NDA 19304

APPROV.
LETTER

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NDA 19-304

DEC 3 1 1993

Fournier Research Inc.
Attention: Mr. R. Lance Boyette
689 Mamaroneck Avenue
P.O. Box 340
Mamaroneck, NY 10543

Dear Mr. Boyette:

Please refer to your New Drug Application (NDA) dated May 30, 1984, and your resubmission dated April 29, 1987, submitted pursuant to section 505(b) of the Federal Food, Drug and Cosmetic Act for Lipidil (fenofibrate) Capsules (100 mg).

We acknowledge receipt of your amendments dated October 26, 1984, and January 29, March 27, May 1, June 25, July 1, July 25, August 22, October 10, and November 7 (2), 1985; March 25, May 20, May 31, July 22, August 3, August 29, September 15, and November 14, 1986; January 20, February 20 and 28, April 29, July 29, August 4, 5, and 17, October 1 and 14, November 4, 6 (2), 17 and 23, and December 1, 1987; February 12, 17 (2), and 24 (2), March 22, April 20, May 18, June 7, 21, 28, September 9, October 3 (3), and December 6, 1988; January 11, March 14, April 7, May 1 and 25, June 2 (2), 6 (2), 7, 9, 14, and 22, August 14, September 13, October 20, 23, 25, and 30, and November 3 and 13, 1989; January 3 (2) and 16, March 1, 5, and 22, April 20, August 27, September 11, October 8, November 15, 1990; January 29, March 22, May 27, June 18, August 23, December 2, 1991; January 13, February 12, 19, 26, April 6 and 24, May 8 and 27, June 15, July 24 and 30, august 17, October 12, November 6 (2), 16, and 25, December 1, 7, 9, 15, 18, and 28, 1992; May 18, June 10, 22, and 29, July 9, August 24 and 26, and November 12, 1993.

This NDA provides for the use of Lipidil as adjunctive therapy to diet for the treatment of adult patients with very high elevations of serum triglyceride levels (Types IV and V hyperlipidemia) who are at risk of pancreatitis and who do not respond adequately to a determined dietary effort to control them.

We have completed the review of this application, as amended, including the revised draft physician insert (PI) labeling submitted November 12, 1993, and the draft carton and container labels submitted August 14, 1989, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the draft PI labeling submitted November 12, 1993. Accordingly, the application is approved effective on the date of this letter.

The final printed labeling (FPL) for the PI must be identical to the November 12, 1993, draft labeling and the August 14, 1989, draft carton and container labels. Marketing the product with FPL that is not identical to this draft labeling may render the product misbranded and an unapproved new drug.

Please submit twelve copies of the FPL as soon as it is available. Seven of the copies should be individually mounted on heavy-weight paper or similar material. For administrative purposes this submission should be designated "FPL for approved NDA 19-304." Approval of this labeling by FDA is not required before it is used.

We note your November 12, 1993, commitments to the following post-approval actions:

1. To complete and file the results of the dose finding studies described in Protocols FEN 8906 and FEN 9107.

2. To conduct, complete, and file the results of the long-term study of fenofibrate in patients with established coronary artery disease, using angiographic end points of effectiveness as described in Protocol FEN 9122 (final protocol submitted November 12, 1993).

3. To develop a new dosing form of fenofibrate approximately equivalent to 50 mg of the present formulation and to study that form to determine its safety and effectiveness.

We request that you describe all submissions relating to these commitments as "Phase 4 commitments for NDA 19-304."

In addition, please submit three copies of the introductory promotional material that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please send one copy to the Division of Metabolism and Endocrine Drug Products and two copies of both the promotional material and the package insert directly to:

Food and Drug Administration
Division of Drug Marketing, Advertising and Communications, HFD-240
5600 Fishers Lane
Rockville, Maryland 20857

Please submit one market package of the drug when it is available.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

Should you have any questions, please contact:

Mr. Stephen T. Trostle
Consumer Safety Officer
Telephone: 301-443-3520.

Sincerely yours,

12/31/93

James Bilstad, M.D.
Director
Office of Drug Evaluation II, HFD-500
Center for Drug Evaluation and Research

cc:
Original NDA orig 12.31.93
HFD-510
HF-2 (with draft labeling)
HFC-130/JAllen
HFD-80 (with labeling)
HFD-230 (with labeling)
HFD-240 (with labeling)
HFD-500/LRipper (with labeling)
HFD-638 (with labeling)
HFD-732 (with labeling)
HFD-510/GTroendle/CNiu/EBarbehenn/EGalliers
HFD-510/STrostle/12/29/93/ft/emg/12/30/rft/emg/12/31/93 \N19304AP.000
Concurrence: AJordan/AJordan for EBarbehenn/12/29/YChiu/12/30/93/
YChiu for CNiu/12/30/GTroendle/EGalliers/GTroendle for SSobel/12/30/93

APPROVAL

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SEP 30 1985

NDA 19-304

G. H. Besselaar Associates
Attention: D.C. Heitz, Ph.D.
103 College Road
East Princeton, New Jersey 08540

Dear Dr. Heitz:

Reference is made to the new drug application submitted on May 31, 1984 pursuant to section 505(b) of the Federal Food, Drug, and Cosmetic Act on behalf of Fournier Laboratories for Fenofibrate Capsules.

We have completed our review and find the information presented is inadequate and the application is not approvable. The deficiencies may be summarized as follows:

The application is not approvable under section 505 (b)(1) of the Act in that the data and information submitted do not establish the safety and efficacy of Fenofibrate Capsules for the proposed indications (i.e., that the drug reduces elevated serum cholesterol and triglycerides and is of benefit in the treatment of severe hyperlipoproteinemias found in some patients in whom dietary measures alone have failed to produce an adequate response). Specifically, the benefits from administering the drug for the proposed indications are judged not to outweigh the risks based on the information submitted and the following information:

1) The drug is a closely-related analogue of clofibrate and the two drugs appear to share a number of pharmacologic and toxicologic effects including hepatic tumorigenicity in rodents and increased lithogenicity in humans (only limited data available for Fenofibrate but data that are available suggest increased lithogenicity).

2) In the World Health Organization (WHO) study, there was a statistically significant higher mortality due to noncardiovascular causes in the clofibrate-treated group compared to the placebo group (half of this difference in mortality was due to malignancy). Although there was a statistically significant decrease in the incidence of nonfatal myocardial infarctions in the clofibrate-treated group, there was no difference in the incidence of fatal myocardial infarctions in the two groups. In the Coronary Drug Project study, there was no significant difference in the incidence of nonfatal or fatal myocardial infarctions, or of noncardiovascular mortality, between the clofibrate-treated and placebo-treated groups.

3) Clofibrate was associated with an increased risk of developing cholelithiasis and cholecystitis requiring surgery in both the WHO and Coronary Drug Project studies.

4) Taking into consideration the above findings, the indications for the clofibrate group of lipid-lowering drugs (clofibrate and gemfibrozil) have been limited as follows:

   i) Adult patients with very high serum triglyceride levels who present a risk of abdominal pain and pancreatitis and who do not respond adequately to a determined dietary effort to control them.

   ii) For clofibrate only: Patients with primary dysbetalipoproteinemia (type III hyperlipoproteinemia) who do not respond adequately to diet).

   In addition, recognition is made of the occasional patient who presents with an unusual combination of severe risk and intolerance or ineffectiveness of all other treatments, for whom this class of drugs may be tried:

   iii) Patients with clearly defined risk due to severe hypercholesterolemia (e. g., individuals with familial hypercholesterolemia starting in childhood) who inadequately respond to appropriate diet and more effective cholesterol-lowering drugs.

5) No information was submitted from well-controlled investigations demonstrating that Fenofibrate Capsules significantly lower triglycerides in patients with very high serum levels or patients with primary dysbetalipoproteinemia. Thus, the application is not approvable for these indications.

   Furthermore, the indication for patients with severe hypercholesterolemia is judged not be be sufficent by itself to approve an NDA for a lipid-lowering drug of the clofibrate class. This judgment is based on benefit-risk considerations including the absence of data from well-controlled studies demonstrating a beneficial effect of this class of drugs on cardiovascular mortality and the safety concerns outlined above in numbered paragraphs 1 through 3.

Additionally, with regard to the manufacturing and controls, we find the following deficiencies:

a) In view of the differences in monograph requirements between the excipients complying with European Pharmacopoeia monograph requirements and United States compendial requirements, it will be necessary that the excipients meeting the United States compendial monograph requirements be used in the manufacture of the finished capsule drug product.

b) In the described synthesis and associated information:

1) Information should be submitted to show that the drug substance used as the reference material has the highest possible purity attainable. It may be a high purity routine lot or one obtained after additional purification. If the latter, the purification procedure should be described and, in any case, the lot, batch, or other identification number given. Its purity should be substantiated by parameters over and above those established for the bulk new drug substance such as elemental or thermal or phase solubility analysis or other independent physical chemical characterization.

2) Of the four different assay procedures submitted for the drug substance, the most precise and accurate procedure should be chosen to be used. Pertaining to the statement on page 8.0126 reading "2. Content 99.98% (as dry product)," the analytical method whereby this result was obtained should be specified.

3) A specification and test procedure for residual isopropanol should be added to the drug substance controls.

4) The submitted controls show the minimum absorption at both 238 um and 240 um wavelengths, the former value on page 8.0131-5, and the latter value on the spectrum. Clarification is requested.

5) What is the exact procedure for draining off the solvent, page 8.0105 steps e and g; how is "constant weight" determined, page 8.0105 step g; and what is the yield of fenofibrate, page 8.0105 step g?

6) The peak assignments in the submitted nuclear magnetic resonance spectrum should be submitted.

7) On page 8.0147, the solubility of the drug substance in hexane should also be added to the submitted solubilities.

8) The chemical name and structure for the impurity 4'-chloro-4-hydroxy-benzophenone is erroneously given on page 8.0168 and should be corrected.

9) Although no hexane wash is specified in the drug substance synthesis, page 8-0150 states that "the marked difference in solubility in hexane between bromoisobutyric acid and fenofibrate would ensure that the former would be removed by washing with hexane". Clarification is requested.

10) Although several testing procedures are submitted for testing of impurities in the drug product, page 8-0112 gives the specification and test procedure for only one impurity. Clarification is requested.

11) Page 8.0177 should be resubmitted with the page numbers filled in.

c) The inconsistency regarding the polyvinyl chloride monomer content in the polyvinyl chloride copolymer plastic used as the blister package laminate requires clarification in that page 8-0311 specifies it to be less than 3 ppm whereas page 8-0325 specifies it to contain not more than 1 ppm.

d) More specific information should be submitted for the varnish in the "aluminum foil complex" which is in contact with the capsules in the blister package.

e) The control numbering system used for the incoming raw materials should be submitted.

f) It is noted that you make use of the bulk fenofibrate drug substance in your assay procedures rather than the reference standard fenofibrate. In this manner you are comparing fenofibrate in the capsules with itself (pages 8.0351-2 and 8.0357) and in our opinion such a procedure is invalid.

g) On page 8-0366, the quantitation instruction for the reference solution for the impurity limits test is in error and requires correction.

h) According to page 625 of Addendum a to the third Supplement to U.S.P.XX, "Weight Variation" testing is not applicable to these finished drug product capsules. It is necessary that "Content Uniformity" testing be used instead.

i) We have the following comments regarding the submitted stability data:

1) As indicated above, weight variation testing of the capsules should be replaced by content uniformity.

2) We note the large variability of the assay results for the finished stored capsules, many lots showing assay increases and several lots showing out-of-specification range assay results.

3) We note that your submitted stability data for the finished capsules do not include dissolution test results.

4) We reserve comment on the proposed five years expiration period until we receive your clarifications on the above manufacturing and controls deficiencies.

5) It is noted in the capsule stability data that TLC was used for the identification of fenofibrate but not for the detection of possible decomposition products during storage. In such circumstances, the UV spectrum assay method may not be stability indicating inasmuch as it may include possible degradation product(s) which may absorb at the same wavelength. It is necessary that you investigate this possibility.

j) With regard to the submitted proposed labeling:

1) In the draft package insert:

i) The DESCRIPTION section should include the fenofibrate chemical structure as required by 21 CFR 201.57(a)(vi).

ii) The format and contents fail to follow the requirements of 21 CFR 201.57. For example, the CONTRAINDICATIONS section should be separated from the WARNINGS section. The hyphen in the middle of "contraindications" should be deleted. A PRECAUTIONS section with its required subsections should be added. Other required sections, i.e. "Drug Abuse and Dependence" and "Overdosage", should be added.

iii) The package insert fails to follow the requirements of 21 CFR 201.10(g)(1), reading, in part: "On any label or page of labeling in which the proprietary name or designation is not featured but is used in the running text, the established name shall be used at least once in the running text in association with such proprietary name or designation and in the same type used in such running text."

iv) The HOW SUPPLIED section is not in accord with 21 CFR 201.57(k) in that it fails to include the strength of the dosage form, "appropriate information to facilitate identification of the dosage form" such as color, "special handling and storage conditions", and the established name.

v) It is suggested that the package insert title section read "Lipantyl Capsules (Fenofibrate Capsules)".

2) In the carton label:

i) Compliance with 21 CFR 201.100(b) is required in the following respects:

The recommended or usual dosage should be transferred to the front panel and have added the statement "See package insert."

The "qsp" on the side panel should be replaced with "qs ad"

The name and address of the manufacturer and distributor should be transferred to the front panel as required by 21 CFR 201.1.

The "Contraindications" and "Warning" sections presently on the side panel should be deleted.

3) In the label submitted on page 4.0010:

It is difficult to determine whether the submitted aluminum foil printed label is for the twelve capsule blister or for each of the twelve rectangles holding one capsule in its blister section. Each blister should have on its back the information contained on the laminate printing submitted. In addition, since the Boston, Massachusetts, facility of Fournier Laboratories does not manufacture the capsules, the name should be preceded by that required by 21 CFR 201.1, e.g. "manufactured for", or "distributed by".

k) In accordance with 21 CRF 207.20 and section 510(g) of the Federal Food, Drug and Cosmetic Act, it will be necessary that you register your firm with FDA Drug Listing Branch, HFN-315.

We have not completed our review of the bioavailability of this product but will do so when the application is resubmitted.

Within 10 days after the date of this letter, you are required to take one of the following actions as described under 21 CFR 314.120:

a) Amend the application or notify us of an intent to file an amendment.

b) Withdraw the application without prejudice to future filing.

c) Request an opportunity for a hearing. Such a request should be submitted to the Division of Regulatory Affairs (HFN-360), Center for Drugs and Biologics, Food and Drug Administration, 5600 Fishers Lane, Rockville, Maryland 20857.

d) Notify us that you agree to an extension of the review period under section 505(c) of the act, so that you can determine whether to respond further under paragraph (a), (b), (c), above. You are required to state the length of such extension.

Sincerely yours,

JBilstad 9/30/85

for Elaine C. Esber, M.D.
Director,
Office of Biologics Research and Review
Center for Drugs and Biologics

cc:NDA Orig.
NWK-DO
HFN-800
HFN-83
HFN-10
HFN-810
HFN-810/RTonelli/10.22.84
rde/10.22.84/7164C
rch/11/1/84
Concur: Berliner, Weston,
Chiu for Kertesz,
Santora, Troendle/10/30/84
Revised:JBilstad/9/26/85/jrs/9/27/85;revised:GTroendle,JBilstad9.30.85/rde/9.30.85
NOT APPROVABLE

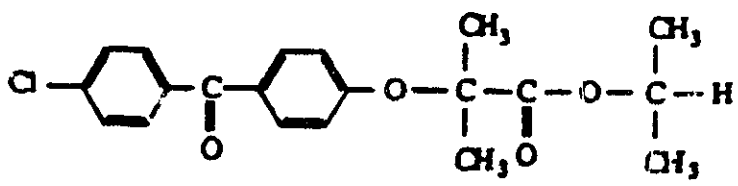
RCB 9/30/85 for S.S.

LBLING

LIPIDIL®
(Fenofibrate Capsules)

DESCRIPTION

LIPIDIL (fenofibrate capsules) is a lipid regulating agent. It is available as capsules for oral administration. Each capsule contains 100 mg of fenofibrate. Each capsule also contains lactose, NF; magnesium stearate, NF; and pregelatinized starch, NF. The chemical name is 2-(4-(4-chlorobenzoyl) phenoxy)-2-methylpropanoic acid 1 methylethyl ester with the following structural formula:



The empirical formula is $C_{20}H_{21}ClO_4$ and the molecular weight is 360.84; fenofibrate is insoluble in water. The melting point is 77-82°C. Fenofibrate is a white solid which is stable under ordinary conditions.

CLINICAL PHARMACOLOGY

The effects of LIPIDIL 100 mg tid on serum triglycerides were studied in two randomized, double-blind clinical trials[1]. 147 hypertriglyceridemic patients (Types IV and V) were treated for eight weeks under protocols that differed only in that one entered patients with baseline triglyceride (TG) levels of 500 to 1500 mg/dL, and the other TG levels of 250 to 500 mg/dL. In patients with hypertriglyceridemia and normal cholesterolemia with or without hyperchylomicronemia (Type IV/V hyperlipidemia), treatment with LIPIDIL decreased primarily very low density lipoprotein (VLDL) triglycerides and VLDL cholesterol. Treatment of patients with Type IV hyperlipoproteinemia and elevated triglycerides often results in an increase of low density lipoprotein (LDL) cholesterol as seen in the following table of changes seen at the end of treatment in patients with triglycerides of 500 to 1500 mg/dL.

Revised: November 12, 1993

Changes in Lipid and Lipoprotein Determinations: *Type IV/V Patients*

	Placebo		LIPIDIL (100 mg tid)		
	Baseline Mean (mg/dL)	% Change	Baseline Mean (mg/dL)	% Change	Net Difference (of %)
Triglycerides					
Total	710	+ 7	726	- 55	- 62
VLDL	537	+ 19	543	- 51	- 70
Cholesterol					
Total	272	0	261	- 14	- 14
HDL	27	+ 5	30	+ 23	+ 18
LDL	100	- 4	103	+ 45	+ 49
VLDL	137	+ 11	126	- 49	- 60

The mechanism of action of LIPIDIL has not been clearly established in man. Fenofibric acid, the active metabolite of fenofibrate, lowers plasma triglycerides apparently by inhibiting triglyceride synthesis, resulting in a reduction of VLDL released into the circulation, and also by stimulating the catabolism of triglyceride-rich lipoprotein (i.e., VLDL). LIPIDIL also reduces serum uric acid levels in hyperuricemic and normal individuals by increasing the urinary excretion of uric acid.

Fenofibrate is well absorbed from the gastrointestinal tract. Following oral administration in healthy volunteers, approximately 60% of a single radiolabelled 300 mg dose of fenofibrate appeared in the urine primarily as fenofibric acid and its glucuronate conjugate, and 25% was excreted in the feces. Peak plasma levels of fenofibric acid occur within 6 to 8 hours after administration, and the compound is eliminated with a half-life of 20 hours. Serum protein binding was approximately 99% in normal and hyperlipidemic subjects. In healthy volunteers, steady-state plasma levels of fenofibric acid were shown to be achieved within 5 days of dosing with 100 mg/day, and did not demonstrate accumulation across time following multiple dose administration. In elderly volunteers 77-87 years of age, the oral clearance of fenofibric acid following a single oral dose of 100 mg was 1.2 L/h, which compares with 1.1 L/h in young adults. This indicates that a similar dosage regimen can be used in the elderly, without increasing accumulation of the drug or metabolites.

In a study in patients with severe renal impairment (creatinine clearance < 50 ml/min), the rate of clearance of fenofibric acid was greatly reduced, and the compound accumulated during chronic dosage.

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However, in patients having moderate renal impairment (creatinine clearance of 50 to 90 ml/min) the oral clearance and the oral volume of distribution of fenofibric acid are increased compared to healthy adults. Therefore, the dosage of LIPIDIL should be reduced in patients who have severe renal impairment, while no modification of dosage is required in patients having moderate renal impairment.

INDICATIONS AND USAGE

LIPIDIL (fenofibrate capsules) is indicated as adjunctive therapy to diet for treatment of adult patients with very high elevations of serum triglyceride levels (Types IV and V hyperlipidemia) who are at risk of pancreatitis and who do not respond adequately to a determined dietary effort to control them. Patients who present such risk typically have serum triglycerides over 2000 mg/dL and have elevations of VLDL-cholesterol as well as fasting chylomicrons (Type V hyperlipidemia). Subjects who consistently have total serum or plasma triglycerides below 1000 mg/dL are unlikely to present a risk of pancreatitis. Improving glycemic control in diabetic patients showing fasting chylomicronemia will usually reduce fasting triglycerides and eliminate chylomicronemia thereby obviating the need for pharmacologic intervention. LIPIDIL therapy may be considered for those subjects with triglyceride elevations between 1000 and 2000 mg/dL who have a history of pancreatitis or of recurrent abdominal pain typical of pancreatitis. It is recognized that some Type IV patients with triglycerides under 1000 mg/dL may, through dietary or alcoholic indiscretion, convert to a Type V pattern with massive triglyceride elevations accompanying fasting chylomicronemia, but the influence of LIPIDIL therapy on the risk of pancreatitis in such situations has not been adequately studied. Drug therapy is not indicated for patients with Type I hyperlipoproteinemia, who have elevations of chylomicrons and plasma triglycerides, but who have normal levels of very low density lipoprotein (VLDL). Inspection of plasma refrigerated for 14 hours is helpful in distinguishing Types I, IV and V hyperlipoproteinemia[2].

The initial treatment for dyslipidemia is dietary therapy specific for the type of lipoprotein abnormality. Excess body weight and excess alcoholic intake may be important factors in hypertriglyceridemia and should be addressed prior to any drug therapy. Physical exercise can be an important ancillary measure. Diseases contributory to hyperlipidemia, such as hypothyroidism or diabetes mellitus should be looked for and adequately treated. Estrogen therapy, like thiazide diuretics and beta-blockers, is sometimes associated with massive rises in plasma triglycerides, especially in subjects with familial hypertriglyceridemia. In such cases, discontinuation of the specific etiologic agent may obviate the need for specific drug therapy of hypertriglyceridemia.

The use of drugs should be considered only when reasonable attempts have been made to obtain satisfactory results with non-drug methods. If the decision is made to use drugs, the patient should be instructed that this does not reduce the importance of adhering to diet.

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Because the benefit/risk ratio of LIPIDIL (fenofibrate) has not been established in clinical trials of primary or secondary prevention to reduce the risk of developing coronary heart disease, LIPIDIL is not indicated for such use. (See WARNINGS and PRECAUTIONS).

CONTRAINDICATIONS

1. Hepatic or severe renal dysfunction, including primary biliary cirrhosis, and patients with unexplained persistent liver function abnormality.

2. Preexisting gallbladder disease (see WARNINGS).

3. Hypersensitivity to fenofibrate.

WARNINGS

1. Because of chemical, pharmacological, and clinical similarities between LIPIDIL (fenofibrate), Atromid-S (clofibrate), and Lopid (gemfibrozil), the adverse findings in 4 large randomized, placebo-controlled clinical studies with these other fibrate drugs may also apply to LIPIDIL. In the first of those studies, the Coronary Drug Project, 1000 subjects with previous myocardial infarction were treated for 5 years with clofibrate. There was no difference in mortality between the clofibrate-treated subjects and 3000 placebo-treated subjects, but twice as many clofibrate-treated subjects developed cholelithiasis and cholecystitis requiring surgery. In a study, conducted by the World Health Organization (WHO), 5000 subjects without known coronary heart disease were treated with clofibrate for 5 years and followed 1 year beyond. There was a statistically significant, 44% higher age-adjusted total mortality in the clofibrate-treated than in a comparable placebo-treated control group during the trial period. The excess mortality was due to a 33% increase in non-cardiovascular causes, including malignancy, post-cholecystectomy complications, and pancreatitis. The higher risk of clofibrate-treated subjects for gallbladder disease was confirmed.

   During the 5 year primary prevention component of the Helsinki Heart Study involving 4081 middle-aged males treated with either gemfibrozil or placebo, and the 3.5 year open extension, total mortality was 22% higher in the original gemfibrozil randomization group (p=0.19, 95% confidence interval for relative risk G:P=0.91-1.64). Cancer deaths trended higher in the gemfibrozil group (p=0.11), while cancers (excluding basal cell carcinoma) were diagnosed in 2.5% of patients in both treatment groups. Because of the more limited size of the Helsinki

Heart Study, the relative risk of death from any cause did not differ statistically from the relative risk of 1.29 clofibrate/placebo observed at the 9 year follow-up of the WHO study. Similarly, the numerical excess of gallbladder surgeries in the gemfibrozil group (0.9% vs. 0.5% with placebo) did not differ statistically from the excess observed in the clofibrate group compared to placebo in the WHO study.

The secondary prevention component of the Helsinki Heart Study involved 628 middle-aged males excluded from the primary prevention study because of known or suspected coronary heart disease and treated with either gemfibrozil or placebo for 5 years. Cardiac deaths trended higher in the gemfibrozil group (17/311 vs. 8/317 placebo patients, p=0.06, hazard ratio 2.2, 95% confidence interval for hazard ratio = 0.94-5.05). Gallbladder surgery was more frequent in the gemfibrozil group (1.9% vs. 0.3%, p=0.07), as was appendectomy (6 cases on gemfibrozil vs. 0 on placebo, p=0.029).

2. **Liver Function: Fenofibrate use at doses of 200 to 300 mg/day is associated with significant increases in serum transaminases [AST (SGOT) or ALT (SPGT)]. Increases to > 3 times the upper limit of normal occurred in 6.3% of LIPIDIL-treated patients taking 200 to 300 mg/day in controlled multiple-dose trials lasting 8-24 weeks.**

Patients with AST or ALT > 3x the Upper Normal Limits in Controlled Clinical Trials vs Fenofibrate (200 to 300 mg/day)

	N	# Events	Events Rate
Control	336	4	1.2%
Fenofibrate	442	28	6.3%

When transaminase determinations were followed either after discontinuation of treatment or during continued treatment, a return to normal limits was usually observed. However, the transaminase determinations remained above normal limits in 2 of the 28 patients (7.1%) at the end of follow-up off treatment. Fenofibrate hepatotoxicity appears to be dose-related. In an 8-week dose-ranging study the incidence of ALT or AST elevations at least three times the upper limit of normal was 13% in patients receiving 200 or 300 mg/day and was 0% in those receiving 100 or 50 mg/day, or placebo. Both hepatocellular and cholestatic hepatitis have been reported. In literature reports, hepatitis associated with fenofibrate has occurred after exposures of weeks to several years.

Regular periodic monitoring of liver function, including serum ALT (SGPT) should be performed

for the duration of therapy with LIPIDIL, and therapy discontinued if enzyme levels persist above three times the normal limit.

3. Cholelithiasis. A gallstone prevalence substudy of 450 Helsinki Heart Study participants showed a trend toward a greater prevalence of gallstones during the study within the gemfibrozil treatment group. Fenofibrate, like clofibrate and gemfibrozil, may increase cholesterol excretion into the bile, leading to cholelithiasis. If cholelithiasis is suspected, gallbladder studies are indicated. LIPIDIL therapy should be discontinued if gallstones are found.

4. Concomitant Oral Anticoagulants. Caution should be exercised when anticoagulants are given in conjunction with LIPIDIL because of the potentiation of coumarin-type anticoagulants in prolonging the prothrombin time. The dosage of the anticoagulant should be reduced to maintain the prothrombin time at the desired level to prevent bleeding complications. Frequent prothrombin determinations are advisable until it has been definitely determined that the prothrombin level has stabilized.

5. Concomitant therapy with LIPIDIL and HMG-CoA reductase inhibitors (such as lovastatin, pravastatin, and simvastatin). No data exists on this combined therapy. The association of the chemically and pharmacologically related similar compound gemfibrozil and Mevacor® (lovastatin) has been associated with rhabdomyolysis, markedly elevated creatine kinase (CK) levels and myoglobinuria, leading in a high proportion of cases to acute renal failure.

In virtually all patients who have had an unsatisfactory lipid response to either drug alone, any potential lipid benefit of combined therapy with HMG CoA reductase inhibitors and LIPIDIL does not outweigh the risks of severe myopathy, rhabdomyolysis, and acute renal failure. The use of fibrates alone, including LIPIDIL, may occasionally be associated with myositis, myopathy, or rhabdomyolysis. Patients receiving LIPIDIL and complaining of muscle pain, tenderness, or weakness should have prompt medical evaluation for myopathy, including serum creatine kinase level determination. If myopathy/myositis is suspected or diagnosed, LIPIDIL therapy should be stopped.

6. The effect of LIPIDIL on coronary heart disease morbidity and mortality and non-cardiovascular mortality has not been established. LIPIDIL should be administered only to those patients described under INDICATIONS AND USAGE. If a significant reduction in fasting chylomicronemia does not occur, LIPIDIL should be discontinued.

Revised: November 12, 1993

PRECAUTIONS

1. **Initial therapy:** Laboratory studies should be done to ascertain that the lipid levels are consistently abnormal before instituting LIPIDIL therapy. Every attempt should be made to control serum lipids with appropriate diet, exercise, weight loss in obese patients, and control of any medical problems such as diabetes mellitus and hypothyroidism that are contributing to the lipid abnormalities. Medications known to exacerbate hypertriglyceridemia (beta-blockers, thiazides, estrogens) should be discontinued or changed if possible prior to consideration of triglyceride-lowering drug therapy.

2. **Continued therapy:** Periodic determination of serum lipids should be obtained during initial therapy in order to establish the lowest effective dose of LIPIDIL. Therapy should be withdrawn in patients who do not have an adequate response after two months of treatment with the maximum recommended dose of 300 mg/day.

3. **Pancreatitis has been reported in patients taking fenofibrate, gemfibrozil, and clofibrate. This occurrence may represent a failure of efficacy or a secondary phenomenon through biliary tract stone or sludge formation and obstruction of the common bile duct.**

4. **Hypersensitivity Reactions:** Acute hypersensitivity reactions including severe skin rashes requiring patient hospitalization and treatment with steroids have occurred very rarely during treatment with *LIPIDIL*. Urticaria was seen in 1.25 vs 0%, and rash in 2.82 vs 1.23% of fenofibrate and placebo patients respectively in controlled trials.

5. **Hematologic Changes:** Mild to moderate hemoglobin, hematocrit, and white blood cell decreases have been observed in patients following initiation of LIPIDIL therapy. However, these levels stabilize during long-term administration. Extremely rare spontaneous reports of thrombocytopenia and agranulocytosis have been received during post-marketing surveillance outside of the U.S. Periodic blood counts are recommended during the first 12 months of LIPIDIL administration.

6. **Skeletal muscle:** The use of fibrates alone, including LIPIDIL may occasionally be associated with myositis. Treatment with drugs of the fibrate class has been associated on rare occasions with rhabdomyolysis, usually in patients with impaired renal function. Myopathy should be considered in any patient with diffuse myalgias, muscle tenderness or weakness, and/or marked elevations of creatinine phosphokinase levels.

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Patients should be advised to report promptly unexplained muscle pain, tenderness or weakness, particularly if accompanied by malaise or fever. CPK levels should be assessed in patients reporting these symptoms, and fenofibrate therapy should be discontinued if markedly elevated CPK levels occur or myopathy is diagnosed.

7. **Drug interactions:**

(A) Oral Anticoagulants: CAUTION SHOULD BE EXERCISED WHEN ANTICOAGULANTS ARE GIVEN IN CONJUNCTION WITH LIPIDIL. THE DOSAGE OF THE ANTICOAGULANTS SHOULD BE REDUCED TO MAINTAIN THE PROTHROMBIN TIME AT THE DESIRED LEVEL TO PREVENT BLEEDING COMPLICATIONS. FREQUENT PROTHROMBIN DETERMINATIONS ARE ADVISABLE UNTIL IT HAS BEEN DEFINITELY DETERMINED THAT THE PROTHROMBIN LEVEL HAS STABILIZED.

(B) HMG-CoA reductase inhibitors: Rhabdomyolysis has occurred when lovastatin was administered in combined therapy with gemfibrozil, a compound of the fibrate class related to fenofibrate. In most patients who have had an unsatisfactory lipid response to either drug alone, any possible benefit of combined therapy with an HMG-CoA reductase inhibitor and LIPIDIL is not outweighed by the risks of severe myopathy, rhabdomyolysis, and acute renal failure. There is no assurance that periodic monitoring of creatine kinase will prevent the occurrence of severe myopathy and kidney damage.

(C) Resins: Since bile acid sequestrants may bind other drugs given concurrently, patients should take LIPIDIL at least 1 hour before or 4-6 hours after a bile acid binding resin to avoid impeding its absorption.

(D) Cyclosporin: Because cyclosporin can produce nephrotoxicity with decrease in creatine clearance and rises in serum creatinine, and because renal excretion is the primary elimination route of fibrate drugs including LIPIDIL, there is a risk that an interaction will lead to deterioration. The benefits and risks of using LIPIDIL with immunosuppressants and other potentially nephrotoxic agents should be carefully considered, and the lowest effective dose employed.

8. **Carcinogenesis, Mutagenesis, Impairment of Fertility:** In a 24-month study in rats (10, 45, and 200 mg/kg; 0.3, 1, and 6 times the maximum recommended human dose on the basis of mg/meter^2 of surface area), the incidence of liver carcinoma was significantly increased at 6 times the maximum recommended human dose in males and females. A statistically significant increase in pancreatic carcinomas occurred in males at 1 and 6 times the maximum

recommended human dose; there were also increases in pancreatic adenomas and benign testicular interstitial cell tumors at 6 times the maximum recommended human dose in males. In a second 24-month study in a different strain of rats (doses of 10 and 60 mg/kg; 0.3 and 2 times the maximum recommended human dose based on mg/meter^2 surface area), there were significant increases in the incidence of pancreatic acinar adenomas in both sexes and increases in interstitial cell tumors of the testes at 2 times the maximum recommended human dose.

A comparative carcinogenicity study was done in rats comparing three drugs: fenofibrate (10 and 70 mg/kg; 0.3 and 1.6 times the maximum recommended human dose), clofibrate (400 mg/kg; 1.6 times the human dose), and gemfibrozil (250 mg/kg; 1.7 times the human dose) (multiples based on mg/meter^2 surface area). Pancreatic acinar adenomas were increased in males and females on fenofibrate; hepatocellular carcinoma and pancreatic acinar adenomas were increased in males and hepatic neoplastic nodules in females treated with clofibrate; hepatic neoplastic nodules were increased in males and females treated with gemfibrozil while testicular interstitial cell tumors were increased in males on all three drugs.

In a 21-month study in mice at doses of 10, 45, and 200 mg/kg (approximately 0.2, 0.7 and 3 times the maximum recommended human dose on the basis of mg/meter^2 surface area), there were statistically significant increases in liver carcinoma at 3 times the maximum recommended human dose in both males and females. In a second 18-month study at the same doses, there was a significant increase in liver carcinoma in male mice and liver adenoma in female mice at 3 times the maximum recommended human dose.

Fenofibrate has been demonstrated to be devoid of mutagenic potential in the following tests: Ames, mouse lymphoma, chromosomal aberration and unscheduled DNA synthesis.

9. **Pregnancy Category C:** Fenofibrate has been shown to be embryocidal and teratogenic in rats when given in doses 7 to 10 times the maximum recommended human dose and embryocidal in rabbits when given at 9 times the maximum recommended human dose (on the basis of mg/meter^2 surface area). There are no adequate and well-controlled studies in pregnant women. Fenofibrate should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

   Administration of 9 times the maximum recommended human dose of fenofibrate to female rats before and throughout gestation caused 100% of dams to delay delivery and resulted in a 60% increase in post-implantation loss, a decrease in litter size, a decrease in birth weight, a 40% survival of pups at birth, a 4% survival of pups as neonates, and a 0% survival of pups to weaning, and an increase in spina bifida.

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Administration of 10 times the maximum recommended human dose to female rats on days 6-15 of gestation caused an increase in gross, visceral and skeletal findings in fetuses (domed head/hunched shoulders/rounded body/abnormal chest, kyphosis, stunted fetuses, elongated sternal ribs, malformed sternebrae, extra foramen in palatine, misshapen vertebrae, supernumerary ribs).

Administration of 7 times the maximum recommended human dose to female rats from day 15 of gestation through weaning caused a delay in delivery, a 40% decrease in live births, a 75% decrease in neonatal survival, and decreases in pup weight, at birth as well as on days 4 and 21 post-partum.

Administration of 9 and 18 times the maximum recommended human dose to female rabbits caused abortions in 10% of dams at 9 times and 25% of dams at 18 times the maximum recommended human dose and death of 7% of fetuses at 18 times the maximum recommended human dose.

10. **Nursing mothers:** Fenofibrate should not be used in nursing mothers. Because of the potential for tumorigenicity seen in animal studies, a decision should be made whether to discontinue nursing or to discontinue the drug.

11. **Use in Children:** Safety and efficacy in children have not been established.

ADVERSE REACTIONS

CLINICAL: Adverse events reported by 1% or more of patients treated with LIPIDIL during the six month and the eight week double-blind, placebo-controlled trials in the U.S.[1,3] are listed in the table below. Adverse events led to discontinuation of treatment in 6% of patients treated with LIPIDIL and in 2% treated with placebo. Skin rashes were the most frequent events, causing discontinuation of LIPIDIL treatment in 2% of patients in double-blind trials.

Revised: November 12, 1993

BODY SYSTEM Adverse Event	LIPIDIL (N = 191)	PLACEBO (N = 183)
BODY AS A WHOLE		
Asthenia/Fatigue	5%	3%
Infections	18%	15%
Flu Syndrome	5%	2%
Localized/Misc. Pain	8%	7%
Headache	5%	4%
CARDIOVASCULAR		
Arrhythmia	1%	1%
DIGESTIVE		
Dyspepsia	5%	7%
Eructation	1%	0%
Flatulence	3%	2%
Nausea/Vomiting	4%	3%
Abdominal Pain	3%	3%
Constipation	3%	2%
Diarrhea	3%	7%
MUSCULOSKELETAL		
Arthralgia	3%	4%
NERVOUS		
Decreased Libido	2%	1%
Paresthesia	1%	2%
Increased Appetite	1%	1%
Dizziness	2%	1%
Insomnia	1%	1%
RESPIRATORY		
Cough	1%	1%
Rhinitis	4%	3%
Sinusitis	1%	1%
SKIN & APPENDAGES		
Pruritus	3%	1%
Rash	6%	2%
SPECIAL SENSES		
Earache	1%	1%
Eye Floaters	1%	0%
Blurred Vision	1%	1%
Conjunctivitis	1%	2%
Eye Irritation	2%	1%
UROGENITAL		
Polyuria	1%	1%
Vaginitis	1%	1%

Revised: November 12, 1993

Additional clinical adverse events reported by fewer than 1% of patients in the U.S. double-blind studies, those reported in other clinical trials, and spontaneously reported in post-marketing surveillance outside the U.S. are listed below, categorized by causality:

PROBABLY CAUSALLY RELATED: Digestive: hepatitis, cholelithiasis, cholecystitis, hepatomegaly; Musculoskeletal: myalgia, myasthenia, rhabdomyolysis; Skin and appendages: photosensitivity, eczema; Respiratory: allergic pulmonary alveolitis.

CAUSAL RELATIONSHIP NOT ESTABLISHED: Body as a whole: facial edema, weight decrease, fever, epistaxis; Cardiovascular: peripheral edema, angina, palpitations, tachycardia, migraine; Digestive: hematemesis, pancreatitis; Respiratory: congestion; Nervous: dry mouth, vertigo, anxiety, sleep disorders, confusion; Skin and appendages: lupus-like syndrome, ichthyosis, telangiectasis, alopecia; Special senses: amblyopia, tinnitus; Urogenital: decreased male fertility, renal lithiasis.

LABORATORY: In the two U.S. placebo controlled studies, serum transaminase determinations (SGPT and/or SGOT) were increased to over three times the upper normal limit in 8 to 10% of patients taking Lipidil at doses of 300 mg/day (See WARNINGS). Other changes that occurred more frequently during Lipidil treatment compared to placebo included increases in creatinine and blood urea, and decreases in hemoglobin and uric acid.

Additional laboratory findings that have been reported during fenofibrate treatment that are probably causally related include: anemia, leucopenia, eosinophilia, thrombocytopenia, and increased creatinine phospholdnase.

DOSAGE AND ADMINISTRATION

Patients should be placed on an appropriate triglyceride-lowering diet before receiving LIPIDIL, and should continue this diet during treatment with LIPIDIL.

LIPIDIL should be given with meals. The initial dose is usually 100 mg per day, depending on the physician's assessment of the patient's risk for pancreatitis (see INDICATIONS AND USAGE). Dosage should be individualized according to patient response, and should be increased sequentially if necessary following repeat serum triglyceride estimations at 4-to-8 week intervals. The maximum dose is 300 mg/day.

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Treatment with LIPIDIL should be initiated at a dose of 100 mg/day in patients having impaired renal function, and increased only after evaluation of the effects on renal function and triglyceride levels at this dose. In the elderly, the initial dose should likewise be limited to 100 mg/day.

OVERDOSAGE

Because fenofibrate is highly bound to plasma proteins, hemodialysis should not be considered.

While there has been no reported case of overdosage, symptomatic supportive measures should be taken should it occur.

HOW SUPPLIED

LIPIDIL (fenofibrate) is available as opaque white hard gelatin capsules. Each capsule contains 100 mg fenofibrate. Each capsule is printed with "LIPIDIL". LIPIDIL is available in bottles of 90 and bottles of 1000.

NDC 0087-0709-41	Bottles of 90
NDC 0087-0709-03	Bottles of 1000

STORAGE

Store in a cool dry place. Protect from temperatures above 30°C (86°F). Avoid excessive light and humidity.

Distributed by

FOURNIER RESEARCH INC.
689 Mamaroneck Avenue
P.O.Box 340
MAMARONECK
N.Y. 10543

CAUTION–Federal law prohibits dispensing without prescription.

Revised: November 12, 1993

REFERENCES

1. Goldberg AC, et al: Fenofibrate for the Treatment of Type IV and V Hyperlipoproteinemias: A Double-Blind, Placebo-Controlled Multicenter US Study. Clinical Therapeutics 11: 69-83, 1989.

2. Nikkila EA: Familial Lipoprotein Lipase deficiency and related disorders of chylomicron metabolism. In Stanbury J.B. et al. (eds.): The Metabolic Basis of Inherited Disease, 5th edition, Mc Graw - Hill, 1983, Chap. 30, pp. 622-642

3. Brown WV, et al: Effects of Fenofibrate on Plasma Lipids: Double-Blind, Multicenter Study in Patients with Type IIA or IIB Hyperlipidemia. Arteriosclerosis 6: 670-678, 1986.

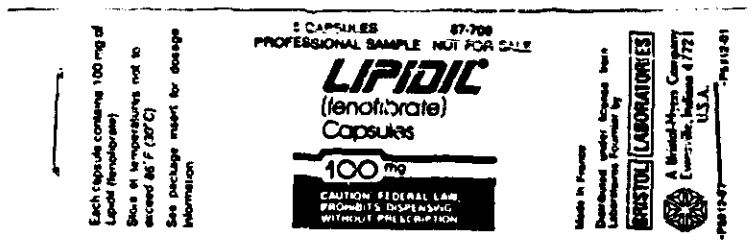
Revised: November 12, 1993

Label for Bottles of 6
(P5912-01)

Dated 8/14/89

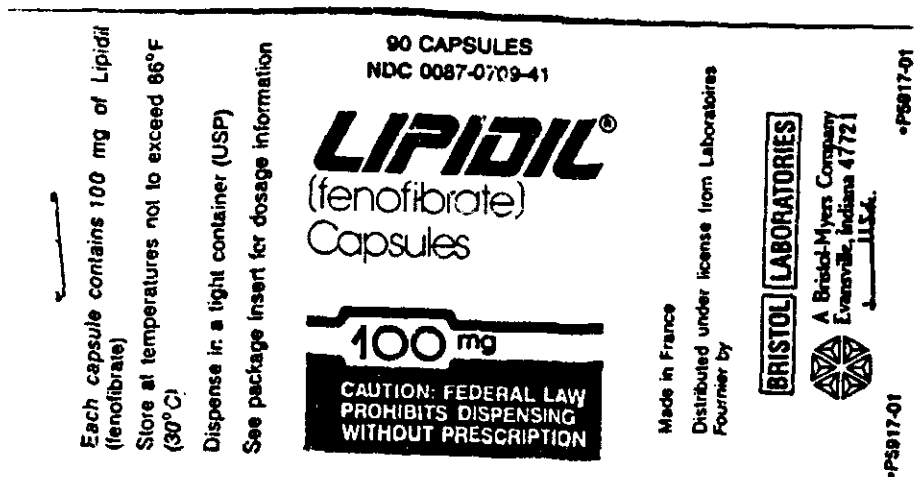
Received 8/18/89

360



Label for Bottles of 90
(P5917-01)

361



(60x)
carton label

362

(front panel)

1000 CAPSULES
NDC 0087-0709-03

LIPIDIL®
(fenofibrate)
Capsules

100 mg

CAUTION: Federal Law Prohibits
Dispensing Without Prescription

(left panel)

Each capsule contains 100 mg of LIPIDIL (fenofibrate)
Store at temperatures not to exceed 86° F (30°C)
Dispense in a tight container (USP)
See package insert for dosage information

(right panel)

Made in France
Distributed under license from Laboratories Fournier by
BRISTOL LABORATORIES
A Bristol-Myers Company
Evansville, Indiana 47721
USA

PATENT& EXCLUSIVITY SUMMARY

DF

EXCLUSIVITY SUMMARY FOR NDA # 19-304 SUPPL # —

Trade Name Lipidil Generic Name fenofibrate

Applicant Name Fournier Research Inc. HFD # 570

Approval Date If Known _____

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following question about the submission.

a) Is it an original NDA?

YES /✓/ NO /___/

b) Is it an effectiveness supplement?

YES /___/ NO /✓/

If yes, what type? (SE1, SE2, etc.) _____

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES /✓/ NO /___/

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

_____

_____

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

_____

_____

d) Did the applicant request exclusivity?

YES /___/ NO /✓/

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule, previously been approved by FDA for the same use?

YES /___/ NO /✓/

If yes, NDA #_____. Drug Name _____.

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

3. Is this drug product or indication a DESI upgrade?

YES /___/ NO /✓/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /___/ NO /✓/

If "yes," identify the approved drug product(s) containing active moiety, and, if known, the NDA #(s).

NDA# _____ _____

NDA# _____ _____

NDA# _____ _____

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES /___/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# _____ _____

NDA# _____ _____

NDA# _____ _____

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. IF "YES" GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES /___/ NO /___/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES /___/ NO /___/

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

_____

_____

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /___/ NO /___/

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion?

YES /___/ NO /___/

If yes, explain: _____

_____

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /___/ NO /___/

If yes, explain: _____

_____

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

_____

_____

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES /___/ NO /___/

Investigation #2 YES /___/ NO /___/

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

_____ _____

_____ _____

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES /___/ NO /___/

Investigation #2 YES /___/ NO /___/

If you have answered "yes" for one or more investigations, identify the NDA in which a similar investigation was relied on:

_____ _____

_____ _____

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

_____ _____

_____ _____

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1	
IND # _____ YES /___/	NO /___/ Explain: _____
	_____
Investigation #2	
IND # _____ YES /___/	NO /___/ Explain: _____
	_____

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1	
YES /___/ Explain _____	NO /___/ Explain _____
_____	_____
_____	_____
Investigation #2	
YES /___/ Explain _____	NO /___/ Explain _____
_____	_____
_____	_____

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /___/ NO /___/

If yes, explain: _____

_____

Stephen T. Troolin
Signature
Title: Consumer Safety Officer

December 29, 1993
Date

Gloria Troolin for Sharf
Signature of
Division Director

12-30-93
Date

EXCLUSIVITY DETERMINATION CHECKLIST

(. #_____ SUPPL. #_____ APPLICANT_____ TR. NAME_____

ACTIVE INGRED._____ POTENCY_____ DOSAGE FORM/ROUTE_____

APPROVAL DATE_____

TYPE OF APPLICATION: FULL NDA____ 505(b)(2)___ EFFIC. SUPP.___ OTHER (SPECIFY)___

EXCLUSIVITY REQUESTED: 5 YR___ 3 YR___ NONE___

QUALIFICATIONS FOR 5 YR EXCLUSIVITY:

Approved for NCE, no salt or ester of which previously approved_____

QUALIFICATIONS FOR 3 YR EXCLUSIVITY:

Approval based on clinical study (other than BIO)? Y___ N___ _____

New Studies:

Previously relied on by Agency for efficacy? Y___ N___

Essential for Approval:

Approval could have been based on literature? N___

Previously approved in another application? N___

Studies conducted by or for applicant:

IND sponsored by applicant? Y___

or

Certification of principal support? Y___

NOTE: If any checks appear in shaded area, it is likely that exclusivity should not be granted. Any exclus. recommendations should be explained below:_____

EXCLUSIVITY RECOMMENDED: 5 YR___ 3 YR___ NONE___

CONCUR _____ SIGNED_____

NON CONCUR_____) DIRECTOR, OFFICE OF GENERIC DRUGS

(

LABORATOIRES FOURNIER S.A.

NDA 19-304
LIPIDIL^{R} (fenofibrate)

ITEM 13

PATENT INFORMATION (21 U.S.C. 355 (b))

1. Active Ingredient	Fenofibrate
2. Strength	100 mg
3. Trade name	LIPIDIL^{R}
4. Dosage Form, Route of Administration	Capsules, Oral
5. Applicant Firm Name	Laboratoires FOURNIER SA
6. NDA Number	19-304
7. Lenght of Exclusivity Period	5 years
8. Patent Information	
(1) Patent Number Date of Expiration	4,058,552 November 15. 1994
(2) Type of Patent	Drug (Formulation or Composition)
(3) Name of Patent Owner	ORCHIMED S.A.
(4) Name of U.S. Agent Authorized to Receive Notice of Patent Certification	Jean M. BOBOC, M.D., M.B.A. FOURNIER RESEARCH, Inc. 689 Mamaroneck Avenue P.O. Box 340 MAMARONECK, N.Y. 10543 Tel. (914) 381-2232

LABORATOIRES FOURNIER S.A.

NDA 19-304
LIPIDIL[R] (fenofibrate)

ITEM 14

PATENT CERTIFICATION (21 U.S.C. 355 (b))

The undersigned certifies that the drug and formulation or composition of fenofibrate is claimed by Patent N° 4,058,552. This product is the subject of a New Drug Application (NDA 19-304) for which approval is being sought.

François PICART
Director,
Industrial Property
LABORATOIRES FOURNIER S.A.

DEBARMENT CERTIFICATION NOT NEEDED
NDA SUBMITTED PRIOR TO JUNE 1, 1992

MED REVIEW

To:the File of NDA-
From: Solomon Sobel M.D..Director, Division of Metabolism and Endocrine Drug Products 2/19/93
Subject: Approval of Lipidil (fenofibrate,Fournier)

The issues to be discussed are:

1.What were the results of the Advisory Committee of 1989?

2. What were the commitments we made in regard to the dose ranging triglyceride study in October 1990

3. Has the company met those commitments ?.

4. What measures do we have of the relative toxicity of fenofibrate in respect to other members of this class in regard to
a.hepatotoxicity
b.hematalogic toxicity
c.allergenicity

5. Are there specific issues in the preclinical toxicology in regard to
a.mutagenicity?
b.hepatotoxicity?

6. What is the evidence for fraud, an issue raised by Dr. Pierce in memos of January 1993?. How is this being addressed?

7. What are the outstanding labeling issues?

1.On June 29,1989 an Advisory Committee meeting was held in regard to the approvability of fenofibrate. The Advisory Committee members agreed that the risk benefit favored the approval of fenofibrate for the indication of lowering triglycerides for the prevention of acute pancreatitis. They felt that the surrogate endpoint of serum triglyceride lowering was sufficent for the indication. There was a majority opinion that a placebo controlled trial to demonstrate a reduction in episodes of acute pancreatitis was not feasible. There was also unaninamous agreement that a dose ascertainment for the lowest dose could be done as a phase 4 study.
Earlier in that meeting a consultant on liver diseases, Dr. Hyman Zimmerman recommended that monitoring of liver enzymes be done indefinitely during treatment with fenofibrate. There were no specific questions on the issue of hepatotoxicity nor did any member raise the issue during the discussion of risk benefit. [for details see pages 93-100 (Dr. Zimmerman)
and pages 214-233(questions) of volume 1 of 1 of the transcript of the meeting].
The issue of the pharmacologic treatment of hypertriglyceridemia to prevent acute pancreatitis is a difficult one. We have maintained that drug treatment of patients with levels above 1000mg/dl is indicated.(the precise sequence of treatment in relationship to good dietary managemnt is not delineated). It is true that many questions remain unresolved. Further studies are needed to

TROSTLE

delineate the comparative effects of dietary management vs. fibrate therapy in regard to lithogenenesis and other adverse reactions (see Dr. Kuller´s comments at the Advisory commitee.) Also one must address the effect that the rise in LDL seen with the reduction of high triglyceride levels may have on the overall risk benefit ratio. The primary question is whether drug treatment is beneficial in reducing episodes of acute pancreatitis in patients with refractory triglyceridemia. We do not have a good prospective study to test the question. Dr. Innerfeld wishes to introduce caveats in respect to the unanswered issues into the label. I think that we should not do this at this time. I believe the issue of the efficacy of fibrates in tghe prevention of acute pancreatitis should be presented to an Advisory Committee; we should then consider action in the labeling of all the fibrates.

2. In a meeting with the firm on October 25,1990, we agreed that drug approval would be considered provided that the final protocol for the triglyceride dose ranging study had been submitted to the Division, the study was underway at each center and that the recruitment projections were realistic.

3. The company has met the commitments under point 2.

4. Fenofibrate has posed special problems in regard to its adverse reaction profile. The spontaneous reporting system in France from 1981 to 1987 based on some 4.3 million patient years of use when compared to an adjusted usage of 800,0000 patient years indicates that fenofibrate is more hepatotoxic. This result is obtained from data that do not include the experience for the first five years of use (the data were not collected during those years). The years following introduction are ordinarily attended by the greatest reporting of adverse events. (see Dr. Pierce´s review of this)

Similar concerns are seen in regard to allergenicity (particularly dermatologic) and hematologic (particularly leukopenia and anemia).

One cannot dismiss the possibility/probability that fenofibrate in the currently recommended doses is more toxic in these respects than the other available fibrates(gemfibrozil and clofibrate). Unfortunately, there are no concurrent comparisons under controlled trial conditions.

I feel that the best approach (as we have discussed) would be to list the adverse reactions in a tabular fashion. It would not be correct to give comparative data. When the dose ranging study safety data are available,they will be a especially important in assessing toxicity since these data are reflective of safety in patients(Type4/5) who may be especially vulnerable to the adverse effects of fenofibrate. Also,if the study results in a lowered dose recommendation this will be helpful in reducing the disparate toxicity if such exists. Preliminary data show that serum liver enzyme elevations above 3 times normal did not occur in the dose of 100 mg /day.
However, sufficient data for approval are now available;labeling changes reflecting the outcome of the dose ranging studies can be made later.

5. The issues of toxicity and carcinogenicity in pre clinical studies has been addressed by Dr. Barbehenn. There is no clear delineation of this fibrate from clofibrate and gemfibrozil. The issue of the dose at which the studies were done in regard to AUC ratios and the MTD was raised. In general, the levels are of the same order of the studies on clofibrate and gemfibrozil. Again

dosage reduction (if that is the outcome of the dose ranging study) will further mitigate this issue.
Extensive mautagenicity studies were negative (see Dr. Dunkle's reports).

6. The issue of the accuracy of reporting must be addressed. We will meet with the scientific monitoring Division. Further auditing is currently being done .

7. Some of the labeling issues have been discussed above. The most difficult area will be the writing of the table for adverse reaction;this must await resolution of the accuracy of the sponsor reports issue.

Recommendation;
I am recommending approval of this NDA. I am submitting this for Dr. Bilstad's parallel review while the remaining issues are addressed,i.e accuracy of reporting and the final label.

DRUG STUDIES IN PEDIATRIC PATIENTS
(To be completed for all NME's recommended for approval)

NDA # 19-304 Trade (generic) names Lipidil (fenofibrate)

Check any of the following that apply and explain, as necessary, on the next page:

____ 1. A proposed claim in the draft labeling is directed toward a specific pediatric illness. The application contains adequate and well-controlled studies in pediatric patients to support that claim.

____ 2. The draft labeling includes pediatric dosing information that is not based on adequate and well-controlled studies in children. The application contains a request under 21 CFR 210.58 or 314.126(c) for waiver of the requirement at 21 CFR 201.57(f) for A&WC studies in children.

____ a. The application contains data showing that the course of the disease and the effects of the drug are sufficiently similar in adults and children to permit extrapolation of the data from adults to children. The waiver request should be granted and a statement to that effect is included in the action letter.

____ b. The information included in the application does not adequately support the waiver request. The request should not be granted and a statement to that effect is included in the action letter. (Complete #3 or #4 below as appropriate.)

____ 3. Pediatric studies (e.g., dose-finding, pharmacokinetic, adverse reaction, adequate and well-controlled for safety and efficacy) should be done after approval. The drug product has some potential for use in children, but there is no reason to expect early widespread pediatric use (because, for example, alternative drugs are available or the condition is uncommon in children):

____ a. The applicant has committed to doing such studies as will be required.

____ (1) Studies are ongoing.
____ (2) Protocols have been submitted and approved.
____ (3) Protocols have been submitted and are under review.
____ (4) If no protocol has been submitted, on the next page explain the status of discussions.

____ b. If the sponsor is not willing to do pediatric studies, attach copies of FDA's written request that such studies be done and of the sponsor's written response to that request.

✓ 4. Pediatric studies do not need to be encouraged because the drug product has little potential for use in children.

____ 5. If none of the above apply, explain.

Explain, as necessary, the foregoing items: _____

Signature of Preparer

2/17/93
Date

cc: Orig NDA
HFD-___ /Div File
NDA Action Package

MEMORANDUM

ORIGINAL

NDA 19304
Fenofibrate
Triglyceride lowering agent

Fournier Laboratories
Label received by MO 5-20-93
Evaluation written 5-21-93

Group Leader's Review of NDA Proposed Package Insert

I have used label proposals from sponsor and with changes suggested by Dr. Innerfield. The following recommendations are for changes from the original proposed by the sponsor and include some of what Dr. I suggested. Further changes will likely be necessary when the prliminary data from the dose ranging study is reviewed.

Page 1, CLINICAL PHARMACOLOGY, replace entire paragraph with: "The effects of LIPIDIL 100 mg tid on serum triglycerides were studied in two randomized, double-blind clinical trials. 147 hyperglyceridemic patients (Types IV and V) were treated for eight weeks under protocols that differed only in that one entered patients with baseline triglyceride (TG) levels of 500 to 1500 mg/dL, and the other TG levels of 350 to 500 mg/dL. In patients with hypertriglyceridemia and normal cholesterolemia with or without hyperchylomicronemia (Type IV/V hyperlipidemia), treatment with LIPIDIL decreases primarily very low density lipoprotein (VLDL) triglycerides and VLDL cholesterol. Treatment of patients with Type IV hyperlipoproteinemia and elevated triglycerides often results in an increase of low density lipoprotein (LDL) cholesterol as seen in the following table of changes seen at the end of treatment in patients with triglycerides of 500 to 1500 mg/dL."

Page 2, table title might say "Type IV/V Patients" instead of "Type IV Patients." Second paragraph, add at the end of line 3, after "in the feces," "Peak plasma levels of fenofibric acid occur within 6 to 8 hours after administration, and the compound is eliminated with a half-life of 20 hours."

INDICATIONS AND USAGE, Add to first paragraph, end of line 6 after sentence ending, "risk of pancreatitis," "Improving glycemic control in diabetic patients showing fasting chylomicronemia will usually reduce fasting triglycerides and eliminate chylomicronemia thereby obviating the need for pharmacologic intervention."

Page 3, 2nd paragraph of INDICATIONS, 5th line, add "~~like~~ thiazide diuretics and beta-blockers" after "Estrogen therapy." In the next sentence, "estrogen therapy" should be replaced with "the specific etiologic agent."

Page 5, last paragraph of WARNING 1. is duplicated in WARNING 5. (to become WARNING 7.). page 6, and should be omitted from WARNING 1.

Page 7 in Dr. I's review includes a table of ALT & AST in patients on lipidil. It is not appropriate to include ADR

frequency data derived from spontaneous reports, because ascertainment of adverse events and the extent of exposure are both uncertain in the extreme. The tendency is to underestimate the number of events and overestimate exposure, leading to wildly inaccurate frequency estimations. However, I do not see that there is any section of either WARNINGS or PRECAUTIONS that addresses liver dysfunction and I think there should be as the second WARNING page 5 as follows:

2. "Liver Function: Fenofibrate use is associated with *significant hepatotoxicity. Increases in serum* transaminases [AST(SGOT) or ALT(SGPT)] to > 3 times the upper limit of normal occurred in 5-10% of LIPIDIL-treated patients in controlled multiple-dose trials lasting 8-24 weeks.

Controlled Clinical Trials
AST or ALT > 3x the Upper Normal Limits

	N	#Events	Event Rate	Hepatitis Rate
Control	339	4	1.18%	0%
Fenofibrate	596	30	5.03%	0.17%

Transaminase elevations returned toward normal when fenofibrate therapy was discontinued, but 57% of the 3-fold elevations remained abnormal at the last observation. Fenofibrate hepatotoxicity appears to be dose-related. In an 8-week dose-ranging study, the incidence of ALT or AST elevations at least 3 times the upper limit of normal was 13% in patients receiving 200 or 300 mg/day and was 0% in those receiving 100 or 50 mg/day, or placebo. Both hepatocellular and cholestatic hepatitis have been reported. In literature reports, hepatitis associated with fenofibrate has occurred after exposures of weeks to several years.

Regular periodic monitoring of liver function, including serum ALT (SGPT) should be performed for the duration of therapy with LIPIDIL (see WARNINGS), and therapy discontinued if enzyme levels persist above 3 times the upper normal limit.

Sections 3. through 5. should be the ones now numbered 2. to 4. and titled "Cholelithiasis," "Concomitant Oral Anticoagulants," "Concomitant Therapy with LIPIDIL and HMG-CoA reductase inhibitors."

Page 6, WARNING 4. (to become 5.), last paragraph, 5th line add "or rhabdomyolysis" after "myothathy."

Page 6, before the current 5., an additional warning should be added as follows: "6. Pancreatitis has been reported in patients taking fenofibrate, gemfibrozil, and clofibrate, including 4/4 positive rechallenges. This occurrence may represent a failure of efficacy, a direct toxic effect, or a secondary phenomenon through biliary tract stone or sludge formation and obstruction of the common bile duct."

WARNING 7. should say, "The effect of LIPIDIL on coronary heart disease morbidity and mortality and non-cardiovascular mortality has not been established. In view of a) liver, pancreatic, and Leydig cell tumor development in fenofibrate-treated rodents at modest multiples of human exposure, b) liver toxicity, c) gallbladder toxicity, increased appendectomies and other gastrointestinal surgical procedures seen in association with the chemically and pharmacologically-related fibrate, gemfibrozil, d) the gallbladder toxicity and increased total and non-cardiovascular mortality with the chemically and pharmacologically-related fibrate, clofibrate, in the WHO study, and e) the potential for rhabdomyolysis, LIPIDIL should be administered only to those patients described under INDICATIONS AND USAGE. If a significant reduction in fasting chylomicronemia does not occur, LIPIDIL should be discontinued.

Page 6, PRECAUTION 3. has been elevated to a WARNING and may be omitted from PRECAUTIONS.

Page 8, PRECAUTION 4., (D)Cyclosporin, third line, following "LIPIDIL," the rest of the line would be smoother if it said "there is a risk that an interaction will lead to deterioration."

Page 8, last sentence of PRECAUTION 5. should say, "Fenofibrate has been demonstrated to be devoid of mutagenic potential in the following tests: Ames, mouse lymphoma, chromosomal aberration and unscheduled DNA synthesis.

Page 9, PRECAUTION 7. Nursing Mothers should say, "Fenofibrate should not be used in nursing mothers. Because of the potential for tumorigenicity seen in animal studies, a decision should be made whether to discontinue nursing or to discontinue the drug."

Page 9, PRECAUTION 8. should be moved to become PRECAUTION 4. second line should say "frequently" rather than "occasionally." Add at the end of the second sentence, "In three U.S. trials, there were 4 patients with treatment emergent granulocytopenia less than 1000/mm^2, and there have been 2 spontaneous reports of agranulocytosis with LIPIDIL. The last sentence should omit "Rarely," and begin, "Cases of leukopenia, thrombocytopenia and..."

Page 10, PRECAUTION 9. should be moved to become PRECAUTION 5.

Page 10, PRECAUTION 11. should become PRECAUTION 3., Hypersensitivity Reactions, add at the end of the paragraph, "~~Anaphylaxis was seen in 0.41 vs 0%~~, urticaria in 1.22 vs 0%, and rash in 3.66 vs 1.23% of fenofibrate and placebo patients respectively in controlled trials."

Page 10, Clinical, replace the second, third and fourth sentences with, "Adverse events led to discontinuation of treatment in 6% of patients treated with LIPIDIL and in 2% treated with placebo. Skin rashes were the most frequent events, causing

discontinuation of LIPIDIL treatment in 2% of patients in double-blind trials.

Page 12, top paragraph should say, "Additional clinical adverse events reported by fewer than 1% of patients in the U.S. double-blind studies, those reported in other clinical trials, and spontaneously reported in post-marketing surveillance outside the U.S. are listed below, categorized by causality:"

Page 13, last paragraph before DOSAGE AND ADMINISTRATION, remove "rarely" from the first line. The DOSAGE AND ADMINISTRATION section must be revised when we have reviewed the preliminary data from the dose-ranging study.

Gloria Troendle
8-20-93

Todd
Troendle

Gloria -
I concur in your comments.
Has the sponsor said when a
final report on the trig/cride
study would be submitted?
Tod

cc: NDA (19304)
HFD-510
HFD-510/GTroendle/STmostko

MEMORANDUM

ORIGINAL

24 June 1993

3

FROM : Gloria Troendle, Division Metabolic Endocrine Drug Products, FDA

TO : Solomon Sobel, Director Division Metabolic Endocrine Drug Products, FDA

SUBJECT: Fenofibrate Labeling Recommendations, Reply to Response of 6-22-93 to Our Proposal of 6-17-93. Also telecon of 6-22-93 between Gloria Troendle and Dr. Irvine and Mr. Boyett.

The Fournier response includes 6 points.

1. Information regarding the liver function number of patients with "hepatitis," was taken from Dr. Innerfield's recommendations. It is based on 1 patient in study FEN8601 out of 596 fenofibrate-treated patients in the studies FEN8104, 8507, 8601, 8802, 8904, 8906. The ALT/AST >3 X ULN are for 14 fenofibrate patients in 8104, 6 in 8601, 2 in 8802, and 8 in 8906, and 3 placebo patients in 8104, and 1 in 8601. Total control (placebo or simvastatin) patients in those studies were 339. Fournier requests this reference to the studies that were included. They also request an explanation of the 57% (I explained it was the 30 patients with >3X elevations of enzymes that had not returned to baseline at the last follow-up. They asked if it would be all right for them to indicate also how many of the patients were followed, and I said I thought so. They will propose such an inclusion for our consideration.

2. Fournier represetatives said that WARNING 6 was a duplicate of WARNING 1. I had intended to remove duplications and had suggested that the final paragraph of WARNING 1 be omitted, so I told them that redundancies could be omitted, but I was not sure at the time what was appearing more than once.

3. This pancreatitis PRECAUTION was based on Dr. Innerfield's suggestion. He says that all of the cases with rechallenge were from our Division of Drug Epidemiology and Surveilance. These reports are on gemfibrozil and should be available on request to FOI.

4. Anaphylaxis was listed wrongly. It was a case in a placebo patient. They asked to remove it anyway, and I agreed. They ask that we provide the source of information for the other hypersensitivity cases. Rash was seen in 14 fenofibrate patients in FEN8104 and 1 in 8601; rash was seen in 3 placebo patients in 8104. Also, urticaria was seen in 4 patients in 8104 and 1 in 8802. In both cases the Ns for denominators were 410 fenofibrate and 244 placebo patients in the 3 studies.

5. I recommended that PRECAUTION 8 on Page 9 should characterize hematologic decreases as frequent rather than occasional, based on Dr. Innerfiel's proposal, but also remembering gemfibrozil data in which such changes were frequent, but rarely marked. Because this sentence specifies mild to moderate changes, I think it is proper. However, the Fournier representatives thought it would "alarm" physicians. They also thought the word "rarely" was appropriate for refering to cases of leukopenia, thrombopenia and eosinophilia, but I think these cases are just cases of WBC or platelets below the lower limits of normal or

eosinophils above the upper limits, and that is hardly "rare" even in patients not taking drug.

6. The company wants to omit the table of adverse events. There seem to me to be 3 tables, none of which contribute much since we have already made WARNINGS and PRECAUTIONS of most of our concerns, and what is left is trivial and probably not drug related. They want to say in a few words, what the residual events were. I thought that would be acceptable.

Gloria Troendle

Gloria Troendle

CC: NDA (19304)
HFD-510
HFD-510/G Troendle/S Trostb

ORIGINAL

(To Dr Truscello
(Concurrence)

NDA 19304
Fenofibrate
Triglyceride lowering agent

MAY 20 1993

Fournier Laboratories
Papers received by MO 5-18-93
Evaluation written 5-20-93

Group Leader's Review of Application and Evaluation of Reviews and Comments from Previous Group Leader

Papers written by Dr. L. Ross Pierce, the previous Group Leader for this drug do not clearly conclude that this drug is or is not approvable, although one paper suggests not approvable without some resolution of the problem he sees as possible data tampering. Some of his papers suggest serious deficiencies or misrepresentations of data, which I am attempting to evaluate, and many have recommendations requesting further data. Because of the long review history of this drug, it is hard to justify further requests unless they are of major importance and would alter the decision on benefit to risk. Most of the requests for data involve issues that might affect wording in the label. This NDA contains much data that has been reviewed over the years and a decision must be made with the least possible delay, so I would prefer to propose stringent ADR labeling, and let the firm, if they wish, submit what they think would make strict labeling unnecessary. I have mentioned here the papers that have material of interest to deciding on approvability and labeling issues and that have recommendations. The 9 papers I include in this paper have apparently been written over several months, but were not completed and say they were terminated due to reassignment of the medical officer (Dr. Pierce). At least some of them were printed 5-14-93 and all bear that date.

ADDENDUM AND COMMENTS TO MOR OF 5TH SAFETY UPDATE (9-17-92) includes review of 18 articles from literature and of data from clinical trials of micronized fenofibrate. The literature is very interesting and well summarized by Dr. Pierce in this review. Studies comparing fenofibrate with simvastatin showed effects of fenofibrate on fatty acid composition of lipoproteins and on LpAII:LpAI and LpAI particle content that were less favorable than the effects of simvastatin. Four cases of photosensitivity to fenofibrate all showed positive dechallenge and positive rechallenge. Severe rhabdomyolysis with renal failure was reported in a patient on fenofibrate and no other known cause of myositis. Another article included 26 cases of myositis and related effects in patients on fenofibrate. One is a case report of hepatitis. The micronized fenofibrate studies were a mixture of open controlled and uncontrolled treatments of questionable value. Dr. Pierce recommends demanding death certificate cause of deaths for 12 patients in the "French Registry" who died for unknown reasons, although the sponsor claims they do not have access to this information. He also wants 1) a randomized, double-blind, placebo-controlled study of Lp(a) and LpAI and LpAII:LpAI particles, 2) baseline and individual patient data for Lp(a) for the simvastatin and lovastatin comparative trials, 3) tables of liver function tests for patients with LFT $\geq$2x ULN for several protocols, 4) further

analyses of safety data for another protocol, 5) details of skin reactions in these studies, and 6) labeling to say it is contraindicated in patients receiving cyclosporin because of high dropout rate for renal dysfunction in heart transplant patients. I do not believe that any of this requested data is essential, and since it was written last September, it was probably either requested then or a decision made not to request it.

GROUP LEADER'S REVIEW OF HEPATOTOXICITY OF FENOFIBRATE (11-16-92) includes anlysis of some patients whose CRFs were reviewed 2-26-93 (see below). Patients are from controlled and uncontrolled studies. It is almost certain that this drug can cause severe hepatotoxicity. The important issue is whether this is clearly different and worse than approved fibrates or whether it can be handled in labeling. Combining controlled trials, literature reports and spontaneous reports, Dr. Pierce seems to conclude that symptomatic aminotransferase elevations in patients on fenofibrate are 20 times the incidence in patients on gemfibrozil. Also, he says that fenofibrate is 100 times more hepatotoxic than lovastatin, and recommends 1) monitoring ALT at baseline and monthly for 15 months, then q 2-3 months for life and 2) a boxed warning for all fibrates. These recommendations for fenofibrate may be acceptable. Fenofibrate label should have a boxed warning if data are comparable to data required for boxed warning on other drugs, but I doubt gemfibrozil or clofibrate will meet that criterion. Monitoring seems reasonable.

GROUP LEADER'S REVIEW OF FRENCH POST-MARKETING SURVEILLANCE REPORTS (11-22-92) covers period from 1979 to 1987 and reports 120 gallstones, 206 hepatic reports, 124 renal, 119 cutaneous, 117 hematological, 102 sexual asthenia, 78 GI and 44 muscle reports in 4.4 million patient-year equivalents of exposure.

GROUP LEADER'S REVIEW OF SKIN/ALLERGIC REACTIONS (11-30-92) is a review of the entire data base apparently beginning with the anaphylaxis referred to in my review of the original submission of the NDA. 35 reports of rash and eosinophilia were noted in 7 studies and 41 allergic reactions in spontaneous reports. No recommendations were made.

GROUP LEADER'S REVIEW OF CASE REPORT FORM OF PATIENT EXPERIENCING ANAPHYLLACTIC REACTION (2-26-93) is simple review of event in which patient was on placebo. No action is recommended.

GROUP LEADER'S REVIEW OF CRF'S OF PATIENTS EXPERIENCING HEPATOTOXIC REACTIONS (2-26-93) includes review of CRF's from a 1989 submission of US type II trial, #8104 and type IV trial 8601. In 8104, 100mg fenofibrate was given TID for 24 wks with an open extension of 24 weeks. In 8601, treatment period was 8 wk. Dr. Pierce found discrepancies in the number of weeks of the study and the number of pills consumed, and omission of symptoms compatible with hepatitis in the tabular listings. It appears that perhaps the tabulation was sloppy and inaccurate, but it is not clear that the differences are great enough to affect the

evaluation of the study. Division of Scientific Investigations is expected to investigate the studies. It is important to get their evaluation of this problem, and to see if they feel that the data reviewed by Dr. Pierce were tampered with by the sponsor. Dr. Pierce recommends this course.

SUMMARY OF SIGNIFICANT VARIATIONS BETWEEN NDA DATA TABULATIONS AND CASE REPORT FORMS (4-12-93) is at least in part a repeat of a previous review of case report forms from studies 8104 and 8601. Conclusion is that important discrepancies call into question the integrity of the NDA. Dr. Pierce says that DSI found a protocol for a long-term safety and efficacy study as an extension of the 24 week US type II trial, 8104, that could not be found in the NDA. Also no report could be found. His recommendations are 1) that safety labeling cannot be accepted without checking CRF's for accuracy of the data, 2) CRFs of patients with skin and allergic reactions should be checked with tabulations, and 3) the firm must be asked to provide the proportion of patients in controlled trials who required hospitalization or ER treatmentfor allergic reactions. I agree that the labeling must be reviewed carefully to be sure it adequately reflects the potential for serious adverse events, including gallstones, myositis, allergic reactions, hepatitis, and perhaps others.

MEMO TO RON INNERFIELD (5-14-93) requests that analyses for demographic variables be looked for in the submissions and if not present, that they be requested of the sponsor as indicated in letter from Carl Peck to Gerald Mossinghoff of PMA dated 31 March 1993. It is very late in review of this drug to make such a request, but I would expect that the dose-ranging study not yet submitted will be analysed for these variables, or numbers provided to show that insufficient patients were studied to warrant such analysis.

HIGHLIGHTS OF EARLY REGULATORY HISTORY OF FENOFIBRATE (5-14-93)is primarily a history, but concludes with recommendations to request the number of patients who, in double-blind placebo trials, were hospitalized or treated for any allergic reaction, or developed eosinophilia, and to repeat previous requests for all adverse events in France 1979 to date and for final reports of all controlled clinical trials not previously submitted to the Division. I believe Dr. Pierce's reviews do suggest the possibility of drug-related allergic reations, and would like the label to reflect this finding. If there are controlled clinical trials not previously submitted, they should be submitted, including the dose-ranging study requested by the Division.

Approval of this NDA was recommended by our Advisory Committee in 1989. It has been subjected to extensive analysis and numerous requests for more data. The sponsor was willing to supply most of what was asked, but has not been afforded the prompt decision making to which all applicants are entitled. At this point, I believe it is imperative that we move as expeditiously as possible toward a final action on this NDA. That action is

dependent primarily on resolving the issue of data tampering and any disputes about labeling. We may not have all of the information that is necessary to complete the labeling. We did tell the sponsor that approval could be granted without information from the dose-finding study if titration was recommended. However, that was a long time ago, and the study has been done. In view of the fact that the study was completed, and toxicity is a serious consideration, and is likely to be dose-dependent, I am unwilling to approve the application without that data. Whatever dose is recommended in the label initially is the one most physicians will learn and use, no matter how persuasive the data are that another dose should be preferred. Finally, all lipid altering drugs have been asked to do phase 4 studies, particularly when the surrogate of lipid alteration is the only endpoint for the approval. A protocol should be submitted and approved prior to approval. Approval is then made with the commitment to conduct the study.

Recommendations:
1) Request that the data from the dose-finding study be submitted immediately.
2) Prepare acceptable labeling.
3) If the DSI audit results in a finding that the data are acceptable, the drug should then be approvable dependent upon the above two recommendations.
4) A phase 4 study should be undertaken, preferably in patients who have a high risk of pancreatitis.

Note: I spoke to R. Lance Boyett 914-381-2232 on 5-20-93 about the data from the dose-finding study. He says it is being analyzed in France, and he will request that they send whatever is available in terms of safety and efficacy data. He also says that they sent us preliminary information on some large studies to be conducted using the micronized product at 200 mg qd. One study in Canada and Europe will be an angiographic study in diabetics. Since they are meeting with us next Wednesday about another compound, they will discuss further with us at that time, and may bring some of the data from the dose finding study with them to that meeting.

cc:Orig NDA
HFD-510
HFD-430
HFD-510/GTroendle/5-20-93
/STROSTER/

Gloria Troendle
d Concur
5/20/93

FAX 914-381-5358

Parke-Davis—Cont.

fatal myocardial infarctions and sudden cardiac deaths). The hazard ratio (Lopid:placebo) for cardiac events was 1.47 (95% confidence limits 0.88–2.48, p = 0.14). Of the 35 patients in the Lopid group who experienced cardiac events, 12 patients suffered events after discontinuation from the study. Of the 24 patients in the placebo group with cardiac events, 4 patients suffered events after discontinuation from the study. *There were 17 cardiac deaths in the Lopid group and 8 in the* placebo group (hazard ratio 2.18, 95% confidence limits 0.94–5.05, p = 0.06). Ten of these deaths in the Lopid group and 3 in the placebo group occurred after discontinuation from therapy. In this study of patients with known or suspected coronary heart disease, no benefit from Lopid treatment was observed in reducing cardiac events or cardiac deaths. Thus, Lopid has *shown benefit only in selected dyslipidemic patients without* suspected or established coronary heart disease. Even in patients with coronary heart disease and the triad of elevated LDL-cholesterol, elevated triglycerides, plus low HDL-cholesterol, the possible effect of Lopid on coronary events has not been adequately studied.

No efficacy in the patients with established coronary heart disease was *observed during the Coronary Drug Project with* the chemically and pharmacologically related drug, clofibrate. The Coronary Drug Project was a 6-year randomized, double-blind study involving 1000 clofibrate, 1000 nicotinic acid, and 3000 placebo patients with known coronary heart disease. A clinically and statistically significant reduction in myocardial infarctions was seen in the concurrent nicotinic acid group *compared to placebo; no reduction was seen with* clofibrate.

The mechanism of action of gemfibrozil has not been definitely established. In man, Lopid has been shown to inhibit peripheral lipolysis and to decrease the hepatic extraction of free fatty acids, thus reducing hepatic triglyceride production. Lopid inhibits synthesis and increases clearance of VLDL carrier apolipoprotein B, *leading to a decrease in* VLDL production.

Animal studies suggest that gemfibrozil may, in addition to elevating HDL-cholesterol, reduce incorporation of long-chain fatty acids into newly formed triglycerides, accelerate turnover and removal of cholesterol from the liver, and increase excretion of cholesterol in the feces. Lopid is well absorbed from the gastrointestinal tract *after oral administration*. Peak plasma levels occur in 1 to 2 hours with a plasma half-life of 1.5 hours following multiple doses. Plasma levels appear proportional to dose and do not demonstrate accumulation across time following multiple doses.

Lopid mainly undergoes oxidation of a ring methyl group to successively form a hydroxymethyl and a carboxyl metabolite. *Approximately seventy percent of the administered* human dose is excreted in the urine, mostly as the glucuronide conjugate, with less than 2% excreted as unchanged gemfibrozil. Six percent of the dose is accounted for in the feces.

INDICATIONS AND USAGE

Lopid (gemfibrozil tablets) is indicated as adjunctive therapy to diet for:

1. Treatment of adult patients with very high elevations of serum triglyceride levels (Types IV and V hyperlipidemia) who present a *risk of pancreatitis and who do not respond* adequately to a determined dietary effort to control them. Patients who present such risk typically have serum triglycerides over 2000 mg/dL and have elevations of VLDL-cholesterol as well as fasting chylomicrons (Type V hyperlipidemia). Subjects who consistently have total serum or plasma triglycerides below 1000 mg/dL are unlikely to present a risk of pancreatitis. *Lopid therapy may be considered* for those subjects with triglyceride elevations between 1000 and 2000 mg/dL who have a history of pancreatitis or of recurrent abdominal pain typical of pancreatitis. It is recognized that some Type IV patients with triglycerides under 1000 mg/dL may, through dietary or alcoholic indiscretion, convert to a Type V pattern with massive triglyceride *elevations accompanying fasting* chylomicronemia, but the influence of Lopid therapy on the risk of pancreatitis in such situations has not been adequately studied. Drug therapy is not indicated for patients with Type I hyperlipoproteinemia, who have elevations of chylomicrons and plasma triglycerides but who have normal levels of very low density lipoprotein (VLDL). Inspection of plasma *refrigerated for 14 hours is helpful in* distinguishing Types I, IV, and V hyperlipoproteinemia (ref. 3).
2. Reducing the risk of developing coronary heart disease only in Type IIb patients without history of or symptoms of existing coronary heart disease who have had an inadequate response to weight loss, dietary therapy, exercise, and other pharmacologic agents (*such as bile acid sequestrants* and nicotinic acid, known to reduce LDL and raise HDL-cholesterol and who have the following triad of lipid abnormalities: low HDL-cholesterol levels in addition to elevated LDL-cholesterol and elevated triglycerides (see *WARNINGS, PRECAUTIONS, and CLINICAL PHARMACOLOGY*). The National Cholesterol Education Program has defined a serum HDL-cholesterol value that is consistently below 35 mg/dL as constituting an independent risk factor for coronary heart disease (ref. 4). Patients with significantly elevated triglycerides should be closely observed when treated with gemfibrozil. In some patients with high triglyceride levels, treatment with gemfibrozil is associated with a significant increase in LDL-cholesterol. BECAUSE OF POTENTIAL TOXICITY SUCH AS *MALIGNANCY, GALLBLADDER DISEASE,* ABDOMINAL PAIN LEADING TO APPENDECTOMY AND OTHER ABDOMINAL SURGERIES, AN INCREASED INCIDENCE IN NONCORONARY MORTALITY, AND THE 44% RELATIVE INCREASE DURING THE TRIAL PERIOD IN AGE-ADJUSTED ALL-CAUSE MORTALITY SEEN WITH THE CHEMICALLY AND PHARMACOLOGICALLY RELATED DRUG, CLOFIBRATE, THE POTENTIAL BENEFIT OF GEMFIBROZIL IN TREATING TYPE IIA PATIENTS WITH ELEVATIONS OF *LDL-CHOLESTEROL ONLY IS NOT LIKELY TO* OUTWEIGH THE RISKS. LOPID IS ALSO NOT INDICATED FOR THE TREATMENT OF PATIENTS WITH LOW HDL-CHOLESTEROL AS THEIR ONLY LIPID ABNORMALITY.

In a subgroup analysis of patients in the Helsinki Heart Study with above-median HDL-cholesterol values at baseline *(greater than 46.4 mg/dL), the incidence of serious coronary* events was similar for gemfibrozil and placebo subgroups (see Table I).

The initial treatment for dyslipidemia is dietary therapy specific for the type of lipoprotein abnormality. Excess body weight and excess alcohol intake may be important factors in hypertriglyceridemia and should be managed prior to any *drug therapy. Physical exercise can be an important ancil*lary measure, and has been associated with rises in HDL-cholesterol. Diseases contributory to hyperlipidemia such as hypothyroidism or diabetes mellitus should be looked for and adequately treated. Estrogen therapy is sometimes associated with massive rises in plasma triglycerides, especially in subjects with familial hypertriglyceridemia. In such cases, *discontinuation of estrogen therapy may obviate the need for* specific drug therapy of hypertriglyceridemia. The use of drugs should be considered only when reasonable attempts have been made to obtain satisfactory results with nondrug methods. If the decision is made to use drugs, the patient should be instructed that this does not reduce the importance of adhering to diet.

CONTRAINDICATIONS

1. Hepatic or severe renal dysfunction, including primary biliary cirrhosis.
2. *Preexisting gallbladder disease* (see *WARNINGS*).
3. Hypersensitivity to gemfibrozil.

WARNINGS

1. *Because of chemical, pharmacological, and clinical simi*larities between gemfibrozil and clofibrate, the adverse findings with clofibrate in two large clinical studies may also apply to gemfibrozil. In the first of those studies, the Coronary Drug Project, 1000 subjects with previous myocardial infarction were treated for 5 years with clofibrate. There was no difference in mortality between the clofi*brate-treated subjects and 3000 placebo-treated subjects,* but twice as many clofibrate-treated subjects developed cholelithiasis and cholecystitis requiring surgery. In the other study, conducted by the World Health Organization (WHO), 5000 subjects without known coronary heart disease were treated with clofibrate for 5 years and followed one year beyond. There was a statistically significant, *44%, higher age-adjusted total mortality in the clofibrate-*treated than comparable placebo-treated control group during trial period. The excess mortality was due to a 33% increase in noncardiovascular causes, including malignancy, post-cholecystectomy complications, and pancreatitis. The higher risk of clofibrate-treated subjects for gallbladder disease was confirmed.

Because of the more limited size of the Helsinki Heart Study, the observed difference in mortality from any cause between the Lopid and placebo group is not statistically significantly different from the 29% excess mortality reported in the clofibrate group in the separate WHO study at the 9 year follow-up (see CLINICAL PHARMACOLOGY). Noncoronary heart disease related mortality *showed an excess in the group originally randomized to* Lopid primarily due to cancer deaths observed during the open-label extension.

During the 5 year primary prevention component of the Helsinki Heart Study mortality from any cause was 44 (2.2%) in the Lopid group and 43 (2.1%) in the placebo group; including the 3.5 year follow-up period since the *trial was completed,* cumulative mortality from any cause was 101 (4.9%) in the Lopid group and 83 (4.1%) in the group originally randomized to placebo (hazard ratio 1.20 in favor of placebo). Because of the more limited size of the Helsinki Heart Study, the observed difference in mortality from *any cause* between the Lopid and placebo group at year-5 or at year-8.5 is not statistically significant from the 29% excess mortality reported in the clofibrate group in the separate WHO study at the 9 year follow-up. Noncoronary heart disease related mortality showed an excess in the group originally randomized to Lopid at the 8.5 year follow-up (65 Lopid, 42 placebo noncoronary deaths).

The incidence of cancer (excluding basal cell) discovered during the trial and in the 3.5 year *trial was completed* was 51 (2.5%) in both of the randomized groups. In addition, there were 16 [illegible] carcinomas in the group originally randomized to [illegible] in the group randomized to placebo ($p = 0.09$). 30 (1.5%) deaths attributed to cancer in the [illegible] nally randomized to Lopid and 18 (0.9%) in the [illegible] nally randomized to placebo ($p = 0.11$). Adverse *including coronary events,* were higher in patients in a corresponding study in men with known or suspected coronary heart disease in the secondary prevention component of the Helsinki [illegible] (See CLINICAL PHARMACOLOGY.)
2. A gallstone prevalence substudy of 450 [illegible] Study participants showed a trend toward a [illegible] *lence of gallstones during the study within the* [illegible] ment group (7.5% vs 4.9% for the placebo to excess for the gemfibrozil group). A trend toward incidence of gallbladder surgery was observed in Lopid group (17 vs 11 subjects, a 54% increase) did not differ statistically from the increased cholecystectomy observed in the WHO study *treated with clofibrate.* Both clofibrate and may increase cholesterol excretion into the bile, cholelithiasis. If cholelithiasis is suspected, studies are indicated. Lopid therapy should be used if gallstones are found.
3. Since a reduction of mortality from coronary disease has not been demonstrated and because *interstitial cell testicular tumors* were [illegible] Lopid should be administered only to those described in the INDICATIONS AND USAGE significant serum lipid response is not obtained, should be discontinued.
4. Concomitant Anticoagulants—Caution should be exercised when anticoagulants are given in conjunction with *Lopid. The dosage of the anticoagulant should be* adjusted to maintain the prothrombin time at the desired level to prevent bleeding complications. Frequent prothrombin determinations are advisable until it has been determined that the prothrombin level has stabilized.
5. Concomitant therapy with Lopid and Mevacor (lovastatin) has been associated with rhabdomyolysis, elevated creatine kinase (CK) levels and myoglobinuria, leading in a high proportion of cases to acute renal failure. IN VIRTUALLY ALL PATIENTS WHO HAVE AN UNSATISFACTORY LIPID RESPONSE TO EITHER DRUG ALONE, ANY POTENTIAL LIPID BENEFIT OF COMBINED THERAPY WITH LOVASTATIN AND GEMFIBROZIL DOES NOT OUTWEIGH THE RISK OF SEVERE MYOPATHY, *RHABDOMYOLYSIS* AND ACUTE RENAL FAILURE (see Drug Interactions). The use of fibrates alone, including Lopid, may occasionally be associated with myositis. Patients receiving Lopid complaining of muscle pain, tenderness or weakness should have prompt medical evaluation, including serum creatine kinase level determinations. If myositis is suspected or diagnosed, *Lopid therapy* should be withdrawn.
6. Cataracts—Subcapsular bilateral cataracts occurred in 10% and unilateral in 6.3% of male rats treated with gemfibrozil at 10 times the human dose.

PRECAUTIONS

1. Initial Therapy—Laboratory studies should be performed to ascertain that the lipid levels are consistently elevated. Before instituting Lopid therapy, every effort should be made to control serum lipids with appropriate diet, exercise, weight loss in obese patients, and treatment of medical problems such as diabetes mellitus and hypothyroidism that are contributing to the lipid abnormalities.
2. Continued Therapy—Periodic determinations of serum lipids should be obtained, and the drug should be discontinued if adequate lipid response is inadequate after 3 months of therapy.
3. Drug Interactions—*(A) HMG-CoA reductase inhibitors:* Rhabdomyolysis has occurred with concomitant gemfibrozil and lovastatin therapy. It may be avoidable in most cases weeks after initiation of combined therapy, but may occur several months. In most subjects who have had an unsatisfactory lipid response to either drug alone, any potential benefit of combined therapy with lovastatin (or other *HMG-CoA reductase inhibitors) and gemfibrozil does not* outweigh the risks of severe myopathy, rhabdomyolysis and acute renal failure. There is no assurance that periodic monitoring of creatine kinase will prevent the occurrence of severe myopathy and kidney

...ents: CAUTION SHOULD BE EXER-
...WHEN ANTICOAGULANTS ARE GIVEN IN
...UNCTION WITH LOPID. THE DOSAGE OF THE
...TICOAGULANT SHOULD BE REDUCED TO
...AIN THE PROTHROMBIN TIME AT THE DE-
...LEVEL TO PREVENT BLEEDING COMPLICA-
...FREQUENT PROTHROMBIN DETERMINA-
...ARE ADVISABLE UNTIL IT HAS BEEN DEFI-
...Y DETERMINED THAT THE PROTHROMBIN
...HAS STABILIZED.

...s. Mutagenesis, Impairment of Fertility—
...studies have been conducted in rats at
...times the human dose (based on surface area,
...). The incidence of benign liver nodules and
...tomas was significantly increased in high dose
...s. The incidence of liver carcinomas increased
...h low dose males, but this increase was not statisti-
...ignificant ($p=0.1$). Male rats had a dose-related
...tatistically significant increase of benign Leydig
...tomas. The higher dose female rats had a signifi-
...increase in the combined incidence of benign and
...liver neoplasms.
...studies have been conducted in mice at 0.1
...times the human dose (based on surface area).
...were no statistically significant differences from
...in the incidence of liver tumors, but the doses
...were lower than those shown to be carcinogenic
...their fibrates.
...microscopy studies have demonstrated a florid
...peroxisome proliferation following Lopid admin-
...to the male rat. An adequate study to test for
...proliferation has not been done in humans,
...changes in peroxisome morphology have been ob-
...Peroxisome proliferation has been shown to oc-
...in humans with either of two other drugs of the fi-
...data when liver biopsies were compared before
...other treatment in the same individual.
...administration of approximately 0.6 and 2 times the
...dose (based on surface area) to male rats for 10
...resulted in a dose-related decrease of fertility.
...subsequent studies demonstrated that this effect was
...reversed after a drug-free period of about eight weeks,
...drug not transmitted to the offspring.
...Pregnancy Category C—Lopid has been shown to pro-
...adverse effects in rats and rabbits at doses between
...and 5 times the human dose (based on surface area)
...no developmental toxicity or teratogenicity among
...offspring of either species. There are no adequate and
...well-controlled studies in pregnant women. Lopid should
...be used during pregnancy only if the potential benefit
...justifies the potential risk to the fetus.
...administration of Lopid to female rats at 0.6 and 2 times
...human dose (based on surface area) before and
...throughout gestation caused a dose-related decrease in
...conception rate and, at the high dose, an increase in still-
...births and a slight reduction in pup weight during lacta-
...tion. There were also dose-related increased skeletal
...variations. Anophthalmia occurred, but rarely.
...administration of 0.6 and 2 times the human dose (based
...on surface area) of Lopid to female rats from gestation
...day 15 through weaning caused dose-related decreases in
...litter weight and suppressions of pup growth during lac-
...tation.
...administration of 1 and 3 times the human dose (based
...on surface area) of Lopid to female rabbits during orga-
...nogenesis caused a dose-related decrease in litter size
...at the high dose, an increased incidence of parietal
...skeletal variations.
...Nursing Mothers—It is not known whether this drug is
...excreted in human milk. Because many drugs are ex-
...creted in human milk and because of the potential for
...carcinogenicity shown for Lopid in animal studies, a deci-
...sion should be made whether to discontinue nursing or
...to discontinue the drug, taking into account the impor-
...tance of the drug to the mother.
...Hematologic Changes—Mild hemoglobin, hematocrit
...and white blood cell decreases have been observed in
...occasional patients following initiation of Lopid therapy.
...However, these levels stabilize during long-term admin-
...istration. Rarely, severe anemia, leukopenia, thrombo-
...cytopenia, and bone marrow hypoplasia have been re-
...ported. Therefore periodic blood counts are recom-
...mended during the first 12 months of Lopid administra-
...tion.
...Liver Function—Abnormal liver function tests have been
...observed occasionally during Lopid administration, in-
...cluding elevations of AST (SGOT), ALT (SGPT), LDH,
...bilirubin, and alkaline phosphatase. These are usually
...reversible when Lopid is discontinued. Therefore peri-
...odic liver function studies are recommended and Lopid
...therapy should be terminated if abnormalities persist.
...Renal Function—There have been reports of worsening
...renal insufficiency upon the addition of Lopid therapy in
...patients with baseline plasma creatinine >2.0 mg/
...dL. In such patients, the use of alternative therapy

	CAUSAL RELATIONSHIP PROBABLE	CAUSAL RELATIONSHIP NOT ESTABLISHED
General:		weight loss
Cardiac:		extrasystoles
Gastrointestinal:	cholestatic jaundice	pancreatitis
		hepatoma
		colitis
Central Nervous System:	dizziness	confusion
	somnolence	convulsions
	paresthesia	syncope
	peripheral neuritis	
	decreased libido	
	depression	
	headache	
Eye:	blurred vision	
Genitourinary:	impotence	retinal edema
		decreased male fertility
Musculoskeletal:	myopathy	renal dysfunction
	myasthenia	
	myalgia	
	painful extremities	
	arthralgia	
	synovitis	
	rhabdomyolysis (see WARNINGS *and Drug Interactions* under PRECAUTIONS)	
Clinical Laboratory:	increased creatine phosphokinase	positive antinuclear antibody
	increased bilirubin	
	increased liver transaminases (AST [SGOT], ALT [SGPT])	
	increased alkaline phosphatase	
Hematopoietic:	anemia	thrombocytopenia
	leukopenia	
	bone marrow hypoplasia	
	eosinophilia	
Immunologic:	angioedema	anaphylaxis
	laryngeal edema	Lupus-like syndrome
	urticaria	vasculitis
Integumentary:	exfoliative dermatitis	alopecia
	rash	
	dermatitis	
	pruritus	

should be considered against the risks and benefits of a lower dose of Lopid.

10. *Use in Children—Safety and efficacy* in children have not been established.

ADVERSE REACTIONS

In the double-blind controlled phase of the primary prevention component of the Helsinki Heart Study, 2046 patients received Lopid for up to 5 years. In that study, the following adverse reactions were statistically more frequent in subjects in the Lopid group:

	LOPID (N = 2046)	PLACEBO (N = 2035)
	Frequency in *percent of subjects*	
Gastrointestinal reactions	34.2	23.8
Dyspepsia	19.6	11.9
Abdominal pain	9.8	5.6
Acute appendicitis (histologically confirmed in most cases where data were available)	1.2	0.6
Atrial fibrillation	0.7	0.1

Adverse events reported by more than 1% of subjects, but without a significant difference between groups:

Diarrhea	7.2	6.5
Fatigue	3.8	3.5
Nausea/Vomiting	2.5	2.1
Eczema	1.9	1.2
Rash	1.7	1.3
Vertigo	1.5	1.3
Constipation	1.4	1.3
Headache	1.2	1.1

Gallbladder surgery was performed in 0.9% of Lopid and 0.5% of placebo subjects in the primary prevention component, a 64% excess, which is not statistically different from the excess of gallbladder surgery observed in the clofibrate compared to the placebo group of the WHO study. Gallbladder surgery was also performed more frequently in the Lopid group compared to placebo (1.9% *vs* 0.3%, $p = 0.07$) in the secondary prevention component. A statistically significant increase in appendectomy in the gemfibrozil group was seen also in the secondary prevention component (6 on gemfibrozil vs 0 on placebo, $p = 0.014$).

Nervous system and special senses adverse reactions were more common in the Lopid group. These included hypesthesia, paresthesias, and taste perversion. Other adverse reactions that were more common among Lopid treatment group subjects but where a causal relationship was not established include cataracts, peripheral vascular disease, and intracerebral hemorrhage.

From other studies it seems probable that Lopid is causally related to the occurrence of MUSCULOSKELETAL SYMPTOMS (see WARNINGS), and to ABNORMAL LIVER FUNCTION TESTS and HEMATOLOGIC CHANGES (see PRECAUTIONS).

Reports of viral and bacterial infections (common cold, cough, urinary tract infections) were more common in gemfibrozil treated patients in other controlled clinical trials of 805 patients. Additional adverse reactions that have been reported for gemfibrozil are listed above by system. Those are categorized according to whether a causal relationship to treatment with Lopid is probable or not established:

DOSAGE AND ADMINISTRATION

The recommended dose for adults is 1200 mg administered in two divided doses 30 minutes before the morning and evening meal.

OVERDOSE

While there has been no reported case of overdosage, symptomatic supportive measures should be taken should it occur.

HOW SUPPLIED

Lopid (Tablet 737), white, elliptical, film-coated, scored tablets, each containing 600 mg gemfibrozil, are available as follows:

NDC 0071-0737-20: Bottles of 60
NDC 0071-0737-30: Bottles of 500
NDC 0071-0737-40: Unit dose packages of 100 (10 strips of 10 tablets each)
Barcode No. 737
Storage: Store below 30°C (86°F).

REFERENCES

1. Frick MH, Elo O, Haapa K, et al: Helsinki Heart Study: Primary prevention trial with gemfibrozil in middle-aged men with dyslipidemia. *N Engl J Med* 1987; 317:1237-1245.

Continued on next page

This product information was prepared in August 1992. On these and other Parke-Davis Products, information may be obtained by addressing PARKE-DAVIS, Division of Warner-Lambert Company, Morris Plains, New Jersey 07950.

...a brown tablet for a *light-colored* tablet nor should ... be taken until you have finished all the *light-colored* tablets, unless your physician or health care provider ... to do so.

...to take tablets according to schedule is ... of its importance in providing you the ... of protection.

MENSTRUAL PERIODS FOR BOTH DOSAGE

...there may be no menstrual period after a cycle of ... Therefore, if you miss one menstrual period but have ... the pills *exactly as you were supposed to*, continue as ... the next cycle. If you have not taken the pills correctly ... miss a menstrual period, *you may be pregnant* and ... taking oral contraceptives until your doctor or ... provider *determines* whether or not you are ... Until you can get to your doctor or health care ... another form of contraception. If two consecutive ... periods are missed, you should stop taking ... It is determined whether or not you are pregnant. ... there does not appear to be any increase in birth ... in newborn babies if you become pregnant while using ... contraceptives, if you do become pregnant, you ... discuss the situation with your doctor or health care ...

...examination

...doctor will take a complete medical and family history ... prescribing oral contraceptives. At that time and ... at least a year thereafter, he will generally examine your ... pressure, breasts, abdomen, and pelvic organs (including ... Papanicolaou smear, ie, test for cancer).

...ARY

...contraceptives are the most effective method, except ..., for preventing pregnancy. Other methods, ... used conscientiously, are also very effective and have ... risks. Although the serious risks of oral contraceptives ... uncommon, some of the risks may persist after you stop ... the pill. On the other hand, the "pill" *is a very convenient* method of preventing pregnancy.

...have certain conditions or have had these conditions in ..., you should not use oral contraceptives because the ... is too great. These conditions are listed in this leaflet. If ... have these conditions, and decide to use the "pill," ... read this leaflet carefully so that you can use the ... most safely and effectively.

...on his or her assessment of your medical needs, your ... or health care provider has prescribed this drug for ..., do not give this drug to anyone else.

...this and all drugs out of the reach of children.

...Federal law prohibits dispensing without prescription.

...1990 0913G156

...in *Product Identification Section, page 422*

R

...Tablets)

...CRIPTION

...gemfibrozil tablets) is a lipid regulating agent. It is ... as tablets for oral administration. Each tablet contains ... mg gemfibrozil. Each also contains calcium stearate, NF; candelilla wax FCC; microcrystalline cellulose, NF; ...propyl cellulose, NF; *hydroxypropyl methylcellulose*, ...; methylparaben, NF; Opaspray white; polyethylene ..., NF; polysorbate 80, NF; propylparaben, NF; colloidal silicon dioxide, NF; pregelatinized starch, NF. The ... name is 5-(2,5-dimethylphenoxy)-2,2-dimethylpentanoic acid.

...chemical formula is $C_{15}H_{22}O_3$ and the molecular weight ...; the solubility in water and acid is 0.0019% and in ... base it is greater than 1%. The melting point is ...°C. Gemfibrozil is a white solid which is stable under ... conditions.

...CAL PHARMACOLOGY

...(gemfibrozil tablets) is a lipid regulating agent which ... serum triglycerides and very low density lipoprotein ...(VLDL) cholesterol, and increases high density lipoprotein ...(HDL) cholesterol. While modest decreases in total and ... density lipoprotein (LDL) cholesterol may be observed ... lipid therapy, treatment of patients with elevated triglycerides due to Type IV hyperlipoproteinemia often results ... in LDL-cholesterol. LDL-cholesterol levels in Type ... patients with elevations of both serum LDL-cholesterol ...triglycerides are, in general, minimally affected by ... treatment; however, Lopid usually raises HDL-cholesterol ...significantly in this group. Lopid increases levels of ... density lipoprotein (HDL) subfractions HDL_2 and ... as well as apolipoproteins AI and AII. Epidemiologic ... have shown that both low HDL-cholesterol and high LDL-cholesterol are independent risk factors for coronary heart disease.

In the primary prevention c...ponent of the Helsinki Heart Study (refs. 1,2), in which 4... male patients between the ages of 40 and 55 were studied in a randomized, double-blind, placebo-controlled fashion, Lopid therapy was associated with significant reductions in total plasma triglycerides and a significant increase in high density lipoprotein cholesterol. Moderate reductions in total plasma cholesterol and low density lipoprotein cholesterol were observed for the Lopid treatment group as a whole, but the lipid response was heterogeneous, especially among different Fredrickson types. The study involved subjects with serum non-HDL-cholesterol of over 200 mg/dL and no previous history of coronary heart disease. Over the 5-year study period, the Lopid group experienced a 1.4% absolute (34% relative) reduction in the rate of serious coronary events (sudden cardiac deaths plus fatal and nonfatal myocardial infarctions) compared to placebo, p = 0.04 (see Table I). There was a 37% relative reduction in the rate of nonfatal myocardial infarction compared to placebo, equivalent to a treatment-related difference of 13.1 events per thousand persons. Deaths from any cause during the double-blind portion of the study totaled 44 (2.2%) in the Lopid randomization group and 43 (2.1%) in the placebo group.

Among Fred...kson types, during the 5-year double-blind portion of the primary prevention component of the Helsinki Heart Study, the greatest reduction in the incidence of serious coronary events occurred in Type IIb patients who had elevations of both LDL-cholesterol and total plasma triglycerides. This subgroup of Type IIb gemfibrozil group patients had a lower mean HDL-cholesterol level at baseline than the Type IIa subgroup that had elevations of LDL-cholesterol and normal plasma triglycerides. The mean increase in HDL-cholesterol among the Type IIb patients in this study was 12.6% compared to placebo. The mean change in LDL-cholesterol among Type IIb patients was −4.1% with Lopid compared to a rise of 3.9% in the placebo subgroup. The Type IIb subjects in the Helsinki Heart Study had 26 fewer coronary events per thousand persons over 5 years in the gemfibrozil group compared to placebo. The difference in coronary events was substantially greater between Lopid and placebo for that subgroup of patients with the triad of LDL-cholesterol > 175 mg/dL (> 4.5 mmol), triglycerides > 200 mg/dL (> 2.2 mmol), and HDL-cholesterol < 35 mg/dL (< 0.90 mmol) (see Table I).

Further information is available from a 3.5 year (8.5 year cumulative) follow-up of all subjects who had participated in the Helsinki Heart Study. At the completion of the Helsinki Heart study, subjects could choose to start, stop, or continue to receive Lopid; without knowledge of their own lipid values or double-blind treatment, 60% of patients originally randomized to placebo began therapy with Lopid and 60% of patients originally randomized to Lopid continued medication. After approximately 6.5 years following randomization, all patients were informed of their original treatment group and lipid values during the 5 years of the double-blind treatment. After further elective changes in Lopid treatment status, 61% of patients in the group originally randomized to Lopid were taking drug; in the group originally randomized to placebo, 65% were taking Lopid. The event rate per 1000 occurring during the open-label follow-up period is detailed in Table II.

Cumulative mortality through 8.5 years showed a 20% relative excess of deaths in the group originally randomized to Lopid versus the originally randomized placebo group and a 20% relative decrease in cardiac events in the group originally randomized to Lopid versus the originally randomized placebo group (see Table III). This analysis of the originally randomized "intent-to-treat" population neglects the possible complicating effects of treatment switching during the open-label phase. Adjustment of hazard ratios taking into account open-label treatment status from years 6.5 to 8.5 could change the reported hazard ratios for mortality toward unity.

Table I
Reduction in CHD Rates (events per 1000 patients) by Baseline Lipids[1] in the Helsinki Heart Study, Years 0–5[2]

	All Patients			LDL-C > 175; HDL-C > 46.4			LDL-C > 175; TG > 177			LDL-C > 175; TG > 200; HDL-C < 35		
	P	L	Dif[3]	P	L	Dif	P	L	Dif	P	L	Dif
Incidence of Evidents[4]	41	27	14	32	29	3	71	44	27	149	64	85

[1] lipid values in mg/dL at baseline
[2] P = placebo group; L = Lopid group
[3] difference in rates between placebo and Lopid groups
[4] fatal and nonfatal myocardial infarctions plus sudden cardiac deaths (events per 1000 patients over 5 years)

Table II
Cardiac Events and All-Cause Mortality (events per 1000 patients) Occurring during the 3.5 Year Open-Label Follow-up to the Helsinki Heart Study[1]

Group:	PDrop N = 215	PN N = 494	PL N = 1283	LDrop N = 221	LN N = 574	LL N = 1207
Cardiac Events	38.8	22.9	22.5	37.2	28.3	25.4
All-Cause Mortality	41.9	22.3	15.6	72.3	19.2	24.9

[1] The six open-label groups are designated first by the original randomization (P = placebo, L = Lopid) and then by the drug taken in the follow-up period (N = Attend clinic but took no drug, L = Lopid, Drop = No attendance at clinic during open-label).

Table III
Cardiac Events, Cardiac Deaths, Non-Cardiac Deaths and All-Cause Mortality in the Helsinki Heart Study, Year 5.0–8.5.[1]

Event	Lopid-at Study Start	Placebo at Study Start	*Lopid:* Placebo Hazard Ratio[2]	CI Hazard Ratio
Cardiac Events[4]	10	131	0.80	0.62–1.03
Cardiac Deaths	36	38	0.98	0.63–1.54
Non-Cardiac Deaths	65	45	1.40	0.95–2.05
All-Cause Mortality	101	83	1.20	0.90–1.61

[1] *Intention-to-Treat* Analysis of originally randomized patients neglecting the open-label treatment switches and exposure to study conditions.
[2] Hazard ratio for risk of event in the group originally randomized to Lopid compared to the group originally randomized to placebo neglecting open-label treatment switch and exposure to study condition.
[3] 95% confidence intervals of Lopid:placebo group hazard ratio.
[4] Fatal and non-fatal myocardial infarctions plus sudden cardiac deaths over the 8.5 year period.

It is not clear to what extent the findings of the primary prevention component of the Helsinki Heart Study can be extrapolated to other segments of the dyslipidemic population not studied (such as women, younger or older males, or those with lipid abnormalities limited solely to HDL-cholesterol) or to other lipid-altering drugs.

The secondary prevention component of the Helsinki Heart Study was conducted over 5 years in parallel and at the same centers in Finland in 628 middle-aged males excluded from the primary prevention component of the Helsinki Heart Study because of a history of angina, myocardial infarction or unexplained ECG changes. The primary efficacy endpoint of t... study was cardiac events (the sum of fatal and non-

Continued on next page

This product information was prepared in August 1992. On these and other Parke-Davis Products, information may be obtained by addressing PARKE-DAVIS, Division of Warner-Lambert Company, Morris Plains, New Jersey 07950.

DEC 15 1993

NDA 19304
Fenofibrate (Lipidil)
Triglyceride lowering

Fournier Labs
Submission dated 11-12-93
Reviewed 12-15-93

Medical Officer's Review of Labeling

ORIGINAL

The labeling is as agreed upon and is acceptable.

The submitted protocol is for a phase 4 study to investigate the effects of 200 mg fenofibrate on coronary artery disease progression/regression in diabetic patients as assessed by quantitative coronary angiography (QCA), to be conducted in cooperation with the World Health Organization. The protocol is final as of July 1993. Study Centers/Principal Investigators are:

University Montreal Hopital Hotel-Dieu/J Genest, Y Latour
University Ottawa/T Chye Ooi, Richard Davies
University Toronto Toronto Hospital/B Zinman, H Aldridge
University Helsinki/M Taskinen, M Nieminen, M Syvanne
University Oulu/A Kesantiemi, M Ikaheimo
Karolinska Institutet Stockholm/S Efendic, A Hamsten

Core Laboratory for QCA is Univ of Toronto, Toronto Hospotal, Peter McLaughlin and Peter Gladstone. The QCA is not further described. Three laboratories for chemistry and lipid analysis are in Vancouver, BC and Helsinki, Finland. Statistical center is Universilty of North Carolina, Chapel Hill. The Safety and Data Monitoring Committee Chairman is Michael Gent, and an Advisory Board includes Matti Henrik Frick of Finland, Yoshiya Hata of Japan, and Paul Zimmet of Australia.

Objectives are: 1) (Primary) to determine by QCA whether long-term correction of dyslipoproteinemia of diabetes with fenofibrate results in decreased progression or regression of preexisting coronary atherosclerosis, 2) (secondary) to determine responses in patients who have had coronary intervention: coronary artery bypass graft (CABG) or percutaneous transluminal coronary angioplasty (PTCA), and 3) to determine long-term safety.

The study will be randomized, double-blind with placebo control. QCA will be done within six months of randomization and 3 years after the final patient is entered. Approximately 300 patients will be randomized, 50 at each center. During 8 weeks of diet (AHA Step I) with single blind placebo, lipid determinations will be done at 4 and 6 weeks, and safety tests, ECG and gallbladder ultrasound will be obtained. Patients will be seen at 4, 8, 16 weeks and then q 4 mo. Patients will be male or female, 40-65 yo, either on approved contraception or not of childbearing potential, and have type II diabetes (FPG>7.8 mmol/L or abnormal GTT when off treatment or actively treated for diabetes with onset 35 yo or more, no ketoacidosis, HbA1c<150% UNL) and lipids after 4-6 w of diet, either TC/HDLC $\geq$4, and LDLC 3.5-4.5 mmol/L and TG $\leq$5.2 mmol/L, or TC/HDLC $\geq$4 and TG 1.7-5.2 mmol/L and LDLC $\leq$ 4.5 mmol/L. To be eligible for randomization, patients must have an adequate quantitative coronary angiogram documenting coronary artery disease. Patients are excluded if they 1) have LDL >4.5 mmol/L or TG >5.2

mmol/L when on diet, 2) have MI, CABG or PTCA within 4 mo, 3) have likely requirement for CABG or PTCA within 6 mo, 4) have ejection fraction <30% or require Rx for CHF, 5) have BMI <18 or >35 kg/m^2, or 6) have renal or other illnesses.

The population to be studied is not necessarily abnormal in LDLC or TG (lower limits 3.5 mmol/L which is about 130 mg/dL LDLC or 1.7 mmol/L which is about 115 mg/dL TG), but will have abnormal TC/HDLC. I have no idea how likely this study is to result in demonstrating a difference between drug and placebo, because the population is not one known to be responsive to altering lipids. However, the high triglycerides of diabetics may be responsible for the associated high morbidity from atherosclerotic heart disease. If that is the study the company is willing to put their money on, I cannot say it is wrong.

The letter should include the committments they make on page 2 of their letter of 12 November 1993, but 3. should not say to develop the 50 mg dosing form for study. It might say they commit:

> To develop and market a dosing form of fenofibrate approximately equivalent to 50 mg of the present formulation.

Recommendation: This drug should be approved.

Gloria Troendle

Gloria Troendle

ORIGINAL

NDA 19-304
Fenofibrate (lipidil)
Triglyceride lowering

Fournier Research
Subm dated 6-29-93
Received by MO 7-23-93
Review written 7-26-93

JUL 26 1993

Medical Officer's Review of NDA Submission

This submission contains statistics on the 50 mg dose intended to show that the 50 mg dose is not effective. It is true that the mean reduction of triglycerides with that dose in the dose-ranging study was less (24.5%) than our arbitrary requirement of 30%, but the 100 mg dose does meet the 30% requirement. Mean change on placebo was an increase of 2.8%, so the drug-placebo difference was 27.3%. For the individual patient, there is a 32% chance of getting a 30% reduction of triglycerides with 50 mg per day. If the patient is at moderate risk of pancreatitis, this may be a very adequate response with minimal risk. This submission does not contribute information that is not in previously reviewed submissions. It should be reviewed by statistics.

Gloria Troendle

Gloria Troendle

Addendum to MOR dated 07/26/93

ORIGINAL

AUG 20 1993

NDA 19-304
Fenofibrate (lipidil)
Triglyceride lowering

Fournier
~~Fax 6-30-93~~ Submission 6-29-93
Review written 6-30-93

Medical Officer's Review of NDA Submission

This submission consists of statistical analyses of triglyceride data from the dose-ranging study. The study was partially reported because of special request, but is still incomplete. The number of treatment successes was less than 50% of the subjects at 50 mg/d. Nevertheless, more than 30 percent of the subjects who were treated with 50 mg/d fenofibrate achieved the 30% reduction in triglycerides that was defined as a successful treatment for the drug. This submission should be sent to statistics for review.

Because of serious concern about hepatotoxicity and evidence that toxicity is considerably less (no patients had >2 x ULN in SGOT or SGPT) at either 50 or 100mg than at 200 or 300 mg/d, it seems appropriate to suggest starting at 50 or 100 and increasing drug if response is not adequate. However, the company does not have a 50 mg dosing form. They made one just for the study, but had no plans to produce it for market. This does not seem like an adequate reason to recommend that all patients begin treatment with 100 mg/d.

Recommend that Statistics and Dr. Sobel be supplied with copies of the triglyceride statistics.

Gloria Troendle
Gloria Troendle

Note: Subsequent information on the % of patients with 30% lowering makes it unnecessary to have statistical ~~s~~ consult.
GJ Troendle
8-20-93

CC: NDA (19304)
HFD-510
HFD-510/GTroendle/STaylor

ORIGINAL

JUL 26 1993

NDA 19-304
Fenofibrate (lipidil)
Triglyceride lowering

Fournier Research
Subm dated 7-9-93
Review written 7-2[illegible]-93

Medical Officer's Review of NDA Submission

Labeling suggestions were sent to Fournier by fax June 17. The suggestions were based in large part on the review by Dr. Innerfield. Subsequently Dr. Innerfield provided references for the suggestions he had made and these were sent to the company June 24. This submission is the sponsor's response to the labeling suggestions.

Figures are adjusted to include adverse events (liver, rash) that were observed in controlled clinical studies. Total number of patients in the controlled studies was 442 fenofibrate and 336 placebo-treated patients.

The response indicates that transaminase elevations were seen only with doses of 200 and 300 mg/d; events occurring in open extension are not included, leaving 28 fenofibrate and 4 placebo patients with transaminase elevations more than three times ULN. The statement about "57% of the 3-fold elevations remained abnormal at the last observation" is removed. Examination of the 28 feno-treated patients with 3-fold elevations (in this submission) shows that 15 patients had elevations above normal at the last follow-up, but all except 2 had returned to no more than 1.5 x ULN, whether or not drug was stopped. Neither of the 2 had determinations after drug was discontinued. I am satisfied with their acquiesence to mentioning only 2 patients with continuing elevations. It does appear that almost all return to normal even if drug is continued.

The statement about pancreatitis rechallenges is removed, because they were not with fenofibrate, but with gemfibrozil. It is not entirely clear that there were 4 rechallenges with gemfibrozil, and I am not impressed. Fournier, of course, does not have this data. If the statement is accepted by sponsor of gemfibrozil and included in their label, it might be included in this label.

For calculating the incidence of rash, only patients in double-blind studies are used. This is not necessarily appropriate; placebo controlled studies are only important if placebo values are to be included, and it appears that is the intention here.

The submission says that if placebo controlled studies are used, the incidence of treatment emergent granulocytopenia less than 1000 /mm^3 is greater in placebo than in fenofibrate patients. I agree to omitting this statement.

Although I agreed that redundant WARNINGS should not be included, I believe that the summary WARNING 6 should retain the summary statement as noted below.

Draft of letter to sponsor:

We are aware of, but do not share, your concerns about recommending an initial dose as low as 50 mg. It appears that more than 30% of patients have at least a 30% lowering of triglycerides at this level. We recommend leaving open the option of starting therapy with 100 mg daily except for the elderly and those with renal dysfunction. For the majority of patients, starting at 50 mg daily appears to be desirable. We understand that a new dosage form is required.

Your proposed changes in the package insert are acceptable, except as follows:

1. CLINICAL PHARMACOLOGY, paragraph 1 and the table of lipid effects: The dose used in the studies that are described should be included. It will probably be necessaary to include the results of the dose-ranging study when they have been submitted and reviewed.

2. The following statement should be retained as part of WARNING 6: "In view of a) liver, pancreatic, and Leydig cell tumor development in fenofibrate-treated rodents at modest multiples of human exposure, b) liver toxicity, c) gallbladder toxicity, increased appendectomies and other gastrointestinal surgical procedures seen in association with the chemically and pharmacologically-related fibrate, gemfibrozil, d) the gallbladder toxicity and increased total and non-cardiovascular mortality with the chemically and pharmacologically-related fibrate, clofibrate, in the WHO study, and e) the potential for rhabdomyolysis, LIPIDIL should be administered only to those patients described under INDICATIONS AND USAGE."

3. The DOSAGE AND ADMINISTRATION second and third paragraphs should read:
"LIPIDIL should be given once a day with the evening meal, and should be initiated at a starting dose of 50 or 100 mg per day, depending on the risk for pancreatitis (See INDICATIONS AND USAGE). Dosage should be individualized according to patient response, and, for most patients, need not exceed 100 mg/d, because response is not usually better and liver abnormalities are increased. If response is not adequate with 50 mg/d as determined by repeat serum triglyceride estimations, 100 mg should be tried. Dose should be reduced from 100 to 50 mg if response is obtained, in order to determine whether the response can be maintained at the lower dose. Dose should also be reduced to 50 mg if gastrointestinal symptoms or rash develop. If a dose that is tolerated without symptoms or liver function abnormalities does not provide adequate control of triglycerides, it is advised that nicotinic acid or another triglyceride-lowering agent be tried.

"Treatment with LIPIDIL should only be initiated at a dose of 50 mg/d in the elderly and in patients having impaired renal function."

Gloria Troendle

Gloria Troendle

ORIGINAL JUL 21 1993

NDA 19304
Fenofibrate (Lipidil)
Triglyceride lowering

Fournier Research Inc.
Received 14 June 1993
Review 18 June 1993
Submission 10 June 1993

Medical Officer's Review and Evaluation of NDA submission

This submission consists of preliminary data on the Fenofibrate dose-ranging study that is still not completely ready for reporting. This data consists of triglycerides, liver function, and certain other safety data.

The study was an 8-week, double-blind trial of 4 doses. Three of the doses (50mg, 100mg, and 200mg) were given once a day, and the other dose and the placebo were given 3 times a day. 28-34 patients were enrolled in each arm and 29 (placebo), 25 (50mg), 28 (100mg), 26 (200mg), and 29 (300mg) completed. Seven patients were discontinued because of adverse events: 1 Placebo patient for mouth ulcers; 50 mg patient for myocardial infarction; 100 mg patient for rash; 200 mg patients for a) SGOT and SGPT more than >2X ULN and b) large red spots (fixed drug reaction); and two 300 mg patients for SGOT and SGPT >2X ULN. No patients on placebo or 50 or 100 mg fenofibrate had SGPT or SGOT >2X ULN. However, 4 and 3 patients had SGPT >3X ULN at 200 and 300 mg/d respectively; 1 patient had SGPT >2<3X ULN at 200 mg; 3 and 2 patients had SGOT >2<3X ULN at 200 and 300 mg/d.

A quick and unchecked talley of clinical adverse event reports indicates that there are probably fewer adverse reports at 50mg/d, but that 100 is not different from 200 and 300 mg/d for total GI events or for dyspepsia or abdominal pain. Pruritis, rash, ulceration, urticaria and pruritic rash are reported in 12 patients on 100 to 300 (16%) (3/26 on 100 = 12%), but in none on 50 or placebo.

In the following table, baseline to endpoint triglycerides are examined. However, the values fluctuated markedly from visit to visit, and many patients had endpoint values not particularly representative of the treatment values overall.

Dose	N	# pts with 30% decr TG	median % change	Per cent lowering of TG at 25th & 10th %iles	
0mg	29	4(14%)	+1.7	22	40
50mg	25	8(32%)	-24	36	44
100mg	28	18(64%)	-38	48	55
200mg	26	18(69%)	-41	51	62
300mg	29	27(93%)	-43	59	66

Thus, the average patient does not obtain greater reduction of triglycerides when he takes doses greater than 100mg, but a few patients might obtain increased triglyceride lowering on taking 200 and 300 mg/d. Even at 50mg, 25% of subjects had at least 36% and 10% had 44% lowering of triglycerides The actual values in individual patients are quite variable, and patients are not consistently benefitted. Probably other factors influence the

visit to visit values - perhaps diet and alcohol intake. An example: Patient 304 had qualifying visit TG of 5.06 mMol/L (448mg/dL), 3.57 (316), 5.42 (480), and 9.84 (872). Baseline is the mean of 3.57 and 5.42, because, at the next visit, she was put on drug before knowing the 9.84 value. Treatment values were 3.90 (345), 4.09 (362), 3.48 (308), 15.41 (1364) and 6.95 (616). Mean of the last two values was the endpoint value, so taking endpoint minus baseline, the treatment effect is a TG increase from 4.5 to 11.18mMol/L, an increase of 600%. It is probably wise to advise patients to modify (reduce) dose if they have GI symptoms or rash and wish to continue the drug, but a reduction based on triglyceride levels at one point would sometimes result in loss of efficacy. Dose adjustment with the intention of reducing risk while obtaining maximum benefit should be based on 2 or 3 TG determinations.

We had agreed to the Advisory Committee recommendation to approve this drug, if our reviews showed it to be otherwise approvable, before having this study done. Therefore, if DSI finds no reason to doubt the data we have received, I recommend approving it with the information we have, including this preliminary report. In addition to the labeling changes I recommended in my review of 5-21-93, the CLINICAL PHARMACOLOGY and DOSAGE AND ADMINISTRATION sections should have the following changes:

CLINICAL PHARMACOLOGY, paragraph 1 and the table of lipid effects should include results of the dose-ranging study when it has been submitted and reviewed.

The DOSAGE AND ADMINISTRATION second and third paragraphs should read:

> "LIPIDIL should be given once a day with the evenin meal, and should be initiated at a starting dose of 50 or 00 mg per day, depending on the risk for pancreatitis (See INDICATIONS AND USAGE). Dosage should be individualized according to patient response, and, for most patients, need not exceed 100 mg/d, because response is not usually better and liver abnormalities are increased. If response is not adequate with 50 mg/d as determined by repeat serum triglyceride estimations, 100 mg should be tried. Dose should be reduced from 100 to 50 mg if response is obtained, in order to determine whether the response can be maintained at the lower dose. Dose should also be reduced to 50 mg if gastrointestinal symptoms or rash develop. If a dose that is tolerated without symptoms or liver function abnormalities does not provide adequate control of triglycerides, it is advised that nicotinic acid or another triglyceride-lowering agent be tried.
>
> "Treatment with LIPIDIL should only be initiated at a dose of 50 mg/d in the elderly and in patients having impaired renal function."

Gloria Troendle
6-21-93

Concur - Abdul
6-22-93

ORIGINAL

JUN 10 1993

Review of Reported Adverse Experiences

NDA: 19-304
Drug: Fenofibrate
Sponsor: Fournier, Inc.
Submission date: Apr 30, 1992
Receipt date: May 1, 1992
Review date: May 26, 1993
MFR Number: n/a
DES Control #: n/a

Hospitalization: Y
Death:
Disability:

Age: 58
Sex: F
Location: QU

Rx Duration (days): 9
Daily dose (mg): 100
Dechallenge: N
Rechallenge: N

Indication: phase iv clinical trial
Concomitant Rx: naproxen 375mg/BID; triazolam
CoStart: AST elevation; confusion; edema; fever (low-grade); hypoalbuminemia; hyponatremia; purpura; rash; renal failure; somnolence; thrombocytopenia; urticaria, vesiculo-bullous [2° to Rx as documented by skin Bx x2]

Data: NIDDM patient with previous reaction to antihistamines, hypertensive, with angina, obesity, and hyperlipidemia was 9 days into a Lipidil phase IV study when she developed a toxic epidermal necrolytic syndrome with severe thrombocytopenic purpura [platelet count of 11,000], obtundation, renal failure, hyponatremia and hypoalbuminemia. Skin biopsies times 2 were felt to be diagnostic for "allergic vesiculobulleuse urticarienne." Bone marrow showed increased megakaryocytes. She responded well to steroid therapy and was discharged after 17 days.

Recommendations: According to the SMOR of Skin/Allergic Reactions for this compound dated 11/30/92, the combined incidence of rash + urticaria in controlled clinical trials was 16% and "much higher than that seen in studies with gemfibrozil ...[1%]." The SMO further cited Sgro and Escouse (Therapie

46:351, 1991)
who listed drug-related skin ADR's as 22.8% of the total fenofibrate events reported to the French Pharmacovigilance surveillance system.

It is obvious to me that a significant number of people are going to suffer because of this compound - even at 100mg/day - and for no well-defined benefit.

Ronald Jay Innerfield, M.D.
Medical Officer

Gloria Troendle 6-10-93

cc: NDA Arch
HFD-510
HFD-426/Gordin
HFD-713/Nevius/Mele

HFD-510/Jordan/Barbehenn/Chiu/Niu/Troendle/Innerfield/Trostle

MAY 14 1993

GROUP LEADER'S REVIEW OF CASE REPORT FORMS OF PATIENTS EXPERIENCING HEPATOTOXIC REACTIONS IN U.S. STUDIES OF FENOFIBRATE

NDA 19304
DRUG: FENOFIBRATE
SPONSOR: FOURNIER
REVIEW DATE 2/26/93

GROUP LEADER'S REVIEW OF CASE REPORT FORMS (CRFs) OF PATIENTS DEMONSTRATING AMINOTRANSFERASE ELEVATIONS > 3X ULN

Source of CRFs: CRFs were included for the type II trial in the original 1984 NDA submission. CRFs were submitted for the U.S. Type IV/V trial as an amendment to the resubmission of the NDA. DSI obtained selected CRFs from one center in the former trial and from 2 centers in the latter trial, which reside in the NDA file. The CRFs used in this review were those contained in volumes 13.1-13.14 of the sponsor's 10/20/89 submission to the NDA.

Study 8104 - U.S. Type II Trial

Brief synopsis of study design:

This was a 3 period study of:

Period	Visit Nos.	Weeks of Visits	Weeks Period
Screening	1-4	0-6	0-6
I SB placebo	5-6	9, 12	7-12
II F vs. placebo	7-12	14,36	13-36
III Open F 300 mg	13-16	38-60	37-60

The dosage of fenofibrate used was 100 mg TID (300 mg total daily dose). Patients were to be on a prudent diet, begun during screening. Safety labs were to be obtained at weeks 0 and 12 during screening and single-blind placebo, and at each visit during DB tx (visits 7-12), and at weeks 38, 45, 52, and 60 during period III. Complete history and physical exam was to be performed at screening, and visit 12 (end of DB) and at visit 16 (end of 24-week open extension).

PT 10-232
ititials

Investigator: Paul Samuel, MD

Center #10
Protocol 502
location: 10/20/89 submission, vol 9, p 120+

Note: While the cover sheet to the CRFs appears to be signed by the investigator of record, Paul Samuel, on 6/10/83, fully 9 months after the patient was removed from the study due to the development of markedly abnormal LFTs (symptomatic), on the CRFs for the individual visits at the "signature of investigator" block appears the signature of R. or Ralph Fenderson for visits v2, v8, v9, but instead the signature of "B. Ch-" appears on the sheets for CRF v6. That the signatures are clearly different conflicts with the fact that the handwriting appears to be of the same individual, comparing, for example, p 154 (v6) with p 177 (v9).

In Fournier's submission of 11/16/92, which represented the computerized database listings of all costart terms for AEs and lab data for any patient with either AST or ALT >= 3X the ULN from any of the trials for which data had been computerized (which omits several controlled trials), this patient was listed as having only asthenia as a reported AE.

Pt was previously txed w gemfibrozil, 1200 mg daily from 6/89 to 3/1/82. No mention of any problems with gemfibrozil is made. Screening date v1 on 4/26/82

Hx: DM

Nl phys exam on screening. Wt 163 for 67 ".

V1 TChol 283
TG 161

FBG 125

v3
T Chol 290

Tg 120

V 5 T chol 285
TG 77

NPH insulin 20 U

	ULN	V1	V7	V8 8/18/82	9/1/82	v9 9/13/82
AST	35	10	18	140	14	135
ALT	45	32	18	303	35	392

ALK PHOS	125	98	85	236	153	401
BILI	1.5	0.4	0.3	0.6	0.3	0.5
CREAT	1.5	1.0	1.2	1.0	0.9	1.2
ABS. EOS		136	61	432		240

Note: labs from 9/1/82 are not recorded by investigator on CRF, but rather have been added as a Monitor's note, initialed KWF, and entered on 3/1/83, 6 months after the fact (p 173 of submission). **CRF indicates that viral studies for hepatitis B were negative, and that patient had 3 days of symptoms of fatigue, anorexia, and low back pain. Adverse reaction report sheet of CRF lists these plus generalized malaise, all of mild severity and continuous. Investigator indicated in 6 distinct places that study drug had been temporarily discontinued** [On p 175, where the box in block C was checked "yes" to the question, if drug was temporarily discontinued was it reintroduced?" and "yes" to the question, "If yes, did reaction reappear", and in block A, Change in test drug dosage, choice 3 was checked, "temp. disc.", but then crossed out by "SS"on 2/16/84, 17 months after the date of the CRF, and choice 4 was checked and circled "disc.", and on p 177, where appears the statement, "Pt took med as directed (was taken off drug for 10 days). In item C on p 175 of the submission (volume 9 of the 10/20/89 submission) where it was indicated that following reintorduction, the reaction reappeared, this was crossed out by SS with the notation "error" on 2/16/84, 17 months after the visit date. It was noted by the investigator on the CRF that drug had been discontinued from 8/23/82 to 9/2/82. This too was crossed out by SS [sp?] on 2/16/84. **This temporary discontinuation would certainly explain why LFTs normalized then reappeared. The investigator listed, on the V9 CRF, after the severe elevations of aminotransferases reappeared, that the relationship to study drug was "remote". Given the suddenness of the reaction, the prompt disappearence and reappearance of marked biochemical abnormalities indicicative of liver dysfunction upon dechallenge and positive rechallenge, the investigator's honesty or biases in this regard are subject to question. It appears that the study monitor may have "corrected" the CRF to remove the suggestion that this hepatitis case included evidence of a positive rechallenge, and would therefore be considered drug-related.**

At visit 7 on 8/2/82, patient was given back box 3, containing 36 capsules, and was issued box #4 containing 72 capsules.

At visit 8, 1 capsule remained from box 3 (indicating that 35 had been taken since v 7) and 12 had been taken from box 4 with 60 returned to the pt, giving a total inter-visit consumption of 47, equivalent to 15 2/3 days. Visit 8 occured on 8/18/82, 16 days following v 7, indicating about 100% compliance. No

irregularities were noted at that point. Box 5 was issued at v 8, containing 6x12=72 capsules.

Visit 9 was on 9/13/82, 26 days from visit 8. 42 capsules were missing from box 4 (30 remained); 18 were missing from box 5 (54 remained). Thus consumption between visits 8 and 9 was ([60-30] from box 4) + 18(from box 5) = 48 = 18 days worth. If therapy were interrupted from 8/23 to 9/2/82 (10 days), as originally noted on tne CRF on p 175 of vol 9 of this submission, that would explain why only 18 days worth had been consumed when there had elapsed 26 days from the previous visit. Also, on p 177 (p 50) of the CRF, the investigator wrote "Pt took med as directed (was taken off drug for 10 days)". **Clearly, the pill counts recorded on the patient compliance sheets on pp 170 and 177 of the submission are incompatible with the "correction" of the CRF on p 175 in which the dates 8/23/82 to 9/02/82 have been crossed out and annotated "error SS 2/16/82 error".**

THE OBVIOUSLY FALSE ALTERATION OF THE CRF BY THE STUDY MONITOR AND THE PECULIAR LEAVING OUT IN THE SPONSORS COMPUTERIZED SUMMARY OF ADVERSE EXPERIENCES IN PATIENTS EXPERIENCING AST/ALT > 3X THE ULN SUBMITTED BY FOURNIER ON 11/16/92, OF THE ADVERSE REACTIONS LISTED BY THE INVESTIGATOR ON THE CRF CONSISTING OF ANOREXIA, GENERALIZED MALAISE, AND BACK PAIN (TOGETHER WITH SIMILIAR OMISSIONS OF POTENTIALLY SERIOUS ADVERSE REACTIONS IN SUMMARIES PROVIDED BY THE SPONSOR) RAISE QUESTIONS OF POSSIBLY DELIBERATE MISREPRESENTATION OF DATA IN THE NDA (FRAUD).

Pt dropped from study on 9/18/82 and returned box #6 intact and 38 caps were left in box #5 of the 54 that had been returned to the patient at v 90 on 9/13/82. Thus, the patient continued to take drug for another 5 days beyond v 9, and consumed 54 - 38 = 16 capsules = 5 1/3 days worth of fenofibrate during this period. The next CRF that is provided in this volume is from v 16 that is dated 03/02/83, nearly 6 months after the patient was discontinued from the study due to hepatotoxicity. The abdominal exam was indicated to be normal on that date, according to the CRF. Of course, the exit physical should have been performed immediately upon discontinuation from the study, rather than 6 months later. We do not know if the patient became jaundiced or developed hepatomegaly as a consequence of the positive rechallenge with fenofibrate. A lipid profile was not done during v "16" on 03/02/83, but safety labs were repeated 6 months after discontinuation of study drug. At this time AST and ALT had normalized at 17 and 31 U, respectively. The CRF for the "16th" visit was signed by "B. Ch-".

On p 186 of vol 9 of this submission (corresponding to p 94 of the CRF for this patient for the exit visit "16" [sic]), which is dated 03/02/83, two adverse reactions are noted consisting of "elevated LF tests" for the periods 8/18/82 to 9/1/82 of severe severity, recurrent periodicity, with choice #3 marked (temp.

disc.) then crossed out on 2/16/84 by "SS("" and changed to #4, (disc.), with outcome to date noted as moderate (discomfort enough to cause interference with usual activity), and relationship to test drug noted as "probable" (among the choices remote, possible, and probable), and elevated LF tests again noted as an adverse reaction on the AR report sheet with onset on 9/13/82 to 9/18/92 (the latter corresponding to the date of discontinuation from study drug as indicated on p 179 of this volume), severity again listed as severe, periodicity as recurrent, change in test drug dosage listed as "disc.", outome moderate, and relationship to test drug probable.

Again, listed in item C of this form, the dates of temporary discontinuation of study drug age listed as 08/21/82 to 09/01/82 and crossed out with the notation "error SS 2/-16-84" (previously listed as 08/23/82 to 09/02/82 on p 175[CRF p 48]), and again the "yes" response to the question, "if yes, did reaction reappear?" has been crossed out with the notation "error", this time with the additional handwritten comment "Meds not reintroduced JZ [indecipherable]".

On p 189 of this vol., corresponding to p 97 of the CRF for pt 232 of investigator 010, the date study drug was discontinued was listed as 09/18/82, but this has been crossed out with the notation, "error" and replaced with 8/20/82 with the initials SS 2/16/84. Drug was indicated to have been stopped due to clinically significant laboratory abnormality, elevated liver function tests. Follow-up lab tests are listed on this same page as having been obtained 9/29/82 (11 days after patient was originally listed on pp 179 & 189 as having discontinued study med definitively) and showed normal AST and ALT values of 19 and 36, but elevated alkaline phosphatase of 168 (nl 31-125, baseline value of 98 at v 1).

On p 185 of this submission (vol 9), corresponding to the slit lamp exam, the notation has been handwritten "Dr. Schonfeld #232 GNBA-502". This page of the CRF does appear to correspond to that of Dr. Samuel's patient #232, insofaras on this and the sheet for the screening slit lamp exam for Dr. Samuel's patient, early bilateral corneal opacities are listed. It is unknown why Dr. Schonfeld's name, the investigator of center #11, is listed on this particular sheet of Dr. Samuel's patient, from center #10.

On p 192 of vol 9 this submission appears a sheet purporting to document changes made to the CRF for this patient. It notes as items 2 and 3 a descripancy between the dates study medication was temporarily discontinued as indicated on p 48 (p 175 of vol 9) and p 94 (p 186 of vol 9) of the CRF [dates of 8/23/82 to 9/2/82 vs. 8/21/82 to 9/1/82, respectively. Either set of dates is plausible for the "10 day" period of drug discontinuation that is noted on p 177 of vol 9 (p 50 of CRF), given that the markedly

abnormal transaminases first were noted from a 8/18/82 blood draw (v 8), and one could anticipate that a few days would elapse to be back the result and contact the patient. A record of this contact should of course, in principle, be contained in the patient's chart. The sheet on p 192 of vol 9 states that another item to be corrected was to "verify if pat. on meds to 9/18/82" with the correction "change date to 8/20/82". Justification for change is listed as a telecom with Estelle Fisher by Gigi Reinhart on 12/5/83. Items 6 and 8 indicate that the resposes to the question "change in test dose" were changed from "temp dc" to "change to discontinued". Items 7 and 9 on p 192 of vol 9, corresponding to question C of the Adverse Reaction CRF sheets on pp 175 and 186 of vol 9 (CRF pp 48 and 94) indicate the "correction" made was to "delete all answers".

Despite the fact that the above "corrections" were signed on this sheet by L. Stevens [sp?], Dr. Besseler, the medical monitor (head of the contract organization monitoring the study), and Paul Samuel, the investigator, it seems inappropriate to have deleted entire responses to item C of the Adverse Reaction CRF forms, particularly because doing so created at least 2 new discripancies: P 177 (CRF p 50) indicated that the drug had been discontinued for 10 days, and on p 189 (CRF p 97), the study drug was indicated to have been discontinued on 9/18/82. This original study discontinuation date fits perfectly with the capsule count, as noted above. Deleting the information originally provided by the investigator that the patient had temporarily discontinued therapy was incompatible with capsule counts at visits 8 and 9, and also incompatible with the time course of the aminotransferase changes.

From the above, it appears that the revised date on which study medication was said to have been discontinued was simply pulled out of thin air. Even if the drug had not been temporarily discontinued (and there is abundant evidence in the original CRFs that drug was, in fact, temporarily discontinued), capsule counts would indicate that drug was taken at least until 9/10/82 [23 (18 +5) days beyond visit 8, which occured on 8/18/82].

Perhaps the motive for changing the record to elimate the record of the temporary interruption in study drug was to make the monitor appear that they were staying on top of emerging severe drug toxicity, or, as previously noted, to eliminate a hepatotoxicity case of well-documented positive rechallenge. Other possibile explanations do not seem readily apparent from the availale data.

CRF REVIEW OF PATIENT 011-161

PATIENT 161

PATIENT INITIALS:

CENTER 011

INVESTIGATOR: Gustav Schonfeld

PROTOCOL GHBA 502

Cover sheet signed by Dr. Schonfeld on 11/10/83 (vol 11, p 269).

Pts age/sex: 54 F

Screening v1: 5/20/82

allergic hx: pcn, sulfa

Dx: IIB HLP

No prior hypoliipidemic tx in prior year

No concom. meds.

No hx of recent GI, liver, or GB disease, or hx of pancreatic disease within the past 3 yrs. No hx of alcohol or drug abuse.

Nl initial abd exam.

Wt 166 lbs for 67.2 inches = 0.0365 lb/in2

Screening v1	total chol	290	V2 293
	TG	120	332
	HDL	48	45
	LDL	218	182

Note: lipid elig. criteria based on v1-v3 and averaged at v4.

Medication dispensed at v 4 on 7/06/82.

Visit #	ULN	v1	v4	v6	v7	v8		v16
Date		5/20		8/27	9/9	9/23/82	10/5/82	5/10/83
AST		17		20	10	113	32	22
ALT		7		19	16	143		26
ALK PHOS		110		123	96	170	143	136
T. BILI		0.4		0.3	0.3	0.6		0.5
ABS. EOS		106		71	165	510	165	0
CREAT		0.8		0.9	0.8	0.9		0.8

GGT 65 179

Repeat GGT on 10/26/82 was sl abnormal at 68; alk phos was nl at 123, ALT was 16, AST 19, abs. eos 180. On 11/30/82, GGT was nl at 35, AST was 35, abs. eos were 50.

During v 6 on 8/27/82, pt's health status was noted to have changed, such change consisting of "recurrent RUQ pain, resolved. TG during this visit were 356.

Recurrent RUQ pain was again noted v7, on 9/9/82, as well as R flank pain. TG on this date were 157. RUQ pain and R flank pain were listed on Adverse reaction report CRF sheet on p 315, were indicated to be of moderate severity and of possible relation to test drug. The adverse reaction was listed as not present prior to study. *Under item C. on p 315, it is indicated that tx with the test drug was temporarily interrupted from 8/5/82 to 8/9/82. This sheet is signed by the investigator, Gustav Schonfeld.* No concom meds were introduced.

At v 8 on 9/23/82, investigator noted "She feels better. RUQ pain decreased in severity but is more or less constant. TG at that visit were 154. At this visit, elevated liver enzymes were added to RUQ pain on the Adverse Reaction Report CRF sheet (p 322). The LFT elevation was listed as moderate severity, not present prior to study, and possibly related to test drug. No potentially noxious or environmental factors were noted to be present. No interruption of medication was listed on this sheet, but on p 326 of v8 CRF (p 45 of CRF), is written "Pt. is on hold at present. Liver enzymes returned to normal p d.c. study medication. Hepatitis survey negative. Pt. will return in 1 month. Will decide if to be rechallenged c study drug. G.B. sonogram & oral cholecystogram w.n.l." [signed by Janet B. Kola, P.A.C. and countersigned by G. Schonfeld on 10/29/82, 36 days after v 8. On this sheet is also the notation, "Repeat liver enzymes AP = 143, SGOT = 32, CPK = 65. SMW 3-09-84.

The next sheet to appear is v 16 dated 5/10/83, nearly 7-8 months after study drug was discontinued. Only at this visit is a record of a physical exam provided. Why was no record made as to the abdominal exam while the patient had been compaining of right upper quadrant and flank pain? At "v 16", the abdomen exam was listed as abnormal, obese, no organomegaly. TG on 5.10/83 were 209. On p 331 of vol 11, it is stated that test drug was d/ced on 10/20/82. Vaginitis was listed on the AR report sheet as having been present form 1/1/83 to 5/10/83 and was felt to be remotely related to test drug.

Appended to the CRF are copies of selected exams, including an echo of the GB showing an echo within the gallbladder which shadows on several of the B scans, which was not reproducible on

real time scanning, read out as suspicious for gallstones. An oral cholecystogram report indicates the GB is well opacified and appears normal. On

v5	v6	v7	v8	v16
7/29	8/27	9/9	9/23/82	5/10/83

remaining
box 1 3,not reissued

issued
box 2 72 consumed

Comment: ran out (vacation)

issued 36 consumed,
box 3 = 12 days worth,
36 reissued 36 consumed

box 4 issued 6 consumed, 6 more cons.
66 reissued 60 remain
"same info
as on p 44 (v 8); pt returned meds then"
box 5 issued none taken

Again, there is lack of concordance between capsule count between visits 8 and 16, during which interval 6 additional capsules were missing, and investigator's statement on p 349 of vol 11 (p 97 of CRF) that study drug was discontinued on 10/20/82. On this sheet it is stated that drug was d/ced due to adverse reaction, namely "gall bladder [sic] symptoms - RUQ pain c elevated liver enzymes". On the next [comments] page (p 350 of vol 11 = p 98 of CRF), Janet B. Kolar P.A. wrote " Pt. d.c.'d study meds in October 1982 secondary to gall bladder symptoms (severe). Could not come in for clear cut visit until today". [countersigned by Ann Goldberg MD on 5/10/83 and G. Schonfeld.

On p 351 of vol 11, item 3 states that the AE BQC was corrected to indicate "reintoo = yes; recurr = no." Justification for this correction of the CRF is listed as "Phys ex. said RQ pain = resolved @ this visit. Again these changes were signed by Besselar and by Anne Carol Goldberg. It is noteworthy, and peculiar, that page 30 (which seems to be the adverse reaction report sheet of visit 6) of this CRF is missing from this submission!
From the correction sheet on p 353 of vol 11 of this submission, it would appear that the original CRF page 42 is missing from the submission as well, and a "clean" replacement sheet has been provided in its place. I say this because the original item to be corrected on p 42 of the CRF is listed as "][up arrow) AGOT, AGPT, alk P)4, on Lab = A.E.; Study Med Temp DC". Nowhere on the CRF page 42 (corresponding to page 322 of vol 11) does it say

any of this; nor is there any indication from item C that therapy was interrupted.

Comment: While the gallbladder echo in this patient was "suggestive" of a stone, the stone was not documented in real time ultrasonography or by OCG. Abdominal pain had been present after visit 5, but had initially resolved by v. 6, only to recurr at v. 7 & 8. Aminotransferases were nl at v6, v7, but > 3X elevated at v8. The investigator indicated that drug had been discontinued prior to visit 6, and had been reintroduced only 7 days prior to v7, possibly not sufficient time to development biochemical evidence of hepatic dysfunction, that was present by visit 8. The presence of eosinophilia of 510/mm3 at v8, coinciding with LFT abnormality and abdominal pain suggests that fenofibrate may have contributed to the AE. Of course, of a gallstone were responsible for the hepatic dysfunction, fenofibrate could certainly have caused the stone, and be indirectly responsible for the hepatic dysfunction.

CRF REVIEW OF

PROTOCOL GHBA 502 (STUDY 8104

INVESTIGATOR #2 (DUJOVNE)

PATIENT: 036

PT INITIALS:

Init. eval. 9/3/82

62 y/o F W

No prior 1 yr drug tx for HLP

Hx arthritis, chr constip

Concom. Meds:

Correctol
calcium
asa
valium 5 mg prn nervousness
V. 4 THERAGRAM M (VIT) ADDED
V. 6 Co-Tylenol, pyroxate
V. 7 Contac

baseline abdominal exam nl

followed AHA rec diet

Baseline lipids:

tot chol AV 317

TG AV 67

HDL

LDL-C

Baseline and on-tx LFTs/labs

Note: Study med (single-blind placebo) dispensed initially at v. 4 on 10/15/82.

VISIT No.:	1	4	5	6	8
DATE:	9/3/82	10/14	11/5	11/19	12/17
AST	20			16	82
ALT	16			18	169
ALK PHOS	75			89	116
T.BILI	0.5			0.4	0.3
GGT					
ABS. EOS.	164			110	700
WBC	4.1'			5.5	5.0
ABS. NEUTROPH.	1845			3300	2500
CREATININE	1.0			0.8	0.9

ULN for ast = 40

uln for alt = 45

At v. 5, which took place 20 or 21 days after dispensing of study med on 10/15 (CRF p 20, p 148 of submis) or on 10/14 (v. 4), 60 tablets were missing from blister packs, equivalent to 20 days of therapy at 100% compliance.

No ADRs listed at v. 5
CHANGES IN HEALTH STATUS/ADRs:

cold with laryngitis 11/13-11/18

cold w nasal congestion V. 7, (12/3/82)

For the 1st time, on V. 7, ADRs are reported on the ADR sheet.

These are (1) cold with nasal congestion and (2) hematuria, felt remotely related to drug. The monitor circled hematuria and wrote at the bottom of CRF 'Hematuria is not considered to be an adverse effect - was present pre-study". **Neither cold, nor hematuria appeared in the Fournier tabular summary of ADRs in pts with AST and/or ALT >= 3x the ULN submitted on 11/16/92.**

ADR sheet p 42 of CRF indicates incr SGPT/SGOT of mild severity, no change in drug dosage, of possible relation to test drug; and hematuria. Lab page indic incr LFTs were asymptmatic on v 8.

Open label tx with feno begun 5/13/83.

For v. 15 on 9/9/83, abs. neutrophil count of 3.6 x 45% = 1800, but annotated abs. ct listed as 1620; noted to be clinically signif by investig. Decr. WBC listed as ADR, felt possibly due to drug. Repeat WBC 4.2 while still on drug.

CRF REVIEW OF

PROTOCOL GHBA 502

INVESTIGATOR #8 (MELLIES)

PATIENT No 181

PATIENT INITIALS:

35 Y/O M

PRIOR LIPID LOWERING MED: CHOLESTYRAMINE 4 G QID D/CED 2/17/82

Abd exam nl at baseline

baseline visits 1-4 ending 5/17/82

visit:	1	3	6	7	8	9
date:	4/7/82	5/3	6/28	7/9	7/26	8/30
T CHOL	295	292	283	274	250	255
TG	113	87	85	59	67	67
AST	18		18	19	35	98
ALT	15		14	9	34	115
ALK PHOS	49		43		37	39
T BILI	0.6		0.8			0.4

GGT					
ABS. EOS.	32	86		369	160
WBC	3.2	4.3			3.2
ABS. NEUT.			1330		1856
CREAT			1.0		1.0

ADVERSE REACTIONS/CHANGE IN HEALTH STATUS RECORDED ON CRF:

v. 8: Incr. SGOT, incr. SGPT, incr. eos, mild, possibly drug-related. No change in test drug.

V. 9 8/30/82 incr. SGOT, incr. SGPT, moderate severity [changed to mild], possibly drug-related, Monospot neg, Hep B antigen neg. No change in tx: "Because of reported trnasient nature of incr. transaminase, will recheck values before stopping medication. Positive alcohol intake at baseline, which was lower on v 2, 3. Drinks/week between visits 3 &4 = 13. Decreased EtoH intake between v. 8 & 9 (max AST/ALT at v 8). Increased Alcohol between v. 11 & v. 12 to 16.5 drinks/week (holidays).

Concom. meds none until v. 12 (Robitussin -DM).

V. 10: incr SGOT/SGPT, levels noted to be decreasing on tx.

V. 11: incr SGOT/SGPT, probable relation to study drug, tx continued.

V. 12: incr SGOT/SGPT, URI sxs x 3 weeks, nearly cleared.

V. 13-16: incr SGOT/SGPT with mildly incr CPK on 2/14

Pt had 100% compliance by pill count.

visit:	10	11	12	13	14	15
date:	9/20/82	11/8*	12/13	12/27	2/14	4/11
AST	72	50	69	40	56	66
ALT	96	63	95	53	66	90
ALK PHOS	41		34			36
T BILI	0.5		0.7			0.3
GGT						

ABS. EOS.	160	58	128	0	93	70
WBC	4.0	2.9				
ABS. NEUT.		1450				
CREAT		1.0				

*Note: date originally recorded at 10/1/82, crossed out and replaced with 11/8/82.

visit:	15a	16
date:	5/25	6/6
AST	28	39
ALT	30	38
ALK PHOS	30	
T BILI		
GGT		
ABS. EOS.		
WBC		
ABS. NEUT.		
CREAT		

CRF review of Pt 128, Study 8104

Investigator: 6 (Robert Knopp)

Pt initials

56 y/o M No hx allergies, hx psoriasis

No prior lipid lowering tx

Randomized to placebo, open label fenofibrate begun week 24.

Nl abd exam baseline and at v. 12 on 1/21/83

Diet at baseline 30-35% tot fat

alt 31 (ABNORMAL) on v. 7 on 8/18

Sreening baseline 5/21/82 - 6/30/82

Adherence to drug 46% at v. 8., 116% on v. 9.

Alcohol intake constant since 7 years prior to and throughout study at 1-2 drinks/day = 3-4 oz.

Visit 13 AST/ALT increase felt to be clinically signif.

Nl range AST 1-25.

Nl range ALT 1-30.

visit:	1	4	6	8	9	12
date:	5/231/82	6/30	8/4	9/1	9/29	1/21
T CHOL	246	286	298	302		346
TG	198	242	129	159		108
AST	25		21	24	34	34
ALT	24		29	41	33	56
ALK PHOS	63		56		63	64
T BILI	0.9		0.4		0.8	0.8
GGT						
ABS. EOS.	108		94			180
WBC	5.4					
ABS. NEUT.						
CREAT	1.3					

visit:	13	14
date:	2/9	4/1/83
T CHOL	223	225
TG	105	93
AST	56	27

ALT	111	30
ALK PHOS	64	
T BILI	0.4	
GGT		
ABS. EOS.	210	
WBC	4.2	
ABS. NEUT.		
CREAT	1.3	

Compliance 98% at v. 14.

No concomitant meds.

ADRs and Change in Pt's Health Status reported on CRF:

V. 10 11/5/82 Stomach pain reported on pp 52 and 59 of CRF, mild, recurrent, not present prior to study, and possibly drug-related (pt on placebo until fenofibrate open label provided v. 12). Investigator notes that pt interrupted tx from 10/22 to 10/27/82 with resolution of pain, followed by recurrence after restarting pills.

V. 11 - 12/10/82 stomach pain, pos drug or EtOH related (no EtOH use noted by dietician until later when documented use of 2 glasses wine/d since 1975 noted).

V. 13: None.

CRF REVIEW OF

PROTOCOL GHBA 502 (STUDY 8104)

INVESTIGATOR #6 (KNOPP)

PATIENT No 122

PATIENT INITIALS:

63 Y/O Oriental M

Screening-baseline 4/19/82 - 6/3/82

No prior lipid-lowering tx.

No concom. meds

Nl. abd exam baseline and at v. 12 on 12/28/82 and at v. 16.

baseline diet AHA prudent; no mention of alcohol.

Randomized to placebo group. Open label fenofibrate given at v. 12; first f/u v. on feno = v. 13 on 1/14/83.

Compliance: "had trouble remembering noontime pill".

visit:	1	4	12	13	14	15
date:	4/19/82	6/3	12/28	1/14/83	3/4	4/22
T CHOL	280	270	290	221	213	205
TG	182	151	167	89	59	113
AST	13		19	35	82	43
ALT	6		16	52	96	41
ALK PHOS	76		77	53	79	51
T BILI	0.5		0.7	0.7	0.9	0.6
GGT						
ABS. EOS.	368		192	177	0	130
WBC	6.7					
ABS. NEUT.						
CREAT	0.9					

ADVERSE DRUG EXPERIENCES AND CHANGES IN HEALTH STATUS REPORTED ON CRF:

v. 13 SGOT/SGPT ELEVATIONS NOTED TO BE CLINIICALLY SIGNIFINCANT.

V. 14 no ADR listed.

V. 15 "Stool change soft & smaller" noted as ADR, mod severity, possibly drug-related.

NOTE: This ADR is not listed in the tabular data listing of all reported ADRs for patients with AST/ALT >3x the ULN on p 158 of

Fournier's 11/16/92 submission to the NDA. This is another example of the inacuracy and unreliability of the Fournier summary data and data tables for fenofibrate. At the exit visit #16 on 6/17/83, AST was 26 and was noted to be borderline elevated "probably drug", and ALT was 24. The subject did not return one blister pack, making compliance assessment unreliable. Whereas "Liver function abnormal" was listed as costart term ADR for this pt for week 26 of the study (v. 13) in the11/16/92 submission, no such ADR was identified by the investigator on the CRF p 74, or on subsequent "Adverse reaction report" sheets.

CRF REVIEW OF

PROTOCOL GHBA 502 (STUDY 8104)

INVESTIGATOR #6

PATIENT No. 335 (vol 13.5 p 377)

PATIENT INITIALS:

45 Y/O W M

No prior lipid-low. tx

No concom meds.

Abd exam nl on screening.

visit:	1	2	3	6
date:	4/24/82	10/11	10/26	12/14
T CHOL	302	331	285	271
TG	167	1225	322	198
AST	26			24
ALT	32			23
ALK PHOS	45			
T BILI	0.9			
GGT				
ABS. EOS.	138			

WBC

ABS. NEUT.

CREAT 0.9

ADRs and CHANGES IN HEALTH STATUS REPORTED ON CRF:

V. 5 (11/30/82) CRF lists flu of mod severity, remote rel to test drug. This does not appear in the tabular listing for ADRs for this pt on p 173 of the 11/16/92 submission to the NDA, probably because this listing only appears to cover the last visit of the single-blind lead-in (visit 6), the DB portion (visits 7-12), and the open label extension (v 13-16).

CRF REVIEW OF
PROTOCOL GHBA 502 (STUDY 8104)

INVESTIGATOR # 8

PATIENT No. 194 (VOL 13.7, P 1; Note there are 2 sets of pp 1-101 in this volume covering different patients!!!)

PATIENT INITIALS:

52 Y/O F

Prior lipid-lowering tx: cholestyramine d/ced 5/30/81

HX: HTN

Concom meds: Renese brand polythiazide, vit. E 400U
Robaxin, vit C.

EtOH at screening 22.5 drinks/week v.1, decreased at v. 2, increased at v. 3.

Screening -baseline 5/20/82 - 6/14/82

Nl abd exam at baseline.

visit:	01	3	5	6	7	8
date:	5/20/82	6/2	7/7/82	7/28	8/16	8/23
T CHOL	347	371	350	384	286	293

TG	92	114	110	124	80	70
AST	21			19	20	89
ALT	19			14	16	111
ALK PHOS	66			62	45	94
T BILI	8.0			0.7	0.8	0.7
GGT						
ABS. EOS.	104			44	50	0
WBC	5.2					
ABS. NEUT.						
CREAT	0.8					

Adverse Reactions/Changes in Health status reported:

v. 5 lower back pain (increased from baseline). Note: THIS IS NOT NOTED ON P 179 OF 11/16/92 SUBMISSION OF COMPUTERIZED DATABASE.

V. 6 "When patient doubles up on capsules, she notices bloating, sxs, ... constipation. ADR sheet lists constip, ABDOMINAL DISCOMFORT, SORENESS LEFT KNEE, WITH NOTATION AT BOTTOM OF P 30 OF CRF (P 33) "Pt st'd onl noticed with abd'l discomfort w bloating, gas, cramping, urge to defecate, when she doubled up on her doses". THE ONLY ADR LISTED ON P 179 OF THE 11/16/92 SUBMISSION IS "FLATULENCE", which is listed for v 7. BY ANY STRETCH, KNEE SORENESS CANNOT BE TRANSLATED INTO THE COSTART TERM, "FLATULENCE"! [It should be noted that elsewhere in chis tabular summary, the sponsor has listed AEs occuring during periods of placebo exposure, such as the abdominal pain occuring during during DB week 12 of pt 6-128 (p 164 of 11/16/92 submission) who is listed as taking placebo during the DB period).

V. 7 indicates no change in health status since last visit, yet lists no ADRs, which is inconsistent.

V. 8 Increased alk phos, increased SGOT and SGPT, moderate severity, clinically significant, no change in test drug dose, possibly drug-related. P 179 OF THE 11/16/92 SUBMISSION LISTS ONLY LIVER FUNCTION ABNORMAL AND CREATININE PHOSPHOKINASE INCREASED FOR WEEK 4 VISIT, THEN NO ADRS ARE LISTED UNTIL WEEK 24 WHEN ABDOMINAL PAIN IS LISTED.

V. 9. PYURIA AND CK AND SGOT/SGPT ARE ALL NOTED TO BE CLINICALLY SIGNIFICANTLY ELEVATED ON LAB SHEET. FLATULENCE, INCR. SGOT/SGPT AND INCR CPK ARE LISTED ON ADR SHEET (AND NOT REPEATED ON 11/16 SUBMISSION TABLE).

v. 12. ABDOMINAL CRAMPING. Letter dated 1/19/83 from Gastrointerologist consultant regarding his evaluation of the subject on 10 Jan 1983 indicates 3 month history of epigastric pain, much worse in intensity x 2 weeks. Consultant noted "There was some tenderness in the epigastrium to the right of the midline" Upper endoscopy performed at that time was normal; transaminases had normalized by this time.

NOTE: In view of the consultant gastroenterologist's ascertainment of epigastric pain overlapping with visits 9 and 10 during which transaminases were clinically significantly elevated and [residual] RUQ tenderness, this patient shall be considered to have had SYMPTOMATIC AMINOTRANSFERASE ELEVATIONS.

visit:	9	10	11
date:	9/20/82	10/18	11/29
T CHOL	296		
TG	60		
AST	36	41	22
ALT	46	43	23
ALK PHOS			
T BILI			
GGT			
ABS. EOS.	0		
WBC			
ABS. NEUT.			
CREAT	0.8		

INVESTIGATOR # 8 (MELLIES)

PATIENT No. 198

PATIENT INITIALS:

Prior tx: Atromid-S (clofibrate)

Baseline TG: 181

Baseline AST 19

Baseline ALT 33, 37

FBS 111, 116

screening/baseline EtOH 12/9 drinks/wk

On-tx EtOH 12/wk, increased, but not quantitated

Concom med: Dyazide for htn

On tx AST 19, 16, 20, 25, 25, 16, 44, 30,

On tx ALT 31, 30, 40, 30, 42, 26, 82, 59

Alk phos: 35

Creatinine: increased from 0.6 to 1.1

ADRs: blurred vision at 5 weeks
incr ALT
cramping lower extremities

visit:

date:

T CHOL

TG

AST

ALT

ALK PHOS

T BILI

GGT

ABS. EOS.

WBC

ABS. NEUT.

CREAT

CRF REVIEW OF

PROTOCOL FEN 8104

INVESTIGATOR # 6 (Knopp)

PATIENT No. 130

PATIENT INITIALS:

Age/Sex 48 M

Ht/Wt 67"/170 lb

Chylos present?

PMHx: allergic rhinitis

Concom. Meds: mitamins, lecithin, chlorpheniramine
Maalox added v 10 for upset stomach
Erythromycin 12/11-12/17/82

No prior lipid-lowering meds.

Diet at screening: prudent AHA

Adverse Reactions Reported by Investigator on CRF:

V 6 URI, mild

V 9 SGOT/SGPT, severe, probable relationship to study drug.

V 10 upset stomach, moderate severity, recurrent, possibly related to drug.

V 11 Flu, mod, remote
V 11 Upset stomach, moderate, possible rel. to drug

V 12 SGOT/SGPT moderate severity, recurrent, probable rel. to drug.

Investig. comments:

V 8 "Pt can't explain overmedicating - he's not aware that he did."

V 9 "alcohol intake is very low"
11/3/82 SGOT + SGPT are elevated considerably - Dr. Knapp recommending recheck.

11/22/82 Recheck now SGOT of 62 and SGPT of 172 [2.5 and 5.7 X the ULN, respectively]. GGT is nl at 24 and the CK is normal. Enzymes at the repeat observation are improving. Pt notess that he has had some lower GI "stomach rumblings" with some gas. This is unusual for him. Otherwise he feels fine. It is decided to continue on the medication until the next visit Dec 6th. Experience with the 'fibrate class is that an SGOT - PT rise on starting a [unintelligible] drug quickly abates. signed by R. Knopp.

V 11 1/23 "Dr. Knopp wrote on lab sheet: These enzyme changes are not an unanticipated effect of this drug and one of the objects of the investigation is to determine the extent of this effect. In the absence of any symptomtology [sic] I would continue - enzyme changes are stable or less than initially [Reviewers note: I pt had reported stomach upset during visits 10 and 11, I don't understand why Dr. Knopp wrote 'in the absence of any symptomology, except that the AE sheet indicates that the abdominal symptoms had resolved 3 days prior to visit 11.]

V 12 abdominal exam nl; small polyp 2" past anus noted on rectal, not noted on earlier exams.

visit:	1	6	7	8	9	10
date:	06/03/82	9/7	9/20	10/4	11/3	12/6
T CHOL	293	301	251	221	247	258
TG	112	93	81	66	64	69
AST	21	20	21	18	131	42
ALT	24	23	11	15	202	87
ALK PHOS	77	59	51	46	43	44
T BILI	0.5	0.7	0.5		0.5	0.6
GGT						
ABS. EOS.	184	220	350		225	204

WBC		
ABS. NEUT.		
CREAT		
Visit No.	11	12
Date	1/17/83	2/24/83
T CHOL	237	237
TG	63	59
AST	52	42
ALT	98	72
ALK PHOS	38	
T BILI	0.5	
GGT		
ABS. EOS.	46	156

NOTE: On sponsor's tabular listing of 11/16/92, it failed to include abdominal pain (upset stomach) at visit 10 or for visit 11, visits when AST and ALT were elevated significantly. In sponsor's table of laboratory adverse events for this study, (Table 2a from 8/23/91 amendment, which had also appeared in previous submissions, including the briefing document for the Advisory Committee, this patient was not counted as he should have been among patients who had clinically significant elevations of AST > 2X the ULN on >= 2 consecutive determinations.

NOTE: This case demonstrated ALT elevation to up to 5.7 X ULN with abnormal levels of AST/ALT lasting about 6 months, eventually resolving on continued therapy. The investigator and this reviewer concludes that this was drug related. Symptoms accompanied marked elevations of AST/ALT consisted of borborygmi, intestinal gas, and abdominal pain.

CRF REVIEW OF

PROTOCOL 8104

INVESTIGATOR # 2 (Dujovne)

PATIENT No. 28

PATIENT INITIALS:

Age/Sex 46 M

Ht/Wt

Chylos present?

PMHx:

Diet at screening: fat > than rec.
At V 6 (end of single blind) % cal from fat > 40%

Concom. Meds:
V 2 7/27 began allopurinol 300 mg qd

V 7 Sorbitrate 10/19 prn chest pain

V 10 oxymetazoline HCl nasal spray prn congest.

Adverse Reactions Reported by Investigator on CRF:

V 2 joint pain

V 5 Pruritis arm

V 6 Pruritis arm
great toe pain x 1 day
Interim visit between V 7 and V 8 on 10/19/82 "Sl tiredness, tightness of chest, sorenesss upon inspiring, transient substernal pain when lying down, SOB, started 10/16/82. Had hot flashes + chills 10/18 during noe. No physical findings Will do ... Only abnormal findings SGPT 54..."

V 8 "Pt not feeling well between visits see comments visit #7. Used Sorbitrate 5 mg tablets SL x 1 10/20 for chest pain with good results."

V 9 viral URI, stuffy nose, headache 11/8 thru 11/16
arm pruritis without rash
No abd pain, nausea, anorexia, or jaundice.
V 10 recovering from viral URI. 6.5 lb wt gain eating fried foods. Nasal congestion, pruritis arm.

V 11 blurred vision, pruritis forearm

V 11 L femoral pulse decreased (not noted at baseline)

V 12 RUQ abdominal pain

Knee pain, ankle pain, rhinorrhea

V 13 Lightheadedness, blurred vision leading to d/c of drug on 3/11/83. Sx improved by 4/19. Change in ECG prompting cardiology referral.

visit:	1	2	6	7	8	8a
/date:	6/29/82	7/13	9/28	10/12	10/26	11/2
T CHOL	309	332	284	242	237	
TG	225	308	169	136	98	
AST	26		31	40	88	56
ALT	26		27	42	165	101
ALK PHOS	74		62	47	69	
T BILI	0.5		0.8	0.5	0.5	
GGT						162
CK						113
ABS. EOS.	66		55	0	116	
WBC						
ABS. NEUT.						
CREAT						

NOTE: On p 7 of attachment 1 of vol 13.7 (p 7 of CRF), physical exam findings for neck and extremities were striken out by a double line, and also completely obliterated with scribbling, by CAD (the invest.)

Neither pruritis nor great toe pain present at V 6 were disclosed for week 0 of DB on p 146 of 11/16/92 submission.

Whereas the tabular listing for this pt on p 146 of the 11/16/92 submission listed for this visit only the AEs fatigue, headache, and chest pain, the CRF also lists SOB (shortness of breath) and pleuritic chest pain, hot flashes, and chills.

Whereas the tabular listing for DB week 12 lists only fatigue, the CRF lists nasal congestion and pruritis arm and does not list fatigue.

Whereas the tabular listing for V 13 (week 26) lists only

"accomodation abnormal", the Adverse reaction report sheet of the CRF (p 74 of vol 13.1) also lists lightheadedness. No mention is made in the tabular listing of the change in ECG or the fact that an outside MD had obtained a PP glucose > 200 mg/dl leading to a prescription of a diabetic diet which, together with the ECG change, seems to have accounted for removal of the patient from the study. The tabular summary incorrectly indicates that the patient was on 100 mg TID of drug at week 33 (V 14) following randomization, whereas the CRF indicates that drug had been d/ced one week prior to the preceding visit (week 25 post-randomization, 10 days after V 12.

The difference in pill counts between visits 8 & 9 is 62 capsules. Twenty-one days separate these visits, so expected consumption is 3 x 21 = 63 capsules. Thus, it cannot be concluded that reduction in dose by patient could explain diminution in LFTs over this interval.

visit:	8c	9	10	10a	11	12
date:	11/9	11/16	12/7	12/29	1/18/83	3/1
T CHOL		295	282		221	244
TG		167	200		98	93
AST	46	49	60	48	39	30
ALT	69	73	115	12	57	41
ALK PHOS		49	44		38	
T BILI		0.4				
GGT						
ABS. EOS.		216	0		85	
WBC						
ABS. NEUT.						
CREAT						

CRF REVIEW OF

PROTOCOL 8104

INVESTIGATOR # 3 FARQUHAR

PATIENT No. 63

PATIENT INITIALS:

Age/Sex 44 F

Ht/Wt 64.5"/ 139 lb

Chylos present?

PMHx: pcn allergy

Concom. Meds: past tx w colestipol
HCTZ
KCl
V. 7 Combid for nausea

Baseline abd exam nl

Diet screening: vegatarian

Adverse Reactions Reported by Investigator on CRF:

V 6 Skin lesion, mild, new, possibly drug related.

V 7 Nausea, severe, recurrent, new, ongoing since 11/10 (10 days), possibly related to study drug.
Fatigue, severe, continuous, new, possibly related to study drug acc to invest., present since 11/10.
1 day of fever to 101, abdominal pain, malaise.
elevated liver enzs, possibly related to drug.
Pt saw PMD for above who noted elevated alk phos of 71 and SGPT of 101. Nausea is not immediately related to time of drug ingestion.

V. 8 Sl. nausea and fatigue.

V. 9 elevated liver enzymes

V 10 Nausea had resolved.

ULN for AST was 70, for ALT 70, according to computer disk from Sponsor for this site.

visit:	01	6	7	8	9	10
date:	8/5/82	10/28	11/19	11/29	12/21	1/20
T CHOL	282	293	277	242	222	243
TG	144	98	148	65	64	73

AST	20	22	130	43	73	63
ALT	24	20	231	59	81	77
ALK PHOS	45	55	57	47	21	
T BILI	0.37	0.69	0.49	0.46		
GGT						
ABS. EOS.	120	91	568	395	105	
WBC						
ABS. NEUT.						
CREAT						

NOTE: Skin lesion, possibly drug related was noted on ADR sheet for visit 6 (p 30 of CRF, p 157 of vol 13.2 of NDA) but not disclosed on tabular summary p 152 submission of 11/16/92 for week 0 of DB (visit 6).

The sponsor failed to disclose that fever and abdominal pain (coincident with 3.3 x ULN elevation of ALT) had been reported on the CRF in its tabular summary of 11/16/92 p 152.

LFTs were indicated to be elevated at week 4 DB on tabular listing, whereas CRF indicated increased LFTs on ADR sheet for Visits 7 & 9 (weeks 2 and 8 of DB).

No abd tenderness or organomegaly V. 8.
Capsule count between v 6 & v 7 suggests 100% compliance (30 caps).

CRF REVIEW OF

PROTOCOL 8104

INVESTIGATOR # 8 Mellies

PATIENT No. 301

PATIENT INITIALS:

Location of CRF reviewed: p 1 of vol 13.8 of submission of 10/20/89. Note: As is typical of the user-unfriendliness of Fournier's NDA, there are two page ones in this volume; this CRF begins after the 3rd yellow tab, about 3/5 of the way through the volume!

Age/Sex 58 F

Ht/Wt 61.4"/118.3 lb

Chylos present?

PMHx:

No history of allergy.

Concom. Meds: None initially. Note: Pt took another investigational drug, Cetaben-Na from 4/21/82 to 7/31/82, terminating 28 days prior to screening for the current study.

Screening diet: fairly good.
No alcohol.

Initial abd exam: s/p histerectomy 1960

Adverse Reactions Reported by Investigator on CRF:

V. 6 eosinophilia, present at baseline also

V. 7 ALT/AST and CPK elevations noted on p 35 of submission for V. 7 to be clinically significant, new, and possibly drug related.

V. 8 incr AST/ALT possibly drug related, "prob drug effect"; incr CPK, remotely related, CPK normal.

V. 9 incr AST/ALT (marked clinically significant) and CPK noted on p 57 of submission (p 48 of CRF), but are not noted on tabular listing on p 183 of 11/16/92 submission.

ULN for AST was 22 and for ALT was 25 at this site, according to computer disk from the sponsor.

visit:	1a	06	7	8	9
date:	9/11/82	12/18	1/3	1/15	2/12
T CHOL	237	283	205	230	228
TG	360	122	128	222	95
AST	14	16	42	71	41
ALT	10	14	54	92	42
ALK PHOS	68	54	44	43	42
T BILI	0.1	0.1	0.5	0.?	0.5

CK		119	75	109
ABS. EOS. 512	455	nd	440	nd
WBC				
ABS. NEUT.				
CREAT				

Note: Tabulation on p 183 of 11/16/92 submission fails to indicate that CRF shows eosinophilia reported at V. 6.

Whereas on CRF for V. 8 increased AST/ALT possibly drug related, "prob drug effect"; incr CPK, remotely related, CPK normal, are listed, no AE events are listed for this visit (DB week 4) or tabular listing.

V. 9 incr AST/ALT (marked clinically significant) and CPK noted on p 57 of submission (p 48 of CRF), but are not noted on tabular listing on p 183 of 11/16/92 submission.

Compliance by pill count v. 7 125%, at v. 8 100%.

Conclusion regarding hepatotoxicity: Investigator and this reviewer conclude that reaction is probably drug related. Elevation of ALT to 3.7 X uln and AST to 3.2 X ULN was associated with 125% compliance by pill count at the preceding visit, when aminotransferases had already begun to rise significantly. Eosinophilia, mild, was present at baseline and did not worsen on drug. While CK was mildly elevated, the AST elevation cannot be attributed to muscle because of the CK/AST ratio value. The reaction was apparently asymptomatic and the enzymes fell on continued therapy (at approximately 100% compliance), but enzymes never normalized. Final elevations were 1.6X ULN for AST and 1.2X ULN at week 48 for ALT. Thus, liver function abnormalities persisted for as long as therapy was continued, namely for nearly a year.

CRF REVIEW OF

PROTOCOL

INVESTIGATOR #

PATIENT No.

PATIENT INITIALS:

Age/Sex

Ht/Wt

Chylos present?

PMHx:

Concom. Meds:

Adverse Reactions Reported by Investigator on CRF:

visit:

date:

T CHOL

TG

AST

ALT

ALK PHOS

T BILI

GGT

ABS. EOS.

WBC

ABS. NEUT.

CREAT

CRF REVIEW OF

PROTOCOL

INVESTIGATOR #

PATIENT No.

PATIENT INITIALS:

Age/Sex

Ht/Wt

Chylos present?

PMHx:

Concom. Meds:

Adverse Reactions Reported by Investigator on CRF:

visit:

date:

T CHOL

TG

AST

ALT

ALK PHOS

T BILI

GGT

ABS. EOS.

WBC

ABS. NEUT.

CREAT

CRF REVIEW OF

PROTOCOL FEN 8601 (U.S. TYPE IV/V STUDY)

INVESTIGATOR 7407 (PICKERING)

PATIENT No. 104

PATIENT INITIALS:

NOTE ON STUDY DESIGN (FEN 8601):

An 8-week (active portion) DB, placebo-controlled parallel study with Hx, PE, and blood chemistry at screening and again at week -4 (v. 1) during Period I (single-blind placebo lead-in period), blood chemistry repeated at week 0, 4, and 8. Lipids were done (profile) at weeks -4, -2, 0, 2, 4, 6, and 8. Beta Quantitation of LDL-C via ultracentrifugation was performed at weeks -4, 0, 4,

and 8.

Visit No.	Week	Chemistries	
1	-4	X	Single blind
2	-2		
3	0	X	Double blind med dispensed
4	2		
5	4	X	
6	6		
7	8	X	

[Provision was planned to have an open extension of 1 year for appropriate patients at centers interested, if negotiated. Several centers took out their individual INDs to continue patients on open label therapy. Follow-up annual reports for these multiple centers treating patients long-term has been received only for the center headed by Elaine Feldman. The sponsor and individual investigators who took out individual INDs were instructed as to the appropriate frequency of safety monitoring for the open extension period and limiting enrollment into open extension to subjects with baseline TG > 500 mg/dL, but never submitted amendments to the INDs to reflect modification of protocols along the lines required.]

Age/Sex: 26 y/o M

Wt 164 lb/ht. 69"

No chylos.

Nl. abd exam at baseline 11/25/86

Note: CRF pages are not numbered!

Visit numbers are not indicated on CRF pages!

100% compliance on 12/9/86 and other visits except 1 dose missed as of 1/20/87 visit and 1 taken day of visit on 2/3/87.

The dietary evaluation record, under food type, indicates for each visit "low chol, low CHO [carbohydrate], low fat". How can

everything be low, unless the patient is on a hypocaloric diet, which is not the intent of the protocol. The pt is said to consume <= 12 oz. scotch 5X per week. Comments indicate pt was instructed in behav. mod. to limit "occ. binging".

Concom. meds: ASA, MVI, propranolol 60 mg for htn, allopurinol 300 mg started 7/83 for gout.

No ADRs (AEs) were reported during the SB placebo lead-in.

The randomization approval sheet, signed and dated 12/23/86, under I. 2. incorrectly states "The serum triglyceride level must be between 350 mg/dl and 1000 mg/dl with or without symptoms of pancreatitis". In fact, the protocol had been amended to allow an upper limit of baseline TG of 1500 mg/dL and only patients who had no prior history of pancreatitis were to be enrolled into the study.

Investigator noted on Lab Evalulation sheet (1 of 2) that "Elevated alcaline phosphatase and SGOTY suggest hemolysis".

Lipid values are not documented on sheet on which investigator certifies that pt meets study inclusion criteria. It is only indicated that, with respect to screening TG level, that it be "markedly elevated" with LDL-C < 175 mg/dL.

Interim History sheets that ask the question, "Were any adverse reaction reports changed? ", are present for the following dates:

12/9/86

12/23/86

1/8/87

1/20/87

2/3/87

The exit summary sheet with the same question about whether any adverse reaction reports changed was dated 2/12/87.

No AEs are listed on the Adverse Reaction Report sheet; the answer to the question, "were any adverse reaction reports changed?" was no on each interim history and the exit sheet.

visit:	1	3	5	7
date:	11/25/86	12/23	1/20/87	2/12/87

T CHOL	238	237	237	213
TG	389	288	308	138
AST	17	26	58	23
ALT	31	35	216	39
ALK PHOS	59	57	139	54
T BILI	0.6	0.7	0.7	0.6
GGT				
ABS. EOS.	67	234	61	294
WBC				
ABS. NEUT.				
CREAT				

CONCLUSION: Single, apparently asymptomatic increase in ALT to 4.3 X ULN with rise in alk phos and AST. No eosinophilia. Spontaneous resolution after 23 days of continued drug tx with approx. 100% compliance by pill count. No clear efficacy of drug on lipids until week 8. I am not aware that hemolysis can lead to such increases in ALT as suggested by the investigator.

CRF REVIEW OF

PROTOCOL FEN 8601

INVESTIGATOR # 7404 (KNOPP)

PATIENT No. 101

PATIENT INITIALS:

Age/Sex

Ht/Wt 63.4/141 lbs.

Chylos present? No

PMHx: Htn, angina

Concom. Meds:

Patient discontinued from study due to ADR? Yes, liver toxicity.

Pt stopped drug on 9/5/86.

Adverse Reactions Reported by Investigator on CRF:

Enlarged liver, moderate severity, related to test drug
according to investigator 9/4-9/10/86

Right upper quadrant pain/indigestion, mild, rel to test drug unkknown 9/4/86-9/25/86

Generalized malaise, mild, related to test drug 9/4/86 continuing

Dark uring, moderate 9/4/86 - 9/10/86

Intermitting itching, moderate, related to test drug 9/4 - 9/15/86

Aching joints, moderate severity 9/10/86 - continuing

Polyuria, mild 9/5-9/15/86

NOTE: On p 195 of 11/16/92 submission of tabular listings of ADRs reported for patients with AST/ALT > 3X the ULN, the sponsor listed only liver damage, arthralgia, and polyuria for this patient as the costart terms corresponding to the reported ADRs. Alan Irvine has emphasized during his telecon with me that the 11/16/92 tablular data listings included all adverse experiences regardless of the investigator's or sponsor's opinion as to whether they were drug related. Because the 3 costart terms reported for this patient in the 11/16/92 submission failed to include hepatomegaly, right upper quadrant or abdominal pain, malaise, pruritis, or dark urine, either the sponsor deliberately failed to transfer these ADRs from the CRF to the tabular data listing we had requested, or the sponsor would appear to be incompetent to accurately prepare data tables that are integral to proper NDA review. This is a clear case of symptomatic drug-induced hepatitis, and, as such, should have undergone careful scrutiny by the sponsor. Leaving important adverse effect data out of the tabular listing for this patient raises important questions as to the integrity of the NDA.

CRF REVIEW OF

PROTOCOL

INVESTIGATOR #

PATIENT No.

PATIENT INITIALS:

Age/Sex

Ht/Wt

Chylos present?

PMHx:

Concom. Meds:

Adverse Reactions Reported by Investigator on CRF:

visit:

date:

T CHOL

TG

AST

ALT

ALK PHOS

T BILI

GGT

ABS. EOS.

WBC

ABS. NEUT.

CREAT

CRF REVIEW OF

PROTOCOL

INVESTIGATOR #

PATIENT No.

PATIENT INITIALS:

Age/Sex

Ht/Wt

Chylos present?

PMHx:

Concom. Meds:

Adverse Reactions Reported by Investigator on CRF:

visit:

date:

T CHOL

TG

AST

ALT

ALK PHOS

T BILI

GGT

ABS. EOS.

WBC

ABS. NEUT.

CREAT

CRF REVIEW OF

PROTOCOL

INVESTIGATOR #

PATIENT No.

PATIENT INITIALS:

Age/Sex

Ht/Wt

Chylos present?

PMHx:

Concom. Meds:

Adverse Reactions Reported by Investigator on CRF:

visit:

date:

T CHOL

TG

AST

ALT

ALK PHOS

T BILI

GGT

ABS. EOS.

WBC

ABS. NEUT.

CREAT

CRF REVIEW OF

PROTOCOL

INVESTIGATOR #

PATIENT No.

PATIENT INITIALS:

Age/Sex

Ht/Wt

Chylos present?

PMHx:

Concom. Meds:

Adverse Reactions Reported by Investigator on CRF:

visit:

date:

T CHOL

TG

AST

ALT

ALK PHOS

T BILI

GGT

ABS. EOS.

WBC

ABS. NEUT.

CREAT

CRF REVIEW OF

PROTOCOL

INVESTIGATOR #

PATIENT No.

PATIENT INITIALS:

Age/Sex

Ht/Wt

Chylos present?

PMHx:

Concom. Meds:

Adverse Reactions Reported by Investigator on CRF:

visit:

date:

T CHOL

TG

AST

ALT

ALK PHOS

T BILI

GGT

ABS. EOS.

WBC

ABS. NEUT.

CREAT

CRF REVIEW OF

PROTOCOL

INVESTIGATOR #

PATIENT No.

PATIENT INITIALS:

Age/Sex

Ht/Wt

Chylos present?

PMHx:

Concom. Meds:

Adverse Reactions Reported by Investigator on CRF:

visit:

date:

T CHOL

TG

AST

ALT

ALK PHOS

T BILI

GGT

ABS. EOS.

WBC

ABS. NEUT.

CREAT

CRF REVIEW OF

PROTOCOL

INVESTIGATOR #

PATIENT No.

PATIENT INITIALS:

Age/Sex

Ht/Wt

Chylos present?

PMHx:

Concom. Meds:

Adverse Reactions Reported by Investigator on CRF:

visit:

date:

T CHOL

TG

AST

ALT

ALK PHOS

T BILI

GGT

ABS. EOS.

WBC

ABS. NEUT.

CREAT

CRF REVIEW OF

PROTOCOL

INVESTIGATOR #

PATIENT No.

PATIENT INITIALS:

Age/Sex

Ht/Wt

Chylos present?

PMHx:

Concom. Meds:

Adverse Reactions Reported by Investigator on CRF:

visit:

date:

T CHOL

TG

AST

ALT

ALK PHOS

T BILI

GGT

ABS. EOS.

WBC

ABS. NEUT.

CREAT

CRF REVIEW OF

PROTOCOL

INVESTIGATOR #

PATIENT No.

PATIENT INITIALS:

Age/Sex

Ht/Wt

Chylos present?

PMHx:

Concom. Meds:

Adverse Reactions Reported by Investigator on CRF:

visit:

date:

T CHOL

TG

AST

ALT

ALK PHOS

T BILI

GGT

ABS. EOS.

WBC

ABS. NEUT.

CREAT

CRF REVIEW OF

PROTOCOL

INVESTIGATOR #

PATIENT No.

PATIENT INITIALS:

Age/Sex

Ht/Wt

Chylos present?

PMHx:

Concom. Meds:

Adverse Reactions Reported by Investigator on CRF:

visit:

date:

T CHOL

TG

AST

ALT

ALK PHOS

T BILI

GGT

ABS. EOS.

WBC

ABS. NEUT.

CREAT

SUMMARY OF ADVERSE EXPERIENCES RECORDED ON CRFs BUT NOT APPEARING ON THE TABULAR SUMMARY OF ALL AEs AND LABORATORY VALUES FOR PATIENTS EXPERIENCING AST/ALT > 3x THE ULN PROVIDED IN THE SPONSOR'S 11/16/92 SUBMISSION:

Eight out of thirteen (62%) of CRFs reviewed failed to have some, often several of the investigator recorded adverse experiences included in the tabular summary of adverse experiences for the same patients in the sponsor's 11/16/92 submission. Omissios of AEs in tabular summaries were seen for patients:

Study 8104:

10-232
2-036
6-122
8-194
6-130
3-63
8-301

Study 8601

7404-101
(only 2 CRFs were reviewed from this study)

For study 8104, 4 CRFs did not have problems in concordance of AEs disclosed both on the CRF and in the tabular summary, but some of these may not have had any AEs recorded. Other problems are evident, and are summarized separately. This includes irregular "corrections" of the CRF by the monitor, and apparent replacement of a CFR page (Pt #011-161, page 42, study 8104) with a "cleaned" page that apparently did not reflect data recorded by the investigator on the original CRF.

RECOMMEND: DSI-ASSISTED AUDIT OF INTERNAL VALIDITY OF NDA DATA SUMMARIES, LABELING VS. CRFS.
This omission cannot be explained by different judgement in translation into COSTART terms. The lack of accuracy of the tabular listing, provided specifically in response to our concern about characterizing the incidence of systematic hepatotoxicity associated with fenofibrate, is of particular concern. The gross inaccuracy of the 11/16/92 submission calls into serious question the veracity and accuracy of the sponsor's proposed labeling, particularly the warnings, precautions, and adverse reactions sections, and the tabular summaries in the original NDA, the tables and discussion of safety in the background document prepared by Fournier for briefing Advisory Committee members, and the tables and summaries in amendments and safety updates. These should all undergo checking to insure data validity. The sponsor

may be asked to correct omissions and inaccuracies in their computerized study database and to resubmit appropriately corrected data.

NOTE: INVESTIGATORS WERE NOT BLIND TO LIPID VALUES; THUS, BECAUSE OF THE REGULAR DECREASE IN TRIGLYCERIDES (OR IN LDL--C AMONG TYPE IIA PTS) SEEN WITH FENOFIBRATE, THE STUDY ESSENTIALLY BECAME UNBLINDED DURING FOLLOW-UP VISITS AS ON-TREATMENT LIPID VALUES WERE INSPECTED.

The center numbers do not appear on the CRFs for study FEN 8601, so that the patient numbers are not unique identifiers without the investigator's name. This makes review cumbersome.

The CRFs for study FEN 8601 are not numbered; nor are the pages of volume 12 of the 10/20/89 submission (vol 13.12) pagenaged, nor do the pink separator sheets indicate the center and patient number, making review more difficult. The index to CRFs is inadeqauate.

For study FEN 8601 there is no signature of the study monitor on any sheets of the CRF or on any sheets submitted in conjuction with the CRFs in the 10/20/89 submission. There is no evidence from the data submitted that any company-sponsored audit of the CRFs was performed.

L. Ross Pierce, MD

Note: Review terminated due to transfer of this reviewer to another Division.

L. Ross Pierce, M.D.
5/14/93
cc
NDA
HFD 510
HFD 510 Pierce/Innerfield/Troendle/Sobel/Trostle
[fenocrf.wp]

Trostle
MAY 14 1993

GROUP LEADER'S REVIEW OF CASE REPORT FORM OF PATIENT EXPERIENCING ANAPHYLLACTIC REACTION IN U.S. STUDY OF FENOFIBRATE

NDA 19304
DRUG: FENOFIBRATE
SPONSOR: FOURNIER
REVIEW DATE 2/26/93

BACKGROUND:

Dr. Gloria Troendle's original NDA review of the 1984 NDA submission indicated that a fenofibrate patient had experienced anaphyllaxis. Checking with the sponsor, it was ascertained that this patient had been randomized to placebo

Protocol 502
Invest. 9
Pt 202
Pt initials

At visit 1, not on diet

TG 108
eos 1.7% at baseline

v 2
TG 129, TChol 395

v3

TG 97, chol 360
No signif changes in dietary status since last v on v 2, 3:

"Diet does not conform to standards for modified fat. Not particular attention is paid to saturated fat or cholesterol. PUFAs are used occasionally."

v 4 diet interview: Have the patient's dietary habits been fairly consistent since the last interview? Ans: yes.

v4 diet interview: " very good recall. Compliance is 75%. Does the patient meet the dietary requirements for continuation for the study? Ans: yes.

v4

TG 114, T Chol 354

concom med propranolol 80 mg

v 11

TG 118
T Chol 368
eos 0.4%

Anaphylactic shock 9/4-9/5/82, severe, hospitalized, med temp d/ced, reintoduced without reappearance of rxn. Rel to test drug rated remote by investigator. Zomax and ASA found to be causative [pt gave screening hx allergy to Zomax and ASA.

Comment: Lack of reduction of TG and chol on test drug would confirm allocation to placebo. NAI regarding this particular case.

L. Ross Pierce, MD

L. Ross Pierce, MD
5/14/93

cc
NDA
HFD 510
HFD-510 Pierce/Innerfield/Trostle
[fenoana]

N19-304 ORIGINAL MAY 14 1993 DRAFT

GROUP LEADER'S FURTHER ADDENDUM TO ADDENDUM/COMMENTS TO MOR OF 5TH SAFETY UPDATE

DRUG: FENOFIBRATE (LIPIDIL)
SPONSOR: LABORATOIRES FOURNIER
SUBMITTED: 4-24-92
MOR SIGNATURE DATE: 5-20-92
DATE OF ADDENUM/COMMENTS: 6-1-92
DATE OF FURTHER ADDENDUM: 9-17-92

Literature review of fenofibrate for period calender year 1991 (plus 1 dated 1986, 1 dated 1990):

1. Pharmacovigilance des hypolipemiants (fibrates et probucol), a partir des donnees de la bangue informatique Systeme Francais de Pharmacovigilance. Therapie 46:345-6, 1991.

For the 5-year period 1985-1990, the Association Francaise des Centres Regionaux de Pharmacovigilance (AFCRP), Department Informatique HCL, Bureau de Pharmacovigilance (PH9) de la Direction de la Pharmacie et du Medicament (DPHM) received a total of 36,875 spontaneous reports of adverse drug experiences for all drugs of any type available in France. Of these, 792 involved lipid-altering drugs.

Of the 792 ADRs with lipid-lowering drugs, 409 were deemed to meet WHO criteria as "suspect". This classification sometimes, but not always involved going back to the complete report, rather than the computerized summary. The 409 ADRs where the lipid-regulating drug was considered suspect (S), included fenofibrate (48%, year of intorduction (YI), 1975), ciprofibrate (19%, YI 1985), gemfibrozil (15%, YI 1985), bezafibrate (14%, YI 1982), clofibrate (2%, YI 1965), and probucol (2%, YI 1080). Relative sales/prescription figures for this period for these drugs are not given.

Of the 409 suspect ADRs, 54 involved muscle, 78 involved liver, and 277 were designated other. No listing by COSTART term or equivalent is provided.

2. N. Agheli , Jacotot, B. Effect of simvastatin and fenofibrate on the fatty acid composition of hypercholesterolemic patients.
Br. J. Clin. Pharmac 32:423-428, 1991.

Fenofibrate 300 mg QD was given to 8 Type II pts for 12 weeks in a DB trial vs. simvastatin 20 mg QD in 7 pts to determine the effect of fatty acid composition of circul. lipoproteins. The effects with fenofibrate were basically those seen previously with clofibrate, namely an increase in the relative content of

saturated fatty acids of chol. esters, phospholipids, and TG in VLDL, IDL, and HDL. The proportion of polyunsaturated fatty acids was decreased in VLDL and IDL. Fenofibrate decreased the P:S ratio in phospholipids of LDL, and in all lipids of VLDL, and in the chol. esters and phospholipids of IDL and LDL. These changes have been suggested to increase the atherogenicity of lipoproteins (Soutar, 1978). Baudet (1984) has reportedly shown that an increase in saturated fat content of LDL decreases its binding, internalization, and protein degradation. Thus, these changes would be expected to be deleterious. These changes in P:S ratio of lipoprotein fatty acids were not seen with simvastatin. However the increase in monounsat. fatty acids seen in chol. esters and phospholipids of all fxs might possibly be expected to help prevent LDL oxidation, according to this FDA reviewer.

3. Lipoprotein particle analysis comparing simvastatin and fenofibrate. Bard JM...et Fruchart JC. Atherosclerosis 91:S29-S34, 1991.

A DB, randomized 10 week study in 189 primary Type II HLP pts with tot. chol > 300 mg/dL and LDL-C > 195 mg/dL and TG < 350 mg/dL 4-6 weeks after d/c all lipid-lowering drugs and on standard lipid-lowering diet, comparing the effects of 200 mg BID of fenofibrate vs simvastatin 20 mg QD (or 40 mg QD if LDL-C > 140 mg/dL at week 6). Lipoprotein particles were determined at weeks 6 and 10.

PERCENTAGE CHANGES FROM BASELINE

	FENOFIBRATE		SIMVASTATIN	
	week 6	week 10	week 6	week 10
lipoprotein particles:				
LpAI	-12.8	-15.1	+2.5	+5.6
LpAII:AI	+13.9	+22.3	+5 (NS)	+2 (NS)
LpE:B	-53.8	-52.2	-33.0	-40.8
LpCIII:B	-35.1	-43.5	-23.8	-31.8
apoliproteins:				
apo A-I	+4.4	+7.4	+3.0	+4.3
apo B	-23.2	-25.3	-30.0	-32.4

The fall and rise, respectively, from baseline in LpAI and LpAII:AI particle concentration was significant for fenofibrate ($P < 0.01$).

Significant reductions were also achieved with both drugs for LpE:B and LpCIII:B particles.

All changes in apo B and the 10 week change for feno only for total plasma apo A-I were signif. ($P < 0.01$).

Conclusion: The changes in LpAI and LpAII:AI particle concentrations induced by fenofibrate would be expected to be deleterious and promote atherosclerosis, in contrast to the effect on apo B. * Low LpAI particle concentration has been shown to be associated with higher rates of CHD, and LpAI particles are thought to mediate reverse cholesterol transport, whereas LpAII:AI particles are thought to antagonize reverse cholesterol transport (Fruchart JC and Ailhaud G. Apoliprotein A-containing particles: physiological role, quantitification, and clinical significance. Clin Chem. 38:793-797). Simvastatin has a better overall profile than fenofibrate for the endpoints studied.

4. Bunte T, Hahmann H, Hellwig N, et al. Regression and decrease in progression of coronary narrowings in hypercholesterolemic patients with long-term fenofibrate therapy. abstract. 9th int'l symp. on atherosclerosis, Rosemont, IL Oct 6-11, 1991.

This seems to be an open, non-randomized study that compares an intervention group (n=21, 98 minor lesions) to a comparison group (n=21 patients, 93 narrowings. Baseline LDL cholesterol in the intervention group was 229 +/- 30 mg/dL and in the comparison group was slightly higher and more varied at 241 +/- 53 mg/dL. Over an average angiographic interval of 21 +/- 6 months, the LDL-C fell by 19.5% in the intervention group and was said to be unchanged in the comparison group. The angiographic entry criteria for lesion severity is not stated, but seems to be limited to "minor coronary narrowings". Categorical assignments of patients in terms of "regression, stillstand, or progression" were based on exceeding "2s" limits of reproducibiligy of the measuring methods (short, medium, or long-term?), and such thresholds are not provided. Change in % plaque area (which is expected to have the same problems as % diameter stenosis in terms of depending on accurate assessment of an uninvolved reference segment to define the baseline of plaque area) is the only parameter described that lead to pt categorization, and handling of mixed progression/regression is not described.

Results: Apparently in contrast to the non-randomized comparison group that had slightly greater baseline cholesterol (and we do not know whether they had greater Lp(a) and lower HDL-C, nor how comparibility to other important risk factors such as smoking compared), the "progression rate" was "lowered" to 33% from 67%, "stillstands" "increased" from 33% to 48%, and the "regression rate" went from 0 to 19%. The angiographic "progress parameters" correlated positively with initial and mean study LDL chol, and negatively with the degree of narrowing in the 1st angiography, by stepwise multiple linear regression (elements of model not

provided).

Comment: In this open non-randomized study "major narrowings tend toward regression, minor narrowings towards progression", which is compatible with regression to the mean. If the non-randomized intervention group had fewer smokers, it could easily explain the results. The study is so small that the treatment groups could easily be unbalanced for factors important to atherosclerotic progression other than LDL-C. The study is not deemed adequate to evaluate possible effects of fenofibrate, either negative or positive, on coronary atherosclerosis,nor on CHD event rates.

5. Fotosensibilidad a fenofibratos. Farm Clin 8:667-72, 1991. Four cases of photosensitivity to fenofibrate are described. Other photosensitizing drugs were screened for similarity of chemical structure to fenofibrate and ketoprofen turned up. All 4 photosensitivity cases with fenofibrate had positive dechallenge and positive rechallenge, so drug-relatedness seems incontrovertable.

6. Farnier M, Bard JM, Lebel P, Fruchart JC. Combination of fenofibrate with simvastatin in severe familial hyperlipoproteinemia: efficacy and safety. abstract. 9th Int'l symposium on Atherosclerosis, Rosemont IL Oct 6-11, 1991.

Ten pts w severe HLP (mean baseline TC 500 +/- 91 mg/dL, LDL-C 386 mg/dL +/- 82, TG 226 +/= 123 mg/dL, apo B 295 +/- 57 mg/dL) were first treated for 3 months with simvastatin 20 mg/day, then for the next 3 months fenofibrate 300 mg QD was added. Simva monotx and simva + feno combination tx resulted in % reductions as follows:

	SIMVASTATIN	FENOFIBRATE + SIMVASTATIN	
TOT CHOL	-27%	-14%	
LDL-C	-29	-12	$p < 0.05$
TRIG	-19	-29	$p < 0.05$
HDL-C	+16	NS	
APO B	-26	-18	$p < 0.01$

One pt on combination tx had a transient rise in CK. No clinical side effects were reported. No signif. changes were seen in creatinine or transaminases. The frequency of CK monitoring was not described.

COMMENT: The estimated frequency of myopathy + rhabdomyolysis

with lovastatin + gemfibrozil is on the order of 5%, with rhabdomyopathy occuring less frequently than myopathy and occuring more frequently in elderly females. The demographics of these patients was not provided. This study of 10 patients does not have sufficient power to exclude the possibility that the incidence of myopathy with this combination may be identical to that seen with L + G. It is not clear from the abstract whether the % changes with simva + feno represent changes vs. simva monotherapy, or whether they represent changes from the pre-simva baseline. The study design, not being DB, randomized, or placebo controlled, is flawed so that one does not know the extent to which further lipid lowering during the simva + feno period relative to simva monotherapy may be due to carry-over and placebo type effects, or to drift in lipid assay standardization.

7. Comparative efficacy of fenofibrate and simvastatin on atherogenic risk factors in IIA and IIB dyslipoproteinemic patients. Farnier M, Bonnefous F, Debbas N, Irvine A, Munoz A. (Fournier Research and Point Medical) abstract 9th Int'l symposium on Atherosclerosis, Rosemont IL Oct 6-11, 1991.

Fenofibrate (200 mg daily, "improved" formulation) or simvastatin 20 mg QD was administered in a double-blind, randomized cross over trial in 60 pts (32 type IIa with mean tot chol 321 +/1 55 mg/dL, trig 85 +/- 29 mg/dL, and LDL-chol 246 mg/dL; and 28 Type IIb pts with mean tot chol 302 +/1 41 mg/dL, trig 230 +/- 91 mg/dL, [LDL-C not given but estimated by reviewer to average around 302 - (230/5 + 40) = 216 mg/dL] for a 3 mo tx period. Population said to be homogen. for smoking, EtOH, physical/professional level of activity, fam Hx of CVD.

Results:

percentage change from baseline:

	FENOFIBRATE		SIMVASTATIN	
PT TYPE:	IIa	IIb	IIa	IIb
LDL-CHOL	-36	-23	-35	-34
HDL-CHOL	NC	+40	NC	NC
TRIG		-52		NC

In pts with a high baseline Lp(a) value (cutoff for defining probable post-hoc subset analysis not given), fenofibrate was associated with a 10 decrease from baseline which was significant from baseline, whereas the change seen with simva (data not given) was claimed not to be significant. It appears the change from baseline or final values were not comared statistically between the two treatments.

Fenofibrate was claimed to be associated with significant decreases in fibrinogen level, plasma viscosity, and uric acid.

Tolerability to both drugs was described at "satisfying"

Comment: No data are provided for inter-assay coefficient of variation for the Lp(a) assay. Because the sponsor analysed only a subset of patients with high initial Lp(a) values, one would anticipate some regression to the mean, which could entirely explain the observed 10% drop in Lp(a) values in the fenofibrate group on repeat measurement. Lp(a) blood level has been reported to rise during therapy with Simvastatin therapy (HMG CoA Reductase inhibitors lower LDL cholesterol without reducting Lp(a) levels. Kostner GM, Gavish D, Leopold B, et al. Circulation 80:1,13-9, 1989.). Thus, the results of this study are compatible with no effect of fenofibrate on Lp(a) and a rise in Lp(a) with simvastatin. Because the study did not include a 3rd (placebo) arm, we cannot know if the standardization (bias) of the assay drifted during the 3 month study, in which case the placebo group would also have shown a 10% decrease from baseline.

8. Rhabdomyolyse avec insuffisance renale aigue: role de l'association fibrate et hypothyroide. Fredenrich A, Sadoul JL, Jambou P, Binti H. Rev Med Interne 12:238, 1991.

A case report of a 66 y/o F hospitalized for severe PROGRESSIVE WEAKNESS of 12 days duration accompanied by myalgia. The pt had been on 50 mcg l-thyroxine with free T4 modertely subnormal at 6 pmol/l (nl 8.4-24 pmol/L), TSH nl at 2.4 mU/L (nl 1-4) and was receiving fenofibrate 300 mg/day, as well as disopyramine for PVCs. On admission, the pt was confused, hypoglycemic at 40 mg/dL, capillary and 2.9, 1.8 and 2.3 mmol/L in plasma, serum creatinine was elevated at 769 micromol/L, serum Na at 126 mEq/L, K nl at 4.6 mmol/L. Hemoconcentration was absent. CK was 25,000 U/L (nl 18-90), plasma myoglobin grossly elevated at 1600 mcg/L (nl 3-8.6). The pt improved after d/c of fenofibrate and disopyramine, with progressive normalization of CK, serum creatinine, and myoglobin. The dose of l-T4 was also increased to 100 mcg daily. MRI of the sella turcica, TRH-LHRH and metyrapone testing gave no indication of pituitary pathology suggestive of secondary hypothyroidism. Rather, acute thyroid sick syndrome would account for low T4 and normal TSH in this pt, casting doubt on the author's conclusion that hypothyroidism favorised the development of rhabdomyolysis. The authors note that disopyramine has been associated with hypoglycemia.

Conclusion: severe rhabdomyolysis with renal failure attributable solely to fenofibrate. Normalization of creatinine after d/c of fenofibrate suggests that baseline renal function was probably normal.

9. Modulation of lipoprotein production in HEP G2 cells by fenofibrate and clofibrate. Hahn SE, Goldberg DM. abstract. 9th Int'l Symposium on Atherosclerosis, Rosemont, IL, Oct 6-11, 1991.

The highly differentiated human hepatoma cell line, Hep G2, was utilized to investigate secretion of apo B and triglycerides in vitro after exposure to feno or clofibrate. At doses > 15 mcg/ml, feno caused a 30% decrease in secreted apo B after 4 days tx, but pulse-chase expt's indicated that this decrease was not due to inhibition of apo B synthesis. TG synthesis of feno-txed Gep G2 cells decreased 30%, and the amt secreted into the medium was reduced by 50%. At 5 mcg/ml, TG secretrion was significantly reduced, while apo B secretion was unchanged.

Comment: this supports the observation that in vivo with ciprofibrate, the minimally effective dose for triglyceride lowering was lower than that required for LDL-C lowering.

Pulse-chase expt's indicated that feno increased apo AI synthesis and raised secreted apo AI levels 200%. While the authors claim that feno was more effective in ihibiting lipoprotein secretion by these liver cells in vitro and only feno increased apo AI secretion, the abstract does not indicate the dosage range utilized in the case of clofibrate. Because clofibrate is used in a clinical dose up to 10 fold greater than fenofibrate, a higher maximum dose of clofibrate should also have been employed in vitro.

10. Harmos G, Ferenc S, Klara B. Gyogyszereink 41:209, 1991.

A Hungarian study of 300 mg/d of feno in 22 pts with primary HLP in which 2 pts were d/ded due to adverse effects of gastric pain, diarrhea, and skin sxs. AST, ALT, BUN, and creatinine rose in this small study.

11. .lwig N et al. Low density cholesterol levels, changes in minor coronary narrowings, and their relationship to left ventricular function in hypercholesteorlemic patients with long term fenofibrate therapy. Abstract, 9th Int'3 Symp on Atheroscl. Rosemont, IL, Oct 6-11 ,1991.

This is the same non-randomized study reviewed above in 21 pts receiving feno for an average of 21 months. Baseline and follow-up estimation of ejection fraction by angiography did not change in feno or control groups. The regression coeff. for the relationship between 2nd and ininitial ejection fxs was determined by MLR to be: EF2 = 0.48*EF1 - 0.75 * %change in plaque area.

12. .Horsch S, Metzenmacher, Nigbur. Corvas 5:217, 1991. In an uncontrolled study using 250 mg feno x 4 mos of only 16 males with IIb HLP and peripheral vascular disease, hematocrit and MCV fell significantly. Walking distances increased, but were not related to the extent of lipid lowering.

13. Jan Ph., Ziegler O, Drouin P. Simvastatin vs. fenofibrate in the treatment of primary hypercholesterolemia: efficacy and tolerability. Annal Medicales de Nancy et de l'Est 30:349-353, 1991.

[Note: This appears be the same study reported in ref #3 above.]

A multicenter DB, randomized study of 204 pts (129 M and 55 F aged 17 to 72, mean age 46) with primary hypercholesterolemia (IIa & IIb with total chol > 300 mg/dL and LDL-C > 195 mg/dL) comparing diet + feno 200 mg BID to diet + simva 20-40 mg q PM for a 10 week tx period, following a 6 week period of diet and also w/d of prior lipid-lowering tx which followed an initial 4 week diet + placebo lead-in. Obese pts, those with TG > 350 mg.dL, and alcoholics with hepatic abnormalities were excluded. Apo B fell 27% from baseline on simva and fell 13% of feno, while LDL-C fell 35 and 22%, respectively. This suggests that the fall in LDL-C is due to reduction in circulating LDL particles rather than change in composition of LDL more in the case of simva compared to feno. TG fell 28% on feno. HDL-C rose 10% on feno vs 7% on simva, difference between groups NS.

Pts in both groups experiencing ADRs numbered 12 each. One feno pt had a fatal MI, another feno pt had a CABG during the short trial period. The only other ADRs presented are those felt to be treatment-related, which included for : abdominal pain (1 feno), 1 each of constip, dyspepsia, functional intestinal disorder, non-infectioys gastrointeritis, and nausea, asthenia (2pts simva, 0 feno), migraine headaches (2 pts simva, 0 feno), rash (1 simva) and impotence (1 feno, 0 simva). One simva pt was d/ced due to elevated ALT and GGT. Another pt on feno was considered to have severe elevation of ALT and CK felt to be drug-related. An abnormality was seen in serum creatinine in 2 feno and 1 simva pt; in AST in 4 feno pts (4%) and in 0 simva pts, ALT in 4 feno and 2 simva pts, CK in 4 feno an 2 simva pts. The authors recommend continued surveillance of liver and muscle enzymes for patients on either drug.

Note: Most of these patients may already have been treated with fenofibrate, according to protocol; thus the patient population would be expected to show a lower incidence of side effects with feno, as these patients would already have demonstrated tolerability to the medication. Pts were only examined at baseline and at end of study. Transient abnormalities may thus have been missed. Medication compliance was not discussed, so some earlier abnormalities may have cleared if the patients d/ced drug prior to f/u.

14. Lavarenne J, Poinas-Caillaud H. Atteintes musculaires et fibrates. Analyse des donnees de la banque informatique du Systeme Francais de Pharmacovigilance. Therapie 46:347-9, 1991.

Muscular adverse reactions attributed to fibrate drugs and

reported to the French pharmacovigilance system numbered 54 for the 5 year period 1985 -89. Most of the reports involved fenofibrate, the most heavily used fibrate in France. These 54 reports comprise 13% of all ADRs (approx. 415) reported with fibrates in France during this period (for all drugs in France, a total of 36890 ADRs were reported for these years)

The paper states that muscular side effects of fibrates are well known, but incompletely understood mechanistically. ADRs included were myalgia, myopathy, muscular pain, muscular cramp, muscular weakness, myositis, polymyositis, muscular degeneration amyotrophy, increased CK, myoglobinuria. Only ADRs considered drug related according to OMS criteria were included. The breakdown of the 54 cases was as follows:

28 M, mean age 56 yrs (25-86)
25 F, mean age 65 years (32-86)
Fenofibrate: 26 cases
Ciprofibrate: 12 cases
bezafibrate: 10 cases
gemfibrozil: 9 cases
clofibrate: 3 cases

Note: Fenofibrate and clofibrate are comparatively old drugs in France in comparison to gemfibrozil which was licensed only in 1985; thus fenofibrate would be expected to be under-reported with respect to gemfibrozil, after correction for comparative usage.

In 48 cases, only a fibrate was considered as causal, in 1 case a fibrate + a lipid-lowering drug of another class was implicated. In 6 cases, 2 different fibrates were Rxed simultaneously; in 2 of these a third lipid lowering drug of another class was given as well.

The dosages reported (44 cases) were within the recommended range (25 times), below recommended (22 times), and exceeded labeled recommendations in 6 cases, not including double fibrate Rxs.

The delay in onset of the muscular reactions varied from 10 days to 5 years (27 < 1 yr, 7 > 1 yr).

Myalgia was reported in 23 cases, elevation of CK in 22 cases, 11 of which also involved reporting of physical symptoms along with the biochemical abnormality.

Drug was stopped in all but 2 cases. Rechallenge was attempted in 5 cases with 3 positive return of rxn.

The outcome of the ADRs was unknown in 6 cases. Cases recovering after w/d numbered 43; 4 cases were progressive at the time of report.

The authors conclude that muscular side effects are a feature of

all fibrates, regardless of lack of mention of them in French package inserts, as reflected in the Dictionnaire Vidal.

15. Sgro C, Escousse A. Effets indesirable des fibrates (hors foie et muscle). (Side effects of fibrates (excluding liver and muscle)). Therapie. 46:351, 1991.

The authors state that rhabdomyolysis and hepatitis resulting from treatment with hypolipidemic drugs of the fibrate class are well-recognized, but that other less well-known toxicities of fibrates exist. The authors summarize ADRs reported in France to the Association Francaise des Centres Regionaux de Pharmacovigilance for all fibrate drugs marketed in France (see above paper) for the years 1985-89 (skipping the 1st 10 years of fenofibrate marketing experience in France). Of those 410 ADRs considered drug-related ("suspect"), 277 (67%) involved target organs other than liver and muscle. The reactions occured among 132 M (mean age 57) and 145 F (mean age 61). Fenofibrate was "incriminated most often among fibrate-related ADRs (123 cases or 30% of reports), and is also reported to be the most-frequently prescribed (data not provided). Ciprofibrate, Gemfibrozil, and bezafibrate each comprised about 10% of reports. The mean dosages reported in these ADR cases coincided with the recommended dosages. The most frequent categories of ADRs to fenofibrate were:

skin (22.8% of reactions)
n=15 for feno

hematologic (9.8% of ADRs)
n=not provided for feno

GI, including pancreatitis, excluding liver (approx. 6%)
n=2 for feno

CNS and PNS (approx 6%)
n=0 for feno

General (including headache!, approx. 6%)
n=3 for feno

Clotting problems due to interaction with anti-vitamin K drugs (5.8%)
n=6 for feno

Kidney (2.9%)
n= not provided for feno

Metabolic - Nutritional (2.9%)
n=3 for feno

Misc. incl. heart, blood vessels, psychiatric, endocr. (5%)
n=6 for feno

About half of the 93 cases of skin reactions involved fibrate monotherapy. Reactions included erythroderma, photo-sensitivity (n=8); urticaria/pruritis (n=8).

31/40 hematologic reactions involving WBC, RBCs, or platelets involved fibrate monotherapy.

About half of kidney, CNS + PNS, and GI (excluding liver) ADRs involved fibrate monotherapy.

Impotence was reported for 4 pts.

Cases involving co-administration of other fibrates accountted for 3.5%.

Three deaths were reported, but these were not attributed to drug (according to whom?). Patients improved in 81% of cases. Patients not recovered numbered 26, and the outcome was unknown for another 27.

It was noted that for certain fibrates, the latent period between initiation of tx and appearance of ADR was somewhat prolonged, suggestive of cumulative toxicity, according to the authors.

16. Lelieur I, et al. Efficacy and Safety of a new Galenic form of fenofibrate in hyperlipidemic patients during 1 year. Abstract, 9th Int's Symp on Atheroscl. Rosemont, IL, Oct 6-11 ,1991

Pts with HLP (n=131) either Type IIa (n=42), IIb (n=33), or IV (n=56) were treated with micronized feno 200 mg/d in an uncontrolled 12 month study, after a 4 week placebo run-in. Dropouts numbered 22 (17%), of which 15 were claimed not to be due to therapy (reasons not given), and 7 w/d due to ADRs as follows: gastric pain (n=4), loss of libido (n=1), elevation of CK (n=1), transaminases > 3x ULN (n=1, others may have had this level of abnormality but may not have been w/d). ADRs not leading to w/d included biliary colic (prexisting gallstone), chest pain & nervousness, gastric discomfort, nausea, and flatulence. TG lowering in Type IV was -35 to -45% from baseline in this uncontrolled study.

17. Liu HF et al. Urinary glucuronide excretion of fenofibric and clofibric acid glucuronides in man. Is it polymorphic? Eur J Clin Pharmacol 41:153-159, 1991.

The urinary excretion of glucuronides of fenofibrate and of clofibrate was studied after single oral doses in 72 healthy volunteers (feno) and 104 subjects (clof). Fenofibrate was excreted more slowly than clofibrate (13.9 vs. 26.6% in 8 hr). Sex and body mass index signif. influenced formation of fenofibryl glucuronide, whereas age and OCs affected excretion of clof. While excretion of clofibric acid and of clofibryl gluycuronide showed a gaussian distrib., fenofibric acid and its

glucuronide showed 2 populations in a bimodal distrib. Subjects comprising 15.3% had 3-fold higher (0.42 vs. 0.15) metabolic ratio of free fenofibric acid to the glucuronide, suggesting a polymorphism in the body's handling capability of fenofibrate, but not clofibrate.

18. Migneco G, et al. Epatite da Clofibrato. Minerva Medica 77:799, 1986.

A case report of a 51 y/o F wnl developed RUQ pain and asthenia after trx for 3 months with clofibrate 500 mg daily for Type IIb HHP. SGOT was 230 - 263 (ULN 39 IU), SGPT was 210 - 280 (N < 35 U/L). The liver was tender to palpation but not enlarged. GB ultrasonography was negative for gallstones. HbSAg and IgM for anti-HAV were negative. After d/c of clofibrate, symptoms resolved rapidly and transaminases resolved gradually and were normal after 4 weeks.

Four months later, the patient had a recurrence of RUQ pain and asthenia, attributed to rechallenge with fenofibrate 100 mg TID that had been begun during the previous month. Again the liver was tender to palpation but of normal size. Icterus was absent in both instances. AST was now elevated on fenofibrate to 133 and ALT to 76, with GGT at 48 (nl < 28), alkaline phosphatase nl, and hepatitis B and A serologies again negative. Transminases normalized 12 days after stopping fenofibrate. The sponsors speculate that fibrate-induced hepatitis may occur on an allergic basis, insofar as a report of granulomatous hepatitis with clofibrate involved portal and parenchymal infiltration with eosinophils (Pierce EH, Chester DL. Possible association of granulomatous hepatitis with clofibrate. NEJM. 299:314, 1978), and a case of overdose with 49 capsules of clofibrate in which no biochemical evidence of cyolytic hepatitis emerged (Greenhouse AH. Attempted suicide with clofibrate. JAMA. 204:402, 1968).

REVIEW OF DATA FROM CLINICAL TRIALS INVOLVING MICRONIZED FENOFIBRATE

Micronized fenofibrate 200 mg has been marketed in France since 2/91, and has been tested in 5 clinical studies plus 4 PK studies. Studies involving a 67 mg micronized formulation have also been conducted in Europe.

Studies with fenofibrate micronized 200 mg:

(Note: these are said to have been conducted according to 1987 French GCPs.)

Two French studies:
FEN 8802
FEN 8904
and 1 in Germany:
FEN 8801

Study 8802
Title: Comparative placebo-controlled study of 2 formulations of fenofibrate: 3 x 100 mg/day and 1 x 200 mg/day micronized fenofibrate.

Investigators: 39 GPs in the Lyon, France region

Time: conducted 12/88-9/89

Author of internal report (study is unpublished): Berthezene, C.

Design: DB, placlebo-controlled, MC, 3 parallel groups of 3 months active duration.
Study population: n=189 randomized(120 Type IIa, 69 IIb), of which 128 evaluable for efficacy (how many evaluable for safety?)

Entry criteria: TChol > 250 mg/dL, TG < 400 mg/dL
IIa or IIb on the basis of TG above or below 150 mg/dL

Results:

Pts were randomized as follows:

Feno 100 TID	Feno 200M	Placebo
n=64	n=64	n=61

Efficacy:

Only compliant pts or those with "minor deviations" were analysed for efficacy. No clear activity on HDL-C or apo A1 was seen with either active formulation when baseline values were "sub-normal". The mean decrease in triglycerides from baseline was not significantly more than placebo for either formulation. This analysis of TG change seems to be limited to IIb patients. Both active treatments produced about the same proportion of subjects with >= 15% decreases in cholesterol levels from baseline (72-73% of subjects compared to 15% with placebo).

Safety:

ADRs (it is believe only those felt drug-related are reported):

Feno 100 TID:

1 each of the following:
edema LEs
tachycardia
abdominal pain
constipation + urinary retention
ulcerative stomatitis
hyperhydrosis

Feno 200 mg M/d:

1 each of:
epigastric pain
gastralgia
pyrosis

Placebo:
1 each of:
gastralgia
pyrosis

Note: All > 2-fold LFT elevations are listed as ADRs, as well as the rises in creatinire above 1.2 x ULN. No rating of severity of ADRs is provided.

More increases in serum creatinine occured within either active group than with placebo. Creatinine rose above 120% of the upper limit of normal (ULN) in 3% of pts on fenofibrate 100 mg TID and in none of the pts in the other 2 groups.

AST was said to exceed 2X (or >3X) the ULN for 5% (0%)of pts in the 100 mg TID group, and in 3% (2%)of patients in the 200 mg micronized/day group, and in none of the placebo subjects. The proportion of subjects experiencing ALT > 2X (or > 3X) the ULN was 6% (2%) and 3% (2%) respectively for 100 mg TID and 200 mg M groups (again, no patients in the placebo group exceeded these thresholds).

FEN 3801

Study title: Long-term evaluation of fenofibrate (200 mg micronized capsule) acceptability. A one-year follow-up study

PI: Y Horel-Luley
Investigators: 14 CPs in France.

Time conducted: 1/89-9/90

Design: Open, uncontrolled, 3 period study with placebo lead-in with 12 month active tx phase.

Population: n=128 "with 7 wrong inclusions" (Type IIa 42 pts, IIb 33 pts, IV 56 subjects)

Lipid entry criteria: II: LDL-C >= 190 mg/dL, TG < or > 200 to differentiate IIa or IIb; Type IV: TG > 250 mg/dL and LDL-C < 190 mg/dL.

Results:

Safety.

ADRs:

22/138 pts dropped out (16%), of which 11/138 (8%) for ADRs. These discontinuations included 4 for GI problems, 1 for loss of libido, 1 for increased CK, and 1 for elevation of transaminases > 3X the ULN accompanied by fatigue and nausea, apparently representing symptomatic drug-induced hepatitis. This patient normalized LFTs 3 months after d/c of drug.

One pt developed choledocholithiasis, possibly attributed to treatment by the sponsor.
One pt interrupted tx for > 30 days because of abd pain and nausea attributed to cholelithiasis diagnosed on echography at baseline.

On ultrasonography, 9/138 treated (6.5%), or 9/114 compliant patients (9/[138-11 dropouts not for ADRs - 13 with undectable drug levels] = 7.9%) had a new diagnosis of gallstone(s) "among which 3 were adequately documented".

Laboratory Safety:

Laboratory safety was determined for 94 compliant pts (68% of those enrolled; 31 Type IIa, 23 IIb, 40 IV).

Thirteen pts were considered non-compliant for never having > 5 mcg/ml fenofibric acid in plasma.

Plasma creatinine and urea rose, leucocytes fell, and AST and ALT rose on fenofibrate.

STUDY FEN 8904

Study Title: 6-mo DB, compar. trial of feno 200M vs. simvastatin in pts w primary HLP Type IIa or IIb (ea. tx period is 3 months).

PI: Farnier

Location: 1 center, Hopital du Bocage

Time conducted: 11/89-6/90

Design: Randomized DB crossover comparison of feno M 200 mg/d to simva 20 mg/d. Two crossover periods of 3 mos ea with no intervening washout.

Population: n=60 IIa or IIb

Lipid entry criteria: chol > 240 mg/dL, TG > or < 130 mg/dL but < 450 mg/dL to differentiate IIa and IIb.

Results:

Compliance: 96% by capsule count; 26/30 in feno group in compliance at end of 1st period.

Safety:

Note: only the first period was analysed by the sponsor because of the lack of between-period washout to re-establish baseline.

Lp(a) fell 14% with feno and 7% with simva in IIa pts. In IIb pts, Lp(a) fell 17% on feno and rose 13% on simva. No info is given on baseline comparability of Lp(a) levels bewtwen tx groups.

Whole blood viscosity rose on fenofibrate.

The sponsor calculated that 72 (95% CI 64-79%) of patients were compliant with fenofibrate, and that 28% had poor acceptability of the drug.

Pooled analyses of the above 3 studies:

True to form, Fournier has pooled results of open uncontrolled and DB, placebo contolled trials of varying lengths. As noted above, the cutpoints for differentiating IIa and IIb by TG level were not even consistent among the pooled studies.

Laboratory safety pooled studies (only includes those nl at baseline)

Test	Tx Group	N with abnormality	% with abnormality
RBC < 90% LLN	FM	4/212	2
	F	0/45	0
	P	0/41	0
Hb < LLN	FM	16/244	6.6
	F	8/58	13.8
	P	0/57	0
Hb < 90% LLN	FM	5/244	2
	F	0/58	0
	P	0/57	0
Hct < 90% LLN	FM	6/189	3.2
	F	2/70	2.9
	P	0/31	0
WBC < 90% LLN	FM	5	11.1
	F	17	7.9
	P	2	4.9
WBC < 3000	FM	0/45	0
	F	0/215	0
	P	0/41	0

Neutrophils	FM	21/103	20.4
	F	10/46	21.7
	P	9/46	19.6
Eosinophils	FM	5/74	6.8
	F	6/20	30
	P	7/24	29.2
Platelets	FM	1	0.5
	F	not done	
	P	not done	
AST > ULN	FM	44	17.8
	F	17	28.8
	P	4	7.7
AST > 2x ULN	FM	4	1.6
	F	3	5.1
	P	0/52	0
AST > 3x ULN	FM	2	0.8
	F	0/59	0
	P	0/52	0

ALT > ULN	FM	46	20.5
	F	12	21.4
	P	2	3.9
ALT > 2X ULN	FM	10	4.5
	F	4	7.1
	P	0/51	0
ALT > 3x ULN	FM	2	0.9
	F	1	1.8
	P	0/51	0
CK > 3X ULN	FM	1	0.6
	F	0	0
	P	0	0
Creatinine rise by > 0.3 mg/dL	FM	55	21.7
	F	3/59	5.1
	P	0/56	0
Creatinine rise by >= 0.5 mg/dL	FM	20	7.9
	F	2	3.4
	P	0/56	0
Bilirubin	FM	2/187	1.1
Lipase > ULN	FM	10/127	7.9%
Fibrinogen > ULN	FM	15/93	16.1
Sodium > ULN	FM	38/131	29
K > ULN	FM	5/110	4.5

All pts regardless of baseline:

Eosinophils	FM	27	22.1
	F	27	44.3
	P	16	27.1
Platelets	FM	2	1
	F	0	0
	P	0	0

Note: FM = fenofibrate micronized 200 mg/d
F = fenofibrate 100 mg TID
P = placebo
Note that inter-formulation omparisons are not strictly comparable because some FM pts were txed 12 months, whereas

placebo and F pts were txed 3 months.

Selected ADRs from 3 pooled French studies:

ADR	Severity
(n = 1 unless otherwise noted)	
micronized fenofibrate 200 mg:	
smell disorder - olfactory sense	moderate
stomache ulcer	2
duodenal ulcer	2
cholelithiasis	2
hypotension	
gastrointeritis	
skin ulceration	2
esophagus/gastritis	
neuralgia	
libido decreased	
kidney calculus/pyelonephritis/sepsis	
biliary pain	
carcinoma/death	
pyelonephritis	2
Zoster	
fenofibrate 100 mg TID:	
pyelonephritis	
duodenal ulcer	
ulcerative stomatitis	
Zoster	
hepatitis 53 y/o F # 28D	

USE OF FENOFIBRATE IN HEART TRANSPLANT PATIENTS

An open uncontrolled study of micronized fenofibrate 200 mg qd in association with cyclosporin in heart transplant patients has been conducted in 43 male pts from 5/90 - 7/91. Drop outs numbered 29/43 = 67%. Among the 29 dropouts, creatinine rose in 16 (37%) and was listed as the cause or one of the causes for discontinuation. Creatinine at time of d/c ranged from 134 to 325 micromol/L.

One patient, said to be an alcoholic, died of acute pancreatitis.

Two pts were d/ced for elevated CK (397, 446 U/L), 5 (12%) were d/ced due to acute allograft rejection, one had biliary colic and another steatorrhea as reasons for d/c.

CONCLUSIONS

The apparent frequency and severity of fenofibrate-associated hepatotoxicity, of severe skin reactions, and incidence of renal impairment as reflected in rises in serum BUN and creatinine are very significantly greater with fenofibrate than that encountered with gemfibrozil. In addition to fenofibrate-induced symptomatic hepatitis having been seen in the relatively small U.S. Studies, we see it again here in 1 patient out of 128 treated in open study FEN 8801 (which employed a lower total daily dose of 200 mg as the micronized formulation). Symptomatic fenofibrate-induced hepatitis has also been reported as individual literature reports and has been seen in post-marketing surveillance in France, and has included fatal cases.

Mechanisms of fenofibrate-induced renal toxicity may include uric acid nephrolithiasis, uric acid nephropathy, rhabdomyolysis, and a direct nephrotoxic effect. A whopping 22% of patients treated with the micronzed 200 mg dosage form of fenofibrate had rises in serum creatinine by > than 0.3 mg/dL and 8% had rises of >= 0.5 mg/dL; the figure for 100 mg TID of the to-be-marketed formulation was 5.1%, compared to zero among parallel placebo patients. Renal failure during treatment with fenofibrate has been reported for patients in the "French Series" of open uncontrolled trials. In one of the studies with the lower 200 mg dose of micronized fenofibrate, nephrolithiasis was complicated by pyleonephritis, a life-threatening condition in the presence of stone-induced obstructive uropathy. Renal toxicity is especially a problem in heart transplant patients who are also on cyclosporin. The high (38%) rate of discontinuations due to renal insufficiency among 43 pts txed with fenofibrate in conjunction with cyclosporin should lead us to consider this drug combination contraindicated.

The high incidence of eosinophilia (8%) documented in the DB, randomized controlled comparative study with simvastatin, taken together with the 11.2% incidence of skin reactions seen among the 116 fenofibrate-treated subjects (>= 1 required hospitalization and systemic corticosteroid treatment) in the double-blind portion of the U.S. Type II trial, plus the 15% rate of withdrawals for skin reactions in the small European study reported in the 1986-1987 literature update, plus the severe skin reaction requiring hospitalization that was seen in the ongoing Canadian study make it clear that unusually severe allergic and dermatologic reactions are to be expected with this drug. Clearly, fenofibrate is the most poorly tolerated fibrate drug ever considered by this Division.

Of additional concern is the fall in LpAI particle concentration seen with fenofibrate, but apparently not seen with gemfibrozil. This would be expected to increase coronary risk, as could the rise in LDL-C regularly seen when hypertriglyceridemic patients are treated with this drug. The study cited above that explored changes in fatty acid composition of lipoproteins may also be

interpreted to suggest, according to the authors, that fenofibrate produces potentially delelterious quantitative effects on lipoprotein composition rendering them more atherogenic.

Another particularly worrisome finding in this submission (Appendix 4 of SU5) is an incidence of 8% among 127 patients of rises in serum lipase above the upper limit of normal. This test result may reflect our previously-expressed concerns that, by increasing bile saturation and facillitating the creation of sludge and gallstones, fenofibrate treatment may actually cause pancreatitis. This casts additional doubt on the validity of using changes in serum triglycerides as a surrogate for alteration of pancreatitis risk among Type V patients with fasting chylomicronemia who are treated with fibrates.
The incidence of newly diagnosed cholelithisis in association with 12 months of fenofibrate therapy was 6.5-8% of 128 subjects in the above-cited study with the 200 mg micronized formulation, which is higher than that seen in either the Coronary Drug Project or WHO study with clofibrate, or in the gallstone prevalence substudy with gemfibrozil, considering the much longer duration of the latter studies.

RECOMMENDATIONS

Ask sponsor to provide primary and secondary causes of death as listed on death certificates for the 12 fenofibrate-txed patients in the "French Registry" who died for "unknown reasons" [Sponsor has claimed they do not have legal access to death certificates]. If there is a legal impediment to this, the sponsor should provide documentation to this effect.

Perform a randomized, double-blind, placebo-controlled study to evaluate the effect of fenofibrate on Lp(a) and LpAI and LpAII:AI particle concentration. The study or studies should included adequate numbers of subjects with levels of Lp(a) > 30 mg/dL and of patients with HDL-C < 40 mg/dL.

In view of the very high dropout rate due to renal dysfunction in heart transplant patients, the proposed labeling of fenofibrate should be revised to contraindicate the drug in patients receiving cyclosporin.

Sponsor to provide the baseline and individual patient data for Lp(a) for the comparative trial with simvastatin and for the comparative trial with lovastatin.

Sponsor to provide a table of the values across time of aminotransferases, alk phos, GGT, and bilirubin, as well as any clinical adverse experiences reported for the subjects from protocols FEN 8801, 8802, and 8804 who had elevations > or = to 2X the upper limit of normal; as well to provide the normal range for AST, total bilirubin, alkaline phosphatase, and for ALT

for each of these studies.

Please provide details of skin reactions seen in the above studies. Were any patients hospitalized and/or treated with systemic corticosteroids for skin or other allergic reactions in the above trials.

For study FEN 8904, were safety data analysed only for the first crossover period? If so, please perform a separate laboratory safety analysis using original baseline data. Please provide the changes in Lp(a) from period 1 to period 2 separately for each randomization group.

L. Ross Pierce

L. Ross Pierce, M.D.
11/13/92 5/14/93

Note: Review terminated due to reviewer reassignment to another division

cc
HFD 510
HFD 510 Pierce/Innerfield/Trostle/Troendle/Sobel
[fenosu5.2]

HFD 500 Bilstad

TROSH MAY 14 1993 DRAFT

GROUP LEADER'S REVIEW OF NDA LITERATURE REVIEW UPDATE - 1986-1987

NDA 19304
DRUG: FENOFIBRATE
SPONSOR: FOURNIER
DATE SUBMITTED: 2/24/88
DATE OF REVIEW: 10/9/92

Selected literature regarding fenofibrate is reviewed as follows:

Note: As is often the case with Founier submissions, the format for review is less than ideal. The references are not numbered; nor are the pages of this submission.

Blane GF. Comparative toxicity and safety profile of fenofibrate and other fibric acid derivatives. Amer J of Med. 83 (5b Suppl.):26-37, 1987.

Comment: Fournier sponsored a "symposium" on fenfibrate which appeared as a supplement in the Amer J of Medicine around the time that the drug's NDA was resubmitted to the FDA for the limited indication in patients with very high triglycerides wtih the aim of reducing pancreatitis risk. None of the articles in the symposium delt specifically with the requested indication, however. This type of activity is being widely scrutinized today from an ethical viewpoint as drug promotional activity. This article is authored by a Ph.D. at Fournier.

Blane provides a list by country of groups of clinical trials, mostly open, totaling 81, involving 3618 subjects, with 5927 equivalent patient-years of exposure.

Adverse reactions are claimed to occur in 2-15% (mean 6.3%) of subjects in European trials of < 6 months duration (these are presumably limited to those ascribed to drug in a causal fashion), and in 7-14% (mean 11.3%) of patients enrolled into trials of >6 months duration. It is believed that, in the case of the latter figure, subjects experiencing ADRs during the initial 6 months of longer trials are not counted!

During the 6-month DB portion of the U.S. Type II Study, 13/116 fenofibrate subjects experienced dermatologic reactions, compared to 1/111 placebo patient (the latter of moderate severity). In the fenofibrate group, the incidence of incapacitatingly severe dermatologic reactions was 4/116, and the incidence of moderate-to-severe skin reactions was 8/116. This is much higher than has been seen in controlled trials of gemfibrozil. Two cases of urticaria were reported, leading to withdrawal of drug.

The abstract of this paper states "In humans, only a small increase in incidence of elevated levels of serum glutamick oxaloacetic transaminase and serum glutamick pyruvidc transaminase seems to be present and is not clearly differemt fromt that of the control groups". This statement is extremely misleading and is a flagrant

misstatement of the truth. In the text of the paper it is stated,

> "...sporadic and short-lived increases in aminotransferase levels have been reported for fenofibrate by a number of authors. There was also a small exess in the treated compared with the placebo group in the United States study...there is evidence that at least on one occasion during the period of observation, approximately 9 percent of patients will have a transmaminase value above the normal laboratory mean. These seem to subside wthout discontinueing fenofibrate treatment in most cases."

Again, Blane misstates the facts in a manner deviating significantly from the actual study results. The incidence of aminotransferases >= 2X the ULN was 21% in the referenced trial. No mention is made that patients had symptomatic hepatocellular dysfunction, nor that abnormalities led to treatment discontinuations and were persistent, rather than transient, in a large number of cases.

Blane states, "there appears to be some slight tendency towards increase in plasma urea and creatinine values during long-term fenofibrate trials, but there is no evidence of any associated renal dysfunction or pathology". Blane makes no reference to reports of renal failure on chronic fenofibrate therapy from published studies and from Fourniers French spontaneous adverse reaction report database.

L. Ross Pierce, M.D.
5/14/93

Note: Cit review terminated due to reviewer reassignment.

cc
NDA
HFD 510
HFD 510 Pierce / Innerfield / Travendle / Sobel //
HFD 500 Bilstad

11021L

GROUP LEADER'S REVIEW OF LITERATURE ON FENOFIBRATE

NDA 19304
DRUG: FENOFIBRATE (LIPIDIL, LIPANTHYL, PROCETOFENE)
SPONSOR: LABORATOIRES FOURNIER
SUBMISSIONS DATED 11-23-87, 2-24-88
DATE OF REVIEW: 1-23-88

MAY 14 1993

"Etude de la tolerance hepatique apres quatre ans de traitement par procetofene" Fromantin et al. La Nouvelle Presse medicale 7:938 (1978)

The article refers to other works that purportedly show mean efficacy for fenotibrate of 25% cholesterol reduction for types IIa and IIb, and of 38% and 50% for triglycerides for Types IIb and IV, respectively. It emphasizes the importance of examining the hepatic tolerance of this fibrate. Experience with the drug among 540 subjects from 3 centers is presented. No statistically significant differences from baseline means to on-treatment means for the time periods 0-12 mos, 0-24 mos, or 0-42 mos was seen for any center except at 1 among a group of 8 patients whose mean SGPT rose from 11.25 +/-1.34 to 14.87 +/-1.04. Numbers of subjects exceeding the ULN were not provided.

"Hepatite medicamenteuse au fenofibrate" Couzigou et al. Therapie 35:403 (1980)

A single case report of a 74 yr old female complaining of pruritis and is found to have a cholesterol of 9 mmol/l, for which she is Rxed fenofibrate, 400 mg/d. Alcohol was not consumed over a subsequent 2 yr tx and the pruritis resolved. Wt loss (7 kg) was accomplished by dieting. Asthenia was then noted and ASAT was elevated at 75 (uln <45) and bilirubin was measured at 50 micromol/l (uln usu approx 18), with chol at 10.5 mmol/l, leading to cessation of fenofibrate. Two months later the pt is hosp. for persistent cholestasis (bili 56 mmol/l, alk phos 409, 5'-nucleotidase at 172 (uln <17), alat (alt, sgpt) 110. Liver span was 14 cm. iv cholycystogram revealed no evidence of bile duct dilitation. Liver biopsy revealed chronic persistant hepatitis. Viral serologies incl anti Hbs, anti Hbc as well as anti mitoch, aANA, anti smooth muscle abs were neg; Fe sat'n normal. Seven months after onset (5 mos after liver bx) hepatomegaly persisted and cholystasis and enzyme elevations persisted, as did liver histology.

"Efficacite et tolerance du fenofibrate au cours de traitement a long term" Fromantin et al. Therapie 36:473-476 ('81).

121 subjects received fenofibrate (usu dose 300 mg/d, 200 mg/d for children, 400 or even 600 mg/d for severe cases)

for a mean duration of 3 years. The drug was "perfectly" tolerated clinically, but 9.2% of subjects had transient and moderate elevations of SGPT (comprising 2% of all determinations). Periodic hepatic transaminase surveillance is recommended for subjects on long term therapy with fenofibrate. After 12 mos, tot chol was decreased from 346 mg/dl to 256 among Type IIa patients; TG fell from 266 mg/dl to 124 among 41 Type IIb patients. No mention was made of controlling subjects' diets. No evidence of therapeutic escape was apparent after 36 mos among 12 IIa or after 48 mos among 12 Type IIb subjects. Two type III subjects experienced a mean decrease in tot chol of 43%. Types IIa and IIb had decreases of 27% on average for tot chol. Maximal effect on lipids was evident at the first time point on drug (3 mos). One case of pancreatis was seen (TG not given, but study included 2 Type Vs and 36 Type IVs: Lab changes with therapy included a sl decrease in alk phos, a signif drop in uric acid (plasma), and a sl rise in BUN. Significant rises in mean SGPT were observed among 66, 57, and 34 subjects at mos 30, 36, and 42 (delta < 4 U for means). 7 subjects had elevations of both SGPT and SGOT concurrently. Two subjects were begun on fenofibrate despite being alcoholics with initital sl transaminase elevations. These were not seen to rise further with continued therapy. The authors point out 2 cases from the lit. of hepatitis in aged subjects (77 and 63) receiving fenofibrate.

"hepatite due au procetofene" Vachon. La Nouv. Press Med. 9:2740, 1980.

A single case report of a 63 y/o f with FH who with other hypolipidemiants maintained a tot chol above 350 mg/dl. She began 12 g Questran and 300 mg fenofibrate daily. Tx w 60 mg Inderal and 3 mg cyclothiazide and 150 mg triamterene was continued. Tot chol fell to 253 by 5 mos of tx; after 6 mos tx w fenofibrate, anorexia, nausea, and hyperbilirubinemia (mild) were noted. Abdominal exam and liver size were normal. SGPT fell after stopping fenofibrate from 110 to 7 after peaking at 130 (uln 12); GGT fell from a peak of 600 to 48 (uln 18); totl bili fell from 25 to 5 and alk phos fell from 45 to 25 (uln 30). HbSAg was neg. The pt was rechallenged with fenofibrate 300 mg/d and after 1 1/2 mos the same symptoms and biochemical evidence of liver dysfunction appeared. GGT peaked 20 days after stopping the rechallenge with fenofibrate, at a level of 300. SGPT fell from 207 to 100 over the same period.

"Hepatite due au procetofene?" Aron et al. La Nouv. Press Med. 8:783, 1979.

A single case report of a 77 y/o m w a hx of cholecystectomy for gallstones 12 yr prior to receiving 200 mg/d of fenofibrate for mild hypercholesterolemia. Concurrent tx

included pyridinol carbamate and amiodarone. After only a few days he developed anorexia, nausea, dyspepsia, and an loss of 6 kg. After 3 mos of continuous tx he was evaluated with a nl examination except minimal esophagitis on endoscopy, nl BE, no hepatomegaly; biochemical abnormalities seen were SGOT of 225, SGPT of 205 (uln 50), bili 21 (17), GGT 100, alk phos nl. Amiodarone and pyridinol were d/ced and after 12 d of hospitalization, transaminases and GGT were unchanged. This was taken to indicate that an alcoholic etiology of the abnormalities was remote. Liver biopsy was interpreted as favoring a diagnosis of drug-induced hepatitis. Some cytoplasmic "clarifications", no steatosis, some pre-necrotic dispersed non-centro-lobular hepatocytes, and slight enlargement of portal spaces [Kiernan's spaces acc to sponsor's translator] by small inflammatory fibrotic elements. Symptoms disappeared promptly after d/c of fenofibrate, but transaminases and GGT elevations resolved over 2 months.

"Elevation des transaminases glutamopyruviques sous traitement par procetofen des hyperlipidemies idiopathiques [:] frequence et importance dans 443 cas traites" DeGennes et al. La Nouv. Press Medicale 7:2398, 1978.

The authors state they have noted that while a greater degree of total cholesterol lowering is seen with fenofibrate that with clofibrate, that SGPT and SGOT elevations are more frequent, of higher elevation, and are more persistant with fenofibrate. 443 subjects were treated (139 f) with 300 - 400 mg/d of fenofibrate for an av duration of 12 mos. Lipids and transaminases were measured regularly q 2-3 mos. Subjects were instructed on a diet consisting of 38% calories as fat, a P:S ratio of >1.6, and a chol intake of <300 mg/d. Abnormalities of SGPT were counted only if a > 2 fold elevation of the ULN (2 x 20 IU = 40 IU) was exceeded, and only if such elevations were observed twice in succession. Measurements of SGPT (ALT) in Karmen (KU) units or Fraenkel (FU) were converted to internat. units (IU) as follows: 1 IU = 2 KU or 2.8 UF. Thus an abnormal value had to exceed the equiv. of 80 KU or 92 FU. Of the 443 cases followed, 85 (19.15) had such elevations of SGPT. Only 26 of these had baseline SGPT values: these allowed calculation of a more than 200% rise in SGPT. 400 mg/d was used by 43% of the subjects. The magnitude of mean SGPT elevation among those with SGPT elevations as defined was the same on either 300 or 400 mg daily. Among 8 subjects receiving over 500 mg/d of fenofibrate, transaminase were normal for 4 and elevated for the remaining half. Children (n=4) had rapid elevations of about 400%, suggesting greater sensitivity to drug. The frequency of elevations of SGPT was similiar among Types IIa (both FH and non FH analyzed separately), IIb + III subjects, except that a higher (36%) frequency of elevations was observed among the 129 subjects with mixed elevations of

chol and TG. Excluding those on concomitant medications gave similar frequencies of SGPT elevation as seen for the group as a whole and the frequencies of such elevations were similiar for all Fredrickson Types studied. 45/240 or 18.9% of subjects taking fenofibrate alone developed SGPT elevations as defined above. HbSAg was looked for systematically and was unifo.mly neg. Among the 15 cases with SGPT >100, no other biochemical abnormality was found except elevated GGT and ornithine carbamyltransferase. Three subjects had SGPT over 200 IU/1. Of 44 subjects with elevations who had their dose of fenofibrate maintained, 48% showed persistent elevations. Among 25 pts who had their dose reducted to 200 mg/d, 32% had persistent elevations of SGPT. Following cessation of therapy in 16 subjects, a persistent elevation was seen in 25%. One subject also on a MAO inhibitor had acute toxic liver atrophy, purportedly a known ADE for MAO inhibitors. Transaminase elevation was seen among 9/11 subjects on perhexiline maleate with or without allopurinol and in 18/31 subjects on allopurinol with our without perhexiline (3/4 for concom. tx w perhexiline only and 12/24 with allopurinol only). The authors suggest transaminase monitoring q 2-3 mos for the first 12 mos of fenofibrate, special caution in children and those on perhexiline or MAO inhibitors.
An internal report by the sponsor analysing DeGennes' data concluded that of 28 subjects who had SGOT or SGPT or both over 70 IU, in 11 drug-relatedness was doubtful. In 11 it was plausible, and in 6 it was judged likely due to therapy with fenofibrate.

15/443 75, u.c.

"Influence of fenofibrate on cellular and subcellular liver structure in hyperlipidemic patients". Bluemcke et al. in Atherosclerosis, 46:105, 1983.

Note: This will be reviewed in greater depth by Dr. Barbehen.

This article is authored by individuals at the Free Univ. of Berlin, Huntigdon Res. Centre, Cambridgeshire (UK), and Lab. Fournier (the sponsor). Subjects (n=23) were treated with fenofibrate for 2 mos to 3 years (mean tx periods of 1.8 yrs for m and 2 yrs for females. Ten control untreated hyperlipidemic subjects also underwent liver bx and EM examination of biopsies. Peroxisomes were described as relatively rare, wihout evidence of the clear proliferation seen in rodents. Variation in nuclear size, mitioch. cont. paracrystaline inclusions, dilated endoplasmic reticulum assoc. with reduced amts of rER, and lipid droplets in hepatocytes were observed. These variations from normal were "in general not much more apparent in samples from the fenofibrate-treated patients that in the untreated group".

"Hyperlipoproteinemies et variations des transaminases", M. Cloarec, La Vie Medicale 31:2781, 1978.

The author studied 324 hyperlipidemic patients treated with fenofibrate for an av. of 18 months, measuring transaminases and GGT every 3 months. The prevalences of transaminase and GGT elevations among this group were as follows:

Type	SGOT>40 IU	SGPT>40 IU	GGT>60 IU
IIa	11/106	11/106	9/106
IIb	14/120	14/120	11/120
IV	52/98	52/98	50/98

These prevalences were compared to those observed among a group of 204 normolipidemic non-treated subjects, as well as to those of a group of 283 untreated hyperlipidemic subjects:

Untreated normolipidemics:

SGOT>40	SGPT>40	GGT>30
11/204	10/204	9/204

Of the 204 subjects in this group, 66 were followed for 12 mos, 106 were followed for 18 mos. and 32 were followed for 24 mos.

Untreated hyperlipidemics:

Type	SGOT>40	SGPT>40	GGT>60
IIA	6/68	6/68	4/68
IIB	15/146	15/146	12/146
IV	46/74	46/74	38/74

42/461 total control subjects had elevations of GGT over 60 IU: 70% of these had normalization of transaminases by altering their diet (limiting fat and/or excess sugar) or reducing/eliminating ethanol intake. [It is assumed that the authors are implying that massive fat or simple sugar intake as well as obesity may be associated with steatosis and transaminase abnormalities]

Among the untreated hyperlipidemics with elevated GGT, cessation of alcohol lead to normalization of the enzyme in 3/4 Type IIa. 9/12 IIb, and 32/38 Type IV subjects with elevations. The authors were careful to exclude from tx with fenofibrate any subjects showing baseline abnormalities of transaminase or GGT, no matter how subtle. This selection may have influenced the authors' observation of no

apparently significant differences in incidence of enzyme elevations among fenofibrate-treated and non-treated subjects. Nevertheless, a small trend of more frequent transaminase elevation was present for fenofibrate-treated IIa and IIb patients, and, more importantly perhaps, is the observation of more persistent abnormalities among fenofibrate users compared to untreated (or diet-treated) hyperlipidemics as depicted in the scattergrams on pp 2784, 2785.

- "Long term-effect of fenofibrate on lipoprotein level and composition in different types of genetic hyperlipidemias", Baggio et al. Pharm. Res. Comm 18:471, 1986

Fenofibrate was administered to 23 patients with primary hyperlipoproteinemia (FH, Type IIb and III). Type III patients had a VLDL-cholesterol:serum TG ratio > 0.3 by ultracentrifugation. Pts were characterized by clinical and biochemical features, fam hx, agarose lipoprotein electrophoresis and isoelectric focusing of apo E2 phenotypes. Fenofibrate was administered as 100 mg TID for 8 mos to Type III and for 10 mos to Type II pts. Pts began an isocaloric diet of 20% protein, 45% CHO, and 35% fat, 300 mg chol with a P:S ratio of 1.8 and 12-15 g fiber/d. The FH pts were monitored for 1 month on diet alone after withdrawal of fenofibrate (f). Safety labs were done at baseline and at 4 and 8 mos of tx. Compliance to diet and pill counts were assessed. No patient was on other drug tx. All other drugs were stopped 3 mos prior to the start of the study. Results (% change in tot cholesterol from baseline):

Type	N	month 4	month 7
FH	12 (5 m)	26%	17%
IIb	5 (3 m)		32%
III	6 (5 m)		48%

Baseline tot chol for FH pts was 333 mg/dl, for "combined hyperlipoproteinemia pts (IIB) was 385 mg/dl, and for Type III subjects was 437 mg/dl. Lipids actually rose during the 2 month dietary lead-in. For the FH patients, LDL decreased by 31% at month 4 and by 20% at month 10; HDL-C rose by 10% at month 7 ($p<0.01$ for both LDL and HDL-C changes). In combined HLP, TG fell by 73% at mo 8, LDL fell by 22% at mo 7, while HDL rose by 9%. In the Type III pts, beta-VLDL was said to disappear as suggested by a fall in the TG:chol ratio in the fraction with d<1.006 g/ml from 0.48 to 0.1 [Table II indicates they mean chol:TG ratio]. Lipid levels as well as lipoprotein levels were described as reaching basal values after 4 weeks of wash-out in the FH pts. Body

wt was stable for FH and Type III pts (data not shown) but ↑ increased during mos 4-6 among "combined" pts. 2/27
SAFETY: Two FH pts discontinued tx because of SGOT and SGPT increases to about 100 (uln 40). These transaminase elevations resolved in a few days after d/cing tx. Three subjects had cutaneous vesicular erythema which resolved on dechallenge. 3/23

"Fenofibrate: influence on circulating lipids and side-effects in medium and long-term clinical use", Elane et al. (lab Fournier), Pharmacol. Control of Hyperlipidaemia p 187-216, 1986 J.R. Prous Science Pub.

This review cites work indicating that while apo B levels are consistently reduced by fenofibrate, apo A is more variably affected. GI complaints are said to occur in 5-20% of treated pts and may resolve with continued tx. Pruritis, erythema, and rash are quoted as being perhaps the most bothersome side effects. Reference is made to the existence of only 2 cases from the lit. of substantial elevation of liver transaminases which were slow to resolve. Two authors are cited who have noted rises in BUN and creatinine with time. Uricosuric activity of fenofibrate is well established, and is fully present by day 4 of tx, resulting in 20-30% decreases in plasma UA conc. The above data were ascertained from subjects treated 1-6 mos in an open fashion.

The paper summarizes and averages results from some 80 (all but one foreign) clinical trials, mostly open with 2 month diet only periods to establish baseline lipid values. The tot no of pts studied has been 3618 for 5927 patient-yrs of exposure. Lipid reductions seen in these trials are listed in Table 2a attached. Tot chol was reduced usu by 20-25% and for IIb and IV pts, TG levels fell by 50-60%. The authors have combined together results from 14 European trials of fenofibrate of up to 6 months duration and separately combined 6 longer-term studies of up to 6 years in length. These studies are described as having case report forms available that correspond to "present day standards" of completeness. The combined shorter term studies included a total of 807 Type IIa patients who displayed a mean diet-only baseline for total chol of 345 mg/dl. After 1 month of f, tot chol dropped to a mean of 261 mg/dl, corresponding to a 24% reduction with 200-400 mg/d (usu as 100 mg TID with meals). Little variation in tot chol was seen over the subsequent 5 mos. Women responded somewhat better than men at mo 6 (chol 253 vs 264 for men, $p<0.05$). Fig 3 (appended) indicates a greater % reduction in tot chol as the baseline chol increases. Thus, for those w baseline chol of >550, a 38% reduction was observed, whereas the figure was about 20% for those w chol 250-350. The 688 type IIb patients saw a mean fall in chol

Note: This literature review of fenofibrate is being terminated due to reassignment of this reviewer to another division.

L. Rafferty, MD
5/14/93

CC NDA
HFD-510
HFD-510/Pierce/Innerfield/Trostle.

NDA 19304
Fenofilerate
Sponsor Laboratories: Fournier S.A.
42 Rue de Longvic -21300 Dijon
France
Agent: G.H. Besselaar Associates
103 College Road
East Princeton, New Jersey 08540
Date of Correspondence: June 7, 1984
Assigned to Albert E. Weiner, M.D.: June 16,1984
NDA 19304 transferred from Albert E. Weiner to
Dr. Santora: 8-15-84
MOR Completed and to typist: 8-22-84

Medical Officer's Review and Evaluation of Fenofibrate

Resume.

Since this NDA was assigned to me for sixty days, including the 45 day in-house meeting on 8-15-84, I wish my evaluation and recommendation to be a part of the record. In my opinion, fenofibrate, because of its very similar actions to its parent drug clofibrate, including liver tumors, cancer, and increased lithogenicity, should not be approved for any human indication. It resembles IND ; and I note that Drs. Hsia and Berliner, FDA pharmacologists, in a review dated Sept. 2, 1983, stated that ' is potentially hazardous for long term administration to patients with hyperlipedemia." The conclusion of Drs. Hsia and Berliner was that "The submitted reports on animal studies do not support the safety of clinical investigations with Pharmacology feels that continuation or initiation of clinical trials should not be permitted."

I believe this statement could as justifiably be applied to fenofibrate.

Dr. Gloria Troendle, group leader for Lipid-Lowering agents stated in her review dated 7-19-83 regarding , "I do not favor returning this problem to the Advisory Committee because I do not think that even with their approval, the drug should be approved." (Review G. Troendle dated 7-19-83 - Wang 1729C).

Similarly, this is my opinion regarding the present NDA (Fenofibrate) 19304 as my final recommendation for its ultimate disposition.

Body of Review:

This review was limited to the Summary Volume I (of 91 volumes) because of the limited amount of days I had this application and others that required timely disposition. Usually 180 days are allowed for the final M.O.R. of a new NDA. Nevertheless, all of the sponsor's summaries are in this volume, and the

9/13/84

toxicology and gallstone incidence and lithogenicity so resemble clofibrate (and) that a full review of the other 90 volumes would not change my recommendation. Naturally, I would have done a full review were the NDA still assigned to me.

Medical Officer's Review of August 22, 1984. Fenofibrate.

I. Name of Drug: Fenofibrate (Trade Name in Europe Lipanthyl). Procetofen. Procetofene.

II. Indication Proposed: Lipid lowering.

III. Chemistry: See chemist's review.

IV. Pharmacology:

There was no input to me on the NDA Fenofibrate from Pharmacology, prior to the 45 day meeting on August 15, 1984. I asked Dr. Berliner during July 1984 for his opinion, and was told that because of a shortage of pharmacologists, the NDA would not be reviewed by Pharmacology until a new additional pharmacologist arrived into his group. Therefore, my opinion re pharmacology is formed from the sponsor's statements in Volume I of NDA 19304.

a. Highlights of Preclinical Studies:

The drug was introduced in France in 1975. Sponsor describes it as "a safe drug with more than six times the potency of clofibrate", and says that fenofibrate demonstrated a more complete profile of activity in all types of hyperlipoproteinemia than gemfibrozil, benzafibrate, the anion resins, and probucol.

b. Pharmacokinetics:

Mean peak plasma concentrations were seen two hours after administration (in rats). Plasma half-life was eight hours. During 5 days after a single dose, 51% was recovered in the urine and 47% in the feces. Fenofibric acid was the main plasma metabolite. Fenofibric acid glucuronide was the major metabolite of fenofibrate in man.

c. Chronic Toxicity Studies (pg. 20015):

Mice:

1) The major target organ for toxicity is the liver.

2) Manifested by increases in liver weights, hepatomegaly, and cholecystasis.

3) Increases in alkaline phosphatases and transaminases.

4) Fenofibrate significantly increased the incidence of hepatic and pancreatic tumors.

5) Hepatic and Pancreatic tumors increased.

Beagle Dogs:

1) Kidney stones were observed in some of the dogs treated with Fenofibrate.

Rats and Hamsters:

1) Proliferation and enlargement of peroxisomes in all animals treated for seven days.

d. Clinical Pharmacology. Efficacy.:

1) 400 mg of fenofibrate per day, administered for one month, reduced total plasma cholesterol by 14%, plasma triglycerides by 46%, and VLDL triglycerides. No significant change was observed in HDL cholesterol.

2) In three studies, the effects of lipid lowering drugs was expressed as a lithogenicity index. In six patients with type IIa or IIb hyperlipoproteinemia treated with 300 mg/day fenofibrate for four to six weeks, "the lithogenicity index increased more than 20% in two patients, and less than 20% in four patients."

Reviewer's note: How much less than 20%? 18%? 4%? In any case, 100% of the six patients treated with fenofibrate for only 4 to 6 weeks had a significant rise of total cholesterol in the bile. To me, this indicates an overall prospect of the hazard of gallstone (cholesterol) formation with fenofibrate, and particularly with longer drug usage. In fact, sponsor reports an incidence of gallstones of 1% in this jacket in patients or fenofibrate.

e. Clinical Safety:

1) Kidney: Adverse Reactions with Fenofibrate

In patients receiving 200 to 400 mg/day of fenofibrate for two months, "transient signifcant increases in mean serum creatinine values were seen with the 200 and 300 mg doses" (pg 20024). This suggests kidney toxicity in the human.

2) Liver Toxicity Safety, Human:

"As expected, the incidence of clinically significant elevations of one or more hepatic enzymes was greater in the fenofibrate group (27 patients, 23%) than in the placebo group (10 patients, 9%). Clinically significant abnormalities in renal function values (BUN, creatinine) were recorded on 1 or more occasions for 21 (18%) patients treated with fenofibrate and 10 (9%) patients treated with placebo." (pg 20032)

f. Safety, Human Studies:

1) "Adverse effects were reported for 218 (9%) of patients treated with fenfibrate. Seventeen investigators either did not observe or did not report any side effects." (pg 20034) (empahsis ours: This, in my opinion, is a severe deficiency of these studies and causes me to discount the reliability of these studies.)

2) "Gallstones and biliary ltihiasis were reported in 1% of patients." (pg 30034) This proves that fenofibrate, aside from increasing the "lithogenicity Index - i.e. cholesterol content of bile...acts like the parent drug clofibrate and does form gallstones in patients given fenofibrate. This is an unacceptable adverse reaction for a lipid lowering agent, meant for long term use. The 5 year study on clofibrate discovered a marked excess in gallstone formation (and necessary cholecystectomy) in patients receiving clofibrate over those receiving placebo with hyperlipedemia, and the third group with low cholesterol receiving placebo. This excess of gallstone formation and resultant excess of cholecystectomy, was responsible for four intraperative deaths with cholecystectomy in the clofibrate-treated group.

It is also very important to note that this excess of gallstone formation was not known or perceived until into the second year of the WHO clofibrate study. I note at this point that the sponser of this fenofibrate IND presents only short term studies, that do not approach the length of treatment time (5 years) in the large WHO Clofibrate Study. Also: In some studies transient increases in serum transaminase concentrations were observed.

3) Also: (pg 20036) "A higher incidence of clinically significant elevations of hepatic enzymes was found among patients treated with fenofibrate than among those treated with placebo."

Also: "A 1% incidence in biliary and gallbladder stones was recorded in foreign studies." This incidence of gallstones I project as increasing over a longer period of observation.

g. Pharmacology:

Sponsor's major comparison of various anti-lipedemic studies compares mainly clofibrate and fenofibrate. Both drugs have similar chemical effects on lipids. Indeed, the marked similarity of action of clofibrate and fenofibrate on blood chemistries, particularly lipids, enhances my concern that fenofibrate would prove to produce the same excess in overall all-cause mortality deaths and in cancer deaths, evidenced in the 5 year clofibrate study.

For example: "Both drugs inhibited cholesterol biosynthesis and formation of hydrocarbon fragments, fatty acid esters, and phospholipids, suggesting that both drugs inhibit cholesterol synthesis at the level of conversion of hydroxmethyl-glutarate into mevalonic acid." (pg 20205) and "In both groups, 90% of radioactivity was found as bile acids." (pg 20206)

h. Summary of Pharmacology:

1) Toxicology and Pathology:

Chronic Toxicology - pg. 20503

Test Animal	Results
Swiss Mice	Intrahepatic cholecystasis degenerative changes in hepatocytes
Swiss Mice	Gross hepatomegaly with cholecystasis fenofibrate and clofibrate

Test Animal	Results
Swiss Mice	Dose related increase in alkaline phosphatase and transaminase elevations in fenofibrate treated groups. Similar but less pronounced pattern in clofibrate group.
Swiss Mice	Increased incidence of modular structures in liver at 200 mg fenofibrate.
Swiss Mice	Increased liver weight at 60 mg and 200 mg with fenofibrate. Changes in clofibrate group (400 mg) similar to fenofibrate group.
Swiss Mice	Increased incidence of hepatocellular hypertrophy, Labular dysplasia, and Kupfer cell pigmentation at 200 mg/kg fenofibrate. Clofibrate group ~~should~~ showed similar changes.
Swiss Mice	Increased incidence of liver tumors at 200 mg and 60 mg fenofibrate. Incidence was greater than in clofibrate group.

Test Animal

Wistar Rats: 2 year study
Dose levels: 10 mg, 45 mg, 200 mg/kg/day fenofibrate
OR: 200 mg/kg clofibrate

Results: Hepatocarcinoma responses with both treatments: Elevated Incidence of hepatic (liver cell carcinomas and adenomas) tumors with hepatomegaly and intrahepatic bile stasis with 45 mg and 200 mg/kg fenofibrate and clofibrate.

Test Animal

Rat, Spraque Dawley: 117 week study
Dose levels: 10 + 60 mg/kg/day fenofibrate; 400 mg/kg/day clofibrate; 250 mg/kg/day gemfibrozil.

Results: Increased incidence of testicular and pancreatic tumors at high dose fenofibrate.

Dog, Beagle: 7 month study
Elevations of transaminases, elevations of alk. phos.
*Cholelithiasis
*Chronic nephritis, renal stone

W1 Star Albino Rat: 7 day study
Dose levels: 3, 10, 30, 100, 300 mg/kg/day fenofibrate

Results: SgoT levels were raised hepatomegaly in all treated rats at doses of 30 mg or above. Peroixsomes proliferation and enlargement in all animals.

2) Sponsor's Summary of Toxicology:

Page 2 0516 volume I (6 week study - fenofibrate in Mice) "Drug-related neoplastic lesions were confined to the liver. Significant increases in the incidence of hepatocellular carcinomas were found....The incidence of hepatocellular adenomas (a precursor of liver cancer) was also significantly increased."

Sponsor States in Conclusion: "Fenofibrate posesses hepatocarcinogenic potential in mice. Increased incidence of hepatocellular carcinoma and adenoma in conjunction with hepatomegaly and cholestasis were drug-related." (In fact, I note that fenofibrate produced more liver tumors than clofibrate.)

Sponsor states: "A dose related increase in the plasma alkaline phosphatase activity was seen in mice,...correlated with increased levels of plasma transaminase activity. A similar, but less pronounced (emphasis mine) pattern was seen in mice given clofibrate.

Sponsor states: Both fenofibrate and clofibrate were associated with an increased incidence of hepatocellular injury, lobular dysplasia (anaplasia), and Kupfter cell pigmentation. The incidence of hepatic tumors was increased in mice given either the intermediate or high dose of fenofibrate or clofibrate; greatest in the high dose fenofibrate.

Sponsor states: Pg. 20519 "It was concluded that the major target organ for toxicity was the liver for clofibrate and fenofibrate...Fenofibrate at doses of 60 and 200 mg/kg/day as well as clofibrate at a dose of 400 mg/kg/day produced increases in plasma alkaline phosphatase and transaminaase activities, hepatomegaly with the development of nodules and hepatocellular carcinoma. These findings were induced at doses of fenofibrate corresponding to 12 and 40 times the therapeutic dose and at a dose corresponding to 12 times the therapeutic dose of clofibrate."

Sponsor's Summary Vol. I (continued) - Chronic Toxicology, Rats:

Dose related increases in liver weights, elevated GPT, and dose-related increases in plasma alkaline phosphatase, for fenofibrate and clofibrate treated animals were correlated with hepatocellular hypertiophy associated with intrahepatic cholestasis and liver cell neoplasia (cancer).

Changes in Blood: "Impaired liver function most likely accounted for dose-related trends in red blood cell counts, hemoglobin, hematocrit, and MCHC noted in the fenofibrate treated animals during the study."
"Dose-related elevations in BUN, etc. ....".

Pg. 20522 "Drug related heoplastic (cancer) lesions were primarily confined to the liver and pancreas for both compounds. Both fenofibrate and clofibrate demonstrated a definitive tumorigenic potential in the liver and pancreatic tissue."

Sponsor states: "In conclusion, this study revealed that fenofibrate and clofibrate elicited hepato carcinogenic responses in rats." Elevated incidences of hepatic (liver cell carcinomas and adenomas) and pancreatic (acinar ~~cell~~ cell carcinomas and adenomas) tumors, in conjunction with hepatomegaly and intrahepatic bile stasis were drug induced." note: gemfibrozil produced similar changes.

Chronic Toxicity in Monkeys:

52 week chronic oral toxicity study: comparison study fenofibrate vs. clofibrate with interval sacrifices starting at month (3) three.

Sponsor states: "There was..." no appreciable difference between the 2 equivalent high dose treatment groups (fenofibrate 60 mg/kg/day and clofibrate 400 mg/kg/day with respect to the number of perox somes seen. (I note that centrilobular peroxisomes were sun in all monkeys treated with fenofibrate 60 mg/kg/day - see chart on page 20530. Note that Reddy et al., 1980 "have subsequently suggested that the peroxisome hypolipedemic drugs should be regarded as a novel class of chemical carcinogens." References: Svoboda and Azarnoff, 1979; Reddy et al., 1980.

Seen

In the present study, the peroxisome proliferative responses to clofibrate and fenofibrate were very similar.

3) My Overall Conclusion:

Fenofibrate is more toxic and at least equally carcinogenic and lithogenic as clofibrate.

4) Sponsor's Summary on Human Clinical Trials:

Human Clinical Study on Bile Lithogenicity, pg. 21012. Sponsor states: "Treatment with clofibrate increased the Lithogenic Index (LI) moderately from 1.1 to 1.4 (P - less than .01) Administration of fenofibrate and bezafibrate for 3 weeks increased the Lithogenic Index from 1.1 to 1.5 (P less than .01) and from 1.4 to 1.8 respectively."

5) My Conclusion:

Fenofibrate is as least as lithogenic and gall-stone producing as clofibrate. Perhaps more so.

V. Medical Officer's Evaluation of Safety Issues Encountered with Fenofibrate and Recommendations as to Approval/Non-Approval:

Unfortunately for the sponsor, I believe that they have followed the wrong path - namely trying to make a clofibrate analogue that was better than clofibrate.

Fenofibrate to me appears significantly similar to clofibrate, only perhaps more toxic and lithogenic in animals than clofibrate. Certainly as likely to produce cancer of the liver and pancreas in animals, and more likely to produce gallstones in humans than clofibrate.

And what has clofibrate now been shown to be with our now-available data from the 5 year WHO study? An embarrasment to those well-meaning people who approved it, and a disaster to those who were given clofibrate, albeit with innocence and good intentions.

Evidence:

The WHO Study (British Heart Journal, 1978, 40, 1069-1118) was a prospective 5 year study involving three randomly assigned groups of males, ages 30 to 59; patients with manifest heart disease or other major disease were excluded. Group I, the treatment group, was a randomly chosen half of the men in the upper third of the serum cholesterol distribution in some 30,000 volunteers. The comparable control group, Group II, comprised the other 5000 men of the upper third of the cholesterol distribution, and these were given a placebo.

A mean reduction of 9% of the initial cholesterol levels was achieved in the treatment group, Group I.

The number of deaths in the treated group I (with clofibrate) significantly exceeded the placebo treated high cholesterol group II. The excess in deaths in the high cholesterol, clofibrate treated Group I (excluding deaths from "accident" and "other vascular causes") was 77 versus 47 - a 36% increased mortality in those receiving clofibrate.

The subgroups with the greatest proportionate excess of deaths is that of conditions related to the liver, the biliary, and the intestinal systems. The cholecystectomy rate for gallstones was 100% higher in the clofibrate-treated Group I, and four deaths were surgical cholecystectomy (gallstone) deaths.

There was an excess of cancer deaths in the clofibrate treated Group I; there was a total malignancy number of 58 deaths in Group I (clofibrate) as compared to 42 deaths in placebo Group II and placebo Group III. Seven of the Cancer Clifbrate treated Group I deaths were "liver, gallbladder, pancreas", and twelve deaths were due to gastrointestinal cancer.

The number of cholecystectomies in clofibrate Group I were 59 as compared to 24 for placebo control Group II and placebo contr`lled Group III. One could go on, but the point is undeniably made that on the basis of new evidence, here outlined, clofibrate does a great deal of harm, and no discernable good.

This opinion is further borne out by the other large study, the Coronary Drug Project, (Jama Jan. 27, 1975 vol. 231, no. 4). The purpose of this trial was to enroll men ages 30 to 64 at entry who had verified evidence of one or more myocardial infarcts, class I or class II, and who were free of other diseases.

These men were randomly assigned to clofibrate or placebo, double-blinded. All surviving patients were in the study at least 54 months, and 96% at least 5 years.

The primary end-point for drug efficacy was total mortality. Clofibrate effected sustained mean reductions of cholesterol of 6% and 22% in triglyceride levels.

The Conclusion of the Study Was: "On balance, there is no evidence from the Coronary Drug Project to lead to a recommendation for the use of clofibrate as a therapeutic agent in men with coronary heart disease." (Clofibrate did not lower cardiac or total mortality.) "There was an increased incidence of cholethiasis among patients taking clofibrate (3.0% vs. 1.3%) in the placebo group.

VI. Recommendation:

Since I see fenofibrate as almost a mirror image of clofibrate, I recommend that it not be approved under any circumstances for any use in humans.

Albert E Weiner MD

Albert Weiner, M.D.

MSR Completed and to typist
8-22-84

cc:
NDA Orig. NDA 19304
HFN-220
HFN-810
HFN-810/AWeiner/8-22-84/KG/9-7-84
Wang no. 6585C
Gloria Trocade MD HFN-180
S Sobel MD
Division file NDA 19304

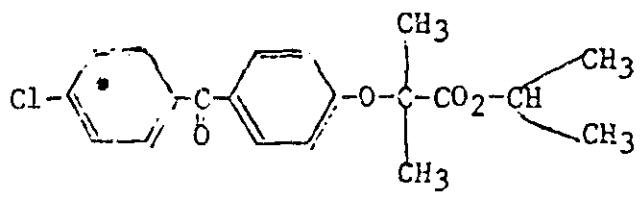
NDA 19-304
Fenofibrate
Lipid altering
Wang 6550C

Laboratoires Fournier S.A.
Submission dated 5-30-84
Received by HO 8-21-84
Review completed 8-31-84

Medical Officer's Review and Evaluation of Original NDA

1. General Information

a. Name of Drug: Generic: Fenofibrate
Tradename: Lipantil, Lipanthyl in Europe
isopropyl 2-[p-(chlorobenzoyl)phenoxy]-2-methylpropionate
$C_{20}H_{21}O_4Cl$



Mol Wt 360.83

b. Pharmacologic Category: lipid altering of the clofibrate class chemically a phenoxyacid

c. Proposed indication: "Lipantil reduces elevated serum cholesterol and triglycerides and is of benefit in the treatment of severe hyperlipoproteinemfas found in some patients, in whom dietary measures alone have failed to produce an adequate response. Lipantil is therefore indicated in appropriate cases of type IIa, IIb, III, IV and V hyperlipoproteinemia."

There is further discussion of diet and risk factors including the following: "Furthermore, it has been shown that a lowering of elevated serum lipids is effective in the prevention of heart disease. The control of such lipid disorders forms the rationale for treatment with Lipantil."

Also: "Plasma uric acid levels are increased in approximately 20% of hyperlipidemic patients, particularly in those with type IV disease. Lipantil has a uricosuric effect and is therefore of additional benefit in such patients."

d. Dosage form and route of administration: 100 mg fenofibrate capsules. For oral administration.
Each capsule contains:

fenofibrate	100	mg
lactose		
magnesium stearate		

e. Related drugs: clofibrate, NDA 16-099
gemfibrozil, NDA 18-422

9/5/84

2. Manufacturing Controls: See Chemistry review.

3. Pharmacology: See Pharmacology review.

a. Pharmacodynamics. Fenofibrate 50-300 mg/kg was found to reduce total lipids and cholesterol in normal rats and in triton or diet induced hypercholesterolemic rats. LDLC and VLDLC were reduced and HDL increased.

In the rat, fenofibrate weakly displaced thyroxine from plasma albumin, reduced incorporation of oleic acid into blood lipids, inhibited bile synthesis without desmosterol accumulation and increased output of bile, increased hepatic clearance of cholesterol and reduced liver cholesterol, and inhibited HMG-CoA reductase. It was moderately ulcerogenic and potentiated anticoagulant activity of acenocoumarol. It was 98-99% albumin-bound.

In dogs, fenofibrate had no effect on blood pressure, EKG, heart rate, respiratory parameters, autonomic nervous system, coagulation factors.

Lecithin cholesterol acyltransferase activity was increased by fenofibrate 25%, by colestipol 12% and by the combination 91%.

Massaroli et al. Activity in inhibiting HMG CoA reductase (HMGR) was suggested by decrease in enzyme activity when fenofibrate was added to incubation medium for human blood mononuclear cells, and when added to assay mixture for HMGR.

Schneider et al. HMGR activity in mononuclear cells from patients with type IIa or IIb who had received fenofibrate for 6 mo was decreased compared to a determination after drug was stopped 2 months. This effect was particularly noted in IIb.

Rubba et al. Lipoprotein lipase activity increased after fenofibrate.

Bosello. Lipoprotein lipase activity was not modified.

Bile lithogenicity increased, but not significantly, in 12 normal males after fenofibrate 2 weeks.

Bile lithogenicity increased more than 20% in 2 patients and less than 20% in 4 patients with type IIa and IIb after 4-6 weeks fenofibrate.

von Bergman et al. After 3 weeks of fenofibrate administration the lithogenic index (Hegardt, Dam and Holzbach) increased from 1.1 to 1.5. After the same period of treatment clofibrate increased the index from 1.1 to 1.4 and bezafibrate increased it from 1.4 to 1.8. The molar ratio of chenodeoxycholic acid to cholic acid in bile was decreased with each of the drugs in some of the patients, but was not significant except with fenofibrate which decreased the ratio in all five of the patients studied.

10 male normolipidemic patients received fenofibrate 300 mg single dose and uric acid clearance increased two-fold.

Kuntz. 5 normal males and 5 normal females received 300 mg/d fenofibrate for 7 days, and plasma uric acid decreased significantly from 0.312 mmoles/l to 0.243.

h. Pharmacokinetics: Single labeled dose administration to rats resulted in 45-50% recovery in urine, 47-50% in feces over 5 days. No label was detected in expired air. Plasma concentration peaked at 2 and 11 hr in males and females respectively. Half-life in plasma was 8 hr. 73-75% of dose was excreted in bile. Steady state was reached in 7 days. Radioactivity was mainly associated with liver, kidneys, GI tract.

In dogs, peak activity occurred at 4-6 hr and half life was 24 hr.

98% of dose was found in urine after single dose in man, 33% in mice, intermediate amounts in rat, hamster, guinea pig. In female rats 36-37% was excreted in urine, in males 39-55%.

Clinical Pharmacokinetics were investigated in 7 studies.

Urien, et al. Protein binding percent was not decreased by increased drug concentration. Amount bound was decreased by cholestasis, but not by salicylic acid or sulfamethoxazole. Phenylbutazone serum binding was decreased by fenofibrate.

^{14}C fenofibric acid to 2 patients, 300 mg single dose: 80-90% of the radioactivity was recovered in urine, mostly within 24 hr.

6 male and 4 female normolipidemic subjects received fenofibrate 300 mg/d for 11 days. Peak plasma level of fenofibric acid was reached at 4-6 hr, and steady state more than 10 mcg/ml by day 5. Half-lives: 5.27 and 21.73 hr. Urinary excretion data indicated 30% absorption.

26 males and 14 females, 23 of them type IIa, 16 IIb and 1 IV received 200-400 mg/d for 1 year. Mean serum level of fenofibric acid at 1 mo was 14 mcg/ml (10-20 mcg/ml, depending on dose).

Jaeger. 5 male and 7 female normolipemic subjects received 300 mg with food, 300 mg without food and 300 mg in water in that order. Mean peak plasma levels were 10.85 mcg/ml at 6 hr, and half-lives were 2.56 and 16.5 hours. There was greater absorption when fenofibrate was given with food (AUC 159 vs 56). When given with food, AUCs in women were similar to men with one exception: a man with higher absorption.

Harvengt et al. 9 subjects with severe or moderate renal disease received 300 mg fenofibrate. 6 subjects with terminal renal disease and 5 other subjects received 100 mg/d for 15 days. There was progressive increase in fenofibrate plasma half-life with increasing renal impairment. In patients requiring dialysis the half-life varied between 2 1/2 and 10 days.

Desager, et al. 6 hemodialysed and 9 hemodialysed subjects received 300 mg fenofibrate. Hemodialysis did not modify the plasma levels, and filtrates contained very small amounts of fenofibric acid. 5 hemodialysed patients received 100 mg for 2 weeks with no serious side effects, but with continued accumulation of fenofibric acid and no correlation of plasma levels with creatinine. The author does not recommend use of fenofibrate in chronic renal failure.

c. Toxicology: 3 month rat studies with fenofibrate 50, 250, 500 and 1000 mg/kg (human dose 6 mg/kg) showed SGOT and SGPT elevated at 500 mg/kg, increased liver weight at 50 mg/kg, decreased weight gain at 100 (sic, pg 2.0502) mg/kg, increased kidney weight at 50 mg/kg.

22 mo mice study with 50 mg/kg showed 100% increase in liver weight with no liver tumors, but cholestasis.

80 wk mice study with 10, 45, 200 mg/kg/d showed dose related increased liver and kidney weight, cholestasis at 200 mg, hepatocellular carcinomas.

104 wk mice study at 10, 60, 200 mg/kg showed increased food consumption at 60 without change in body weight, increased alkaline phosphatase, transaminase, increased liver nodules at 200, increased liver weight at 60, increased hepatocellular hypertrophy, increased liver tumors at 60.

2 yr rat study at 10, 45, 200 mg/kg showed hepatocarcinogenic response with increased hepatic and pancreatic carcinomas and adenomas and intrahepatic bile stasis.

117 wk rat study at 10 and 60 mg/kg showed increased testicular and pancreatic tumors at 60.

7 mo dog study at 50 and 100 mg/kg and 24 mo dog study at 25 mg/kg showed loss of weight and decreased food consumption, changes in transaminases at 25 mg, elevations of alkaline phosphatases, renal microlithiasis at 50, chronic nephritis with renal lithiasis at 25, cholelithiasis.

52 wk study in rhesus monkeys at 12, 50 and 200 mg/kg showed "no treatment-related" effects in hematology blood chemistry, urinalysis and ophthalmology and no increase in peroxisomes in liver.

Some embryolethality and toxicity was seen with very high doses in rats, mice and rabbits during gestation, but no teratogenicity. Fertility was not affected but loss and smaller litters was seen, as well as dystocia, stillbirths, and reduced survival.

4. Clinical Background. This drug has been marketed in Europe for several years. Adverse reactions from that experience are reviewed with the published literature under Other studies, 5.b. below.

5. Clinical Studies

a. Controlled studies: One multicenter study is identified as "controlled." Eleven investigators studied 240 subjects. Results were combined for analysis.

1) Investigators for the study were:

	No pts studied
Virgil Brown,MD, Mt. Sinai School Medicine, New York	7
Carlos Dujovne,MD, Univ Kansas Med Ctr, Kansas Cty	21
John W. Farquhar,MD, Stanford Univ Sch Med, Palo Alto	32
Elaine B. Feldman,MD, Med Coll of Georgia, Augusta	16
Scott M. Grundy,MD, Univ Texas Health Sci Ctr, Dallas	13
Robert H. Knopp,MD, Northwest LRC, Seattle	38
Norman L. Lasser,MD,PhD, N J Med Sch, Newark	8
Margot J. Mellies,MD, Univ of Cincinnati, Cincinnati	36
Robert H. Palmer,MD, Columbia Presbyt Med Ctr, New Yrk	15
Paul Samuel,MD, Cornell Univ Med Col, Manhasset, NY	27
Gustav Schonfeld,MD, Washington Univ Sch Med, St Louis	27

2) Objectives: To compare the effect of fenofibrate 300 mg/d with that of placebo on plasma cholesterol, plasma cholesterol fractions, and plasma triglycerides in patients with type IIa or IIb hyperlipoproteinemia under double-blind conditions for 24 weeks, and to collect additional information on long-term safety and tolerability of fenofibrate in a 24-week open-label period following the double-blind treatment.

3) Rationale: This study was to provide a controlled study for the NDA submission. The drug has been marketed in France since 1975. Studies done in Europe showed efficacy for cholesterol lowering.

4) Experimental Design: The study was randomized and double-blind.

Patient population:
Patients were 18-65 years of age, male or postmenopausal females not on estrogen.
Diagnosis of type II was based on LDLC at one of the prestudy visits of at least 175 mg/dl, and diagnosis of either type IIa or type IIb depended on whether mean TG at the three prestudy visits was less than 250 mg/dl or was at least 250 mg/dl. Also, average TC of the three visits had to be at least 250 mg/dl.
Mean age of 116 fenofibrate patients entering the double blind period was 52, and of 111 placebo patients was 51.7, mean weights were 165.1 and 164.9 respectively.
The fenofibrate group contained 82 male and 34 female subjects, the placebo group 71 and 40. 104 and 98 were caucasian, 6 and 9 negro, 0 and 2 hispanic, and 6 and 2 were "other."
92 and 89 were IIa, 24 and 22 IIb. Two subjects who entered the placebo group had LDLC less than 175 and two who entered the fenofibrate group had TC less than 250.
42 fenofibrate and 31 placebo patients had had previous hypolipidemic therapy, which was probucol for 3 of the IIa patients.

Of the type IIa's, 4 patients had had previous myocardial infarctions, 26 had hypertension, 4 angina and 3 other coronary artery disease. Of IIb's, 2 had previous MI, 6 hypertension, 3 angina.
Concomitant medications included aspirin 26.7%, hydrochlorothiazide 12.5%, propranolol 12.5% and nitroglycerine 5%.

5) Procedure:

A 6-week washout period preceeded the study, during which history and physical were obtained, screening for elegibility was done, dietary interview was conducted and instruction in a prudent diet given, and lipid determinations were done. The lipid determinations at week 0, 2 and 6 included total cholesterol (TC), plasma triglycerides, and plasma high density lipoprotein cholesterol (HDLC), from which low density lipoprotein cholesterol (LDLC) was calculated. Lipid quantification was done at week 4 and included measurement of plasma VLDLC by centrifugation. Blood chemistry, prothrombin time, hematology, urinalysis, and ECG were also done at week 0.

A 6 week placebo-treatment period followed during which compliance was evaluated, and subjects excluded from further study if they appeared to be non-compliant. The above lipid determinations and lipoprotein quantifications were repeated at weeks 3 and 6 respectively, as well as blood chemistries, prothrombin time, hematology, urinalysis, ECG and slit-lamp examination.

A 24 week double-blind treatment period then followed during which lipid determinations were done at weeks 2, 4, 8 and 18, lipoprotein quantification at weeks 12 and 24, blood chemistries, hematology and urinalysis at weeks 2, 4, 8, 12, 18 and 24, prothrombin time and ECG at week 24. Treatment was either 100 mg fenofibrate tid or placebo.

24 weeks of further treatment was offered those who completed the double-blind period with followup visits at 2, 9, 16 and 24 weeks, similar laboratory examinations, slit-lamp examination at 24 weeks.

Of the 92 fenofibrate type IIa patients (FIIa) who entered the double-blind portion of the study, 10 discontinued treatment for the following reasons: adverse reactions 5, increased liver enzymes 3, lost to followup 2. From the 89 control IIa patients (CIIa) 9 discontinued for: adverse reactions 1, increased liver enzymes 2, lost to followup 3 and noncompliant 3. Of the 24 IIb fenofibrate patients (FIIb) 4 discontinued because of adverse reactions. Of the 22 IIb control patients (CIIb) none discontinued.

6) Efficacy. Body weight changes were minimal, and type IIa patients had gained 1-1.1% by the last visit or by visit 24 in both F and C groups. Type IIb patients had lost 0.1 or gained 0.2% in F group and gained 2.6% in C group.

Variable/Type & Rx	IIa drug	IIa control	IIb drug	IIb control
Number patients	92	88	24	22
Total cholesterol				
Baseline	301.7	310.2	300.9	308.2
Endpoint	252.4	311.9	254.1	322.5
Percent change	-16.2	0.5	-14.8	4.7
LDL cholesterol				
Baseline	219.8	227.2	180.1	198.6
Endpoint	176.3	228.3	169.7	197.7
Percent change	-19.6	0.7	-2.7	1.2
HDL cholesterol				
Baseline	49.4	49.0	41.9	40.1
Endpoint	54.9	48.4	47.6	38.7
Percent change	11.7	-0.9	13.5	-3.2
Triglycerides				
Baseline	153.8	159.5	349.3	317.9
Endpoint	97.5	155.1	195.4	388.7
Percent change	-33.6	-1.6	-40.9	26.0
LDL/HDL cholesterol				
Baseline	4.8	5.2	4.5	5.3
Endpoint	3.6	5.2	3.9	5.3
Percent change	-27.3	0.2	-14.2	2.4
VLDL cholesterol/# pts	81	78	23	19
Baseline	22	26.5	64	66
Endpoint	15.5	26.5	32.5	91
Percent change	-34.1	2.6	-52.7	4.8

Total cholesterol. In FIIa mean TC fell to -13.2 at week 2 and remained at -15.3 to -18.4 through week 24, when it was -16.5%. In FIIb mean TC fell to -14.6% at week 2 and stayed between -12.8 and -16.9 through week 24 when it was -14.8.

Low Density Lipoprotein Cholesterol. 60% of all subjects on fenofibrate had at least a 15% reduction in LDLC from baseline, but only 14.8% of control patients had that amount of reduction. Reduction was 15.9% at week 2 and -17.1 to -22.7 through week 24 when it was -19.5% for FIIa. For FIIb, reduction was -2 to -10.5% during the period and mean reduction was -4.3%.

High Density Lipoprotein Cholesterol. 49.2% of all F patients and 18.4% of all C patients had at least a 10% increase in HDLC. Increase was 5.9% at 2 weeks and continued to increase with the exception of week 18 until it was +11.3% at week 24 in FIIa. Increase was 8.7% at 2 weeks and continued to increase to 16.4% at week 12 in FIIb.

Triglycerides. 59.5% of all fenofibrate patients and 14.6% of control patients had decreases in TG of at least 30%

In all fenofibrate patients with baseline TC more than 315, TC was reduced a mean of 18.6%, but in those with TC not more than 270 it was reduced 10.5%.

In those with baseline LDLC more than 231, LDLC was reduced 20.4%, and in those with LDLC not more than 180 it was reduced 5.8%. In those with baseline HDLC not more than 40 HDLC was increased 15.6%, and in those with HDLC more than 54 it was increased 9.3%. In those with baseline TG more than 240, TG were reduced 43.6% and in those with not more than 115 they were reduced 28.9%.

5. a. 6) In males, TC was reduced 13.6%, LDLC 11.8%, TG 34.1%, and in females TC was reduced 21.5%, LDLC 26.6%, and TG 37.6%. At the same time differences between males and females in the control groups were very little for TC, but LDLC decreased 1.7% in males and increased 5.2% in females, and TG increased 6.9% in males and decreased 1.4% in females. HDLC increased 10.1% in males and 16.8% in females with only slight changes in controls.

In some cases, the variations between investigators were substantial, but can generally be explained by the small numbers and the variation in type, age, sex, and previous treatment of the subjects.

LDLC. Dujovne (10 patients) and Samuel (14 patients) had mean reductions of LDLC of 20.9% at endpoint, but Mellies (19 patients) had only 10.5% LDLC reduction. Both the Dujovne and Samuels patients were a little older and more of them were female than the Mellies patients. Also, the Dujovne patients had had less previous hypolipidemic treatment than the Mellies patients.

VLDLC. VLDLC was increased 10.5% in two Brown patients and 33.3% in one Lasser patient, but decreased 60.2% in 6 Palmer patients at endpoint. The Brown patients were one male and one female IIa, the Lasser patient was male IIa, and Palmer patients were 1 male, 4 IIa. TG reduction was -25.9% for 8 Feldman patients (only one was IIb and one was female) to -59.7% for 6 Palmer patients.

HDLC. HDLC increased 22.4% in Dujovne and 22.6% in Palmer (6) patients, but declined 10.6% in Grundy (3) patients at endpoint. 3/4 Lasser patients who had determinations after 4 weeks also had mean decreases of 4.4% at week 24. The 3 Grundy patients were all male IIa, and were younger than the others which were 6 male and 10 female, and 12 IIa, 4 IIb. The 4 Lasser patients were male and 3 were IIa. Dujovne had the greatest reduction (-35.8%) in LDL/HDL ratio and Grundy the least (-7%).

Dr. Mellies determined cholesterol on fractions of HDL and determined levels of apo AI and apo AII. AI is inversely correlated with CHD and is present in greater concentration in HDL_2 than in HDL_3. Apo AI increased from placebo phase 126.66 to 24 week 142.39 (12%) and apo AII increased from 32.77 to 41.91 (28%). HDL_2C decreased from 24.13 to 22.83 (-5%) and HDL_3C increased from 25.03 to 33.41 (33%). The increase in HDL is therefore in the HDL_3 fraction which is not known to be associated with decrease in CHD.

In an effort to see what happened to individual patients, I looked at one of the largest groups (patients of Dr. Farquhar) to see how many had good results for LDLC and at least no adverse change in HDLC. I found only 3 females and 4 males, so I looked also at the other two groups (Knopp and Mellies) with more than 30 patients each. I selected those who had at least 15% lowering of LDLC and from that group those who had at least no reduction in HDLC. I also decided to discard those who had 15% reduction in LDLC at the end determination, but had had much higher levels throughout, but actually found only one such who was discarded for having decreased HDLC anyway. Two subjects not have HDLC on the appropriate table and were not counted.

Of the total of 53 fenofibrate-treated patients, 20 qualified as good responders. Three of 51 placebo patients similarly qualified as good responders.

Of the 20 fenofibrate responders, 6 had less than 10% increase in HDLC.

Of the 53 subjects, 10 were female. 7/10 females and 13/43 (30%) males were good responders. All 6 of those with little change in HDLC were men.

All 20 responders were IIa.

8/13 male and all of the female responders had elevated SGOT or SGPT on at least one occasion.

Thus a minority of men are "benefited" as judged by our biochemical parameters, and some may have adverse effects (either increase in LDLC or decrease in HDLC) in spite of taking drug.

Comments: This drug appears to have efficacy similar to clofibrate and gemfibrozil in lowering lipids. The lowering of LDLC in type IIa may be better than with clofibrate or gemfibrozil, but that is not possible to determine from this study since clofibrate was not studied. The lowering of LDLC in type IIb with fenofibrate is statistically significant, but not clinically significant and does not meet our standard of 15% lowering in order to have the indication in the label. The increase in HDLC may be similar to that seen with gemfibrozil and greater than that with clofibrate, but again it is impossible to be sure, because they were not studied. With all of these clofibrate-family drugs, the increase of HDL may not have any relevence to CHD risk. At least no relationship has been established by epidemiologic studies.

5. a. 7) Safety review of combined investigators. In the following discussion I have underlined those adverse findings which are of greatest concern to me. They are mentioned later in the Comments following the safety review of this study.

There was one death during the study, from "hypertensive atherosclerotic cardiovascular disease." This patient was 48 and was in the single-blind placebo period.

Five patients were discontinued from the study because of abnormal laboratory results during the double-blind period. All had increased liver enzymes. Three were on fenofibrate:

Feldman pt 85 had mild <u>increases in CPK, SGOT and SGPT</u>.

Samuel patient 232 had fatigue, anorexia, back pain, malaise and severely increased liver enzymes.
Schonfeld patient 161 had right upper quadrant pain and moderately elevated liver enzymes.

Two were on placebo:
Dujovne patient 27 had moderately increased SGOT and SGPT on day 1.
Samuel patient 254 had abdominal discomfort and moderately increased liver enzymes.

Ten patients were discontinued because of adverse reactions.
Nine of them were on fenofibrate:
Feldman patient 77 had moderately severe rash.
Grundy patient 99 had moderately severe diabetes.
Lasser patient 133 had mild PVC's.
Samuel patient 257 had moderately severe indigestion, fatigue and decreased libido.
Samuel patient 259 had severe urticaria.
Samuel patient 260 had pituitary tumor.
Schonfeld patient 156 had melanoma of the eye.
Schonfeld patient 157 had severe hives.
Schonfeld patient 169 had moderately severe nausea, heartburn, malaise, and RUQ pain.

One was on placebo:
Dujovne patient 31 had hepatitis with severe fever and back pain.

Abnormal Laboratory Values. Because some of those patients included in baseline laboratory results did not have end-of-study determinations for some of the variables, totals at end of study in the group high, or low at baseline are used below.

Hematocrit was low in 6 fenofibrate patients (F) and in 4 placebo patients (P) at baseline. 2 of each were still low at the end of therapy, but 8 F and 5 P additional patients were low. For hemoglobin, 3 F and 5 P were low at baseline, 2 of each remained low, and 15 F and 3 P patients became low. This is compatible with the results for clofibrate (C) and gemfibrozil (G), mild depression of hemoglobin and hematocrit. Summary statistics are not separated for men and women. Mean hematocrit at baseline was 44.7 and fell to 43 at week 18. Hemoglobin fell from 15 to 14.4 at week 18. Falls in the placebo group were from 44.4 to 43.9 and from 14.9 to 14.8.

WBC was low in 9 F and 15 P at baseline, of which 9 and 6 remained low. Additionally, 5 and 3 became low. This means that 9 F and 15 P started low, but 14 F and 9 P finished low, almost a reversal. Also compatible with C and G reports. Mean WBC in F went from 6.1 to 5.8 at week 18 and number of patients with low WBC increased from 9 to 15 at week 24, while in placebo patients mean went from 6.0 to 5.9 and number of lows from 15 to 13 at week 18.

Uric acid was high in 14 F and 17 P at baseline, and in 1 F and 17 P at end. Mean from 6.1 to 4.7 and number high from 14 to 0.

Alkaline phos was high in 8 F and 12 P at baseline, in 3 F and 10 P at end. Mean 65.3 to 44.1 and number low from 3 to 10.

SGOT was high in 4 F and 4 P at baseline, in 22 F and 6 P at end. Mean from 20.4 to 30.7 at week 4, number of high from 5 to 25.

SGPT was high in 5 F and 12 P at baseline, in 24 F and 11 P at end. Mean from 21.5 to 38.1 at week 4, number high from 5 to 25.

BUN was high in 14 F and 11 P at baseline, in 18 F and 7 P at end. Mean from 16.2 to 18.5, number high from 14 to 18 at week 18.

Creatinine was high in 5 F and 6 P at baseline, in 12 F and 4 P at end. Mean from 1.0 to 1.2 at week 18 and number high from 5 to 15.

Phosphorous mean decreased from 3.3 to 3.0 and number of low increased from 16 to 23 at week 4.

CPK increased from 77.8 to 110.3, number of high from 9 to 14 at week 24. In P, CPK increased from 70.7 to 99.5, number high from 9 to 5 at week 8.

Adverse reactions, double-blind period. The same patient may be counted under several reactions in the tabulation below. I have listed all reactions in which fenofibrate incidence was twice that in placebo patients and was at least 3 reports.

Infections occurred in 32.8% of fenofibrate and 25.2% of placebo patients. Increased numbers of infections occurred in genitourinary (6 vs 3) and viral (5 vs 2) infections and in tooth abscesses (3 vs 0).

Gastrointestinal symptoms were similar in the two groups (27.6 vs 27%).

Nervous system reactions occurred in 20.7% of fenofibrate and in 13.5% of placebo patients. Fatigue (12 vs 4), headache (11 vs 4) and sleep disorders (3 vs 0) were increased in F.

Musculoskeletal reactions were similar in the two groups (12.1 vs 16.2%).

Dermatologic reactions occurred in 15.5% of F and 5.4% of P. "Skin rash" was seen in 8 vs 3 and pruritus and hives in 8 vs 3.

Respiratory reactions were similar (9.5 vs 9.9%), but rhinitis was seen in 5 F vs 1 P.

Cardiovascular events occurred in 10.3 F vs 6.3% P with cardiac ischemia in 6 vs 5 patients, but arrhythmia was seen in 4 F vs 2 P.

Ophthalmic reactions occurred in 8.6% F and 3.6% P, but no single reaction was as frequent as 3 reports. Visual alterations, irritation, puffy eyes, lacrimation defect, tired eyes, spots, eye floater, light flashes were all more frequent or occurred only in the fenofibrate group.

Mouth-throat reactions occurred similarly in both groups (5.2 vs 3.6%).

Genitourinary reactions were more frequent in the P (2.6 vs 6.3%). This was due to increased urination (1 vs 3), and kidney stones, dysuria and epididymitis, urinary burning, erectile dysfunction occurring once in P but not in F.

Endocrine reactions were similar (1.7 vs 1.8%) with diabetes and pituitary tumor in F and menopausal syndrome and gynecomastia in P.

Other adverse reactions included ear ache, tinnitus, chills, allergies, gout, anaphylactic shock, prickly sensation, warm feeling and breast carcinoma, all in very small numbers.

When fenofibrate was given to patients who had been on placebo, 4 were withdrawn for adverse reactions, and 3 F who continued were withdrawn for adverse reactions. Two F and one P were withdrawn for abnormal laboratory values.

Farquhar F patient 45 was withdrawn for moderately severe flu.
Mellies F patient 300 was withdrawn for severe head pain.
Schonfeld F patient 159 was withdrawn for severe CVA.
Feldman P patient 81 was withdrawn for moderate fatigue.
Mellies P patient 199 was withdrawn for severe rash.
Palmer P patient 201 was withdrawn for MI.
Samuel P patient 248 was withdrawn for severe cholecystitis and cholelithiasis.
Dujovne F patient 26 was withdrawn for severe decreased WBC.
Knopp F patient 127 was withdrawn for severe nausea, dizziness, rash, swelling, flushing and moderate increase in liver enzymes.
Samuel P patient 231 was withdrawn for moderate increase in liver enzymes.

Results for laboratory values similar to those seen in double blind period in F were observed in P when they were started on fenofibrate for uric acid, alkaline phos, SGOT, BUN, creatinine.
Adverse reactions were similar in patients continued from the two groups for most categories, but were slightly increased in P (patients newly put on fenofibrate) for several categories.
Gastrointestinal reactions were reported in 22.4% F and 28.7% P with increases in diarrhea (4 vs 9), abdominal pain (3 vs 7), constipation (1 vs 4), flatulence (1 vs 3).
Infections were reported in 15.3% F and 20.2% P, no specific kind increased.
Ophthalmic reactions were 7.1% in F and 11.7% in P with cataract in 0 F vs 2 P, and one each lacrimation defect, puffy eyes, iritis and pseudopannus in P and none in F.

Cardiovascular events were 6.1% in F and 9.6% in P with cardiac ischemia 2 F vs 6 P and arrhythmia 0 F vs 2 P.
Dermatologic reactions were 4.1% F and 8.5% P with rash 1 F vs 6 P and pruritis 0 F vs 4 P.

Comments. The visible toxicity of this drug is minor, in the same way that toxicity of clofibrate in short term studies is minor. The toxicity is similar to that seen in the multicenter trial with gemfibrozil. The possible problems with this drug include ones familiar from review of clofibrate and gemfibrozil. Elevated liver enzymes, rashes and sensitivity reactions, arrhythmias, decreased libido, decreased hemoglobin and hematocrit, decreased WBC, increased BUN, and cholecystitis and cholelithiasis were seen in the Coronary Drug Project in clofibrate-treated subjects. Increased infections, increased liver enzymes, decreased hemoglobin and hematocrit and decreased WBC were seen in the gemfibrozil multicenter trial. This trial was just not large enough to identify some of the other problems such as cholecystitis and cholelithiasis. I am not aware of problems with the CNS or ophthalmic reactions, but they are diffuse enough and appear only when the system totals are considered, so they may not be real.

5. b. Other Studies. This section consists of a review of literature. I have used the NDA summary for reports with reprints referenced in the IND but not included in this submission rather than getting them from the IND submission.

There are 22 controlled studies, of which 3 are double-blind, 2 single-blind and 17 open.

Double blind studies.

1) Lauwers. 28 male and 2 female patients 46-76 years of age, 18 with type IIa, 10 with IIb, 1 with III and 1 with IV hyperlipidemia were treated 1 month with fenofibrate 300 mg/d. 12 were then continued on fenofibrate and 10 on placebo for another month. The 22 were then treated with fenofibrate 300 mg/d for a third month. During the first month the 12 "fenofibrate patients" had 29% reduction in TC and 36% reduction in TG, while the "placebo patients" (on fenofibrate) had 32 and 27% reductions. During the double-blind second month reductions of 27 and 31% continued in the fenofibrate group, but placebo reductions fell to 6 and 11%. During the 3rd month reductions in the "fenofibrate patients" were 27 and 28%, in the "placebo patients" were 26 and 26%. One patient died during the first month, one was withdrawn for not taking drug regularly and 3 for reasons unrelated to the trial. What happened to the other 3 is not stated. One patient had a cerebrovascular accident during the run-in period, 1 had gastric discomfort during the first month, and 1 had hematuria from "interaction with anti-coagulant."

2) Brunova. 18 male and 5 female patients with mean age 49.7 years, 8 type IIa, 8 IIb and 7 IV, were randomized to fenofibrate 300 mg/d or placebo for 3 months and then crossed over to the other medication for 3 months. Four of the patients stayed on fenofibrate for 6 months.

Cholesterol was reduced 18% after 3 months, 30% after 6 months. TG was reduced 38 and 65% at 3 and 6 mon. It appears likely that good responders were chosen to remain on fenofibrate for the second 3 months. 2 patients had dyspepsia and all completed 6 months treatment.

3) Verdonk & Afschrift. 18 male and 11 female patients 30-76 years 19 type II and 10 type IV were treated with fenofibrate 300 mg/d or placebo for 2 months and then crossed over to the other medication for 2 months. 7 type II had 6% reduction of TC and 9% reduction of TG during placebo treatment. 4 type II had 21% reduction of TC and 45% reduction of TG during fenofibrate treatment. For type IV, TC was not measured, but TG increased 39% on placebo and decreased 45% on fenofibrate. There were no adverse reactions and no reported dropouts although some did not always have lipids measured.

Comments: About 70 patients were studied in 1-3 mo periods and compared to placebo. Lipoproteins were not studied. Randomization was used in at least one of the studies. Overall the information we have is not adequate to use these studies in efficacy evaluation.

6. b. Single-blind studies.

4) Harvengt. 12 male and 7 female patients 35-69 years, 5 with type IIa, 2 with IIb, 6 with IV and 6 with V not responsive to clofibrate took placebo 6 weeks and then fenofibrate 300 mg/d for 1-2 yr. In IIa TC was reduced 30%, in IV 20%, in 5 V 15%. TG was reduced in type IV 60%, in V 50%. Creatinine phosphokinase increased in 3 patients who had myalgia. Serum transaminases increased slightly in 3 cases, and one patient had 2-fold rise in GOT, GPT, CPK. 2 nonresponders to fenofibrate were not included in the analysis. There is a discrepancy between the summary and the actual report in that page numbers overlap but are not the same, and the report of these patients is only a single paragraph at the end of a report of 3 or 4 other studies of pharmacokinetics in normals and in patients with renal failure showing markedly prolonged half-life "up to 362 hr". Fenofibrate-colestipol interaction and uricosuric action were also studied in normals, with the finding of no interaction with colestipol and a two-fold increase in uric acid clearance after fenofibrate.

5) Ciswicka-Szmajderman. 15 male and 15 female patients, 14 type IIa, 9 IIb and 7 IV took 300 mg/d fenofibrate for 2 months and then washed out 1 month and took 2 g/d clofibrate the fourth and fifth months. TC reductions on fenofibrate were 29, 33 and 35% in IIa, IIb and IV. TC reductions on clofibrate were 6, 8 and 25%. TG reductions were 33, 29 and 53% on fenofibrate, 28, 38 and [illegible] on clofibrate. No withdrawals and no adverse reactions.

6. b. Open studies.

6) Szajd. 12 male and 14 female patients, mean age 51.3, 15 IIa, 3 IIb, 18 IV received 300 mg fenofibrate (21 patients) or placebo (15) 6 mos. When on fenofibrate, IIa patients had 32 and 43% reduction of TC and of TG, 22% increase in HDLC and 22% reduction in uric acid. Type IV had 10 and 49% decrease in TC and in TG, 7% increase in HDLC, and 6% decrease in uric acid. On placebo, TC and HDLC reduced 1 and 14%, TG increased 34%. No withdrawals and no ADRs. Concomitant, ? randomized.

7) Fromantin. 12 male and 12 female, IIa patients received probucol 100 mg (Should this be 1000 mg, which is the usual dose?) or fenofibrate 300 mg/d for 3 months. On fenofibrate, TC was reduced 25%, TG 34%, apoB 19% and uric acid 22%. On probucol, reductions were 15, 0, 9 and 3%. SGPT was increased and RBC decreased. Concomitant, ? randomized.

8) Ciswicka-Sznajderman. 51 male and 29 female patients, 19 IIa, 24 IIb, and 37 IV received 300 mg fenofibrate (40 patients) or 1500 mg clofibrate (40 patients) for 6 months. In the type II TC was reduced 23% and TG 47% and HDLC increased 14% with fenofibrate, and TC reduced 12%, TG 21% and HDL increased 4% with clofibrate. In type IV, TC was reduced 20 and TG 63% and HDLC increased 4% with fenofibrate, TC decreased 15, TG 52% and HDLC 17% with clofibrate. No withdrawals and no ADRs are reported. Concomicant, ? randomized.

9) Cloarc & Belcour. 352 males and 48 females 30-55 years of age with IIa or IIb received no medication (200), diet only (100) or diet and fenofibrate 300 mg/d for 3 years. This was apparently not a randomized study. HDLC increased in 0, 26 and 40% of the patients in the 3 groups. No withdrawals or ADRs are reported. Not concomitant?, ?randomized.

10) Lehtonen & Viikari. 13 patients, 32 to 55 years, 10 IIa, 3 IIb took placebo 1 mo, fenofibrate 300-600 mg/d for 3 mo, cholestyramine 12 g for 3 mo. Reduction was 21 and 18% in TC for the two drugs, 23 and 20% in LDLC, 57 and 32% in TG. HDLC increased 10% on fenofibrate and decreased 12% on cholestyramine. Aminotransferase increased in 2 patients and thrombocytes decreased below normal in one. No withdrawals reported and no ADRs. Not concomitant controls.

11) Abaurre, et al. 27 males and 20 females, 35-60 years, 10 IIa, 27 IIb and 10 IV received placebo 15 days, fenofibrate 300 mg 30 days and then placebo another 15 days. After the fenofibrate, TC was reduced 27%, TG 48%, pre-beta lipoprotein 32% and beta lipoprotein 5%; alpha lipoprotein increased 30%. 2 patients had abdominal pain. Not concomitant controls.

12) Capurso, et al. 10 IIa and IIb patients received fenofibrate 300 mg/d for 3 months, then placebo 1 month. After fenofibrate, TC was reduced 15%, TG 46%, VLDLC 44%, LDLC 13%, VLDLTG 56%, LDLTG 36%, apoB 17% and apoCIII 29%; HDLC increased 25% and apoAI 6%. No ADR or withdrawals were reported. Not concomitant controls.

13) Schwartzkopff. 38 males and 24 females, averaging 54 to 63 years, 12 IIa, 19 IIb, and 31 IV, received placebo 6 weeks, fenofibrate 24 weeks, placebo 6 weeks and then bezafibrate 600 mg 24 weeks, or drugs in the reverse order. Apparently the assignment was not random, but the first half of the patients received bezafibrate first and the second half fenofibrate first. Analysis was difficult due to rebound effects observed after the first treatment periodwith each drug.

Fenofibrate and bezafibrate changes (percent of placebo) for IIa were TC -21 and -19%, TG -22 and -34%, LDLC -25 and -25%, HDLC -6 and -2%; for IIb they were TC -16 and -12%, TG -37 and 39%, LDLC -15 and -9%, HDLC +8 and +27%; and for IV TC -17 and -10%, TG -45 and -46%, LDLC +3 and +2% , HDLC +18 and +19%. Blood glucose was slightly lower, alkaline phosphatase was decreased, urea and creatinine were increased, uric acid decreased, RBC and WBC decreased. One patient had epigastric pain. Probably concomitant controls, ? randomized.

14) Mordasini. 10 males and 8 females age 27-69, 12 IIa and 6 IIb received placebo 1 mo and fenofibrate 12 weeks. TG was reduced (percent of change on placebo) 35%, TC 15%, LDLC 12% and apoB 20%. HDLC was unchanged. SGPT was increased, uric acid decreased. One patient was withdrawn for non-compliance and 1 for cholelithiasis. Two patients had abdominal pain and nausea. Not concomitant controls.

15) Rossner and Oro. 43 males and 13 females 33 to 71 years, 10 IIa, 7 IIb, 4 III and 33 IV received placebo 1 mo, fenofibrate 200 mg 1 mo, 300 mg 1 mo, and 400 mg 1 mo, then some randomly received fenofibrate 400 mg while others received clofibrate 2 g for 2 months, then drugs were reversed in the two groups for 2 mo. In one publication, column heads were apparently wrong so that reported HDLC and LDLC were wrong. The column heads are corrected in pen on the copy. After fenofibrate (400 mg) and clofibrate in IIa TC was changed (percent of value on placebo) -29 and -9%, TG -16 and -20%, in IIb TC was changed -25 and -14%, TG -53 and +7%, in III TC was changed -38 and -8%, TG -70 and -38%, and in type IV TC was changed -14 and -10%, TG -48 and -19%. Percent changes were not in the article, but appear to have been calculated for the summary, probably by the company. Lipoprotein values are not in the summary and it appears that in IIa, HDLC values were lower on fenofibrate than on placebo or on clofibrate. Also in IIb HDLC was lower on fenofibrate than on clofibrate. However, in IV LDLC appears to be lower on fenofibrate than on placebo or on clofibrate. Creatinine rose initially, SGOT and SGPT increased, bilirubin and alkaline phosphatase decreased. When treatment was continued 4 years in 21 cases lipoprotein reductions were maintained, but blood glucose was raised and ASAT and creatinine increased spasmodically. Concomitant controls, randomized.

16) Schwartzkopff. 32 patients 38-73 years, 8 IIa, 11 IIb, 5 IV received placebo 6 weeks, fenofibrate 300 mg 12 weeks, placebo 6 weeks, fenofibrate 300 mg 12 weeks, and placebo 6 weeks. In IIa TC was reduced (percent of change on placebo) 16-19%, TG 20%. In IIb TC was reduced 10-11%, TG 40-46%. In IV TC was reduced 11-13%, TG 38-42%. Alkaline phosphatase and uric acid were reduced, SGOT and creatinine showed transient rises. 4 were withdrawn for non-compliance, 1 for gastralgia, and 4 moved away. Not concomitant controls.

17) Schwartzkopff. 25 males and 16 females 61-67 years, 21 IIa, 11 IIb, and 9 IV received etofibrate 500 mg and fenofibrate 300 mg for 24 weeks each. 27 males and 13 females 56±11 years, 20 IIa, 6 IIb and 14 IV received etofibrate 500 mg and bezafibrate 600 mg for 12 weeks each. Etofibrate was less active than either of the other drugs.

After fenofibrate and bezafibrate treatment in IIa TC was changed -20 and -18%, TG -30 and -22%, LDLC -19 and -25%, HDL +2 and +8%. In IIb TC was changed -18 and -16%, TG -41 and -37%, LDL -16 and -16%, HDL -5 and +25%. In IV TC was changed -20 and -8%, TG -48 and -36%, LDLC +2 and 0%, HDLC 0 and +2%. Transaminases and creatinine rose slightly, alkaline phosphatase and uric acid decreased. About 1/3 of patients entered were excluded from evaluation mainly for doubtful compliance and lack of cooperation. 3 patients had headache, 4 gastric pain, 2 nausea. Probably not concomitant controls.

18) Canzler. 32 patients, 12 IIa, 7 IIb, 5 III, 5 IV received placebo 8 weeks, fenofibrate 300 mg for 6 months and then placebo for 8 weeks. TC was reduced 10% and TG 20% in 21 of 26 at 1 mo and in 17 of 24 at 6 mo. In percent of reduction on placebo, TC was reduced 25% in IIa, 22% in IIb and III, 10% in IV, and TG 24, 45 and 47% in the same groups. LDL_2C was decreased 21% in IIa with no change in HDLC. Neither LDLC nor HDLC were changed in IIb. LDLC increased 42% in IV. In III LDL was lowered 15-23%. Not concomitant controls.

19) Daubresse. 45 patients mean age 54, 14 IIa, 15 IIb, 16 IV received clofibrate 2 g for 2 months, fenofibrate 300 mg for 8 months and clofibrate 2 mo. After clofibrate and fenofibrate therapy, in IIa and IIb TC was reduced 16 and 25%; in IIb and IV TG was reduced 32 and 48%. There were slight increases in urea, creatinine, SGPT. One patient was withdrawn for digestive intolerance and two others had digestive intolerance, 1 rash. 2 year followup revealed 1 gallstones and 1 suspected gallstones. Not concomitant controls.

20) Lehtonen. 33 patients 28-61 years, 16 IIa, 7 IIb, 10 IV received placebo 1 mo, fenofibrate 300 mg for 6 months. Dose was increased to 600 mg in 17/33 patients because response was not satisfactory. In percent of reduction on placebo, TC was reduced 20% and TG 34% in IIa, TC 30 and TG 67% in IIb, TC 17 and TG 46% in IV. In all patients, HDLC increased 46%, apo AI increased 3%, apoB decreased 16%, apoAI.B increased 31%, apoAI/HDLC decreased 10% and apoB/VLDL+LDLC increased 15%. Not concomitant controls.

21) Fromantin. 32 males and 6 females 30-70 years, 13 IIb, 4 III and 21 IV were treated. 21 received clofibrate 2 g for 75 days, fenofibrate 300 mg 90 days and 17 received the same drugs in reverse order 90 and 75 days. After fenofibrate and clofibrate TC was reduced 22 and 14% and TG 56 and 50% from diet levels. uric acid was decreased. 6 patients reported asthenia, digestive symptoms and dizziness. One patient withdrew because of dizzy spells. Probably concomitant controls.

22) Rouffy. 78 patients received clofibrate 2 g 1 mo, wash out 1 mo, and then 300 mg fenofibrate. Clofibrate reduced TC 15% and TG 25% over diet alone. Fenofibrate reduced TC 22 and TG 35%.

Comments: All together the published literature indicate efficacy just about as found in the U.S. controlled study: effective at lowering LDLC for a majority of IIa. However what evidence we can get from these studies

indicates that, as with both clofibrate and gemfibrozil, LDLC goes up in type IV. HDLC is probably increased in a majority of subjects.

Uncontrolled studies. Another 18 studies are reported as uncontrolled studies. Some of these were fairly large studies and are described briefly below with consideration of safety only. The first study contained some information on CHD so that is briefly reviewed.

23) Rouffy. 260 males and 115 females 18-77 years received 200-400 mg for 0.5 to more than 5 years. Gamma-GT, alk phos, and uric acid decreased, and urea and creatinine increased. There were 15 digestive upsets, 6 muscle cramps, 3 alopecia and 11 sexual asthenia. Patients prematurely withdrawn from the study included 2 cancer, 1 T.B., 1 alcoholism, 1 hypothyroidism, 7 sudden death, 3 accidents, 4 GI problems and 7 failures of the drug. Of the 375 subjects 263 were free of CHD, 49 had coronary failure without MI (presumably angina) and 63 were post MI. Average treatment duration was 36-39 mo in all of these categories. Four of the angina subjects improved. 255, 41 and 55 of the subjects in the 3 groups had no change in disease status. 3 of those without CHD developed "coronary failure" and 1 in each of the other groups had worsening of the disease. MI occurred in 4, 1 and 1 subjects and sudden death in 1, 1, and 6 patients.

24) Schwartzkopff. 176 males and 94 females were treated with 200-400 mg fenofibrate for 1mo to 4 years. Uric acid and alk phos were reduced, creatinine rose. ADR included 16 headaches, 12 GI, 6 insomnia, 4 fatigue, 1 muscle pains, 1 sexual asthenia. Liver biopsies done on 42 patients showed no peroxisome proliferation. Fat droplets were slightly greater in the fenofibrate group. A "variation in nuclear size" was seen in 5 of 28 fenofibrate patients.

25) Fromantin. 81 males and 40 females 10-72 years took 200-900 mg for 5 years. Uric acid and alk phos decreased, and urea, SGPT increased.

26) Debry. 138 males and 30 females received 200-600 mg for 18 mo to 4 years. Uric acid and alk phos decreased and urea rose.

27) DeGennes. 223 males and 85 females received fenofibrate 300 mg for 5.07 yr. Transaminases were transiently elevated in 28. ADRs included GI upset 23, muscle pains 3, articular pains 2, itching 2, cardiac or vascular events 14, liver or GB pathology 28, renal pathology 3, tumors 4, hematological 2, dermatological 2, gastroenterological 6 and other 9.

28) Drouin. 61 males and 59 females 18-79 years received 5 mg/kg for 24 mo. Alk phos was decreased and transaminases increased after 3-6 mo in 4.

5. b. Safety Summary for the above published studies. A total of 2862 subjects entered the studies and 2427 received fenofibrate. 191 (7.8%) were withdrawn before the end of the treatment period. Reasons for withdrawal included: gastrointestinal, gastralgia 15, unspecified illness or adverse effect 8, body weight change 6, unspecified intercurrent illness 5, depression 4, general indisposition 3, cancer

2, and 1 each of pruritus, dizziness, tuberculosis, alcoholism, hypothyroidism, surgery, nausea and muscular pains, sweating, dizziness and angina, cholelithiasis, elevated transaminases, and unspecified adverse effect. In addition 43 were withdrawn because of inappropriate treatment, change of drug or unresponsive to treatment, and 13 for non-compliance. 8 deaths were reported.

A total of 218 other reports of adverse reactions from the reported trials were included. These were: gastrointestinal 79, fatigue, headache, insomnia and vertigo 31, sexual asthenia 13, cardiac or vascular events 15, alopecia, itching, rash 11, myalgia and muscle cramps 13, hematuria and lithiasis 4, liver and cholelithiasis 27, tumors 4, articular pains 2, hematologic 2, cytolytic hepatitis 1, bad odor 1, and 15 others which are described as alopecia, asthenia, digestive upsets, dizziness, headaches, sexual asthenia. Physician's voluntary reports of adverse reactions in France included: skin disorders 140, gastrointestinal 100, hematologic disorders (neutropenia, leukopenia, eosinophilia, raised ESR, anemia, phlebitis, hypercoagulability, epistaxis, petechia, thrombocytopenia, hemolytic anemia, hemorrhage, retinal hemorrhage) 70, liver disorders 68, renal disorders 50, weight loss 42, impotence 32, headaches and vertigo 30, alopecia 28, muscle disorders 20, pancreatitis 10, biliary lithiases and related 9, gout 7, and others 6.

Comments: Safety of this drug is hard to assess, because the following question cannot be answered by 6-month studies in a few hundred patients: "Does fenofibrate have the toxicity that resulted in increased mortality in the clofibrate-treated patients in the WHO study?" In the absence of a study large enough to detect it (5000 patients/group studied for 5 years), it is necessary to answer, "maybe." In spite of our inability to identify the cause of those deaths, there is evidence (in the similarity of adverse findings) to suggest that the toxicity does apply. All of the phenoxyacids we have show similar biochemical and hematological effects. It has always appeared that one candidate for the cause of the adverse effect on mortality had to be a subtle effect on the immune system, perhaps through effects on hematological parameters. Fenofibrate may have less effect on hemoglobin, hematocrit and WBC than clofibrate and gemfibrozil do, but nevertheless the effect on infections is still suggested by the adverse effects reported. Our review of the gemfibrozil NDA revealed that the greatest difference between incidence of adverse reports in drug and placebo groups was for cough and urinary tract infection. Similarly, the number of infections reported as ADRs was greater in drug than in placebo group in the multicenter study for this NDA.

This toxicity may apply, but it is still possible that the benefits of the drug might outweigh this risk. There is no justification for taking figures from the WHO and coronary primary prevention (CPPT) trials and applying them to the fenofibrate studies, but just for rough estimation of risk: The increased total mortality in the WHO study resulted in 4.9 deaths/1000 per annum in the clofibrate-treated group compared to 3.8 deaths/1000 per annum in the placebo-treated group, a 29% increase. In the CPPT, an overall reduction in LDLC of 20.3% was associated with a reduction in total mortality of only 7%. The LDLC reduction of 19.6% with fenofibrate is very close to that seen with the CPPT, and that means an estimated benefit of 7% decreased risk of death is up against an increased risk of 29%, a very unfavorable ratio.

This reasoning is all very similar to what led to our limiting of the indication for clofibrate and to our approving gemfibrozil for the same indication, that is for reducing triglycerides, because of the risk of pancreatitis, in patients with levels over 750 mg/dl. This drug is apparently similar enough to clofibrate and gemfibrozil to warrant similar treatment. However, it has not been studied for its effect in patients with that degree of hypertriglyceridemia. Neither of the other drugs had been studied in this population, but they had been studied in the population susceptible to sudden and unpredictable increases in triglycerides, type IV HLP. This is not true of the type IIb patients who were studied in the fenofibrate trials. Triglyceride lowering in IIa and IIb patients with fenofibrate appears to be comparable to that seen with gemfibrozil and clofibrate. Nevertheless, approval can not be given for treatment of type IV and V with triglycerides more than 750 mg, when the drug has not even been studied in type IV patients.

Recommendation: This drug is not approvable for the proposed indication, because of uncertainties about toxicity that cannot be resolved with the submitted studies, and that result in an unfavorable benefit to risk ratio for the drug. Meeting is planned with the company to discuss this drug.

Gloria Troendle

cc:Orig NDA
HFN-810
HFN-810/AWeiner
HFN-810/ASantora
HFN-810/GTroendle
HFN-340.

NDA 19-304
Fenofibrate

Fournier Labs
Submission dated: 5/1/85
Reviewed by M.O.: 7/22/85

Medical Officer's Review and Evaluation of NDA Amendment

Dr. Boboc has submitted data relevant to the effects of fenofibrate on triglycerides in Type IV and V hyperlipoproteinemic patients, from European studies. There was one original article and a summary of the combined result of all other studies.

The complete submitted study is that of James Shepherd and co-workers from the Royal Infirmary and Hairmyres Hospaital, Glasgow. The support of the study was from the Medical Research Council and the Scottish Home and Health Department. No pharmaceutical company support was acknowledged. The subjects were seven male patients with fasting chylomicronemia and raised circulating VLDL without evidence of another disease causing the hypertriglyceridemia. The patients would probably be classified Type V hyperlipoproteinemia, although one may have been a Type I. None of the patients was diabetic or "excessively obese." The study was unblinded and lipids, lipoproteins and turnover of radioiodinated LDL were measured before and after fenofibrate 200 mg/ twice a day (The usual dose in other NDA studies was 300 mg/day.)

Plasma triglyceride decreased from an average of 16.6 mmol/l (1469 mg/dl) to 3.8 mmol/l (336 mg/dl). Total cholesterol decreased from 9.0 mmol/l (347 mg/dl) to 5.3 mmol/l (205 mg/dl). LDL-C increased from 1.9 mmol/l (73 mg/dl) to 2.7 mmol/l (104 mg/dl) as did HDL-C from 0.9 mmol/l (35 mg/dl) to 1.3 mmol/l (50 mg/dl). HDL_2 mass did not change but HDL_3 mass increased from 162 to 225 mg/dl (note: total mass not cholesterol). The fractional clearance rate of the LDL-choleseterol pool decreased during fenofibrate treatment on average from 0.67 pools/day to 0.43 pools/day. This change in clearance was apparently due to a reduction in the receptor-independent LDL-C clearance pathway while the fractional rate of clearance by the receptor-dependent pathway clearance did not change. All of the patients except the patient who probably had type I hyperlipoproteinemia had pre-drug triglycerides greater that 750 mg/dl (8.47 mmol/l) and all but 1 had a triglyceride less than 300 mg/dl during therapy; that other patient started with a triglyceride of 25.2 mmol/l (2230 mg/dl) which decreased to 11.7 mmol/l (1035 mg/dl).

Comment: Fenofibrate appears to reduce triglycerides in type V hyperlipoproteinemics although there was no diet-only control. Also, the end-point is triglyceride change rather than decrease in pancreatitis frequency.

The sponsor has also presented a summary of open protocols from Europe in which the effect of fenofibrate on triglycerides of type IV hyperlipoproteinemic patients was determined. Patients were on a "Prudent Diet" beginning 2 months before drug therapy and about 2/3 of 302 patients were studied for 6 months. I am uncertain how the data averages were calculated since data from several studes were pooled and patients who completed a full six-months of study may have had a different mean triglyceride level than did the group of patients having baseline pre-drug

JUL 22 1985

triglyceride measurement. Remembering the limitations of the data, the average triglyceride decreased from 583 to 250 mg/dl after 6 months. The reduction was present after only 1 month of treatment. Change in women studied was about the same as that in men. There were 52 patients with initial triglycerides greater than 750 mg/dl, average 1638. In 41 patients completing 6 months of therapy, decrease in triglyceride was to an average of 488 mg/dl. The magnitude of the decrease in triglyceride is greater in patients with higher initial levels; those with initial levels 450-550 mg/dl had a 41% decrease while the average decrease in those with initial triglycerides greater than 750 was 70%.

Comment: Although the effect appears good, the studies were not placebo controlled or blinded.

Recommendation: The sponsor must demonstrate the effect of fenofibrate on serum triglycerides in a controlled, double-blind study of hypertriglyceridemic patients felt to be at risk of pancreatitis due to thier lipid abnormality. Patients studied should have fasting serum triglycerides greater than 500 mg/dl on appropriate diet therapy, or have lesser degrees of hypertriglyceridemia but have actually had pancreatitis, or frequent abdominal pain or eruptive xanthomata due to hypertriglyceridemia. Patients should ideally have type V hyperlipoproteinemia however type IVs with episodic abnormal chylomicronemia would also be acceptable. The question of an appropriate phase IV study remains. I believe it should include a pancreatitis prevention end-point.

7/22/85
Arthur C. Santora II, M.D., Ph.D.

7-23-85

cc:
Orig. IND
HFN-810
HFN-810/AC Santora
Wang #2065D

NDA 18,304
Drug Fenofibrate

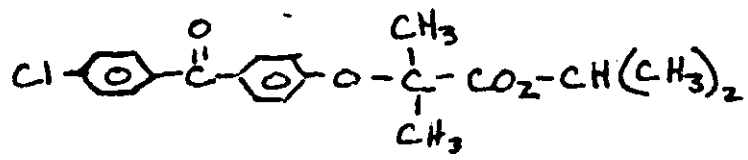
Sponsor: Laboratoires Fournier
M.O.:A.Troendle
Reviewed by M.O.: 11/30/87

Medical Officer's Review and Evaluation of NDA and Supplements
Dated 4/29/87, 8/17/87, 10/14/87, and 11/19/87

MAR - 3 1988

I. GENERAL INFORMATION:

A. Name of Drug: Generic: Fenofibrate
Tradename: Lipidil, Lipanthyl in Europe
isopropyl 2-[4-(4-chlorobenzoyl) phenoxy]-2-methylpropionate
$C_{20}H_{21}ClO_4$



Mol Wt 360.84

B. Pharmacologic Category: lipid altering of the clofibrate class, chemically a phenoxyacid

C. Proposed Indication: There is a discussion of diet, reduction of alcohol intake, and exercise as important measures in the prevention of coronary heart disease due to hyperlipidemia, treatment of secondary causes of hyperlipidemia. A reference to the Warnings section for toxicity of the class is also mentioned. The specific indications are as follows:

" LIPIDIL may be considered for the treatment of adult patients with very high triglyceride levels (Type IV or Type V hyperlipoproteinemia) who present a risk of abdominal pain and pancreatitis and who do not respond adequately to a determined effort to control them. Patients with triglyceride levels in excess of 750 mg per deciliter are likely to present such risk. LIPIDIL (fenofibrate) lowers elevated cholesterol in most subjects. However, the physician should be selective and confine fenofibrate treatment to patients with clearly defined risk due to severe hypercholesterolemia (e.g., individuals with familial hypercholesterolemia starting in childhood) who inadequately respond to appropriate diet and more effective cholesterol-lowering drugs."

" LIPIDIL is not known to be useful for the treatment of patients with Type I hyperlipidemia."

"In December 1984, a National Institutes of Health Consensus Development Conference Panel concluded that lowering definitely elevated blood cholesterol levels (specifically blood levels of low-density lipoprotein cholesterol) will reduce the risk of heart attacks due to coronary heart disease. However, the effect of fenofibrate-induced reduction of serum cholesterol or triglyceride levels or elevation of HDL levels on morbidity or mortality due to coronary heart disease has not been established. "

D. Dosage form and route of administration: 100 mg fenofibrate capsules for t.i.d. oral administration.
Each capsule contains: fenofibrate 100 mg

E. Related drugs: clofibrate, NDA 16-090
gemfibrozil, NDA 18-422

II. MANUFACTURING CONTROLS: See Chemists Review

III. PHARMACOLOGY: See Pharmacology Review.

Most of the pharmacology data was previously submitted and unavailable for this MOR. This is particularly true for the toxicology data. The material presented here is taken in part from the original pharmacology review for submitted 7/31/81 and the MOR review of the original NDA submission of 5/30/84.

A. Pharmacodynamics:
In the rat, fenofibrate reduces the incorporation of oleic acid into blood lipids, inhibits bile synthesis without accumulation of desmosterol, increases the output of bile by the liver, increases hepatic clearance of cholesterol and reduces liver cholesterol, and inhibits HMG-CoA Reductase.

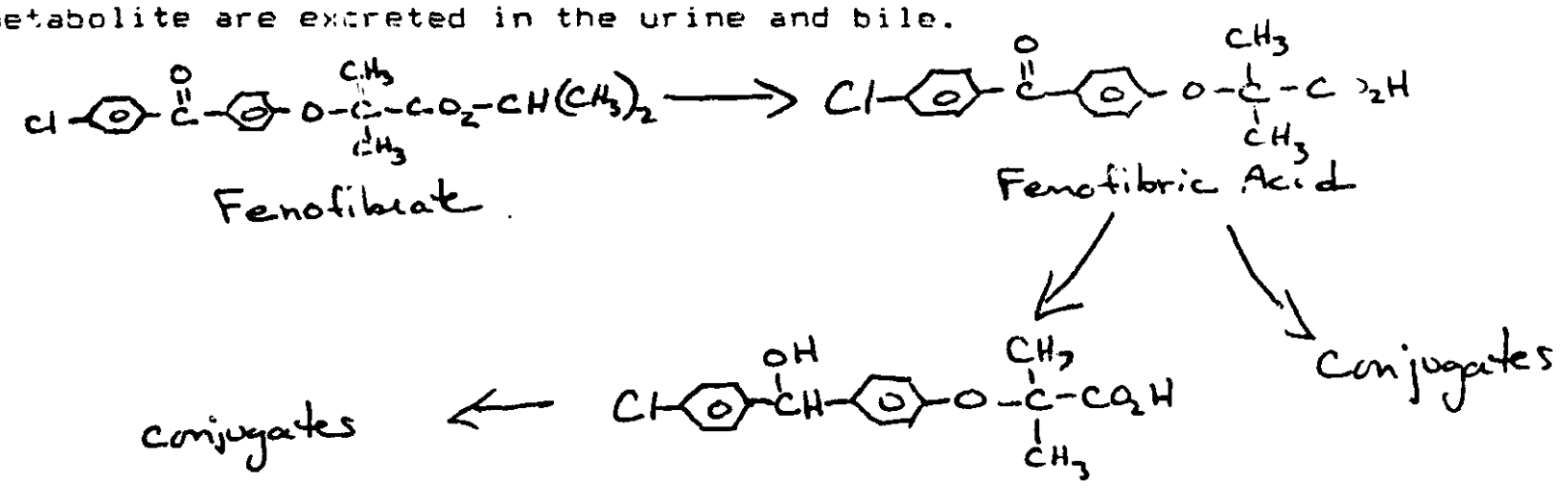
In dogs, fenofibrate had no effect on blood pressure, EKG, heart rate, respiratory parameters, autonomic nervous system, or coagulation factors. Lecithin cholesterol acyltransferase activity was increased.

In humans, fenofibrate reduces serum triglycerides and variably decreases LDL-C without decreasing HDL cholesterol. Bile lithogenicity is increased and uric acid clearance is increased approximately two-fold.

[redacted]

B. Pharmacokinetics:

Fenofibrate is a water-insoluble carboxylic acid ester that is rapidly hydrolyzed after oral administration to Fenofibric acid (the major plasma metabolite in all species). Small amounts of the benzhydrol analog of fenofibric acid is also found in plasma, but unchanged fenofibrate is usually not detected. Various proportions of free and conjugated fenofibric acid and free and conjugated benzhydrol metabolite are excreted in the urine and bile.



RAT-----

Rats were given 25 mg/kg [carbonyl-14C]-fenofibrate dissolved in ethyleneglycol:water (4:1). Radioactivity recovery was approximately 50% in urine and 50% in feces. 75% was secreted in the bile and the plasma half-life was 8 hours. No unchanged fenofibrate was detected in the plasma, but free and conjugated fenofibric acid was detected with CMAX of 5-7 mcg/ml for fenofibric acid. 53% of the urinary radioactivity was due to the benzhydrol analog.

DOG-----

Dogs were given 25 mg/kg [carbonyl-14C]-fenofibrate dissolved in oil; recovery of radioactivity was approximately 70% in feces and 25% in urine. Unchanged fenofibrate was not detected in plasma and the major form was the reduced benzhydrol metabolite with peak levels at 5 hours and half-life of 24 hours.

Human-----

After 14C-labeled fenofibrate given orally with a meal, about 60% of label is excreted in the urine and 25% in feces. Urinary radioactivity was primarily free and conjugated fenofibric acid (approximately 90%) with lesser free and conjugated benzhydrol metabolite. No unchanged fenofibrate was detected in the plasma. Dose proportionality is not seen between 100 and 500 mg and is probably due to decreased absorption at higher doses. The terminal elimination half-life of fenofibric acid is approximately 20 hours and steady state is achieved in 5 days. Fenofibric acid is highly (>99%) bound to plasma proteins, but does not displace warfarin from serum albumin. Fenofibric acid decreases binding of phenylbutazone. In the elderly, the half-life and volume of distribution is greater than in young adults, but clearance is the same. There is no significant difference between males and females.

NDA 19,304
Drug Fenofibrate

Sponsor: Laboratoires Fournier
M.D.:A.Troendle
Reviewed by M.D.: 11/30/87

A study in 12 male volunteers given 100 mg fenofibrate orally with and without a fatty meal at capsule or suspension in water gave the following results for plasma fenofibric acid:

	cap/fast	cap/fed	susp/fast	susp/fed
CMAX(mcg/ml)	1.01±.9	3.67±1.4	.82±.7	3.97±.9
tMAX(h)	6.2	7.3	7.7	7.6
T1/2(h)	25	20	30	23
AUC(mcg.h/ml)	37±24	95±35	36±31	99±35

It is clear that a fatty meal increases bioavailability approximately three-fold and reduces the proportional variability.

Single doses of 14C-fenofibrate 300 mg in capsule form was given to 8 healthy male volunteers. CMAX was 9.9 mcg/ml fenofibrate equivalents at 6 hours based of radioactivity. In the same study, CMAX was 9.5 mcg/ml at 6 hours based on fenofibric acid levels.

In 10 healthy volunteers given 300 mg fenofibrate per day for 10 days steady state was reached in 5 days with fenofibric acid levels of 10 mcg/ml and half-life of 20 hours.

In a study of 6 male volunteers, plasma levels and urinary excretion of fenofibric acid were measured when fenofibrate was given alone and with colestipol. No effect of colestipol on fenofibrate pharmacokinetics were observed.

In a study by Harvengt et al, 9 subjects with moderate to severe renal disease were given 300 mg fenofibrate. There was a progressive increase in fenofibric acid plasma half-life with increasing renal impairment. Patients on dialysis had half lives between 2.5 and 10 days.

C. Toxicology:
MOUSE-----
1) 22 month study at 50 mg/kg/d. Hepatomegally, intra-hepatic cholestasis, and some degenerative changes were seen.

2) 18 month study at 10, 45, and 200 mg/kg/d. At 200 mg/kg, hepatocellular carcinoma was seen in 27.5% of males and 16.7% of females (vs. 4.7 and 2.7% of controls. Liver cell adenoma was also increased to 22.5% of males and 6.9% of females (vs. 5.9% and 1.6%). At 10 mg/kg, carcinoma was seen in 15.8% of males.

NDA 19,304
Drug Fenofibrate

Sponsor: Laboratoires Fournier
M.O.:A.Troendle
Reviewed by M.O.: 11/30/87

RAT-----

1) 2 year study at 10, 45, and 200 mg/kg/d and clofibrate 200 mg/kg/d. The following was found:

a) Depressed weight gain in HD males and females and in clofibrate males.

b) Dose related decrease in Hgb, Hct, MCHC in fenofibrate males.

c) Increased Alk Pase and SGPT in all groups.

d) Dose related increase in liver and kidney weights in fenofibrate groups and in clofibrate group.

e) Liver Adenomas and Carcinomas- 3.8% control males
27.7% MD males
90.6% HD males
39.7% HD females
41.3% clofibrate males
9.4% clofibrate females

f) Pancreatic Carcinomas- none in controls
6.3% clofibrate males
2.0% LD males
7.7% MD males
16.7% HD males
3.2% HD females

g) Testicular Leydig Cell Tumors- none in controls
6.6% HD
3.3% clofibrate

2) 117 week study at 10 and 60 mg/kg/d and clofibrate 400 mg/kg/d and gemfibrozil 250 mg/kg/d. The following was found:

a) Decreased food consumption and weight loss at 60 mg/kg

b) Liver adenomas increased in all groups

c) Liver cell carcinomas- 54% and 20% clofibrate M and F.
4% and 2% gemfibrozil M and F.
none in fenofibrate groups

d) Pancreatic adenomas increased in all groups.

e) Testicular interstitial cell tumors- 16% HD fenofibrate
14% clofibrate
10% gemfibrozil

DOG-----

A 7 month study at 50 and 100 mg/kg and a 24 month study at 25 mg/kg/d showed weight loss, decreased food intake, change in transaminases at 25 mg/kg, elevations of Alk Pase, renal microlithiasis at 50 mg/kg, chronic nephritis and renal lithiasis at 25 mg/kg, and cholelithiasis in both studies.

MONKEY-----

A 52 week Rhesus monkey study at 12, 50, and 200 mg/kg demonstrated no treatment-related toxic effects.

The conclusion and recommendation of the reviewing pharmacologist based on the above toxicology studies and other pre-clinical studies submitted in the IND of 7/31/81, was the following:

" Based on the results of the submitted pre-clinical studies, we conclude that fenofibrate is similar to clofibrate in its lipid

lowering activity (although more potent), its mechanism of action, target organs of toxicity, tumorogenic potential, and effect on reproductive performance in the rat. At equal multiples of human dose, fenofibrate appears to show lesser degree of adverse effects than clofibrate or gemfibrozil in the rat. In the dog, the observed cholelithiasis and kidney stones would seem to be unique for fenofibrate. "

Reviewers Comments:

VI. CLINICAL STUDIES:

A. Background- On May 30, 1984, Laboratories Fournier submitted an NDA for use of Fenofibrate in patients with hypercholesterolemia.

On September 30, 1985, FDA issued a not approvable letter. However, it was agreed that the studies in Type II patients, included in the original submission, could serve as the primary safety data in a submission for triglyceride lowering. It was anticipated that the only new clinical studies required for such a submission would be two relatively small, short term trials for analysis of efficacy and safety issues unique or more frequent in the target population of type IV and V hyperlipidemics. Laboratories Fournier began such trials and requested FDA begin review early, with an interim look at the data. This request was granted and, after submission of the interim report dated 4/29/87, I began review of the submission. Although the new trials were viewed as the pivotal efficacy studies for the triglyceride reduction indication, no lipid values were submitted in the interim report. Because of this, my review centered on safety issues and the data from the original submission of 5/30/84. In that review, I discovered numerous discrepancies between tabulated lipid values and those on the case report forms. For this reason, I requested that case report forms be submitted for all subjects in the new triglyceride trials, along with efficacy data, when the final report was completed.

On 8/17/87 the completed report of the triglyceride lowering trials was submitted, but contained neither efficacy data nor case report forms. I immediately requested both be made available for review.

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Drug Fenofibrate

Sponsor: Laboratoires Fournier
M.O.:A.Troendle
Reviewed by M.O.: 11/30/87

On 10/1/87 the tabulated lipid values for patients in the trials were submitted. No case report forms were included. My review of the data uncovered several spurious LDL-C values (below 10 mg/dl) without explanation. After relaying my concerns to Mr. Vodra on 10/14/87, he said case report forms would be made available immediately (received 10/15/87) and an explanation of all unrealistic lipid values, as well as a description of how lipid measurements were done at each clinical center, would follow (received 11/19/87).

The case report forms have been found to be useless. With the exception of occasional transcription errors, the tabulated data is the same as that in the case reports, including the spurious values. There is no separation of primary from calculated values, and thus no way to determine the cause of the incorrect values.

The explanation (received 11/19/87) of spurious lipid values is incomplete. An attempt was not made to check with each individual lab to determine how lipid subfraction measurements were done, but instead an analysis was made of values in the case report forms to find relationships and infer methods. The following can be concluded from that analysis and selective inquiries at study centers by the company:
1) The case report forms and tables do not contain all lipid measurements performed during the trial.
2) Many investigators performed lipid profiles in addition to sending blood for lipid quantification. The values reported are an assortment of calculated values and measurements done by the investigators and lipid laboratories.
3) Nine of the ten clinical centers measured LDL-C as required by protocol. One of the centers (Dr. Pickering) used the Friedewald's approximation, and calculated some very low LDL-C values (including negative values).

In spite of the explanations and corrections offered by the most recent submission, many questions remain. Values as low as 2 for LDL-C in Dr. Pickering's data and values as low as 26 in untreated patients of other investigator's data remain. A full accounting of all lipid measurements done in conjunction with the new trials, including source and methods, is needed for a complete evaluation of the study. This should include validation data on each lab with information on how measurements at each lab differ from the LRC standard. It is understood that populations with high triglycerides often have low LDL-C, but the values in this population seem unusually low. To compare LDL-C values in this study with epidemiologic data, we must know how the methodology used here compares with the LRC standard.

B. **Pivotal Safety Study:** This was done in a population of type IIa and IIb patients for an anticipated cholesterol indication. The study was a multicenter controlled study of 240 male and postmenopausal female subjects 18 to 65 years of age. The study contained a dietary lead-in and 6 week placebo single blind period followed by 24 weeks of double-blind, controlled treatment and 24 weeks of open extension in which all subjects were treated with fenofibrate 100 mg t.i.d.. The

diagnosis of type II hyperlipoproteinemia was based on an LDL-C of at least 175 mg/dl at one of the pre-study visits. The diagnosis of type IIa or IIb depended on whether the mean TG at the three pre-study visits was less than 250 mg/dl or at least 250 mg/dl. Also, the average T-C of the three visits had to be at least 250 mg/dl.

Results: 116 subjects were randomized to fenofibrate and 111 to placebo. This included the following groups:

1) 92 Type IIa treated with fenofibrate (10 discontinued: 5 adverse reactions, 3 liver transaminase abnormalities, 2 lost to follow-up)

2) 89 Type IIa given placebo (9 discontinued; 1 adverse reaction, 2 liver transaminase abnormality, 3 lost to follow-up, 3 non-compliance)

3) 24 Type IIb treated with fenofibrate (4 discontinued: all for adverse reactions)

4) 22 Type IIb given placebo (none discontinued)

Weight changes were minimal over the study. Overall, 59.5% of all fenofibrate patients and 14.6% of control patients had a decrease of TG of at least 30%. The following table gives the changes in lipid parameters by group:

	IIaFeno	IIaPlacebo	IIbFeno	IIbPlacebo
# patients	92	88	24	22
T-C				
baseline	302	310	301	308
endpoint	252	312	254	323
% change	-16.2	.5	-14.8	4.7
LDL-C				
baseline	220	227	180	199
endpoint	176	228	170	198
% change	-19.6	.7	-2.7	1.2
HDL-C				
baseline	49	49	42	40
endpoint	55	48	48	39
% change	11.7	-.9	13.5	-3.2
TG				
baseline	154	160	349	318
endpoint	98	155	195	389
% change	-33.6	-1.6	-40.9	26

-12 subjects on fenofibrate were discontinued during the double-blind phase:
- -mild increase in CPK, SGOT, SGPT
- -fatigue, anorexia, backpain, malaise, severely elevated LFT's
- -moderately elevated LFT's
- -moderately severe rash
- -moderately severe DM
- -mild PVC's
- -moderately severe indigestion, fatigue, decreased libido
- -severe urticaria
- -pituitary tumor
- -melanoma of eye
- -severe hives
- -moderately severe nausea, heartburn, malaise, RUQ pain

-3 subjects on placebo were discontinued during the double-blind phase:
- -moderately elevated LFT's(day 1)
- -abdominal discomfort, moderately elevated LFT's
- -hepatitis

-A number of trends in laboratory values were observed during the double-blind portion of the study. The following table gives mean values and number of patients with values outside the normal ranges in parentheses:

	Fenofibrate		Placebo	
	baseline	endpoint	baseline	endpoint
Hgb*	15.0(3)	14.4(17)	14.9(5)	14.8(5)
WBC*	6.1(9)	5.8(14)	6.0(15)	5.8(7)
Uric acid	6.1(14)	4.7(1)	(17)	(17)
Alk Pase	65.3(8)	44.1(3)	(12)	(10)
SGOT	20.4(4)	30.7(22)	(4)	(6)
SGPT	21.5(5)	38.1(24)	(12)	(11)
CPK	77.8(9)	110.3(14	70.7(9)	99.5(5)
BUN	16.2(14)	18.5(18)	(11)	(7)
Creatinine	1.0(5)	1.2(12)	(6)	(4)

* endpoint values taken at 18 weeks

-The following adverse reactions, occurring in the double-blind phase, were at least twice as common in the fenofibrate group and had at least 3 reports:

	Fenofibrate	Placebo
Infections	32.8%	25.2%
genitourinary	6	3
viral	5	2
tooth abscess	3	0
Nervous system reactions	20.7%	13.5%
fatigue	12	4
headache	11	4
sleep disorders	3	0
Dermatologic reactions	15.5%	5.4%
skin rash	8	3
pruritis and hives	8	3
Cardiovascular events	10.3%	6.3%
arrhythmia	4	2
Ophthalmic	8.6%	3.6%

(no single reaction was as frequent as 3 reports, but visual alterations, irritation, puffy eyes, lacrimation defect, tired eyes, spots, eye floaters, and light flashes, were all more frequent or only occurred in the fenofibrate group.)

-During the open extension 10 patients were withdrawn from drug for the following reasons: (FF=fenofibrate throughout trial, PF=placebo switched to fenofibrate at 24 weeks)

FF moderately severe flu
FF severe headache
FF severe CVA
FF severe decreased WBC
FF severe nausea, dizziness, rash, moderately elevated LFT's
PF moderate fatigue
PF severe rash
PF MI
PF severe cholecystitis and cholelithiasis
PF moderately elevated LFT's

Reviewers Comments: A paradoxical rise in LDL-C has been described in the literature in patients taking fibric acid derivatives and is more common in patients with high triglycerides. This is assumably due to greater clearance of VLDL particles to LDL and thus is explainable by our current knowledge of lipoprotein metabolism. In an attempt to look at subgroups of patients at risk of this adverse change in lipid parameters while on fenofibrate, lipid values determined during this trial were entered into DBase III plus and subgroup analysis was done.

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Information on how this database (FENO_1.DBF) was generated is contained in Appendix 1 and the results are presented in Table 1.

Table 1 is a complex matrix of data presented as a single table to facilitate comparison of changes in lipid parameters and subgroups of patients. The table gives average lipid values, change in lipid values, and ratios for groups of patients stratified by baseline triglycerides. Baseline triglyceride levels divide the table into columns across the top and subgroups are identified along the left edge dividing the table into rows. All values in parenthesis refer to the number of records (patients) in the database averaged for that particular entry. The quantity averaged in the body of the table depends upon which section of the table it lies within; there are 6 parts as follows:

1) Part 1 contains 5 rows. Each entry is structured as follows:

PCLDL/ACLDL(N)

where PCLDL refers to the percent change in LDL-C from baseline to average endpoint during the double-blind treatment period, ACLDL refers to the absolute change in LDL-C from baseline to average endpoint (ie. endpoint minus baseline), and N refers to the number of records averaged. The five rows contain these values for all fenofibrate treated patients of: Type IIa; Type IIb; any type; any type showing greater than 50% drop in triglycerides from baseline to endpoint; and any type showing greater than a 70% drop in triglycerides from baseline to endpoint respectively.

2) Part 2 contains 3 rows. It has the same information as part one but for placebo patients. The three rows contain PCLDL/ACLDL(N) values for all patients that were placebo treated and: Type IIa; Type IIb; and any type, respectively.

3) Part 3 contains 3 rows with baseline LDL-C values for all fenofibrate treated patients of: Type IIa; Type IIb; and any type, respectively.

4) Part 4 contains 2 rows and gives HDL-C information on all fenofibrate treated patients. Each entry in the first row is structured as follows:

PCHDL/ACHDL(N)

where PCHDL refers to the percent change in HDL-C from baseline to average endpoint during the double-blind treatment period, ACHDL refers to the absolute change in HDL-C from baseline to average endpoint (ie. endpoint minus baseline), and N refers to the number of records averaged. The second row of part 4 contains average baseline HDL-C values for fenofibrate treated patients.

5) Part 5 has 4 rows and looks at the LDL-C:HDL-C ratio in fenofibrate treated patients. The first row reports the ratio at baseline and the next 3 rows give the percent change in the ratio from baseline to endpoint for: all fenofibrate treated patients; fenofibrate treated patients showing greater than a 50% drop in triglycerides from baseline to endpoint; and fenofibrate treated

patients showing greater than a 70% drop in triglycerides from baseline to endpoint.

6) Part 6 gives the percent change in LDL-C/HDL-C ratio for all placebo patients for comparison to part 5.

The results in Table 1 demonstrate that all treated groups with entry triglycerides below 300 mg/dl show substantial decreases in LDL-C, small increases in HDL-C, and a favorable change in the LDL-C/HDL-C ratio. Also, those patients within each group showing the greatest decrease in triglycerides, show the greatest decrease in LDL-C. Thus, patients with the greatest response to fenofibrate (in terms of triglyceride drop), due to greater compliance or sensitivity to the drug, show no tendency to increase LDL-C in all groups up to an entry level of 300 mg/dl for triglycerides. This cannot be said for patients with baseline triglycerides above 300 mg/dl. LDL-C in this group is increased on average and patients with the greatest response to therapy, in terms of triglyceride drop, show the largest increases in LDL-C.

If we accept fully the HDL version of the lipid hypothesis (and in particular accept that the mechanism of rise and subclass profile of HDL rise given by fibric acid drugs is as beneficial as a naturally higher total level of HDL-C would appear to be from epidemiologic data), the adverse effect of increased LDL-C, in patients with baseline triglycerides above 300 mg/dl is, in part, offset by the rise in HDL-C seen in this group. HDL-C is raised to a much greater extent in the population of subjects with entry triglycerides above 300 mg/dl value of an HDL-C. However, the change in LDL-C/HDL-C ratio, favorable for low triglyceride groups, drops off rapidly in the subjects with triglycerides above 300 mg/dl.

C. **Pivotal Efficacy Trial:**

1) Purpose: To compare the safety and efficacy of 100 mg fenofibrate t.i.d. taken with food with that of matching placebo in the treatment of Type IV and V hyperlipoproteinemia and baseline triglyceride levels of 350 to 1500 mg/dl. The study was broken into 2 groups in order to stratify baseline triglyceride values to 350-499 (group A) and 500-1500 (group B). This study was designed as the pivotal efficacy study for the indication of triglyceride lowering in patients with Type IV and V hyperlipoproteinemia and at risk of pancreatitis.

2) Investigators: This is a multicenter trial involving 10 centers:
Elaine Feldman,MD Med College of Georgia, Augusta
Henry Ginsberg,MD Columbia University, New York
Donald Hunninghake,MD Univ of Minnesota, Minneapolis
William Insull,MD Methodist Hospital, Houston,Texas
Robert Knopp,MD Univ of Washington, Seattle
Peter Kwiterovich,MD Johns Hopkins Hospital, Baltimore

Margot Millies,MD Univ of Cincinnati, Cincinnati
Jack Pickering,MD Jefferson Med College, Philadelphia
Paul Samuel,MD Long Island Jewish-Hillside Med Center, Manhasset
Gustav Schonfeld,MD Washington Univ, St. Louis

3) Design: The study was expected to randomize 128 patients with 32 per sub-group. The design was double-blind, placebo-controlled, with a 2 month treatment period. Entry criteria include age 18 to 70, male or post-menopausal female not on estrogens or surgically sterile or IUD users, no acute medical problems, TG 350 to 1500 mg/dl, no history of pancreatitis. Exclusion criteria include use of lipid altering drug in past month, secondary hyperlipidemia, or acute alcohol abuse. The study was broken into 3 periods.
a) Dietary Lead-In: A 6 to 12 week period of dietary counselling with follow-up each 2 weeks to encourage a low fat diet.
b) Placebo Lead-In: A 4 to 6 week period of single-blind t.i.d. placebo treatment with follow-up each 2 weeks. Patients were to have a mean TG level on the last two visits of this period of 350 to 1500 mg/dl in order to qualify for entry into the double-blind treatment period. Also, TG levels during the placebo period were to be reasonably stable with the highest value being no more than 150% of the lowest value. Patients were assigned to group A or B based upon the mean TG value in this period. By protocol, lipid values at visits 1, 3, 5, and 7 (weeks 2 and 4 of the placebo baseline and weeks 4 and 8 of the double blind period) were to include a beta-quantification in which LDL-C would be determined by subtracting HDL-C in the d > 1.006 fraction from the total cholesterol in that fraction. As mentioned in the background section above, this was not uniformly followed.
c) Double-Blind Treatment: Patients randomized to placebo or 100 mg fenofibrate t.i.d. taken with food and seen every two weeks.

4) Results:
a) Demographics- 147 subjects were randomized; 55 in group A (27F, 28P) and 92 in group B (48F, 44P). The treatment and placebo groups had no statistically significant differences in age, weight, sex, or race. There was no statistically significant baseline difference between treatment sub groups in total triglycerides, VLDL-TG, T-C, LDL-C, or HDL-C.

b) Discontinued Prematurely- 13 patients were dropped from the study during the double-blind period, 8 on fenofibrate and 5 on placebo:
- Patient 101 (Center7404) Group A, Fenofibrate- dropped due to allergic hepatitis response.
- Patient 101 (Center7409) Group A, Fenofibrate- dropped due to elevated LFT's.
- Patient 102 (Center7400) Group A, Fenofibrate- dropped due to non-qualifying triglycerides
- Patient 209 (Center7402) Group B, Fenofibrate- dropped due to hyperglycemia.
- Patient 204 (Center7406) Group B, Fenofibrate- dropped due to urticarial skin rash requiring hospitalization.
- Patient 210 (Center7409) Group B, Fenofibrate- dropped due to elevated liver enzymes.

- Patient 208 (Center7400) Group B, Fenofibrate- dropped due to concurrent hormonal therapy.
- Patient 211 (Center7403) Group B, Fenofibrate- patient withdrew consent.
- Patient 104 (Center7406) Group A, Placebo- dropped due to sleep disorder.
- Patient 106 (Center7406) Group A, Placebo- lost to follow-up.
- Patient 203 (Center7401) Group B, Placebo- dropped due to elevated triglycerides.
- Patient 206 (Center7406) Group B, Placebo- dropped due to hyperglycemia.
- Patient 204 (Center7407) Group B, Placebo- dropped due to anxiety.

c) Efficacy- Final weights were available for 139 of the 147 patients entered into the trial. In the treated patients, the mean weight decreased by 1.3lb (182.5 to 181.2) and in placebo patients the mean weight increased by .8lb (185.4 to 186.2). These changes were not statistically significant and individual weights or weight changes are not tabulated for individual patients. There was a statistically significant greater decrease in percent change from baseline in total triglyceride for fenofibrate over placebo subgroups in both group A and group B.

The company submitted lipid values and liver transaminase values in a DBase III file for my analysis. Visit 3 values were taken at the time of randomization and visit 7 values were taken at the end of the 8 week trial. Measurements at visits 1, 3, 5, and 7 included a beta-quantification for LDL-C. In order to evaluate lipid changes in all patients over the double-blind treatment period; baseline was taken as visit 3 if available, or if not, visit 1; end-point was taken as visit 7 if available, or if not, visit 5. In this way, all 147 patients are evaluable and only quant values are used for LDL-C. The following table summarizes these efficacy results:

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	GROUP A		GROUP B	
	FENOFIB (N=27)	PLACEBO (N=28)	FENOFIB (N=48)	PLACEBO (N=44)
TOTAL TG				
baseline	415	456	674	685
endpoint	219	426	296	762
% change mean	-47	-7	-56	11
mean % change	-44	-3	-46	19
LDL-C				
baseline	128	121	105	101
endpoint	137	132	128	90
% change mean	7	9	22	-11
mean % change	16	15	44	-1
HDL-C				
baseline	34	36	31	28
endpoint	40	36	35	28
% change mean	18	0	13	0
mean % change	18	4	21	8

As previously mentioned, both Fenofibrate groups showed a statistically significant greater decrease in triglycerides than placebo. Additionally, the company's analysis indicated a statistically significant greater increase in LDL-C and HDL-C in the group B treated patients over placebo.

d) Safety- The following table shows within treatment group changes from baseline to endpoint for laboratory parameters showing a significant sign test.

TEST	GROUP A mean change	p	GROUP B mean change	p
Alk Pase	-22 mg/dl	.001	-28 mg/dl	.001
Creatinine	.13 mg/dl	.007	.17 mg/dl	.001
Uric Acid	-1.4 mg/dl	.001	-1.3 mg/dl	.001
Hgb	-.59 gm%	.002	-.4 gm%	.014
Hct	-1.84 %	.002		
RBC	-.19 X10^6	.001	-.1 X10^6	.038
Basophils	.43 %	.006		
Platelets	19.4 K/mm^3	.004	31.7 K/mm^3	.001
SGOT			5.2 u/l	.028
SGPT			9.7 u/l	.004

The placebo groups showed only three changes in laboratory values with significant sign test: group A had increases in Hct of .63% (p=.043)

and RBC of .09X10⁶ (p=.015); group B had a decrease in CPK of 10.8 u/l (p=.008).

The company did a further analysis counting the number of patients with normal laboratory value at baseline and excursion to outside the normal range (elevation for enzyme, decrease for hematologic parameter) during the double-blind treatmert period. The combined results for groups A and B are as follows:

Parameter	Fenofibrate	Placebo
SGOT	16	3
SGPT	22	9
CPK	11	4
CREATININE	9	3
Hgb	10	2
Hct	11	1
RBC	16	1
WBC	5	1

The company further analyzed the degree of elevation for LFT's and the degree of decrease for hematologic parameters. The table below gives the number of treated patients with LFT elevations in the given ranges (corresponding values for placebo patients are given in parenthesis):

Parameter	1-2 X ULN	2-3 X ULN	>3 X ULN
SGOT	11(8)	2(0)	3(0)
SGPT	15(8)	3(1)	4(0)
CPK	11(4)	0(0)	0(0)

A similar table for decreases in hematologic parameters in relation to the lower limit of normal follows:

Parameter	90-100% LLN	<90% LLN
Hgb	7(2)	3(0)
Hct	8(1)	3(0)
RBC	15(1)	1(0)

An analysis of the relation of LFT elevation to entry triglycerides and treatment was done by this medical officer. Elevations of liver transaminases were consistently greater in the treated groups, but showed no apparent relation to the entry triglyceride level.

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Reviewers Comments: Subgroup analysis of lipid changes by entry triglyceride was done on the data submitted in DBase III file using the same baseline and end-point values as the above efficacy analysis. The results are presented in Table 2 in the same manner as Table 1, but without the separation into Type IIa and IIb groups and without the final column containing values for patients regardless of entry triglycerides. This final column is contained in Table 3 due to lack of room on Table 2.

From our look at the results of the fenofibrate trial in Type II patients (Table 1), we might expect an increase in LDL-C for patients with all but the lowest triglyceride levels on entry. However, the extent and consistency of the LDL-C elevation is amazing. LDL-C is unchanged in patients with entry TG 200-400, increased 33% in those with entry TG 400-600, increased 55% in those with entry TG 600-800, increased 33% in those with entry TG 800-1000, increased 92% in those with entry TG 1000-1200, and increased 158% in those with entry TG 1200-1700. Within each TG group, the increase in LDL-C is greatest in those subjects with the greatest response to therapy, as measured by drop in TG's. The modest rise in HDL-C is dwarfed by the rise in LDL-C in all groups but the lowest entry TG one, such that the LDL-C/HDL-C ratio is raised by 21-84% on average. The significance of this rise is unknown, but without evidence to the contrary, we must assume that the lipid hypothesis is valid in this population. There is a low overall level of LDL-C in this study group, but such patients may still be at substantial risk of coronary artery disease by virtue of low HDL-C. The increase in LDL-C/HDL-C ratio is adverse and marked.

In an attempt to determine if other Fibric acid derivatives are similar in regards to LDL-C elevation, a multicenter Gemfibrozil trial in Types II and IV hyperlipoproteinemia submitted to the Gemfibrozil NDA (18-442) was looked at. The lipid values in that trial were entered into DBase III and an analysis similar to that of the Fenofibrate data was done. A description of the Gemfibrozil trial and information on how the data was utilized for analysis is relegated to Appendix 2 and the results are presented in Tables 4 and 5. Tables 4 and 5 are identical in arrangement to Tables 1 through 3, but with subgrouping for Types IIa, IIb, and IV hyperlipoproteinemia.

It is readily apparent that Gemfibrozil is very similar to Fenofibrate under this analysis. Again, subjects with entry triglyceride levels below 300 mg/dl have a beneficial change in LDL-C and LDL-C/HDL-C ratio. Above a level of 300 mg/dl for entry triglycerides, there is a progressively more adverse change in both parameters. It should be noted that the entry level of LDL-C is higher in the Type IV patients of the Gemfibrozil trial than that of the same group in the Fenofibrate trial. For instance, baseline LDL-C is above 130 mg/dl in Type IV patients with triglycerides 400-600 in the Gemfibrozil trial and only 115 in the same group of the Fenofibrate trial. The question of which level more accurately represents the target population of therapy and if these values are comparable to the LRC standard is important for evaluating the change in risk a given increase in LDL-C will cause.

While on the subject of Gemfibrozil, it should be mentioned that a report of the Helsinki Heart Trial recently appeared in the New England Journal of Medicine (Vol 317, No.20; 11/12/87). Th[illegible] reports a statistically significant decrease in non-fatal MI [illegible] Gemfibrozil group; a finding similar to that found in the WHO [illegible] Clofibrate. The average baseline TG level in the Helsinki [illegible] 175 mg/dl with a SD of 118 mg/dl. Thus, most patients had [illegible] triglycerides below 300 mg/dl and a favorable change [illegible] the LDL-C/HDL-C parameters while on therapy. Unfortunate[illegible] trial did not have the power to measure changes in tot[illegible] even cardiovascular mortality) and we are left with th[illegible] that Gemfibrozil causes an adverse change in total mor[illegible] of the effect on arteriosclerotic heart disease. Despite thi[illegible] failing, the Helsinki trial offers persuasive evidence [illegible] change caused by these drugs is beneficial and that th[illegible] at present) measure of increased risk for ischemic hear[illegible] Type IV patients using this drug is the LDL-C/HDL-C ratio [illegible]

Discussion of Benefit/Risk Analysis: Fenofibrate is simila[illegible] approved drugs of the Fibric Acid class (Gemfibrozil and Clofi[illegible] in toxicity and lipid changes. All these drugs are carcinogen[illegible] animals, increase lithogenicity of bile, and show significa[illegible] toxicity. Gemfibrozil and Fenofibrate cause large, graded, adverse changes in LDL-C and the LDL-C/HDL-C ratio in patients with TG's above 300 mg/dl. The graded nature of these changes leads me to believe that patients with higher triglyceride levels than studied in this submission will experience even greater increases in LDL-C and LDL-C/HDL-C ratio.

[illegible]

On the benefit side, we have poorly documented improvement in pancreatitis due to hypertriglyceridemia. A controlled study of these drugs in a patient population at substantial risk of pancreatitis has yet to be done. Studies submitted in this NDA report evidence for TG decrease in patients with entry TG's as high as 1500 mg/dl. Despite several months of untreated baseline (except diet) in all patients and two months further placebo treatment in the control group, not a single case of pancreatitis is reported. Surely this population is not at high risk of pancreatitis due to elevated triglycerides. On the other hand, we have seen significant toxicity from treatment, including one case of allergic hepatitis.

The labeling for Gemfibrozil and Clofibrate states that these drugs are indicated for prevention of abdominal pain and pancreatitis due to elevated triglycerides and that patients with a TG level above 750 mg/dl are likely to present such risk. This is clearly misleading. Pancreatitis due to elevated triglycerides must be considered rare in patients with TG's below 2000 mg/dl. Also, many patients with TG's

NDA 19,304
Drug Fenofibrate

Sponsor: Laboratoires Fournier
M.O.:A.Troendle
Reviewed by M.O.: 11/30/87

RECOMMENDED REGULATORY ACTION:

August Troendle

August Troendle, M.D.
Medical Reviewer

cc:
NDA 19,304
HFN-810 RPierce,ATroendle,EBarbehenn

See Group Leaders Review of Literature on fenofibrate and comments on NDA 19,304

L. Ross Pierce 1-11-88

NDA 19,304
Drug Fenofibrate

Sponsor: Laboratoires Fournier
M.O.:A.Troendle
Reviewed by M.O.: 11/30/87

TABLE 1
LIPID CHANGES IN TYPE II FENOFIBRATE TRIAL

	ENTRY TRIGLYCERIDE VALUES					
	(000-100)	[100-200)	[200-300)	[300-400)	[400-900)	[000-900)
T IIa	-22/-51(21)	-24/-55(41)	-14/-30(14)	27/33(4)	-------	-19/-46(80)
T IIb	-------	-14/-30(3)	-11/-28(6)	-14/-34(4)	4/6(4)	-9/-22(17)
T TOT	-22/-51(21)	-23/-54(44)	-13/-30(20)	6/-1(8)	4/6(4)	-17/-41(97)
T >50	-36/-71(1)	-31/-77(9)	-14/-30(4)	14/8(4)	12/18(2)	-15/-41(20)
T >70	-------	-35/-86(1)	-30/-56(1)	-------	12/18(2)	-10/-27(4)
P IIa	-2/-8(14)	-1/-5(52)	-6/-15(14)	2/4(2)	-------	-2/-7(82)
P IIb	-------	-15/-35(4)	4/6(7)	-6/-20(6)	0/4(4)	-3/-10(21)
P TOT	-2/-8(14)	-2/-7(56)	-3/-8(21)	-4/-14(8)	0/4(4)	-2/-8(103)
TLDLa	221(21)	233(41)	216(14)	140(4)	------	222(80)
TLDLb	------	188(3)	192(6)	224(4)	160(4)	191(17)
TLDLt	221(21)	230(44)	209(20)	182(8)	160(4)	217(97)
PAHDL	8/4(4)	9/4(44)	15/6(20)	26/10(8)	16/4(4)	12/5(97)
HDL2	57(21)	50(44)	42(20)	42(8)	36(4)	49(97)
L/H	4.1(21)	4.8(44)	5.1(20)	4.5(8)	4.6(4)	4.7(97)
C(L/H)	-26.8(21)	-27.4(44)	-22.9(20)	-12.4(8)	-7.2(4)	-24.3(97)
C >50	-53.4(1)	-35.4(9)	-25.4(4)	-1.1(4)	-15.9(2)	-25.5(20)
C >70	------	-39.6(1)	-26.9(1)	-------	-15.9(2)	-24.6(4)
C(L/H)	-6.6(14)	0.0(56)	-0.4(21)	3.2(8)	-1.3(4)	-0.8(103)

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Sponsor: Laboratoires Fournier
M.O.:A.Troendle
Reviewed by M.O.: 11/30/87

TABLE 2
LIPID CHANGES IN TYPE IV FENOFIBRATE TRIAL

	ENTRY TRIGLYCERIDE VALUES					
	(200-400)	[400-600)	[600-800)	[800-1000)	[1000-12..)	[1200 1700)
T TOT	2/-1(22)	33/25(28)	55/38(10)	33/24(5)	92/40(6)	158/64(2)
T >50	4/1(7)	43/41(13)	68/46(8)	34/26(4)	92/40(6)	158/64(2)
T >70	-------	60/46(4)	95/62(5)	53/34(1)	115/54(5)	183/66(1)
P TOT	2/-2(18)	9/4(26)	2/-13(15)	20/10(7)	-49/-61(1)	-4/-2(3)
TLDLt	144(22)	115(28)	86(10)	89(5)	97(6)	42(2)
PAHDL	14/5(22)	12/4(28)	44/9(10)	8/2(5)	34/7(6)	49/9(2)
_2	36(22)	32(28)	27(10)	30(5)	30(6)	24(2)
L	4.1(22)	3.9(28)	4.4(10)	3.1(5)	2.6(6)	1.8(2)
C /H)	-4.4(22)	26.6(28)	21.3(10)	22.6(5)	39.1(6)	84.3(2)
C >50	-6.6(7)	9.3(13)	31.9(8)	21.5(4)	39.1(6)	84.3(2)
C >70	------	13.0(4)	52.6(5)	27.6(1)	53.6(5)	82.8(1)
C(L/H)	6.3(18)	8.8(26)	-2.2(15)	11.7(7)	-42.4(1)	-8.4(3)

NDA 19,304
Drug Fenofibrate

Sponsor: Laboratoires Fournier
M.O.:A.Troendle
Reviewed by M.O.: 11/30/87

TABLE 3
LIPID CHANGES IN TYPE IV FENOFIBRATE TRIAL

	ENTRY TRIGLYCERIDE VALUES [200-1700)
T TOT	35/21(73)
T >50	53/34(40)
T >70	95/54(16)
P TOT	5/-2(70)
TLDLt	113(73)
PAHDL	19/5(73)
_2	32(73)
L	3.8(73)
H)	18.9(73)
C >50	20.5(40)
C >70	43.4(16)
C(L/H)	4.6(70)

NDA 19,304
Drug Fenofibrate

Sponsor: Laboratoires Fournier
M.O.:A.Troendle
Reviewed by M.O.: 11/30/87

TABLE 4
LIPID CHANGES IN GEMFIBROZIL MULTICENTER TRIAL OF TYPES II AND IV

	ENTRY TRIGLYCERIDE VALUES (000-200)	[200-300)	[300-400)	[400-500)	[500-600)	[600-700)
T IIa	-10/-26(48)	1/0(6)	-------	-------	-------	-------
T IIb	-11/-27(17)	-4/-13(19)	5/8(9)	-10/-22(1)	-------	-------
T IV	3/-1(23)	-1/3(38)	26/32(17)	37/35(14)	33/31(5)	20/11(5)
T TOT	-6/-19(88)	0/-5(63)	19/24(26)	34/31(15)	33/31(5)	20/11(5)
T >50	-16/-38(25)	-3/-10(33)	21/24(19)	28/20(7)	40/46(3)	40/54(2)
T >70	-------	-11/-22(1)	29/22(3)	44/38(2)	-------	40/64(1)
P IIa	-2/-6(40)	4/10(3)	40/84(2)	-------	-------	-------
P IIb	4/5(24)	0/-4(16)	4/7(9)	1/3(5)	-10/-18(2)	-------
P IV	1/0(16)	-1/-4(27)	3/0(26)	10/5(15)	16/10(6)	0/-26(8)
P TOT	0/-1(80)	0/-3(46)	6/6(37)	8/4(20)	9/3(8)	0/-26(8)
TLDLa	235(48)	241(6)	-------	-------	-------	-------
TLDLb	226(17)	231(19)	229(9)	213(1)	-------	-------
TLDLIV	166(23)	173(38)	146(17)	149(14)	132(5)	180(5)
TLDLt	215(88)	197(63)	175(26)	153(15)	132(5)	180(5)
PAHDL	18/9(88)	19/7(63)	16/6(26)	21/7(15)	22/5(5)	27/7(5)
HDL2	52(88)	41(63)	41(26)	36(15)	37(5)	32(5)
L/H	4.4(88)	5.0(63)	4.4(26)	4.7(15)	3.8(5)	5.8(5)
C(L/H)	-16.5(88)	-12.8(63)	5.3(26)	14.4(15)	21.1(5)	-4.0(5)
C >50	-33.9(25)	-20.4(33)	4.0(19)	5.5(7)	2.4(3)	-7.4(2)
C >70	-------	-31.8(1)	-4.6(3)	2.3(2)	-------	-16.5(1)
C H)	-4.1(80)	2.9(46)	4.6(37)	8.8(20)	-4.0(8)	-4.2(8)

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Drug Fenofibrate

Sponsor: Laboratoires Fournier
M.O.:A.Troendle
Reviewed by M.O.: 11/30/87

TABLE 5
LIPID CHANGES IN GEMFIBROZIL MULTICENTER TRIAL OF TYPES II AND IV

	ENTRY TRIGLYCERIDE VALUES [600-700)
T IIa	-8/-23(54)
T IIb	-5/-14(46)
T IV	14/12(102)
T TOT	4/-3(202)
T >50	3/-5(89)
T >70	29/26(7)
P IIa	1/-1(45)
P IIb	2/2(56)
P	3/-2(98)
P TOT	2/-1(199)
TLDLa	236(54)
TLDLb	229(46)
TLDLIV	162(102)
TLDLt	197(202)
PAHDL	19/8(202)
HDL2	45(202)
L/H	4.6(202)
C(L/H)	-9.0(202)
C >50	-15.9(89)
>70	-8.2(7)
C(/H)	0.3(199)

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Drug Fenofibrate

Sponsor: Laboratoires Fournier
M.O.:A.Troendle
Reviewed by M.O.: 11/30/87

APPENDIX 1
FENO_1.DBF

Numerous discrepancies between tabulated efficacy results and case report forms lead to use of case report form values. Case report forms for 233 patients were found; 119 treated and 114 placebo.

Patients were seen at weeks 3 and 6 of the single blind placebo baseline period and at weeks 6, 12, 18, and 24 of the double blind treatment period. At week 6 of the single blind period and at weeks 12 and 24 of the double blind period, a lipoprotein quantification was done to measure VLDL-C, T-C, LDL-C, HDL-C, and plasma triglycerides. At all other visits, T-C, HDL-C, and triglycerides were determined only. Values included in the database were T-C, LDL-C, HDL-C, and TG and weeks 3 and 6 of the single blind period and weeks 12 and 24 of the double blind period. Thus, all values in the database were directly determined except for the 1st baseline LDL-C value which was calculated using the Friedewald's's approximation.

DBase III plus was used on an IBM-PCAT and IBM-PS/2 model 60. All lipid values were taken from the case report forms in the NDA. After entry, all values were printed out and double checked for accuracy. Absent values were entered into the database as zero and not used in the analysis. Time points containing 2 or more values were averaged. The following field names were used:

INVEST	-	2 characters to identify the center
PATIENT	-	3 characters for patient identification
TYPE	-	1 char "a" for Type IIa and "b" for Type IIb
TREATMENT	-	Logical True = treated, False = placebo
TC1	:	3 digit numeric for each T-C at weeks 3 and 6
TC2	:	of the single blind placebo lead-in and weeks
TC3	:	12 and 24 of the double blind treatment period,
TC4	:	respectively
LDL1	:	3 digit numeric for each LDL-C at weeks 3 and 6
LDL2	:	of the single blind placebo lead-in and weeks
LDL3	:	12 and 24 of the double blind treatment period,
LDL4	:	respectively
HDL1	:	3 digit numeric for each HDL-C at weeks 3 and 6
HDL2	:	of the single blind placebo lead-in and weeks
HDL3	:	12 and 24 of the double blind treatment period,
HDL4	:	respectively

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TG1 TG2 TG3 TG4	4 digit numeric for each TG at weeks 3 and 6 of the single blind placebo lead-in and weeks 12 and 24 of the double blind treatment period, respectively
ABTC ABLDL ABHDL ABTG	Numeric value representing the average baseline for T-C, LDL-C, HDL-C, and triglycerides. The average uses both values at weeks 3 and 6 of the placebo baseline when available.
AETC AELDL AEHDL AETG	Numeric value representing the average end-point for T-C, LDL-C, HDL-C, and triglycerides. The average uses both values at weeks 3 and 6 of the double blind period when available.
PC1TC PC1LDL PC1HDL PC1TG	Percent change from average baseline to average end-point for T-C, LDL-C, HDL-C, and triglycerides.
PC2TC PC2LDL PC2HDL PC2TG	Percent change from value 2 (week 6 of baseline) to average end-point for T-C, LDL-C, HDL-C, and triglycerides.
AC1TC AC1LDL AC1HDL AC1TG	Absolute change (verage end-point minus average baseline) for T-C, LDL-C, HDL-C, and triglycerides
AC2TC AC2LDL AC2HDL AC2TG	Absolute change (average end-point minus value 2) for T-C, LDL-C, HDL-C, and triglycerides

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APPENDIX 2
GEMFIBROZIL MULTICENTER TRIAL DATABASE (LOPID.DBF)

The results of the Gemfibrozil multicenter trial were submitted in the Gemfibrozil NDA 18-422. It included 8 placebo controlled trials with protocol numbers 64, 67, 68, 69, 70, 71, 74, and 75. The study was double-blind and placebo-controlled without use of diet. It utilized a 6 week placebo baseline, 18 week double-blind treatment, and 6-week washout followed by 18 weeks of open label treatment of all patients. The double-blind treatment period was divided into three 6 week periods with treatment at increasing doses of 800, 1200, and 1600 mg/d.

427 patients entered the double-blind phase and were evaluated [299 men and 138 women age 22-76 years (mean=54.5)]. There were 108 (25.3%) Type IIa with mean pre-treatment T-C=323 and TG=135; 107 (25.1%) Type IIb with mean pre-treatment T-C=317 and TG=237; 212 (49.6%) Type IV with mean pre-treatment T-C=268 and TG=318.

Follow-up was every 2 weeks in the following scheme:

	BASELINE			800 mg/d			1200 mg/d			1600 mg/d			WASHOUT		
STUDY WEEK	1	3	5	7	9	11	13	15	17	19	21	23	25	27	29
VISIT #	1	2*	3*	4	5*	6	7*	8	9	10*	11	12	13*	14	15

Lipoprotein quantification measurements were done at the visits marked with asterisk only. Values for TG, LDL-C, and HDL-C from visit numbers 2, 3, 7, 10, and 13 were entered into the database. Note that visit 7 represents the first day of 1200 mg/d treatment and is thus the day following the last treatment with 800 mg/d. Therefore, the database utilized only quantification values for LDL-C and contained two baseline values and a single treatment value at the end of each dosage. Although this is straight-forward in principal, the results were not that simple. Patients often had lipid values at times other than indicated by the above protocol and yet assigned the closest visit number. For example, visit 13 represents one or more weeks into the washout period for many subjects and is the primary reason for the lack of dose response between 1200 and 1600 mg/d found by the company's analysis.

NDA 19,304
Drug Fenofibrate

Sponsor: Laboratoires Fournier
M.O.:A.Troendle
Reviewed by M.O.: 11/30/87

427 patient records were located and reported values were entered into DBase III, then printed out and double checked. The database was assigned the following fields:

STUDY	-	2 characters to identify the center
PATIENT	-	3 characters for patient identification
TREATMENT	-	Logical True = treated, False = placebo
TYPE	-	1 char "A" for Type IIa, "B" for Type IIb, or "C" for type IV
HDL1	:	3 digit numeric for each HDL-C at visits 2 and 3
HDL2	:	of the single blind placebo lead-in and visits
HDL3	:	7, 10, and 13 of the double blind treatment
HDL4	:	period, respectively
HDL5	:	
LDL1	:	3 digit numeric for each LDL-C at visits 2 and 3
LDL2	:	of the single blind placebo lead-in and visits
LDL3	:	7, 10, and 13 of the double blind treatment
LDL4	:	period, respectively
LDL5	:	
TRI1	:	4 digit numeric for each TG at visits 2 and 3
TRI2	:	of the single blind placebo lead-in and visits
TRI3	:	7, 10, and 13 of the double blind treatment
TRI4	:	period, respectively
TRI5	:	
ABHDL	:	Numeric value representing the average baseline
ABLDL	:	for HDL-C, LDL-C, and triglycerides.
ABTRI	:	The average uses both values at visits 2 and 3
	:	of the placebo baseline when available.
AE1HDL	:	Numeric value representing the average end-point
AE1LDL	:	for HDL-C, LDL-C, and triglycerides.
AE1TRI	:	The average uses all three values at visits 7, 10
	:	and 13 when available.(As many as available)
AE2HDL	:	Numeric value representing the average end-point
AE2LDL	:	for HDL-C, LDL-C, and triglycerides.
AE2TRI	:	The average uses values at visits 7 and 10 only to
	:	avoid use of measurements taken during the washout
PC1HDL	:	Percent change from average baseline to
PC1LDL	:	average end-point using AE1 values
PC1TRI	:	
PC2HDL	:	Percent change from average baseline to
PC2LDL	:	average end-point using AE2 values
PC2TRI	:	
PC3HDL	:	Percent change from average baseline to
PC3LDL	:	visit 10 value (for best estimate of changes
PC3TRI	:	at dose of 1200 mg/d)

AC1HDL AC1LDL AC1TRI	Signed absolute change from average baseline to average end-point using AE1 values
AC2HDL AC2LDL AC2TRI	Signed absolute change from average baseline to average end-point using AE2 values
AC3HDL AC3LDL AC3TRI	Signed absolute change from average baseline to visit 10 value (for best estimate of change at dose of 1200 mg/d)

An analysis of the database was done identical to that done for the two fenofibrate studies. This analysis was carried out using the average of values at visits 2 and 3 for baseline and three ways for end-point measures for end-point:

1) Average of visits 7, 10, and 13 as many as available

2) Average of visits 7 and 10 only as available

3) Visit 10 measurement only

The results were virtually identical regardless of endpoint used so the results for only the first analysis are presented in Table 4 and 5. This method of calculation allowed the largest number of subjects to appear in the averages (401 records).

MOR OF NDA AMENDMENT

NOV 15 1989

DRUG: FENOFIBRATE (LIPIDIL)
SPONSOR: LAB. FOURNIER
INDICATION: SEVERE HYPERTRIGLYCERIDEMIA
SUBMITTED: 11-3-89
REVIEW DATE: 11-15-89

This submission contains a draft protocol for a dose-response study for triglycerides in response to our Division's request for such a study to be performed (letter of 7-24-89). We had proposed a 6-month study in patients with fasting triglycerides > 400 mg/dl, randomized to receive either 50, 100, 200, or 300 mg as a single daily dose, or placebo, or 100 mg TID. Most studies with fenofibrate have employed 100 mg TID.

Fournier proposes to perform a 2 month study at the proposed doses in subjects with TG 400-800 mg/dl, and a second 24-week safety and efficacy study comparing the lowest effective dose found in the above study to the 100 mg p.o. TID regimen. Only a draft of the 2 month protocol is included.

PROPOSED STUDY TITLE: Dose ranging of fenofibrate in patients with Type IV or V hyperlipoproteinemia-- an efficacy/safety study

OBJECTIVE: Compare effect of 100 mg fenofibrate taken 3 x daily with meals to that of matching placebo and to 50, 100, 200, and 300 mg fenofibrate capsules with supper on levels of total plasma triglycerides and cholesterol, as well as their respective lipoprotein fractions in pts with Types IV or V HLP during an 8 week tx period. To obtain safety data.

DESIGN:

Randomized, double-blind, parallel, multicenter, with 30 patients per treatment group (180 pts per total of 6 groups).

Inclusion criteria: M or F pts aged 18-70 not on estrogen with TG after >= 12 hr fast 400-800 mg/dl, diagnosed as Type IV or V HLP, on stable concomitant meds. The Tg levels at QV1 and QV2 must be within 150% of the lower value. The lead in may be extended up to one additional month to achieve this level of TG stability.

Exclusion criteria: Use of lipid-lowering tx within the past 4 weeks, or probucol in the past 6 months.

Obesity > 40% IBW

Any condition that could cause secondary HTP incl. hypothyroidism, nephrotic syndrome, hypercortisolism, FBS > 140 mg/dl, glycogen storage disease, uremia, lipid-storage disease, dysproteinemia, idiopathic hypercalcemia.

Hx of severe GI disease (PUD, gastric ulcer) within 3 mos

Liver or GB disease within 6 mos (including evid. gallstones).

Hx EtOH or drug abuse wit' .n 6 mos.

PT > 2x nl or anti-coagulant tx.

MI or unstable angina within 3 mos.

Use of hormonal tx.

Sensitivity to fibrates.

Fertile females.

ANALYTICAL METHODS

The single last lipid determination at randomization will serve as baseline. The 8 week values will serve as end-point, or, if not available, the last on-treatment values. The primary response variable will be the natural log of the endpoint/baseline ratio [only for TG?]. This is done to normalize the data, to enable a 2-way analysis of variance valid only for normally-distributed data to be employed. A secondary analysis of percentage change from baseline will be performed using a non-parametric procedure based on ranks, ignoring possible study-center interaction. Significance will be defined at the alpha 0.05 level (two-sided not stated) for efficacy, and at the 0.1 level for safety parameters.

POWER

Stated to be >90% for detecting a 30 % difference from treatment and placebo groups at the alpha 0.05 level, based on the previous [US] trial of fenofibrate in Type IV/V pts, using 25 pts per group. The power to detect differences between active treatments is not stated.

Dropouts may be replaced if not due to ADR.

LIPID MEASUREMENTS

Every 2 weeks during baseline (min 4) and treatment: Tot chol, TG, HDL-C

At randomization, weeks 4 and 8: lipoprotein quahtitation of VLDL-C, VLDL-TG?), and LDL-C

SAFETY EVALUATION

Every 2 weeks blood will be drawn for ALT, AST, uric acid, creatinine, glucose, alkaline phosphatase, CK, tot bili, LDH, PT, CBC with diff. At the same times, UA with microscopic will be done.

RECOMMENDATIONS:

1. Because it has been suggested that steady-state plasma levels of HDL-C are not reached with fenofibrate until at least 12 weeks of therapy, and because we have no information as to whether lower doses of fenofibrate might require a longer time to reach steady state in terms of their effects on triglycerides and chylomicronemia, the dose-ranging study should be carried out for a minimum of 12 to 14 weeks.

2. It is felt desirable to enroll subjects with TG values from 400 to 1500 mg/dl. Subjects enrolled with TG levels over 1000 mg/dl should not have a history of acute pancreatitis that occured despite satisfactory dietary compliance.

3. Treatment groups should be blocked by sex, and baseline levels of triglycerides (400-600, 600-800, etc).

4. Subjects should not be encouraged to increase the fat content of the diet to comply with the study diet. The 30% calories as fat in the NCEP step one diet proposed is inappropriately high for most patients with Type V hyperlipoproteinemia (HLP). A study diet oflower fat content should be encouraged, but failure to comply with a given level of fat intake should not be cause for exclusion. A constant fat and carbohydrate content of the diet should, of course, be encouraged, after the appropriate diet is instituted.

5. Provide the methodology of dietary assessment and analysis. Quantitative food records, prospectively collected, must be obtained. The treatment groups must be compared for % of Calories as total fat, % of Calories as carbohydrate, and grams of fat per day divided by ideal body weight. Simple and complex carbohydrates should be distinguished. Between-group and across-time within-group comparisons must be performed.

6. Non-parametric methods should be utilized to assess comparibility of baseline triglycerides between groups.

7. Provide the calculations that test whether the natural log of the ratio of endpoint to baseline triglycerides was normally distributed for the data from the completed US study in Type IV/V pts.

8. Fasting chylomicrons should be quantitated by differential flotation at the time of each lipoprotein ultracentrifugation. Consideration may be given to determining chylomicron remnants by oral retinyl palmitate labeling.

9. Consideration may be given to comparing the results of HDL-C determinations by precipitation of non-HDL lipoproteins from the d>1.006 fraction vs by precipitation of the non-HDL lipoproteins from total plasma.

10. It is felt preferable to define the baseline as the mean of lipoprotein values obtained at weeks -2 and 0, or -4, -2, and 0. The endpoint lipid values should be redefined as the mean of 2 or 3 measurements, each taken 1 to 2 weeks apart (ie, weeks 10, and 12, or weeks 10, 12, and 14.

11. Apolipoproteins A1 and B should be determined. Consideration should be given to determining apolipoprotein B in the LDL density fraction at the time of each ultracentrifugation.

12. Lipoprotein (a) levels should be obtained.

13. Consideration may be given to doing HDL subfractionation. The dose-response curve for various HDL subfractions may differ.

14. Only subjects that drop out due to geographic relocation should be replaced.

15. A questionaire should supplement prior spontaneous volunteering of perceived adverse reactions/symptoms on the part of patients. This should include questions relating to sexual functioning.

16. BUN and creatinine clearance should be added to safety parameters.

17. The incidence of AST and ALT elevations above 2 x the ULN and >= 3x the ULN should be reported separately for each group. The incidence of transaminase elevations accompanied by right upper quadrant pain, jaundice, weight loss over 6 lbs, or anorexia should be provided in the study report.

18. Provide the rationale for excluding patients over 40% of ideal body wt. Condider raising this to up to 50% over IBW.

19. Provide the estimated power to detect a 30% difference between active treatment groups in percent triglyceride lowering from baseline (net after subtracting change from baseline in placebo group).

20. Consider increasing the size of each active group to 40 subjects, and increasing the size to the placebo group to 60 subjects.

Ross Pierce

Ross Pierce, MD
Group Leader, HFD 510

cc
NDA 19304
IND
HFD 510
HFD 510 Pierce/Troendle/Sobel/Hassal/Thomas/Aurecchia

MOR OF NDA AMENDMENT

DRUG: FENOFIBRATE (LIPIDIL)
SPONSOR: FOURNIER
INDICATION: SEVERE HYPERTRIGLYCERIDEMIA
NDA: 19304
SUBMITTED: 9-13-89
DATE OF REVIEW: 11-17-89

This submission addresses points 7 to 11 and # 15 of our letter to the sponsor dated 7-24-89. The remaining points are said to be addressed in the subsequent submission of 10-20-89.

Point 7. The upper limits of normal was doubled to define the threshold of "abnormal" in the NDA reporting of transaminase elevations of the French Registry. Upper limits of normal for ALT (SGPT) ranged from >25 to >40 (2 x ULN from >50 to >80) at the 5 centers: ULN for AST (SGOT) varied from >27 to >41 (2x ULN = >54 to >82.

Point 8. Corrected percentages for the incidence of transaminase elevations in the French Series are presented after eliminating from the denominator in the calculation those who never had a transaminase determination while on treatment. The summary "Background Information" presented to the advisory committee indicated an encidence of "enzyme disorders (mainly increases in transaminases)" of 1.8% (p 172). and the incidence could have been calculated as 1.74% for increased AST + AST from the table on p 173 of the Background Info (BI) document. In fact, the corrected figures (TAble 2 of 9-13-89 submission). show a combined incidence of 23.8% for the 5 centers (range 17% to 33.4% for ALT exceeding the ULN) and 3.2% (range 2.9 to 6%) for > 2 times the ULN for AST.

Point 9. The mean interval between testing for serum transaminase levels is presented in Table 3. The two largest retrospective series had mean intervals between testing of transaminases of 7 months. Center 103 (Rouffy) had a mean of over 20 months (1 year and 10 months) between determinations. [Lipid values were determined much more frequently, which I guess says something about the relative importance of efficacy over safety evaluations among these investigators] The maximum interval between transaminase determinations varied from 36 to 106 months!

"One must keep in mind that the "French Registry" is not a formal. prospective study, but a retrospective survey of data from patients for whom we know some information relating to fenofibrate treatment exists. This allows us to obtain information beyond that generated by a post-martketing surveillance system based on spontaneous

reporting, yet without the depth and accuracy of a fjormal, long-term trial."

"In previous submissions refering to the "French Registry", patients lost to follow-up were not removed from the series in calculating the number on which incidence data were determined. As the number of patients remaining in the Registry is in constant evolutino, we have only considered incidences globally, i.e., how many patients experienced an event out of a total number of patients (1149) with documented treatment."

It is unfortunate that the above state of affairs was not disclosed to the advisory committee, either in the writted BI provided to members, or during Fournier presentations.

Information regarding causes of dropouts from the "French Registry" are listed in Appendix 1 of the submission, as well as "survival (still on tx) curves for ea center. Pooling data from all centers (n=1149), it appears that 433 remain in the Register through the present time; those lost to follow-up total 638; 49 are said to have dropped out for reasons not related to tx; 12 died of unknown cause; an additional 17 deaths were classified not related to treatment with fenofibrate. The mode for dropouts is at year 5. The mode for deaths for unknown reason is at year 8 (n=4), and for deaths not attributed to fenofibrate, it is at year 5 (n=5).

The "survival curve" for the number of patients remaining in the registtry shows about 50% remaining after about 7 years.

Discontinuation reasons in the French Registry included 1 for hepatitis, 1 for elevated transaminases, 4 for renal failure (including one acute with pulmonary edema), 5 for nephropathy, 2 for lung cancer, 1 for generalized cancer, 1 for viral hepatitis B (fatal), and 4 for ulcer.

Point 10.
We had inquired why, in one of Fournier's consultant's presentations to the Advisory Committee, a side was shown showing only 3 cases of gallstones between 1984 and 1988. (In fact, I received a call subsequent to the meeting who was similiarly confused by the apparent discrepancy in this data. Fournier responds that, in fact 33 cases of gallstones were reported between 1984 and 1988 (plus another 95 collected haphazardly from 1979-1983, giving a total of 128 gallstone cases). Dr. Brown's slide had apparently been abstracted from a table in the BI document listing only "severe" ADRs from 1984-1988. These three gallstone events were severe because they resulted in hospitalization. Of the 128 cases, 6 are considered definitely not drug-related; these latter cases were omitted from the 6-89 Safety Update.

Point 11. Post-marketing surveillance data are presented for other European countries. Rxs for fenofibrate in France account for 75% of total. It is stated that very few countries have a formal post marketing surveillance system, and that where one exists it may not be "as scrupulously implemented" as in the U.S., U.K., or France. Foreign ADRs from 1984 to 1988 include 2 gallstones, 1 benign tumor, 1 renal failure, 6 myositis, 2 sexual dysfunction, and 11 urticaria/allergic skin rxn, 1 of cholestatic jaundice, 4 or leukopenia, 1 of retinal bleeding, another of glaucoma, 1 of veritgo, 3 of asthenia, 1 of pericarditis, an 2 of non-bacterial orchitis.

In France post marketing, from 1984 to 1988, 12 cases of ranal insuff or failure, 3 of rhabdomyolysis, 4 myositis, 33 of sexual dysfunction, 1 of angioedema, and 63 of urticaria /skin allergic rxn are listed in table 4.

COMMENT AND RECOMMENDATION:

In labeling, any reference to the incidence of ADRs and laboratory abnormalities observed from the "French Registry" should make it explicit that the ADR figures are not corrected for the considerable number of subjects lost to follow-up and that transaminases were determined very infrequently. The true incidence of transaminse elevations may be significantly higher than given in the French registry data.

Because it can be anticipated that fenofibrate will be used in the treatment of Types IIa and IIb HLP, despite labeling only for severe Type V, it should be noted that the ratio of the frequency of transaminase elevations seen with fenofibrate is about an order of magnitude greater than that seen with lovastatin. (It is also an order of magnitude greater that that seen with gemfibrozil for AST in the HHS). In the EXCEL (lovastatin expanded use) trial, among over 7500 subjects treated for 48 months, 33 (0.44%) had greater than 3 fold elevations on repeat (within 1 week). Only 1 patient at lovastatin 20 mg (out of about 1500) had a >3 x ULN elevation of transaminases, giving an incidence of less than 0.1%. While the French Registry data do not provide the number of confirmed (by a second determination) elevations, it should be noted that in the Type IV/V US study, the incidence of SYMPTOMATIC transaminase elevations exceeding 3 fold the upper limit of normal was about 8%. No patient in any controlled trial of lovastatin (including 744 pts followed since 1984) has had SYMPTOMATIC elevations of transaminases recorded. This points out the desirablity to better characterize the hepatotoxic potential of fenofebrate in Type IV/V patients over a much longer time period than studied in the completed US 8 week study. Combining the data from the French Registry and post-marketing data, a total of 21 cases of renal failure/renal insufficiency

appear. This is worrisome, in view of the consistent rises in creatinine and BUN seen in the long term studies of Rouffy and others, seen also in the US controlled studies, and in view of the severe nephropathy seen in the dog.

Ross Pierce, MD

cc
NDA
HFD 510
HFD 510/Pierce/Troendel/Sobel/Thomas/Hassal

DIV

01/29/91

MOR OF NDA AMENDMENT

DRUG: FENOFIBRATE (LIPIDIL)
SPONSOR: FOURNIER
INDICATION: SEVERE HYPERTRIGLYCERIDEMIA
NDA: 19304
SUBMITTED: 10-20-89
DATE OF REVIEW: 11-17-89

This submission addresses points 1 to 6, 12, and 13 of our letter to the sponsor dated 7-24-89. The remaining points were addressed in my review dated 11-17-89 of a separate submission dated 9-9-89.

1. The sponsor was asked to exclude open extension data from the tabular listings and figures of laboratory abnormalities [for U.S. study data]. In the NDA and background information (BI) document for the advisory committee, the sponsor had counted many patients twice, which tended to inflate the denominator and gave a falsely low impression of ADR and abnormal lab incidences. The sponsor's response to this request is not satisfactory, in that it is limited to "clinically significant abnormal values at 2 or more consecutive visits". The definition of "clinically significant" is not provided, and one does not know if standard criteria were used, or if this was determined by each investigator. It happens not infrequently that a potentially clinically significant laboratory abnormality may not necessarily be labeled by an investigator as a laboratory adverse event. In the Type I 6 month study, there were 116 patients evaluated on fenofibrate and 111 on placebo. The number of lab ADRs in each group were:

test	feno	placebo
increases:		
AST	3	0
ALT	5	2
ALK PHOS	1	0
UREA	2	1
CREATININE	3	2

In the open extension of this study, in which all patients continuing (98 who had been on feno for 6 months already, and 94 previously on placebo) received fenofibrate 100 mg TID, the incidence of AST and ALT ADRs was 1.5 and 2%, respectively, 3% in those with longer exposure (feno-feno group). The incidence of creatinine ADRs increased to 6.1% in the feno-feno group and to 4.3% in the placebo-feno group, somewhat suggestive of a increased incidence with greater cumulative exposure, even over a constant observation interval (6 months). In those exposed to feno for 1 yr, the cumulative incidence of ALT ADRs was 6.1%, of

CPK ADRs was 3.1%, of creatinine ADRs was 7.1%, of WBC ADRs was 11.2%.

In the U.S. Type IV 2-month study, there were 75 pts evaluated on feno and 72 on placebo. Here, clinically significant abnormal values at any visit are totaled and expressed as %:

test	FENO	PLACEBO
increases:		
AST	6.7	0
ALT	10.7	1.4
CREAT	1.3	0
decreases:		
Hb	4.0	0
Hct	4.0	0
RBC	1.3	0

A table 5 appears on p 7 summarizing combined data for the U.S. studies, in which the incidence of AST ADRs is 6.8% for fenofibrate, 1.6% for placebo.

2. The sponsor has recalculated the entries into tables of clinical ADRs for the U.S. studies. Previously, open extension patients were counted twice. The tables, 6-10, are appended to this review. Whereas in the Type II study the incidence of digestive ADRs was similiar for feno and placebo, in the Type IV study it was higher (18.7 vs. 12.5%). Skin, appendages, and mucosa (including many cases of rash and uritcaria, some requiring systemic corticosteroid therapy) ADRs were 12.1% in the feno group and less than 1% in the placebo group in the Type II study. Whereas nervous system ADRS were equal during the double-blind phase, they doubled to 11% during the 6 month open extension of the Type II study. In the Type V study, urogenital ADRs were seen in 4% of feno pts vs. zero for placebo. ADRs are only tablulated if the investigators considered them probably or possibly drug-related.

3. The response to request #3 combined ADR data from the first 2 months of the 6-month Type II study with the 2 month data from the Type IV/V study to correct for the differences in length of drug exposure in the 2 studies. Two sets of tables are presented, the first includes ADRs regardless of the investigator's assessment of drug-relatedness, the second is limited to those felt either possibly or probably drug related (vs. remote) in the Type II study, and unknown or related to drug (vs. not-related) in the Type IV/V study. Exemplary of the possible lack of usefullness of the investigator's assessment of drug-relatedness is asthenia, a rather vague and not uncommon clinical complaint, reported 6 times for fenofibrate out of 191 patients, but felt to be of unknown, possible, probable, or definite relation to drug in

2 subjects. Thus the investigators were absolutely sure that 4 patients' asthenia bore no or only a remote relation to drug therapy. This level of certainty of the event not being drug-related seems to me unlikely.

Selected ADRs are presented from the first table:

ADR	% feno	% placebo
angina	1.6	0
anorexia	1.0	0
constip	1.0	1.1
diarrhea	3.7	3.8
dyspepsia	4.7	3.3
hepatomeg	0.5	0
nausea	3.1	2.2
vomiting	1.6	0.5
anemia	0.5	0
eosinoph	1.6	0
dec plat	0.5	0
CPK incr	0	0.5
hyperglyc	0.5	0
hyperkal	0.5	0
AST incr	9.4	0.5
ALT incr	12.0	1.6
musc/skel	4.7	3.8
nervous s	4.2	2.1
resp	15.7	12.0
skin	9.4	1.1

4. Attachment 1, Tables 4-A and 4-B, and present all AST, ALT, alk phos, and bilirubin data for each patient for each visit, so that the time course of LFT abnormalities can be appreciated. Table 4-A list the actual values whereas table 4-B lists them as multiple of the particular labs ULN, to one decimal place. Table 4-C lists all symptoms or PE abnormalities recorded and the treatment day when recorded for all subjects having AST or ALT >= 2x the ULN to aid in the determination of the incidence of symptomatic hepatitis.

5. This item in attachment 1 lists patients who has a >= 50% rise in mean on-treatment creatinine compared to the mean of screening and randomization creatinine values.

6. This item in attachment 1 lists patients having decreases of >= 10% in either Hb, Hct, or RBC.

Case report forms are included in the submission as attachment 2 for those patients listed in items 4, 5, and 6.

12. The sponsor states that Dr. Pickering's center (7407) had provoked "original suspicions about the use of Friedewald's approximation". It is stated that at that center, VLDL-cholesterol was assayed directly from the

D<1.006 ultracentrifugation fraction. The sponsor calculated estimated VLDL-cholesterol by TG/5 and scored the number of times this gave a value +/- 1 mg/dl from that reported on the CRFs for VLDL-cholesterol. The proportion of determinations reaching this level of agreement was very small at each center and overall was 14/627 in group B and 16/376 in group A (lower baseline TG) stratum. The sponsor therefore concludes that VLDL-cholesterol values reported must be ultracentrifugally determined.

13. LDL-C values for the Type IV/V study were determined by ultracentrifugation only at visits V3 (randomization) and V7 (week 8). The mean % change from baseline, including Dr. Pickerings center was a rise of +50.5% for the fenofibrate group B (high baseline TG) subjects and -1.1% for the placebo group B stratum. This is the figure for LDL-C change that must appear in the labeling, as it is best reflective of the anticipated LDL-C change in the population targeted by the labeled indication (those with very high TG at risk of pancreatitis). The VLDL-C change should similiarly come from the ultracentrifugal data: -48.9% for group B feno and +17.2% for placebo group B. The TG efficacy values should come from the means of the 2 pre-randomization visits as baseline and the mean of weeks +4 and +8 on treatment, however, as called for in the protocol.

COMMENT AND RECOMMENDATION:

In labeling, advertising, and/or the SBA, any reference to the incidence of ADRs and laboratory abnormalities observed from the "French Registry" should make it explicit that the ADR figures are not corrected for the considerable number of subjects lost to follow-up and that transaminases were determined very infrequently. The true incidence of transaminse elevations may be significantly higher than given in the French registry data.

Because it can be anticipated that fenofibrate will be used in the treatment of Types IIa and IIb HLP, despite labeling only for severe Type V, it should be noted that the ratio of the frequency of transaminase elevations seen with fenofibrate is about an order of magnitude greater than that seen with lovastatin (It is also an order of magnitude greater that that seen with gemfibrozil for AST in the HHS). In the EXCEL (lovastatin expanded use) trial, among over 7500 subjects treated for 48 months, 33 (0.44%) had greater than 3 fold elevations on repeat (within 1 week). Only 1 patient at lovastatin 20 mg (out of about 1500) had a >3 x ULN elevation of transaminases, giving an incidence of less than 0.1%. While the French Registry data do not provide the number of confirmed (by a second determination) elevations, it should be noted that in the Type IV/V US study, the incidence of SYMPTOMATIC transaminase elevations exceeding 3 fold the upper limit of normal was about 8%. No

patient in any controlled trial of lovastatin (including 744 pts followed since 1984) has had SYMPTOMATIC elevations of transaminases recorded. This points out the desirablity to better characterize the hepatotoxic potential of fenofibrate in Type IV/V patients over a much longer time period than studied in the completed US 8 week study.

Combining the data from the French Registry and post-marketing data, a total of 21 cases of renal failure/renal insufficiency appear. This is worrisome, in view of the consistent rises in creatinine and BUN seen in the long term studies of Rouffy and others, seen also in the US controlled studies, and in view of the severe nephropathy seen in the dog.

RECOMMENDATIONS:

The sponsor's response to request #7 of our letter of 7-24-89 is not satisfactory, in that it is limited to "clinically significant abnormal values at 2 or more consecutive visits". The definition of "clinically significant" is not provided, and one does not know if standard criteria were used, or if this was determined by each investigator. Recalculate the entries for these tables utilizing all subjects experiencing a laboratory abnormality defined as being outside the normal range for the particular laboratory employed and occuring on one or more occasions during the double-blind portions of the study only. In addition, calculate the cumulative hazard rates for experiencing an elevation of 1) > or = 2x the ULN and 2) > or = 3 x the ULN for either ALT or AST (or both) on one or more occasions during the double-blind portions of each domestic trial (combining the low and high baseline TG strata of the Type IV/V Trial), as well as the cumulative hazard rate for those subjects in the Type II trial who were randomized to fenofibrate treatment during the initial 6 months DB portion and who remained on fenofibrate treatment during the open extension period.

2. Provide a duplicate of Attachment 1 of your 10-20-89 submission, which was missing from the review copy.

3. Prepare revised tables of the incidence of adverse drug reactions during the double-blind portions of both domestic trials, excluding the open extension data from the Type II trial, and including all adverse experiences regardless of the investigators' or the sponsor's opinion of whether the reactions may have been drug related. ADR incidences for groups A and B patients of the Type IV/V study should be presented separately as well as being combined into 1 table.

Ross Pierce

Ross Pierce, MD

6

Approved 1-29-91

cc
NDA
HFD 510
HFD 510/Pierce/Troendel/Aurecchia/Thomas/Cheever

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUGS AND BIOLOGICS

DATE: SEP 30 1987

TO: Elizabeth K. Barbehenn, Ph.D., HFN-810
Division of Metabolism and Endocrine Drug Products

FROM: Group Leader, Statistical Application & Research Branch, HFN-715

SUBJECT: Data Request, NDA 19-304, Fenofibrate Rat Carcinogenicity study

For evaluating the dose-response relationships more information is needed for the following tumor types:

I. For males

a. Adrenals Cortical Ademoma
b. Thyroids C-cell Adenoma
c. Testes interstitial Cell Tumor
d. Nervous Tissue Astrocytoma

II. For females

a. Thyroids C-cell Adenoma
b. Pancreas Acinar Adenoma
c. Uterus Endometrial Polyp
d. Mammary Gland Adenocarcinoma
e. Liver Neoplastic Nodule

We have also prepared a blank form for the sponsor. Please request the sponsor to complete this form for the controls and dose groups, 2, 3, 4 and 5.

The ten-week intervals should be used for completing these forms. The interim (if any) and terminal sacrifices should be reported separately. In the column "start", the number of animals alive in the beginning of that interval should be entered.

For any further information, the sponsor can contact Mr. Mordecai Friedberg who is working on this project at (301) 443-4710.

Suresh C. Rastogi 9/30/87
Suresh C. Rastogi, Ph.D.

Data Table

Drug Name: Fenofibrate
Animals: Rat
Animal Sex: ☒ Male ☐ Female

Time Intervals (weeks)	Group ( )						
	Deaths			Tumor Types			
	Start	D	S	N	TT1	TT2	TT3	TT4
0-10								
11-20								
.								
.								
.								
Interim Sacrifices (if available)								
.								
.								
.								
Last Time Interval of the Study								
Terminal Sacrifices								

Notes:
D = Number of Animals died
S = Number of Animals Sacrificed Moribund
N = Number of necropsies
TT1= No. of animals with Adrenals Cortical Adenoma
TT2= No. of animals with Thyroids C-cell Adenoma
TT3= No. of animals with Testes Interstitial Cell Tumor
TT4= No. of animals with Nervous Tissue Astrocytoma

Data Table

Drug Name: Fenofibrate
Animals: Rat
Animal Sex: ☐ Male ☒ Female

Time Intervals (weeks)	Group ( )							
	Deaths			Tumor Types				
	Start	D	S	N	TT1	TT2	TT3	TT4	TT5
0-10									
11-20									
.									
.									
.									
Interim Sacrifices (if available)									
.									
.									
.									
Last Time Interval of the Study									
Terminal Sacrifices									

Notes:
D = Number of Animals died
S = Number of Animals Sacrificed Moribund
N = Number of necropsies
TT1 = No. of animals with Thyroids C-cell Adenoma
TT2 = No. of animals with Pancreas Acinar Adenoma
TT3 = No. of animals with Uterus Endometrial Polyp
TT4 = No. of animals with Mammary Gland Adenocarcinoma
TT5 = No. of animals with Liver Neoplastic Nodule

STAT REVIEW

ORIGINAL

Statistical Review and Evaluation
(An Addendum)

JUN 23 1989

NDA #: 19-304 Date:

Applicant: Fournier Laboratories, Inc.

Name of Drug: Fenofibrate (Lipidil)

Documents Reviewed:

Information and data sent to Division of Biometrics by Dr. Elizabeth K. Barbehenn.

I. Background

A carcinogenicity study in rats included in this NDA submission has been reviewed by the Division of Biometrics. Recently the sponsor submitted additional requested data. Dr. Elizabeth K. Barbehenn, HFD-510 who is the reviewing pharmacologist of this NDA had requested the Division of Biometrics to test if the positive dose-response relationship is significant in pancreatic acinar adenoma in both sexes, and nervous tissue astrocytoma and pancreatic acinar adenocarcinoma in male rats. The results of this review have been discussed with Dr. Barbehenn.

In this review, the phrase "positive dose-response relationship" refers to the increasing linear component of the effect of treatment, and not necessarily to a strictly increasing tumor or mortality rate as dose increases.

II. c. Reviewer's Analyses and Comments

The prevalence method for incidental tumors and the death rate method for fatal tumors described in Peto et al. ("Guidelines for Simple, Sensitive Significance Tests for Carcinogenic Effects in Long-Term Animal Experiments", In Long-Term and Short-Term Screening Assays for Carcinogens: A Critical Appraisal, International Agency for Research on Cancer Monographs, Annex to Supplement 2, World Health Organization, 311-426, 1980) were used to test the positive dose-response relationship in the tumor data. Since the p-values from the Peto method are not stable and reliable for tumor types with small number of occurrences across treatment groups, therefore, the exact permutation trend test was applied to tumor types with total number of five or less occurrences across treatment groups. The time intervals 0-52, 53, 54-80, 81-117 weeks and terminal sacrifice were used in these methods. The sponsor has indicated that Fenofibrate was administered in the diet to rats for 117 weeks. However, the sponsor used the time intervals 1-100, 101-110, 111-120, and terminal sacrifice to summarize the tumor data. With the concurrence of

Dr. Barbehenn, the reviewer did not compare any treatment related responses produced by Fenofibrate with those produced by two other hypolipidaemic compounds, Clofibrate and G250.

As indicated in Peto et al. (1980, p. 375), "Misclassifying incidental tumors as fatal tumors tends to make the treatment of groups with poor intercurrent survival appear more carcinogenic than it really was, while, conversely, misclassifying fatal tumors as incidental tends to make the treatment of groups with poor intercurrent survival seem less carcinogenic than it really was. (In this context, 'poor intercurrent survival' means high death rates from causes other than the tumor type of interest during the period during which such tumors were arising.)"

Since the uncertainty about which contexts of observation (definitely incidental, probably incidental, probably fatal, or definitely fatal) should be estimated for the nerous tissue astrocytoma, the reviewer has applied both the prevalence method and the death rate method to this tumor. The actual dose levels 0, 10 and 60 were the scores assigned to the control, low, and medium dose groups, respectively.

The results of the analyses show that there is a significant positive dose-response relationship in pancreatic acinar adenoma in both sexes (male: $p = 0.00095$; female: $p = 0.0422$). No significant positive dose-response relationship was found in nervous tissue astrocytoma either observed in a fatal context ($p = 0.074$) or observed in an incidental context ($p = 0.088$) in male rats. In addition, there is no statistically significant positive dose-response relationship in pancreatic acinar adenocarcinoma in male rats ($p = 0.266$). The incidence rates of the tumor types with significant positive dose-response relationships are given in Tables 1 to 2.

III. Summary

In this review, the phrase "positive dose-response relationship" refers to the increasing linear component of the effect of treatment, and not necessarily to a strictly increasing tumor or mortality rate as dose increases.

Our analyses show that there is no statistically significant positive dose-response relationship in pancreatic acinar adenocarcinoma in male rats, nor is there a significant positive dose-response relationship in nervous tissue astrocytoma in male rats. However, there is a significant positive dose-response relationship in pancreatic acinar adenoma in both sexes (male: $p = 0.00095$; female: $p = 0.0422$).

Daphne Lin 6/20/89

Daphne Lin, Ph.D.
Mathematical Statistician

Concur: Karl K. Lin 6/20/89
Karl K. Lin, Ph.D., Group Leader, SARB

WR7 6/22/89
William R. Fairweather, Ph.D., Chief, SARB

cc: Original NDA 19-304
HFD-510/Dr. Solomon
HFD-510/Dr. Barbehenn
HFD-710/Chron
HFD-715/Dr. Fairweather
HFD-715/Dr. Karl Lin
HFD-715/Dr. Daphne Lin
HFD-102/Dr. Chah
HFD-715/DRU 2.1.1, Fenofibrate, Fournier Laboratories, Inc.

Table 1
Tumor Incidence Rates
Male Rats, Pancreatic Acinar Adenoma

Weeks	Control		Low		Medium	
	T	N	T	N	T	N
0-52	0	2	0	3	0	5
53-53	0	10	0	9	0	9
54-80	0	4	0	4	0	4
81-117	0	22	0	22	3	16
Terminal	0	22	1	22	4	26
Total	0	60	1	60	7	60

Table 2
Tumor Incidence Rates
Female Rats, Pancreatic Acinar Adenoma

Weeks	Control		Low		Medium	
	T	N	T	N	T	N
0-52	0	1	0	5	0	1
53-53	0	10	0	10	0	10
54-80	0	9	0	7	0	6
81-117	0	25	0	22	2	24
Terminal	0	15	0	16	1	19
Total	0	60	0	60	3	60

Notes: T: Number of necropsies with the above tumor.
N: number of necropsies.

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MEMORANDUM OF CONSULTATION

DATE: May 17, 1990

BETWEEN: Leland R. Pierce, M.D. (HFD-510)

AND: Daniel N. Marticello (HFD-713)

SUBJECT: NDA 19-304, Fenofibrate submission dated March 5, 1990

In a statistical review and evaluation dated May 3, 1990, I concluded that the data included in the sponsor's January 16, 1990 submission was insufficient to define a dose-response effect. The sponsor's current submission dated March 5, 1990 does not include data which would allow me to alter this conclusion.

Given that the sponsor's "valid" studies are capable of providing statistically meaningful dose response information, (which they are not as stated in the May 3 statistical review), the methodology employed by the sponsor in their current submission has a logical basis.

However, it is not apparent that the sample sizes (2 x 100mg: 23 II b, 23 IV, 3 x 100mg: 31 II b, 7 IV) were sufficient to detect clinically meaningful differences between the Type II b and Type IV patients. In fact, the sponsor's methodology would probably be unnecessary if such sample sizes were available.

In addition, the fact remains that only 12 Type IV patients (2 x 100mg: 10, 3 x 100mg: 2) were included in the sponsor's 2 x 100mg versus 3 x 100mg analysis.

Consequently, the sponsor's current submission does not allow me to rescind my May 3, 1990 recommendation that the sponsor should conduct a double-blind randomized dose-response study in order to define a fenofibrate dose-response effect.

David N. Marticello

Daniel N. Marticello
Mathematical Statistician

JAN 15 1991
JAN 15 1991

Statistical Review and Evaluation

NDA #: 19-304/Drug Class: 1C

Applicant: Fournier Research Inc.

Name of Drug: Lipidil (fenofibrate)

Document Reviewed: Draft Study Protocol included in August 27, 1990 submission

Medical Reviewer: This review has been discussed with the Medical Officer, Leland R. Pierce, M.D. HFD-510).

Relevant Issues Discussed in This Review

1. The sponsor's randomization blocking factor was not specified.

2. Statistical tests should be conducted to justify the use of the sponsor's proposed logarithmic transformation. Results should be presented in terms of the original variable rather than the transformed variable for ease of interpretation.

3. The sponsor's 30% efficacy and equivalence criteria should be assessed for its clinical relevance by the reviewing clinicians.

4. The sponsor's proposed sample size of 180 patients does not appear to be adequate in regard to arriving at meaningful equivalence conclusions.

5. Intent-to-treat endpoint analyses should be conducted with regard to the primary efficacy variable.

6 Results should be provided by center so that they may be examined for consistency.

7. Consideration should be given to stratifying the randomization based on baseline TG levels and on conducting an analysis of covariance with the baseline TG as the covariate.

Key Words: analysis of covariance, blocked randomization, carry-forward, diet, endpoint, equivalence criteria, hyperlipoproteinemia, hypertriglyceridemia, intent-to-treat, logarithmic transformation, sample size, stratification, triglyceride

8. The Wilcoxon Rank Sum Test rather than sign test should be utilized to compare treatment groups with regard to clinical laboratory values.

The sponsor has submitted a protocol which describes a randomized, double-blind, placebo-controlled, multi-center dose-ranging study which will compare the efficacy and safety of five dosage forms of fenofibrate to placebo in patients with Type IV or V hyperlipoproteinemia.

The study will consist of a screening and diet initiation visit followed by an 8-week stabilization/baseline placebo phase and an 8-week double-blind treatment phase.

Patients who satisfy protocol criteria which includes a baseline triglyceride level (TG) between 300 and 750mg/dl will be randomized to receive either a once daily dose of fenofibrate 50mg, 100mg, 200mg, 300mg, or fenofibrate 100mg tid or placebo for 8-weeks. Matching placebo capsules will be administered up to three times daily to maintain the blind. In addition, all patients will be maintained on a "Step One Diet" throughout the study.

The primary objective of the study will be to compare the effect of fenofibrate taken at the above mentioned doses to that of placebo on total plasma triglyceride levels.

Reviewer's Comments (may be conveyed to the sponsor)

Page 12 of the protocol states that the randomization schedule will be generated using a blocked random number generator program. However, the blocking factor was not specified by the sponsor.

The main efficacy criterion will be the relationship between the baseline and endpoint total plama triglyceride levels. The repsonse variable will be the natural logarithm of the endpoint to baseline ratio as the sponsor claims that the logarithmic transformation will normalize the triglyceride data. In support of this argument, the sponsor should conduct appropriate statistical tests on their resulting data set to justify the utilization of their proposed transformation. Also, results should be presented in terms of the original variable rather than the transformed variable for ease of interpretation.

The protocol states that an efficacious anti-hypertriglyceridemia drug is defined as one which allows a decrease of at least 30% from baseline triglyceride levels and that a specific fenofibrate dose will be considered efficacious if its endpoint/baseline ratio does not exceed .7 and if it can be statistically differentiated from placebo.

The above mentioned 30% criterion appears to be arbitrary and should be investigated for its clinical relevance by the reviewing clinicians.

The same may be said with regard to the sponsor's statement that a specific fenofibrate dose will be declared equivalent in effectiveness to fenofibrate 100mg tid if the difference in response is less than 30%. Furthermore, any sponsor equivalence claims need to be supported by sound statistical results.

The protocol states that a total population of at least 405 patients would be necessary to "assess equivalent effectiveness" of a specific fenofibrate dose to fenofibrate 100mg tid. However, the sponsor failed to relate this estimate to a specific equivalence criterion. As only 180 patients are to be randomized to double-blind treatment, the adequacy of this study to arrive at meaningful equivalence conclusions is in question.

The protocol did not indicate whether or not protocol violators and/or dropouts would be included in the efficacy analysis. In addition to analyses conducted on a sponsor defined efficacy population, an intent-to-treat endpoint analysis in which patients last TG measurements are carried forward as well as an intent-to-treat analysis on the subset of patients who complete the double-blind treatment phase should be conducted in order to assist us in an assessment of whether or not the efficacy population results are affected by any such patient exclusions. Results should also be provided by center so that they may be examined for consistency across centers.

Consideration should be given to the medical officer's recommendations that the randomization should be stratified by baseline TG levels and that an analysis of covariance with baseline TG level as a covariate be conducted.

The following remarks are made in response to specific questions raised in the medical officer's November 19, 1990 review:

1. The use of the Van Elteren Test is appropriate.

2. The Wilcoxon Rank Sum Test should be utilized to compare treatment groups with regard to clinical laboratory values rather than the sign test as proposed by the sponsor.

3. The utilization of the Stuart-Maxwell or McNemar Test is appropriate for within treatment clinical laboratory comparisons.

David N. Marticello
Daniel N. Marticello
Mathematical Statistician

Statistical Review and Evaluation

MAY 3 [illegible]

NDA #: 19-304

Applicant: Fournier Laboratories

Name of Drug: Fenofibrate

Indication: Triglyceride-lowering

Document Reviewed: "Review of the Relative Efficacy and Use of Various Dosing Regimens of Fenofibrate dated January 16, 1990.

Medical Reviewer: This review has been discussed with the clinical reviewer, Leland R. Pierce, M.D. (HFD-510).

Relevant Issues Discussed in this Review:

1. The results exhibited in the sponsor's submission are insufficient to define a fenofibrate dose-response effect. In order to define such an effect, a parallel double-blind randomized dose-response study should be conducted by the sponsor. The doses selected for this proposed study should be agreed upon by the sponsor and the FDA in order that a minimum effective fenofibrate dose may be recommended.

2. There is no sound statistical basis for pooling the sponsor's five "valid" studies each of which is not capable of providing statistically meaningful information regarding a fenofibrate dose response effect. Consequently, the pooled p-values supplied by the sponsor should not be given any credence.

Background

Due to the fact that a comparative analysis of hepatotoxicity, hematologic toxicity, and possible renal toxicity strongly suggests that fenofibrate is significantly more toxic than gemfibrozil (an approved triglyceride-lowering fibrate) the clinicians felt that the sponsor should submit satisfactory data to be able to recommend the lowest effective fenofibrate dose.

The sponsor's January 16, 1990 submission is in response to the Division of Metabolism and Endocrine Drug Products request for an analysis of dose-response data for fenofibrate's triglyceride lowering effect.

Key Words: dose-response effect, hypotriglyceridemic, minimum effective dose, open studies, pooling, triglycerides

The sponsor considered five studies valid for the review of the hypotriglyceridemic effect of fenofibrate 200mg, 300mg, or 400mg administered daily. Validation was based on the following criteria:

1. Patients were treated for at least one month.

2. A "sufficient" number of patients with elevated triglycerides were required in each dose group.

3. Treatment was not to be allocated on the basis of lipid levels.

4. Case report forms or individual lipid level raw data was to be available.

Brief comments on each of the sponsor's valid studies follow:

Aubertin Study 8

Twenty-six patients received fenofibrate 200mg or 300mg daily in this open study for durations ranging from fifteen days to in excess of nine months.

The sponsor submitted descriptive results which indicated that fenofibrate 200mg patients experienced a triglyceride mean reduction of .87g/L (3.47g/L to 2.60g/L) compared to a 2.72g/L (4.42g/L to 1.70g/L) experienced by fenofibrate 300mg patients. Based on these results, the sponsor concluded that a more pronounced decrease in triglyceride levels was achieved by fenofibrate 300mg patients than by fenofibrate 200mg patients.

However, patients were not randomized to treatment nor treated in a parallel fashion. Also, five patients received both treatment regimens. In addition, data was not broken down by Fredrickson type as desired by the reviewing clinician and some patients were treated less than the one month validation criterion.

Consequently, in the opinion of this reviewer, the results of this study do not provide statistically meaningful information regarding a fenofibrate dose response effect.

Raynaud Study 9

Twenty-five patients received fenofibrate (2 200mg, 5 300mg, 18 400mg) daily in this open study for durations ranging from one month to one year.

Based on a categorization scheme, the sponsor concluded that fenofibrate 300mg was the optimum dose. However, treatment group means were not supplied by the sponsor and due to the lack of well-defined randomization procedure, the treatment allocation was extremely unbalanced.

Consequently, as with regard to the Aubertin Study, the results submitted by the sponsor do not provide statistically meaningful information regarding a fenofibrate dose response effect.

Aumann Studies 10 and 11

In Study 10, 119 patients were treated in an open fashion with fenofibrate 300mg daily for six months. Fifty-one of these patients had their daily dose reduced to 200mg for an additional three to six months. In Study 11, the same investigators treated 14 patients in an open fashion with fenofibrate 200mg daily for six months.

Baseline data was not available for Type IV patients in Study 10 which is a violation of one of the sponsor's validation criteria. Also patients were not randomized to treatment nor treated in a parallel fashion.

In addition, all Study 11 patients received the same treatment regimen.

Consequently, as with regard to the above reviewed studies, the results submitted by the sponsor do not provide statistically meaningful information regarding a fenofibrate dose response effect.

Rossner Study 12

Thirty-nine patients were titrated from fenofibrate 200mg daily to 300mg daily to 400mg daily every two months in an open fashion. They were then administered fenofibrate 400mg daily or clofibrate 200mg daily for two months and then crossed over to the alternate treatment for an additional two months. In addition, 16 other Type IV patients received a constant 200mg dose for 2 months.

The sponsor submitted only 400mg data which is a violation of one of their validation criteria.

As with the above reviewed studies, the design of this study precludes it from providing statistically meaningful information regarding a fenofibrate dose response effect.

Reviewer's Concluding Comments (may be conveyed to the sponsor)

The sponsor pooled the results of their five "valid" studies in order to perform statistical procedures to compare the effects of the fenofibrate treatment regimens.

Based on these comparisons, the sponsor arrived at several conclusions, one of which was that "a daily fenofibrate treatment regimen of 300mg is significantly more effective than the 200mg regimen in reducing elevated triglycerides."

However, there is no sound statistical basis for pooling these studies, each of which is not capable of providing statistically meaningful information regarding a fenofibrate dose response effect.

Consequently, the pooled p-values supplied by the sponsor in the opinion of this reviewer should not be given any credence.

In conclusion, the sponsor's submitted data are clearly insufficient to define a fenofibrate dose-response effect. In order to define such an effect, a parallel double-blind randomized dose-response study should be conducted by the sponsor. The doses selected for this proposed study should be agreed upon by the sponsor and the FDA in order that a minimum effective fenofibrate dose may be recommended.

David N. Marticello

Daniel N. Marticello
Mathematical Statistician

This review consists of 4 pages of text.

Concur: Dr. Chi 4/27/90

Dr. Dubey 4-30-90

cc:
Original: NDA 19-304
HFD-510
HFD-510/Dr. Sobel
HFD-510/Dr. Pierce
HFD-510/Mr. Eastep
HFD-344/Dr. Lisook
HFD-713/Dr. Dubey [File: 1.3.2 NDA]
HFD-713/Dr. Chi
HFD-713/Mr. Marticello
Chron.
D.N.Marticello:x34594:SERB:skj:04-23-90:#2130n

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUGS AND BIOLOGICS

DATE: SEP 30 1987

TO: Elizabeth K. Barbehenn, Ph.D., HFN-810
Division of Metabolism and Endocrine Drug Products

FROM: Group Leader, Statistical Application & Research Branch, HFN-715

SUBJECT: Data Request, NDA 19-304, Fenofibrate Rat Carcinogenicity study

For evaluating the dose-response relationships more information is needed for the following tumor types:

I. For males

a. Adrenals Cortical Ademoma
b. Thyroids C-cell Adenoma
c. Testes interstitial Cell Tumor
d. Nervous Tissue Astrocytoma

II. For females

a. Thyroids C-cell Adenoma
b. Pancreas Acinar Adenoma
c. Uterus Endometrial Polyp
d. Mammary Gland Adenocarcinoma
e. Liver Neoplastic Nodule

We have also prepared a blank form for the sponsor. Please request the sponsor to complete this form for the controls and dose groups, 2, 3, 4 and 5.

The ten-week intervals should be used for completing these forms. The interim (if any) and terminal sacrifices should be reported separately. In the column "start", the number of animals alive in the beginning of that interval should be entered.

For any further information, the sponsor can contact Mr. Mordecai Friedberg who is working on this project at (301) 443-4710.

Suresh C. Rastogi 9/30/87
Suresh C. Rastogi, Ph.D.

Data Table

Drug Name: Fenofibrate
Animals: Rat
Animal Sex: ■ Male ☐ Female

Time Intervals (weeks)	Group ( )						
	Deaths			Tumor Types			
	Start	D	S	N	TTI	TT2	TT3	TT4
0-10								
11-20								
.								
.								
.								
Interim Sacrifices (if available)								
.								
.								
Last Time Interval of the Study								
Terminal Sacrifices								

Notes: D = Number of Animals died
S = Number of Animals Sacrificed Moribund
N = Number of necropsies
TTI= No. of animals with Adrenals Cortical Adenoma
TT2= No. of animals with Thyroids C-cell Adenoma
TT3= No. of animals with Testes Interstitial Cell Tumor
TT4= No. of animals with Nervous Tissue Astrocytoma

Data Table

Drug Name: Fenofibrate
Animals: Rat
Animal Sex: ☐ Male ☒ Female

Time Intervals (weeks)	Group ( )							
	Deaths			Tumor Types				
	Start	D	S	N	TTI	TT2	TT3	TT4	TT5
0-10									
11-20									
.									
.									
.									
Interim Sacrifices (if available)									
.									
.									
Last Time Interval of the Study									
Terminal Sacrifices									

Notes: D = Number of Animals died
S = Number of Animals Sacrificed Moribund
N = Number of necropsies
TTI= No. of animals with Thyroids C-cell Adenoma
TT2= No. of animals with Pancreas Acinar Adenoma
TT3= No. of animals with Uterus Endometrial Polyp
TT4= No. of animals with Mammary Gland Adenocarcinoma
TT5= No. of animals with Liver Neoplastic Nodule

ORIGINAL

Statistical Review and Evaluation
(An Addendum)

2 3 1989

NDA #: 19-304 Date:

Applicant: Fournier Laboratories, Inc.

Name of Drug: Fenofibrate (Lipidil)

Documents Reviewed:

Information and data sent to Division of Biometrics by Dr. Elizabeth K. Barbehenn.

I. Background

A carcinogenicity study in rats included in this NDA submission has been reviewed by the Division of Biometrics. Recently the sponsor submitted additional requested data. Dr. Elizabeth K. Barbehenn, HFD-510 who is the reviewing pharmacologist of this NDA had requested the Division of Biometrics to test if the positive dose-response relationship is significant in pancreatic acinar adenoma in both sexes, and nervous tissue astrocytoma and pancreatic acinar adenocarcinoma in male rats. The results of this review have been discussed with Dr. Barbehenn.

In this review, the phrase "positive dose-response relationship" refers to the increasing linear component of the effect of treatment, and not necessarily to a strictly increasing tumor or mortality rate as dose increases.

II. c. Reviewer's Analyses and Comments

The prevalence method for incidental tumors and the death rate method for fatal tumors described in Peto et al. ("Guidelines for Simple, Sensitive Significance Tests for Carcinogenic Effects in Long-Term Animal Experiments", In Long-Term and Short-Term Screening Assays for Carcinogens: A Critical Appraisal, International Agency for Research on Cancer Monographs, Annex to Supplement 2, World Health Organization, 311-426, 1980) were used to test the positive dose-response relationship in the tumor data. Since the p-values from the Peto method are not stable and reliable for tumor types with small number of occurrences across treatment groups, therefore, the exact permutation trend test was applied to tumor types with total number of five or less occurrences across treatment groups. The time intervals 0-52, 53, 54-80, 81-117 weeks and terminal sacrifice were used in these methods. The sponsor has indicated that Fenofibrate was administered in the diet to rats for 117 weeks. However, the sponsor used the time intervals 1-100, 101-110, 111-120, and terminal sacrifice to summarize the tumor data. With the concurrence of

Dr. Barbehenn, the reviewer did not compare any treatment related responses produced by Fenofibrate with those produced by two other hypolipidaemic compounds, Clofibrate and G250.

As indicated in Peto et al. (1980, p. 375), "Misclassifying incidental tumors as fatal tumors tends to make the treatment of groups with poor intercurrent survival appear more carcinogenic than it really was, while, conversely, misclassifying fatal tumors as incidental tends to make the treatment of groups with poor intercurrent survival seem less carcinogenic than it really was. (In this context, 'poor intercurrent survival' means high death rates from causes other than the tumor type of interest during the period during which such tumors were arising.)"

Since the uncertainty about which contexts of observation (definitely incidental, probably incidental, probably fatal, or definitely fatal) should be estimated for the nervous tissue astrocytoma, the reviewer has applied both the prevalence method and the death rate method to this tumor. The actual dose levels 0, 10 and 60 were the scores assigned to the control, low, and medium dose groups, respectively.

The results of the analyses show that there is a significant positive dose-response relationship in pancreatic acinar adenoma in both sexes (male: $p = 0.00095$; female: $p = 0.0422$). No significant positive dose-response relationship was found in nervous tissue astrocytoma either observed in a fatal context ($p = 0.074$) or observed in an incidental context ($p = 0.088$) in male rats. In addition, there is no statistically significant positive dose-response relationship in pancreatic acinar adenocarcinoma in male rats ($p = 0.266$). The incidence rates of the tumor types with significant positive dose-response relationships are given in Tables 1 to 2.

III. Summary

In this review, the phrase "positive dose-response relationship" refers to the increasing linear component of the effect of treatment, and not necessarily to a strictly increasing tumor or mortality rate as dose increases.

Our analyses show that there is no statistically significant positive dose-response relationship in pancreatic acinar adenocarcinoma in male rats, nor is there a significant positive dose-response relationship in nervous tissue astrocytoma in male rats. However, there is a significant positive dose-response relationship in pancreatic acinar adenoma in both sexes (male: $p = 0.00095$; female: $p = 0.0422$).

Daphne Lin 6/20/89

Daphne Lin, Ph.D.
Mathematical Statistician

Concur: Karl K. Lin 6/20/89
Karl K. Lin, Ph.D., Group Leader, SARB

WR7 6/22/89
William R. Fairweather, Ph.D., Chief, SARB

cc: Original NDA 19-304
HFD-510/Dr. Solomon
HFD-510/Dr. Barbehenn
HFD-710/Chron
HFD-715/Dr. Fairweather
HFD-715/Dr. Karl Lin
HFD-715/Dr. Daphne Lin
HFD-102/Dr. Chah
HFD-715/DRU 2.1.1, Fenofibrate, Fournier Laboratories, Inc.

Table 1
Tumor Incidence Rates
Male Rats, Pancreatic Acinar Adenoma

Weeks	Control		Low		Medium	
	T	N	T	N	T	N
0-52	0	2	0	3	0	5
53-53	0	10	0	9	0	9
54-80	0	4	0	4	0	4
81-117	0	22	0	22	3	16
Terminal	0	22	1	22	4	26
Total	0	60	1	60	7	60

Table 2
Tumor Incidence Rates
Female Rats, Pancreatic Acinar Adenoma

Weeks	Control		Low		Medium	
	T	N	T	N	T	N
0-52	0	1	0	5	0	1
53-53	0	10	0	10	0	10
54-80	0	9	0	7	0	6
81-117	0	25	0	22	2	24
Terminal	0	15	0	16	1	19
Total	0	60	0	60	3	60

Notes: T: Number of necropsies with the above tumor.
N: number of necropsies.

CHEM REVIEW

ORIGINAL

REVIEW OF CHEMISTRY AND MANUFACTURING CONTROLS

NDA #19-304

Division: DMEDP, HFD-510
Chemistry Review: #6

FEB 12 1992

Sponsor: Fournier Laboratories
Address: 42 Rue de Longvic
21300 Chenove
France

Date Completed: 2/12/92

Product Name(s):
Proprietary: Lipidil
Non-proprietary: Fenofibrate Capsules
USAN: Fenofibrate
Code name/number: LF 178

Dosage Form(s) and Route(s) of Administration:
Hard gelatin capsules, 100 mg, oral

Pharmacological Category and/or Principal Indication:
Lipid-lowering agent

Initial Submission: May 31, 1984

Amendment: December 2, 1991

Remarks:

(1). The revised draft package insert provided in this amendmentis acceptable from chemistry viewpoint.
(2). The Labeling and Nomenclature Committee has no objection to the proposed name, Lipidil (see the attached).
(3). The method validation by the FDA laboratories has been completed. This information is currently under review.

Conclusion and Recommendation:
The application is approvable from chemistry viewpoint. However, we have not received a response to the request for the final update of the EER for manufacturers of the drug substance and the drug product forwarded to Division of Manufacturing & Product Quality on December 10, 1990.

Chien-Hua Niu, Ph.D.
Review Chemist

cc: IND/NDA Orig.
HFD-510
HFD-510/CNiu/2/12/92/Disc IBM/NDA19304.006
R/D init: 2/12/92

REVIEW OF CHEMISTRY AND MANUFACTURING CONTROLS

MAR 1 4 1990

NDA # 19,304

Division: DMEDP, HFD-510
Chemistry Review: # 5

Sponsor: Fournier Laboratories
Address: 42 Rue de Longvic
21300 Chenove
France

Date Completed: 3/15/90

ORIGINAL

Product Name(s):
Proprietary: Lipidil™
Non-proprietary: Fenofibrate Capsules
USNA: Fenofibrate
Code name/number: LF 178

Dosage Form(s) and Route(s) of Administration:
Hard gelatin capsules, 100 mg, oral

Pharmacological Category and/or Principal Indication:
Lipid-lowering agent.

Initial Submission: May 31, 1984

Amendment: August 14, 1989 & March 1, 1990

Conclusion and Recommendation:

~~Acceptable~~ The new drug application remains ~~Acceptable~~ approvable from chemistry viewpoint. The package insert and bottle label have been revised according to our recommendation (see Chem. Rev. # 3). Method validation by the FDA laboratories has been completed. This information is currently under review. ~~Acceptable Comments.~~

Chien-Hua Niu, Ph.D.

cc: IND/NDA Orig.
HFD-510
HFD-510/CHNiu/3/15/90/Wang # 1245c
R/D init. by: C. Chiu 3/14/90

DEC 22 1988

REVIEW OF CHEMISTRY AND MANUFACTURING CONTROLS

NDA # 19,304

Division: DMEDP, HFD-510
Chemistry Review: # 4

Sponsor: Fournier Laboratories
Address: 42 Rue de Longvic
21300 Chenove
France

Date Completed: 12/22/88

Product Name(s):
Proprietary: Lipidil™
Non-proprietary: Fenofibrate Capsules
USNA: Fenofibrate
Code name/number: LF 178

Dosage Form(s) and Route(s) of Administration:
Hard gelatin capsules, 100 mg, oral

Pharmacological Category and/or Principal Indication:
Lipid-lowering agent.

Initial Submission: May 31. 1984

Remarks:
In the attached memorandum issued by the Division of Manufacturing and Product Quality (HFD-320) on ~~Per~~ cGMP compliance, all the manufacturing sites except were found acceptable. Meanwhile, been put into category of cGMP non-compliance in the manufacture of sterile products. However, on December 22, 1988, during the telephone conversation with Mr. Paul B. Mckim, Non-Sterile Drug Branch, Division of Manufacturing and Product Quality, he confirmed that - used for manufacturing non-sterile capsules are inspected and acceptable.

Conclusion and Recommendation:
As stated in Chem. Rev. # 2, the only pending chemistry issue was on cGMP compliance. Since all the facilities involved in manufacturing this drug are acceptable by the office of Compliance, this new drug application now becomes approvable from chemistry viewpoint. The approvable letter, if to be issued, should include the request delineated in the draft letter.

Chien-Hua Niu, Ph.D.
Review Chemist

cc: IND/NDA Orig.
HFD-510
HFD-510/CHNiu/12/22/88/Wang # 0735c
R/D init. by: C. Chiu 12/22/88

MAY 26 1988

REVIEW OF CHEMISTRY AND MANUFACTURING CONTROLS

NDA # 19,304

Sponsor: Fournier Laboratories
Address: 42 Rue de Longvic
21300 Chenove
France

Division: DMEDP, HFN-810
Chemistry Review: # 3

Date Completed: 5/26/88

Product Name(s):
Proprietary: Lipidil™
Non-proprietary: Fenofibrate Capsules
USNA: Fenofibrate
Code name/number: LF 178

Dosage Form(s) and Route(s) of Administration:
Hard gelatin capsules, 100 mg, oral

Initial Submission: May 31, 1984

Amendment: February 12, 1988

Conclusion and Recommendation:

Information submitted for Lipidil capsules packaged in HDPE bottles is satisfactory. This application is approvable from chemistry viewpoint provided the packaging facilities at are found to be in compliance with cGMP regulations.. Regarding the bottle labels, the applicant should be asked to:

(1) Change the trade name of the drug from "Lipidil™" to "Lipidil™ Capsules".

(2) Change the statement "Bristol Laboratories" to "Packaged by Bristol Laboratories" so to comply with 21 CFR 201.1h(2) & (6).

(3) Change the statement to "Made in France".

The sponsor has submitted three-month stability data of Lipidil capsules packaged in high density polyethylene (HDPE) bottles which are stored at accelerated (40 and 50 C) and room temperature (30 C), under intense fluorescent light, or in a high relative humidity environment. The results presented in the amendment indicate that Lipidil capsules in HDPE bottles are extremely stable even in accelerated temperature. Since Lipidil capsules in blister package has been granted with a shelf life of 36 months, it is recommend that Lipidil capsules in HDPE bottles also bear an expiry dating of 3 years.

Chien-Hua Niu, Ph.D.

cc: IND/NDA Orig.
HFD-510
HFD-510/CHNiu/YYChiu/5/26/88/Wang # 0350c
D init. by: 5/26/88

REVIEW OF CHEMISTRY AND MANUFACTURING CONTROLS

NDA # 19-304

Division: MEDP, HFN-810
Chemistry Review #2

Applicant: Laboratoires Fournier
Address: 42 Rue de Longvic
21300 Chenove
France

Date Completed: October 5, 1987

Product Name(s):
Proprietary: Lipidil™
Non-proprietary: Fenofibrate Capsules
USAN: Fenofibrate
Code name/number: LF 178

Dosage Form(s) and Route(s) of Administration:
Hard gelatin capsules, 100mg, oral.

Pharmacological Category and/or Principal Indication:
Lipid-lowering agent.

Structural Formula and Chemical Name:
The MW of fenofibrate is 360.84.

Initial Submission: May 31, 1984.

Resubmission: Correspondence date: April 29, 1987; Date received by TL: May 7, 1987.

Amendment(s): 8/3/86(responses to chemistry deficiencies in FDA letter of 9/30/85), 9/15/86(error in 8/3/86 response), 2/20/87(new manufacturing site)

Related Documents:

Remarks:
This is a resubmission of NDA 19-304 originally submitted on May 30, 1984. In this resubmission the only information submitted which is relavent to chemistry is draft labeling.

Conclusion and Recommendation:
The firm has properly responded to the chemistry deficiencies communicated to them in the FDA letter of September 30, 1985. It is therefore approvable from the chemistry point of view provided the facilities are found to be in compliance with cGMP regulations. The requested expiry period of 36 months is granted for the finished dosage form.

Theresa Lee
Theresa Lee, Ph.D.
Review Chemist

cc: NDA Orig.
HFN-810
HFN-102/Kumkumian
HFN-810/TLee/10/5/87
Wang 0086r

R/D initialed by J. Chin 10/13/87

REVIEW OF CHEMISTRY AND MANUFACTURING CONTROLS

NDA 19-304 (ORIG.)

Applicant: Fournier Laboratories
Chenove, France
via: . H. Besselaar Associates
Princeton, New Jersey

Division: NEDP, HFN-810
Chemist Review #1
Reviewing Chemist: N. Weston

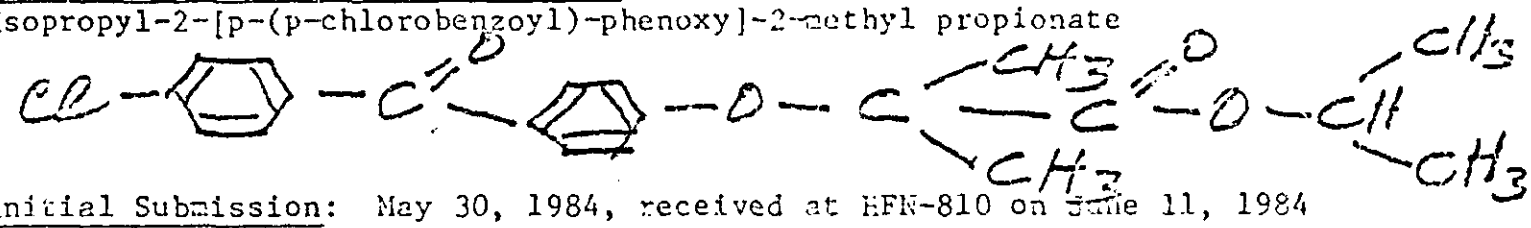
Date Completed: July 25, 1984

Product Names: Lipantyl Capsules (in U.S.)
Proprietary: Lipanthyl Capsules (in Europe)
Non-proprietary: Procetofen Capsules; Procetofene Capsules
USAN: Fenofibrate (Capsules)
Code Name: LF 178

Dosage Form and Route of Administration: Hard-shell gelatin capsules each containing 100 mg of fenofibrate for oral administration.

Pharmacological Category: Lipid altering agent - is 30% to 38% absorbed after oral administration.

Structural Formula & Chemical Name:
Isopropyl-2-[p-(p-chlorobenzoyl)-phenoxy]-2-methyl propionate



Initial Submission: May 30, 1984, received at HFN-810 on June 11, 1984

Related Documents: ; similar in chemical structure to clofibrate and bezafibrate.

Remarks: Components and Composition:
Applicant submits the formulations for the Fenofibrate Capsules 100 mg and

Conclusions and Recommendations: A deficiencies letter to issue regarding the manufacturing, controls, and technical aspects of the labeling

N. Weston

N. Weston, Chemist

cc:
Orig. NDA
HFN-810
HFN-102/Kumkumian
HFN-810/NWeston/7/25/84/sw/8/3/84
R/D init. by: DJKertesz/7/30/84
Wang No. 6309C

ET

WHEN THE ORIGINAL CHEMISTRY REVIEW WAS COMPLETED IN 1984, CDER POLICY DID NOT REQUIRE, FOR A NEW MOLECULAR ENTITY, A SEPARATE ENVIRONMENTAL ASSESSMENT REVIEW BY AN ENVIRONMENTAL EXPERT IN ODE I

MICRO REVIEW

NO MICROBIOLOGY REVIEW

PHARM
REVIEW

Trostle

NDA 19-304 November 3, 1993

Fournier Research
Mamaroneck, NY

Submission: July 24, 1992

Pharmacology Review of Revised Labeling

Drug: Fenofibrate (Lipidil)
Category: lipid altering (triglyceride lowering)

Carcinogenesis, Mutagenesis, Impairment or Fertility:

1) Add mg/kg in addition to mg/square meter:
Page 8; second paragraph should read:
"In a 24-month study in rats (10, 45, and 200 mg/kg; 0.3, 1, and 6 times the human dose on the basis of mg/square meter of surface area), the incidence..."

"In a second 24-month study in a different strain of rats (doses of 10 and 60 mg/kg; 0.3 and 2 times the human dose based on mg/sq meter surface area), there were..."

Page 8; third paragraph should read:
"A comparative carcinogenicity study was done in rats comparing three drugs: fenofibrate (10 and 60 mg/kg; 0.3 and 1.6 times the human dose), clofibrate (400 mg/kg; 1.6 times the human dose), and gemfibrozil (250 mg/kg; 1.7 times the human dose) (multiples based on mg/sq meter surface area). Pancreatic acinar adenomas were increased in males and females on fenofibrate; hepatocellular carcinoma and pancreatic acinar adenomas were increased in males and hepatic neoplastic nodules in females treated with clofibrate; hepatic neoplastic nodules were increased in males and females treated with gemfibrozil while testicular interstitial cell tumors were increased in males on all three drugs."

Page 8; fourth paragraph should read:
"In a 21-month study in mice at doses of 10, 45, and 200 mg/kg (approximately 0.2, 0.7, and 3 times the human dose on the basis of mg/square meter surface area), there were statistically significant increases in liver carcinoma at 3 times the human dose in both males and females. In a second 18-month study at the same doses, there was a significant increase in liver carcinoma in male mice and liver adenoma in female mice at 3 times the human dose."

Page 8; fifth paragraph should read:
"Fenofibrate has been demonstrated to be devoid of mutagenic potential in the following tests: Ames, mouse lymphoma, chromosomal aberration, and unscheduled DNA synthesis."

P. 9; Second paragraph should end with (as previously requested): "and an increase in spina bifida."

The data in study #745-00088 shows that the incidence in the high dose fenobrate-treated rats was 2.3% compared to 0% in concurrent control and 0.14% in historical controls; thus, the reference should remain.

Elizabeth Barbehenn

Elizabeth Barbehenn, Ph.D.

A Jordan 11/3

cc: NDA Arch
HFD-510
HFD-510/Jordan/Barbehenn/Innerfield/Trostle
Labelfen.#3

D;V

NDA 19-304 August 31, 1992

Fournier Research
Mamaroneck, NY

Submission: July 24, 1992

Pharmacology Review of Revised Labeling

Drug: Fenofibrate (Lipidil)
Category: lipid altering (triglyceride lowering)

Carcinogenesis, Mutagenesis, Impairment of Fertility:
Page 8; First paragraph is fine.

Page 8; Second paragraph should read:
"A comparative carcinogenicity study was done in rats comparing three drugs: fenofibrate (at 0.3 and 1.7 times) and clofibrate and gemfibrozil (at 1.7 times) the human dose (mg/sq meter surface area). Pancreatic acinar adenomas were increased in males and females on fenofibrate; hepatocellular carcinoma and pancreatic acinar adenomas were increased in males and hepatic neoplastic nodules in females treated with clofibrate; hepatic neoplastic nodules were increased in males and females treated with gemfibrozil while testicular interstitial cell tumors were increased in males on all three drugs."

Page 8; Third paragraph is fine.

Page 8; Fourth paragraph should read:
"Fenofibrate has been demonstrated to be devoid of mutagenic potential in the following tests: Ames, mouse lymphoma, chromosomal aberration, and unscheduled DNA synthesis."
(Comment: Dr. Virginia Dunkel stated that sister chromatid exchange in CHO cells is no longer considered a valid test.)

P. 9; Second paragraph should end with (as previously requested):
"and an increase in spina bifida." data (study #745-00088):

	CONTROL	FENOFIBRATE (mg/kg/day)		CLOFIBRATE (mg/kg/day)
	0	300	75	15	300
Bifed vert.	0	9	0	2	0
No. pups	287	397	260	238	282
% affected	0	2.3	0	0.8	0

Historical control data:

MALFORMATIONS:	CONTROL	TREATED
vertebrae- malformed/agenesis	16/5002 = 0.14%	30/6709 = 0.44%
inhibition osteogenesis	32/5002 = 0.28%	50/6709 = 0.74%

RECOMMENDATION: Since the incidence in the high dose fenofibrate-treated rats was 2.3% compared to 0% in concurrent control and 0.14% in historical controls, the reference to spina bifida should remain in the label. The second and fourth paragraphs (page 8) have been modified (see above).

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HFD-510/Jordan/Barbehenn/Pierce/Innerfield/Short
Labelfen.#2

EB

If we're going to include the comparative EA study, it should be in the label of the other fibrates as well

Alex

ORIGINAL

FEB 7 1992

NDA 19-304
SWBM 12/2/91
Fournier Research, Inc.

February 7, 1992

FENOFIBRATE LABELING (Pharmacology)

Carcinogenesis, Mutagenesis, Impairment of Fertility

In a 24-month study in rats at approximately 0.3, 1, and 6 times the human dose (on the basis of mg/square meter of surface area), the incidence of liver carcinoma was significantly increased at 6 times the human dose in males and females. A statistically significant increase in pancreatic carcinomas occurred in males at 1 and 6 times the human dose; there were also increases in pancreatic adenomas and benign testicular interstitial cell tumors at 6 times the human dose in males. In a second 24-month study in a different strain of rats at 0.3 and 2 times the human dose (based on mg/sq meter surface area), there were significant increases in the incidence of pancreatic acinar adenomas in both sexes and increases in interstitial cell tumors of the testes at 2 times the human dose.

In a 21-month study in mice at doses approximately 0.2, 0.7 and 3 times the human dose (on the basis of mg/sq meter surface area), there were statistically significant increases in liver carcinoma at 3 times the human dose in both males and females. In a second 18-month study at the same doses, there was a significant increase in liver carcinoma in male mice and liver adenoma in female mice at 3 times the human dose.

Pregnancy Category C. Fenofibrate has been shown to be embryocidal and teratogenic in rats when given in doses 7 to 10 times the human dose and embryocidal in rabbits when given at 9 times the human dose (on the basis of mg/square meter surface area). There are no adequate and well-controlled studies in pregnant women. Fenofibrate should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Administration of 9 times the human dose of fenofibrate to female rats before and throughout gestation caused 100% of dams to delay delivery and resulted in a 60% increase in post-implantation loss, a decrease in litter size, a decrease in birth weight, a 40% survival of pups at birth, a 4% survival of pups as neonates, a 0% survival of pups to weaning, and an increase in spina bifida.

Administration of 10 times the human dose to female rats on days 6-15 of gestation caused an increase in gross, visceral and skeletal findings in fetuses (domed head/hunched shoulders/rounded body/abnormal chest, kyphosis, stunted fetuses, elongated sternal ribs, malformed sternebrae, extra foramen in palatine, misshapen vertebrae, supernumary ribs).

Administration of 7 times the human dose to female rats from day 15 ofgestation through weaning caused a delay in delivery, a 40% decrease in live births, a 75% decrease in neonatal survival, and decreases in pup weight, at birth as well as on days 4 and 21 post-partum.

Administration of 9 and 18 times the human dose to female rabbits caused abortions in 10% of dams at 9 times and 25% of dams at 18 times the human dose and death of 7% of fetuses at 18 times the human dose.

Nursing mothers: It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for tumorigenicity shown for fenofibrate in animal studies, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

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cc: NDA Arch
HFD-510 (19-304)
HFD-510/Jordan/Barbehenn/Pierce
Fenof.lab

A Jordan
2/7/92

APR 1 8 1989

ORIGINAL

NDA 19-304 March 28, 1989

Laboratoires Fournier
Dijon, France

Submission: April 29, 1987

Pharmacology Review of NDA

Drug: fenofibrate

Category: lipid altering

Clinical status: The drug is given at a dose of 100 mg t.i.d. (6 mg/kg/day) for the lowering of triglycerides in types IV and V hyperlipidemia.

Previous reviews: December 14, 1981 and August 31, 1984 (NDA 19-304). These reviews cover Pharmacology, Toxicology, Reproduction, Carcinogenicity, and Mutagenicity.

The first NDA submission was May 30, 1984 as a drug to lower cholesterol which was denied due to lack of efficacy. The current submission is for triglyceride lowering.

New toxicity data in this submission

1) Effects on bone marrow chromosomes of the rat
#86/FOU009/034 November 1985

No effects on chromosome structure were seen after exposure to single doses of 200, 1000, or 5000 mg/kg to CD rats.

Only one time was examined for the two lower doses (24 h post treatment) and the drug effect may not be evident at that time point.

2) Sensitizing potential by topical application to guinea pigs
June 1987.

Application of 0.2 or 0.4 g did not cause any reactions, according to the summary. However, no positive controls were run so we do not know if the study was carried out properly, and it is stated, in French, that erythemas could not be seen because of the color of the drug. The drug was wiped away but the skin was not examined for 6 hours.

(Submitted May 30, 1984 and not previously reviewed)
93-week oral carcinogenicity study in mice (Foreign data)
#493/17. May 1979-February 1981.

Treatment: Six groups of CD-1 mice (50/s/g) were given in the diet 0, 10, 60, or 200 mg/kg/day of fenofibrate (1.7, 10, and 33X HTD) or 0 or 400 mg/kg/day of clofibrate (10X HTD). The clofibrate mice were obtained as a separate batch and may have been a week younger. In week 46, each group was divided into two subgroups "of approximately equal size". One group continued to receive the same diet; the other received a diet with a 10-fold increase in vitamin A via a mixture of retinyl acetate and palmitate (from 3000 I.U./kg to 32,000 I.U./kg of feed). No reason was given for this.
(Doses of 60 mg/kg/day (fenofibrate) and 400 mg/kg/day (clofibrate) are both 10 times the HTD.)

Results
Mortality: no drug effects

Clinical signs: none drug-related but no data presented

Drug concentration in diet: calculated weekly and agrees with expected

Body weight: no drug effects (fenofibrate); females gained (clofibrate)

Food consumption: significantly increased M and HD males and females (fenofibrate)

Hematology (weeks 53 and 94)
No drug effects but large standard deviations makes detection of significant findings unlikely.

Clinical chemistry (GOT, GPT, ALP, cholesterol, TG; weeks 26, 53 and 94):
ALP: increased as a function of dose 2-12 times males (± vit A)
increased HD fenofibrate females (± vit A)
cholesterol: no drug effects
triglycerides: no drug effects
liver transaminases: trend to slight raises (2-fold maximum) in HD males (fenofibrate) and clofibrate males, but S.D. very large

Pathology
Organ weights (as % of body weight):
liver: (males) increased 2-3X M and HD fenofibrate; 1.8X clofibrate
(females) increased 2X HD fenofibrate; 50% clofibrate

Histopathology (non-neoplastic)
Groups= 0, 10, 60, 200 mg/kg/day fenofibrate; 0, 400 mg/kg/day clofibrate

No vitamin A
liver:

basophilic hepatocellular alteration:	4, 4, 3, 37;	15, 16% (males)
Kupffer cell pigmentation	4, 0, 52, 77;	0, 52% (females)
biliary proliferation	0, 0, 0, 15;	0, 0% (females)
	0, 0, 0, 20;	0, 4% (males)
lymph node: hyperplasia	7, 4, 4, 19;	4, 0% (males)

vitamin A (doses as above in 6 groups)
liver:

basophilic hepatocellular alteration	0, 0, 4, 29;	0, 4% (females)
Kupffer cell pigment	0, 0, 10, 22;	0, 25% (males)
	0, 4, 48, 67;	0, 52% (females)
hepatocellular hypertrophy	0, 0, 4, 25;	0, 48% (females)
	0, 0, 5, 22;	0, 13% (males)
lobular dysplasia	0, 0, 0, 43,	0, 4% (males)
	0, 0, 0, 8;	0, 0% (females)

Histopathology (tumor)
no vitamin A
liver:

carcinoma complex	4, 11, 27, 30;	4, 16% (males)
adenoma single	4, 4, 4, 19;	0, 12% (females)

with vitamin A
liver:

carcinoma complex	9, 5, 5, 52;	13, 21% (males)

Evaluation of Mouse Carcinogenicity Study

a) The mouse carcinogenicity has several deficiencies: doses were too low (making it a very insensitive test which would be invalid by today's standards; higher doses might have turned up more target organs and/or carcinogenicity in females) and histopathology listings were minimal (cyst was the only item under pituitary whereas a mouse carcinogenicity study had 8 categories). The breakup of the 6 major groups to test the effect of vitamin A meant that 12 groups had to be analyzed and group size became too small to obtain statistical significance without pooling data (7-11 males/g and 11-16 females/g at 93 weeks in +/- vitamin A subgroups).

b) Non-neoplastic findings

The liver was clearly the major target organ with the facts as presented:
1) alkaline phosphatase was elevated in M and HD males and HD fenofibrate females
2) liver weight increased 2-3X in M and HD fenofibrate males and HD fenofibrate females (as well as clofibrate males and females)
3) basophilic hepatocellular alteration and hypertrophy, Kupffer cell pigmentation, biliary proliferation, and lobular dysplasia in M and HD fenofibrate and clofibrate treated mice
4) possible increases in serum transaminases (difficult to evaluate due to large standard deviations although says positive)

c) Neoplastic findings

Liver carcinoma increased as a function of dose in fenofibrate males in both +/- vitamin A groups (4, 11, 27, 30% and 9, 5, 5, and 52% -/+ vit A)
Liver adenomas increased in HD females (4, 4, 4, and 19% - vit A).

d) General

There was also an interesting effect on metabolism in that food consumption increased significantly (at 10X and 33X the HTD with fenofibrate) without any increase in body weight. Although no electron microscopy was done in this study, other studies in rats (and in people) have shown changes in mitochondrial morphology implying that there could be an effect on oxidative phosphorylation.

Summary of Significant Neoplastic findings

Mouse Carcinogenicity Studies

Laboratory (strain)	Multiples Tested	% Affected (control/treated)	Organ	Tumor
(CF-1)	0,2X,8X,33X	5,16,6,28 (M)	Liver	Carcinoma
		3, 5,0,17 (F)	Liver	Carcinoma
(CD-1)	0,2X,10X,33X	15,16,32,82 (M)	Liver	Carcinoma
		2, 4, 4,19 (F)	Liver	Adenoma

Rat Carcinogenicity Studies

Laboratory (strain)	Multiples Tested	% Affected (control/treated)	Organ	Tumor
(Wistar)	0,2X,8X,33X	3,0,11,70 (M)	Liver	Carcinoma
		3,1, 1,25 (F)	Liver	Carcinoma
		1,1,13, 8 (M)	Liver	Adenoma
		3,3, 3, 8 (F)	Liver	Adenoma
		0,1, 5,10 (M)	Pancreas	Carcinoma
		0,0, 1, 9 (M)	Pancreas	Adenoma
		0,0, 0, 4 (M)	Testis	Leydig cell
(Sprague-Dawley)	0,2,10X	0, 2, 10 (F)	Liver	Nodules
		0, 2, 14 (M)	Pancreas	Adenoma
		0, 0, 6 (F)	Pancreas	Adenoma
		2, 2, 16 (M)	Testis	Leydig cell
		0, 0, 4 (M)	Brain	Astrocytoma

ADDENDA

A) [redacted] rat study problems:

1) Inconsistent data Data submitted on frequency of tumors was inconsistent (each submission different) + data on mortality as a function of time (for each tumor type) had missing animals in every case making statistical analyses impossible.

2) Low survival in the females (28%, 32% and 40%; 0, L, HD) at the end of the study at week 117 lowered ability obtain statistical significance for females.

3) Low doses Doses were set too low (1 and 10 X HTD).

B) [redacted] rat carcinogenicity study results

1) Dose trend

dose trend in males for liver (carcinoma)
pancreas (adenoma and carcinoma)
testis (any tumor)

dose trend in females liver (carcinoma) and mammary (adenoma).

2) Earlier onset of tumors vs clofibrate:

fenofibrate males (10X HTD) tumors were statistically significant at:
week 30 (liver adenoma) vs week 52 for clofibrate
week 41 (liver carcinoma) vs week 78 for clofibrate
week 78 (pancreas adenoma and carcinoma) vs week 94 for clofibrate adenoma

fenofibrate females (33X HTD): tumors were statistically significant at
week 20 (malignancy any organ)
week 52 (liver carcinoma)
week 36 (mammary fibroadenoma)

clofibrate females (10X HTD): week 78 (uterine polyps)

C) No effect levels in rodent carcinogenicity studies
Studies:)

male rats:
2X HTD for liver adenomas/carcinomas (W-L);
2X HTD for Leydig cell tumors (testis); 8X (W-L)
8X HTD for pancreas adenoma and carcinoma (W-L)
2X HTD for pancreas adenoma (HZ)
2X HTD for brain astrocytoma (HZ)

female rats:
8X HTD for liver adenoma and carcinoma (W-L); 2X for liver nodules (HZ)

male mice:
8-10X HTD for liver carcinoma (W-L and HZ)

female mice:
8X HTD for liver carcinoma (W-L)
10X HTD for liver adenoma (HZ)

Considerations related to toxicity of fenofibrate

I) Pharmacokinetics

A) Long elimination half life

fenofibrate = 20 hours (vs 2 hours for gemfibrozil)

B) High plasma drug levels

1) Human plasma levels

Fenofibrate (5 mg/kg/day)	18 ug/ml (Biopharm Rev.2/2/89)
Gemfibrozil (24 mg/kg/day)	20 ug/ml (Biopharm Rev. 7/15/89)

2) Absorption in humans using 14-C fenofibrate
(Pharmacology Review 12/14/81)

species	dose (mg/kg/day)	plasma level	ratio
rat	25	34	1.4
dog	25	25	1.0
man	5	29	4.8

3-4X higher than dogs or rats which means that potential for toxicity is higher

II) Genotoxicity

Of the seven tests done, none were done by GLP procedures, and all had important deficiencies (analyzed by Dr. Leonard Schectman, HFV-154, with the results conveyed to this reviewer). The result is that one can not draw the conclusion that all were negative, as Fournier has done. The test laboratory conducting the studies concluded that there were several positive findings:

A) "weak clastogenic activity" (chromosomal aberrations)

B) "some activity in inducing high levels of thymidine incorporation in HeLa cells in culture in the presence of rat liver post mitochondrial supernatant"

III) Cytoxicity

(effects of fenofibrate on cultured human liver and skin cells)
(The plasma drug level in humans averages 14 ug/ml; range 6-25 ug/ml)

Fenofibrate added early in culture

A) Cell adhesiveness decreased as a function of dose (at 1 and 10 ug/ml)
B) "Severe" cell alterations increased " " " (" " " ")
C) Cell division delayed at 1 ug/ml
D) Detachment of confluent cells + accumulation of vacuoles, lipid globules, and lysosomes (1 ug/ml and above)

Fenofibrate added later in culture

A) Fenofibrate added after cells cultured 18 or 48 hours: cell division delayed (10 ug/ml) and detached (100 ug/ml)

B) "Severe" delay in cell proliferation when added after "several weeks of culture: 10 ug/ml requires 18 days to reach confluence vs 6 for control (1st subculture) and 31 days vs 5 days for control (2nd subculture)

The no effect dose level = 0.1 ug/ml

"a cytotoxic action should be considered simply as an additional possible mechanism of carcinogenesis..." Fed. Reg., March 14, 1985, p[illegible]

"One of the earliest factors identified as associated with teratogenicity is cytoxicity." MHL Snow in "Approaches to Elucidate Mechanisms in Teratogenicity", p. 84, Frank Welsch, ed. (1986)

IV) Carcinogenicity

(direct comparison vs clofibrate by _____ Wistar rats)

A) Tumors appear earlier (statistically significant at similar [illegible] of HTD)

B) There are more target organs

(direct comparison vs clofibrate and gemfib. by Sprague-Dawley rats)

A) Astrocytomas in males at levels higher than historical and concurrent control (4% vs 1% historical control, biologically significant)

B) Other tumor frequencies same except liver carcinoma higher with clofibrate

V) Toxicity

increases in serum transaminases; decreases in hct (rat/dog/monk[illegible]
cholethiasis/microstones (dog gallbladder)
lithiasis (dog kidney)
steatosis (dog liver)

VI) Maternal and Developmental Toxicity

RAT

Segment I (females): treated 2 weeks before and throughout gestation; doses were 2.5, 13, and 50X HTD; 8X HTD clofibrate; groups for delivery/weaning

DAMS

A) weight gain depression (dams)
5, 14, 33% (L, M, HD); 29% clof. (gestation, term sacrifice subgroup)
4, 4, 64% (L, M, HD); 34% clof. (gestation, deliver and wean subgroup)

	% 0, L, M, HD ; clofibrate
B) % delay in delivery:	10, 29, 21, 100%; 6% clofibrate
C) % post-implantation loss:	8, 15, 10, 68%; 28% clofibrate

D) litter size: decreased (p less than 0.01) M and HD; clofibrate (term sacrifice)

FETUSES

A) % survival at birth:	97, 94, 97, 37%;	79% clofibrate
B) % survival neonate:	100, 91, 90, 4%;	77% clofibrate
C) % survival at weaning:	98, 93, 81, 0%;	89% clofibrate
D) pup wt decreased, wean. (females)	9, 25%;	10% clofibrate
(males)	8, 25%;	14% clofibrate

pup wt significantly decreased at term, birth, day 4 and weaning for M and HD males and females and clofibrate

p less than 0.01 for HD for all except maternal weight (not calculated)

RAT
Segment II (dosed days 6-15 gestation; doses 0, 2, 20, 60X HTD; 8X clofibrate)
Dams
No mortality or clinical signs
Weight gain dams = 36, 33, 27, -6; -12 grams (days 6-15 of gestation)
Weight gain dams = 154, 153, 150, 118; 110 grams (days 0-21 of gestation)
Food consumption = 21, 21, 20, 18; 15 g/rat/day (days 0-21 ")

Fetuses (individual data only, no litter data available)
Total number of findings (0, L, M, HD; clofibrate)
Gross and visceral: 3, 0, 11, 93; 9 clofibrate
Skeletal: 204, 223, 377, 577; 117 clofibrate

Individual categories (0, L, M, HD; clofibrate; see also Table 1)

Domed head/hunched shoulders/ rounded body/abnormal chest:	0, 0, 0, 2%;	0% clofibrate
Kyphosis:	0, 0, 0.5, 5%;	0% clofibrate
Stunted:	1, 0, 3, 30%;	4% clofibrate
Elongated sternal ribs:	0, 0, 0, 2%;	0% clofibrate
Malformed sternebrae:	0, 0, 0, 2%;	0% clofibrate
Extra foramen in palatine:	3, 2, 14, 10%;	12% clofibrate
Misshapen vertebrae:	13, 4, 19, 41%;	7% clofibrate
Extra ossification C7 extension:	0, 0.7, 0, 3%;	0% clofibrate
Supernumerary ribs:	18, 31, 34, 60%;	23% clofibrate

*Historical control data agrees with concurrent controls in all cases.

Gemfibrozil: no effects on female fertility/teratogenicity up to 10X HTD (maximum tested)

RABBIT (2.5, 25, 50X; clofibrate 5X)
Dams
Weight gains: not a function of dose (LD lost more wt than HD days 0-6)
Abortions/deaths:
HD: 5/20 aborted; 2/20 died (10 additional does added)
MD: 2/20 aborted (fenofibrate); 1/20 died (clofibrate)
LD/control: no effects

Fetuses
Dead fetuses: 0/100, 0/58, 2/82, 5/75 (0, L, M, HD); 2/73 clofibrate
Findings in fetuses: no drug effects due to either drug

Medical Problems (Medical Officer Review, October 30, 1987)
1) No long term human safety data (and patients will use a long time)
2) No substantial benefit over other drugs of this class already available
3) Never tested in the patient population in which it is intended (people at risk of pancreatitis)
4) Numbers of people tested in double blind trials low: 116 treated + 111 placebo for 6 months (type II); 75 treated + 72 placebo for 2 months (type IV) (=NDA indicated group)
5) The higher the TG, the higher the elevation of LDL-C as a result of treatment and the lower the ratio of LDL-C/HDL-C; "adverse and marked"
6) Significant toxicity seen: significant decreases in hematologic parameters and elevation of LFT's in treated groups (also seen in rats, dogs, and monkeys) plus one case of allergic hepatitis
7) If approved, patient population should be "subjects with a previous episode of abdominal pain and/or pancreatitis with a markedly elevated triglyceride level"

Summary and evaluation: Fenofibrate is a member of the "fibrate" family of drugs which, in addition to fenofibrate, includes two approved drugs, clofibrate and gemfibrozil as well as two in the IND stage, Clofibrate was approved February 8, 1967 and gemfibrozil December 21, 1981.

There were 2 rat and 2 mouse carcinogenicity studies for the fenofibrate NDA. Fenofibrate was carcinogenic in all four studies: in 2 strains of each species (in both sexes of rats and mice) and in at least 3 organ systems (liver, pancreas, testis). In addition, there were 2 astrocytomas/50 males at 10X HTD in the Hazelton rat study (4%) with none in controls, LD, clofibrate or gemfibrozil treated male rats and with a historical control rate in males of 1%.

Although all the fibrates are carcinogens when tested in rats and/or mice in the standard rodent bioassay, much has changed in our way of analyzing and understanding carcinogenicity and mutagenicity data since approval of clofibrate and gemfibrozil:

1) It was thought that 5 or 10 times the human dose was adequate for carcinogencity testing; none of the carcinogenicity studies were done with the "maximum tolerated dose" as is currently required. Under those conditions, when only male rats tested positive, sponsors could say that carcinogenicity was a finding restricted to male rats (Doses used for mouse carcinogenicity studies were the same as those given in rat carcinogenicity studies; mice with higher metabolic rates normally require higher doses to be comparable to rats).

2) It was thought that peroxisomal proliferation seen in rats was specific to that species. It has now been shown that peroxisomal proliferation can be induced by ciprofibrate in cats, chickens, pigeons, and 2 species of monkey after exposure for 3-7 weeks. Proliferation was a dose-dependent but not a species-specific phenomenon (Reddy, et al., 1984, Am. J. Path., 171-183). There was no data on electron microscopy of liver in any species in the fenofibrate IND and N but it is assumed to behave like the class.

It was thought that these changes did not occur in human liver. However, two studies with clofibrate (1980 and 1983) showed strutural changes in mitochondria (atypical arrangement and proliferation of cristae, paracrystalline inclusions and giant mitochondria), increase in smooth and rough endoplasmic reticulum (SER and RER), as well as increased numbers of mitochondria and peroxisomes. The increase in SER and RER and numbers of mitochondria and peroxisomes "persisted for months" after stopping clofibrate treatment in 3/27 patients (Hanefeld, et al. Atherosclerosis: 36, 159-172 and 46, 239-246). Significant increases in peroxisomes in human liver have also been seen after ciprofibrate treatment (IND); changes in morphology have been seen after gemfibrozil treatment (Atherosclerosis, 43, 19-37, 1982).

Fenofibrate was not studied in people with biopsies before and after drug treatment; therefore, nothing can be said about peroxisome numbers. In fact, there does not appear to have been an EM study of rodent liver. However, paracrystalline inclusions were seen in mitochondria, marginal plates in microsomes, as well as dilated ER, in human liver cells in treated patients (Blumcke et al., 1983; de la Iglesia, 1982).

Although it has been widely assumed that peroxisomal proliferation is the mechanism involved in the rodent liver tumors, this has not been proven. Furthermore, liver peroxisomal proliferation does not explain the tumors in pancreas and testis although a careful analysis of these tissues for peroxisomal changes has apparently not been done (these tissues have microperoxisomes which are more difficult to visualize, Novikoff).

3) It was thought that the occurrence of mouse liver tumors had no relevance to man. It has now been shown that tumors induced in B6C3F1 mice by furan and furfural are the result of activation of the H-ras oncogene by point mutations (Reynolds et al., 1987, Science, 237, 1309-1316). This is a general mechanism of carcinogenicity, not something unique to mice.

4) It was thought that negative results in the Ames in vitro mutagenicity test meant that a drug was not carcinogenic. We now know that all peroxisome proliferators are negative in this test in spite of being carcinogenic (Glauert et al., 1986, Cancer Res., 46, 4601-4606). One possible mechanism may involve free radical production by the hydrogen peroxide produced by peroxisomes.

Conclusion: Fenofibrate is carcinogenic in both mice and rats, in two strains each, in both sexes, in four organs (liver, pancreas, and testes as well as brain). It is fetotoxic and teratogenic.

The drug plasma levels are similar to those of gemfibrozil although the HTD dose is only 20% as high on a mg/kg basis; the halftime for fenofibrate is approximately 10 times longer (20 vs 2 hours) meaning that the body burden is significantly higher. Based on a radiolabeled study, man absorbs 3 to 5 times as much fenofibrate as do rats and dogs; thus, we can expect more toxicity and a possibly greater potential for tumors than would be apparent from the carcinogenicity studies. However, because of the long lag time in tumor development, this may not become clear for many years and then only with careful reporting.

Fenofibrate is cytotoxic and possibly genotoxic. Although we lack comparable information on gemfibrozil and clofibrate, we cannot ignore the information that we do have on fenofibrate. Fenofibrate is cytotoxic in human cell lines at drug plasma levels seen in vivo. Cytotoxicity affects fetal development and is one mechanism of carcinogenicity. There is some evidence for direct damage to DNA; however, the data were from flawed studies and, as a result, we are requesting further testing for genotoxicity and cytotoxicity of all three drugs by Fournier.

Fenofibrate causes hepatic toxicity in humans. The clinical and hepatic histological profile resembles "lupoid" autoimmune chronic active hepatitis with anti-organelle antibodies found in patients with drug-induced hepatis. Fenofibrate is listed as one of "the most common culprits" (Sherlock, S., The Spectrum of Hepatotoxicity Due to Drugs in The Lancet, pp. 440-444, August 23, 1986); also Hepatology 5, pp. 904-909 and 722-727, 1985). In the small study submitted with the NDA, there have been elevations of liver enzymes that have never returned to normal even after withdrawing drug (Dr. Ross Pierce Review) and even in the small sample of 43 people, a case of allergic hepatitis (Dr. August Troendle Review).

Elizabeth Barbehenn

Elizabeth K. Barbehenn, Ph.D.

cc: NDA Arch.
HFD-345
HFD-510 (19-304)
HFD-510/Jordan/Barbehenn/Pierce
HFD-502/Weissinger
Wang #0238r

A Jordan
4/13/89

NDA 19-304

August 31, 1984

Laboratories Fournier
Dijon, France
US agent: C.H. Besselaar Associates
Princeton, New Jersey

Submission date May 30, 1984

Review and Evaluation of Pharmacology and Toxicology Data

Drug: Fenofibrate

Related
Category: lipid lowering agent

The reports for the pharmacological and toxicological investigations on fenofibrate are presented in the NDA in the format of summaries of the individual tests, and as tabulations containing the description of the study methodologies and their results. All these investigations had been conducted under and are referenced in the summaries and the tabulations for their location in the IND.

A comprehensive review and evaluation of these investigations reported in the IND was performed and described in the Pharmacology Review of December 14, 1981 by S.P. Hsia, Ph.D., pharmacologist of this division, for the IND of fenofibrate. Because of the high scientific caliber and completeness of Dr. Hsia's review made from the raw data of the tests, their new review is deemed superfluous, and instead, the review by Dr. Hsia is applied for the actions by Pharmacology on the NDA. As an aid to obtain a concise picture of the large number of performed preclinical investigations covering the broad spectrum of the pharmaco-physiological and therapeutic functions of fenofibrate, these tabulations by the sponsor are included in the present review material because they are by their high professional caliber usable for the evaluation procedure. It can be stated at this stage that the entire material for the preclinical investigations submitted by the sponsor is of high professional quality in every respect.

In the following discussion an effort is made to highlight the critical parameters of fenofibrate for its pharmacological functions and toxicological effects.

Pharmacology

Depending from the target substrate, such as the cause for the hypercholesterolemic state in the test animal (high cholesterol diet, treatment with triton, age) fenofibrate is four to six times as potent (on a weight basis) as clofibrate for the reduction of blood lipids and cholesterol. While both drugs are capable to reduce LDL and VLDL lipoproteins, fenofibrate was shown to increase the levels of HDL lipoproteins while clofibrate does decrease their level. Both drugs are similar in their mode of action for interfering with cholesterol synthesis by acting at the stage of mevalonic acid formation.

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This step is ascribed by the sponsor to a specific property of fenofibrate, its inhibitory action on HMG CoA reductase (hydroxy-methyl glutaryl CoA reductase), the enzyme that mediates cholesterol synthesis. However, this inhibitory property is not unique or specific for fenofibrate, for it is also a function of clofibrate, and, more important, it is a property now found for drugs not of the clofibrate class that have the advantage of not causing the adverse effects of fenofibrate and of clofibrate and its analogues, principally their carcinogenic and peroxisome stimulating potential and hepatotoxicity.

Toxicology

The main target organ for all members of the clofibrate type, including fenofibrate, is the liver, followed by the pancreas, and kidney, to a lesser degree, testicular interstitial tissue. A carcinogenic action of fenofibrate was found to be dose dependent and, like that of clofibrate, appears to be limited to the mouse and rat species. However, the tests conducted in dogs used only small numbers of animals (2/sex/dose groups of 25, 50 and 100 mg/kg/day) with only the last two dose groups given for 24 months that resulted in some clinical indication for heptotoxic effects even though without hepatomegaly, and other toxic effects were indicated by cholelithiasis and chronic nephritis in the treated animals. Rhesus monkeys on 12, 50 and 200 mg/kg/day treated for 52 weeks, with 9 animals/sex per group did not show toxic effects from either the doses of fenofibrate, nor in 8/sex control animals on clofibrate at 200 mg/kg/d. No treatment related increase in the incidence of liver peroxisomes was noted, but this does not demonstrate a superior property for fenofibrate because other drugs with peroxisome (microbody) stimulating properties evidenced in rats, are also ineffective for this action in monkeys. The tests in Swiss mice gave a clear indication for a carcinogenic potential of fenofibrate by doses higher than 10 mg/kg/day in one study by the incidence of liver carcinomas while in another study the liver lesions were described as nodular structures, but with similar changes noted also in the clofibrate group.

In a rat study with a large group population of Wistar strain rats of 80/sex/dose of 10, 45 and 200 mg/kg/d for 2-years both drugs were prominently carcinogenic affecting the liver and pancreas, with other non-neoplastic alterations in livers resulting in hepatomegaly and intrahepatic bile stasis. Somewhat divergent results were obtained in another study in rats of the Sprague-Dawley strain of 60/sex/group on 10 and 60 mg/kg/d with a group of same size on 400 mg/kg/d clofibrate. This study was conducted by in England. No liver tumors or carcinomas were found in either dose group of fenofibrate but pancreatic tumors were caused by the 60 mg/kg dose. These variations in drug effects can be ascribed to variable factors, strain of rats, test procedures in different laboratories, pathological interpretations, etc.

Clinical laboratory tests conducted in the course of the chronic tests with fenofibrate and clofibrate and other clofibrate derivatives persistently showed elevated values for SGOT and SGPT indicating their hepatotoxic property which was not diminished for fenofibrate. Liver enlargement to the extend of noticeable hepatomegaly was present in fenofibrate treated animals with above 30 mg/kg. Proliferation of microbodies (peroxisomes) was also noted to occur with fenofibrate as with others of this class of drugs.

The general conclusion for the safety assessment of fenofibrate on the basis of the available information from the preclinical investigations has to be that its claimed greater potency as a cholesterol reducing agent has resulted in the significantly smaller size of the human therapeutic dose form, but the increase in potency dose not provide an improvement in the risk factor for induction of liver toxicity and hepatic carcinomas in consideration of the fact that the "no-effect" dose for the adverse reactions including carcinogenesis is 10 mg/kg which is only 1.5 times the Human Dose, a very narrow margin for even minor toxic effects.

The pathway of action by which fenofibrate performs its lipid lowering function is not established in the animal model to an extent to demonstrate that it is superior in effectiveness and safety compared to other presently existing drugs of this class. Its claimed action through inhibition of HGM CoA reductase function was not demonstrated by in-vivo tests in animals, and the sponsor himself stated in the discussion that it is perhaps medicated through this route, but even if so, it is not unique for fenofibrate. The only superiority of fenofibrate might be that it increased the level of circulating HDL cholesterol in some animal models. For these considerations, it cannot be concluded to recommend the approval of the NDA for fenofibrate on the basis of the information accumulated by the investigations in animals.

V. Berliner

V. Berliner, Ph.D.

cc:
Orig. NDA
HFN-810
HFN-340
HFN-810/pharmacology
HFN-810/VBerliner/8/31/84/DB/9/5/84
Wang No.6643C

2.050D

2. D.2. Toxicology and pathology

FENOFIBRATE

TOXICOLOGY SUMMARY TABLE

REPRODUCTION: FERTILITY
PERI AND POST NATAL

Location Vol/Page	Species/ Strain	Route of administration	Frequency	Dose levels	No. Animals M F	Findings
	Rats/CD	p.o. in diet	each day for 61 days to male and 15 days to female	0, 15, 75, 300 mg/kg/day fenofibrate. 300 mg/kg/day clofibrate	Controls 50 50 Treated 200 200 (50/sex/dose)	No effect on male fertility. No effect on female fertility, but greater pre-implantation loss and smaller litters at 75 and 300 mg/kg/fenofibrate. Delayed parturition (2 to 3 days) and dystocia in high dose fenofibrate treated females. With both drugs, greater post-implantation loss, higher rate of stillbirths and drastic reductions in survival and body weights of F_1 neonates at the high dose levels. Incidence of abnormalities in F_1 within normal historical limits. Reproductive performance of F_1 was normal. No drug-related abnormalities in F_2.
	Rats/CD	p.o. in diet	once each day from day 15 of gestation until weaning day 20	0, 15, 75, 300 mg/kg fenofibrate 400 mg/kg clofibrate	100 (20/dose)	Food intake depression was severe at the high dose and slight at 75 mg/kg. The gestation period was slightly increased at 75 and 300 mg/kg. Fetal wastage was significantly higher at 300 mg/kg. Fetal size, growth and survival were all reduced at 300 mg/kg, with many dams showing complete maternal neglect.

FENOFIBRATE

TOXICOLOGY SUMMARY TABLE

REPRODUCTION: TERATOLOGY

Location Vol/Page	Species/ Strain	Duration of study	Route of administration	Dose levels	No. Animals M F	Findings
	Mice	Day 6 to 15	p.o.	0,70,370, 2000 mg/kg	(1063 fetuses)	Embryolethality was increased in mice and rabbit fetuses from mothers treated with the highest dose, as a result of general maternal toxicity.
	Rat	Day 6 to 15	p.o.	0,70,260, 1000 mg/kg	(900 fetuses)	No teratogenicity.
	Rabbit	Day 7 to 14	p.o.	0,35,115, 400 mg/kg	(386 fetuses)	
	Albino Rat/ CD	Day 6 to 15	p.o.	0,14,12*, 361 mg/kg fenofibrate 321 mg/kg clofibrate	100 (20/dose)	Maternal and embryo toxicity including kyphosis and weight gain depression at high dose. No teratogenicity with fenofibrate. Slight maternal and embryo toxicity; no teratogenicity with clofibrate.
	Rabbits/ Dutch-Belted	Day 6 to 18	p.o.	0,15,150 300 mg/kg fenofibrate 200, 300 mg/kg clofibrate	140 (20-30/dose)	Maternal toxicity except at low dose fenofibrate. No teratogenicity.

FENOFIBRATE

TOXICOLOGY SUMMARY TABLE

SPECIAL TOXICOLOGY STUDIES

Location Vol/Page	Species/ Strain	Duration of study	Route of administration	Frequency	Dose Levels	No. Animals M F	Findings
	Albino rat/ Wistar	7 days	p.o. in 1% gum tragacanth with normal diet and with high cholesterol diet	once each day	3-10-30-100-300 mg/kg. feno. 20-60-200-600 mg/kg clofibrate	Treated 100 (10/dose/diet) 80 (10/dose/diet) Controls 60	SGOT levels were raised. Dose related hepatomegaly in all trented rats at doses above 30 mg/kg/day. Proliferation and enlargement of peroxisomes in all treated animals.
	Albino rat/ Wistar male	7 days	p.o. in 1% g.a tragacanth with normal diet and with high cholesterol diet	once each day	100 mg/kg feno-fibrate 200 mg/kg clofibrate	Treated 12 (6/dose/diet) 12 (6/dose/diet) Controls 12 (6/diet)	

	fenofibrate		clofibrate	
	normal diet	high cholesterol	normal diet	high cholesterol
Hepatomegaly	+	+	+	+
Coumarin hydroxylase	reduced	unchanged	reduced	unchanged
Glucose-6-phosphatase	unchanged	Increased	unchanged	Increased
Aminopyrine demethylase	reduced	Increased	reduced	Increased
Microsomal phospholipid	unchanged	unchanged	unchanged	unchanged
Microsomal protein	unchanged	unchanged	reduced	unchan

FENOFIBRATE

TOXICOLOGY SUMMARY TABLE

CHRONIC TOXICOLOGY

Location Vol./Page	Species/ Strain	Duration of study	Route of administration	Frequency	Dose levels	No. Animals M F	Findings
	Rat/ Sprague Dawley	117 weeks	p.o.	⇒	10 + 60 mg/kg/day fenofibrate 400 mg/kg /day clofibrate 250 mg/kg /day gemfibrozil	Controls 60 60 Treated 240 240 (60/sex/dose)	No change in morbidity and mortality with fenofibrate. Increased incidence of testicular and pancreatic tumors at high dose (60 mg/kg/day) but no evidence of a tumorigenic effect on the liver. Hepatic neoplastic nodules and hepatocellular carcinoma with gemfibrozil and clofibrate. No adverse effects at 10 mg/kg/day fenofibrate for 117 weeks.
	Dog/ beagle hound	7 months	p.o. (capsules)	7 days a week	50 + 100 mg/kg/day	Controls 1 1 Treated 2 2	No death. Loss of weight and decreased food consumption. Transient changes in transaminases at 25 mg/kg. Elevations of alkaline phosphatases. Renal microlithiasis in 2 females and one male (50-100 mg/kg) and chronic nephritis with renal lithiasis in one female at 25 mg/kg. No hepatomegaly. Cholelithiasis. Prostatic adenoma in 1 dog.
		24 months	p.o. (capsules)	7 days a week	25 mg/kg/day	Controls 1 3 Treated 2 2	
	Rhesus Monkeys	52 weeks	p.o. (in banana & apple-sauce)		fenofibrate mg/kg/day 12 50 200 clofibrate mg/kg/day 200	9 9 9 9 10 10 3 3 Controls 8 8	No mortality or other adverse effects. No treatment-related effects in hematology blood chemistry, urinalysis and ophthalmology. Gross pathology: no lesions. No treatment-related increase in the incidence of peroxisomes in the liver.

FENOFIBRATE

TOXICOLOGY SUMMARY TABLE

CHRONIC TOXICOLOGY

Location Vol/Page	Species/ Strain	Duration of Study	Route of administration	Frequency	Dose Levels	No. Animals M / F	Findings
	Rats/ Wistar	2 years	p.o. in diet	once each day	10, 45, 200 mg/kg/day fenofibrate 200 mg/kg clofibrate	Controls 120 / 120 Treated 320 / 320 (80/sex/dose)	Hepatocarcinogenic responses with both treatments: Elevated incidence of hepatic (liver cell carcinomas and adenomas) and pancreatic (acinar cell carcinomas and adenomas) tumors with hepatomegaly and intrahepatic bile stasis with 45 + 200 mg/kg fenofibrate and clofibrate.

FENOFIBRATE

TOXICOLOGY SUMMARY TABLE

CHRONIC TOXICOLOGY

Location Vol/Page	Species/ Strain	Duration of Study	Route of Administration	Frequency	Dose Levels	No. Animals M	No. Animals F	Findings
NDA	Mice/ Swiss albino CD-1	104 wks.	p.o. in diet	Daily	0 mg/kg 10,60,200 mg/kg/day fenofibrate	50 150 (50/sex/dose)	50 150 (50/sex/dose)	- Increased food consumption at 60 & 200 mg fenofibrate; slight increase with clofibrate. However, no change in body weights. - Dose-related reduction in incidence of palpable masses in males given fenofibrate.
					0 mg/kg 400mg/kg/day clofibrate	50 50	50 50	- Dose-related increase in alkaline phosphatases associated with transaminase elevations in fenofibrate-treated groups. More pronounced in males than females. Similar but less pronounced pattern in clofibrate group. - Increased incidence of nodular structures in liver at 200 mg fenofibrate. - Increased liver wts at 60 & 200 mg fenofibrate, more pronounced in males. Changes in clofibrate groups similar to 60 mg fenofibrate group. - Increased incidence of hepatocellular hypertrophy, lobular dysplasia and Kupffer cell pigmentation at 200 mg fenofibrate. Clofibrate group showed similar changes. - Increased incidence of liver tumors at 200 mg fenofibrate and at 60 mg in males. Incidence was greater than in clofibrate group. 10 mg fenofibrate similar to controls. - Vitamin A had no significant effect on incidence or severity of above changes.
					Vitamin A given to ½ each subgroup after week 46			

FENOFIBRATE

TOXICOLOGY SUMMARY TABLE

CHRONIC TOXICOLOGY

Location Vol/Page	Species/ Strain	Duration of study	Route of administration	Frequency	Dose Levels	No. Animals M F	Findings
	Mice/ Swiss	22 months	p.o. in diet	once each day	0 and 50 mg/kg	40 40 (20/sex/dose)	Despite a 100% increase in liver weight in treated animals, no liver tumors. Intrahepatic cholestasis and some degenerative changes in hepatocytes.
	Mice/ Swiss	80 weeks	p.o. in diet	once each day	0, 10, 45 or 200 mg/kg/day fenofibrate 200 mg/kg/day clofibrate	Controls 100 100 Treated 200 200 (50/sex/dose)	No treatment-related mortality. No effect on body weight or food consumption. Dose-related increases in liver and kidney weight. Gross hepatomegaly with cholestasis at 200 mg/kg fenofibrate and clofibrate. Increased incidence of hepatocellular carcinomas with high dose fenofibrate. Increased incidence of alveologenic adenocarcinomas and lymphoid tumors in male with clofibrate.

2/0 x 50

10 mg

FENOFIBRATE

TOXICOLOGY SUMMARY TABLE

SUB-ACUTE TOXICOLOGY

Section/ Ref/Page	Species/ Strain	Duration of study	Route of administration	Frequency	Dose levels	No. Animals M F	Findings
	Rat/Wistar	3 months	p.o. in arabic gum	6 days/week	0,50,250,500 and 1000 mg/kg fenofibrate	50 (10/dose)	One death in each group, 50, 100 and 250 mg/kg. No significant changes in hematology or urinalysis. Depression of blood lipids at all dose levels. SGOT elevated at 500 and 1000 mg/kg doses. Tendency of SGPT to be high at the upper dose levels. Dose-related increase in liver weight at all doses. No histopathological changes of toxicological significance. Dose dependent decrease in weight gain at 100, 250, 500 and 1000 mg/kg. Significant increase in kidney weight at all doses.

FENOFIBRATE

TOXICOLOGY SUMMARY TABLE

ACUTE TOXICOLOGY

Location Vol/Page	Species/ Strain	Duration of study	Route of administration	Frequency	Dose levels	No. animals M	No. animals F	LD50
	Mice/Swiss		p.o.*		400,800,1600, 2400,3200 mg/kg	75	75	>3200 mg/kg
	Mice/Swiss		i.p.		800,1600,2400, 3200 mg/kg	60 (15/sex/dose)	60	>3200 mg/kg
	Rats/Wistar		p.o.*	One Single Administration	400,800,1600, 2400,3200 mg/kg	50	50	>3200 mg/kg
	Rats/Wistar	7 days	i.p.		800,1600,2400 3200 mg/kg	40 (10/sex/dose)	40	>3200 mg/kg
	Mice/Swiss		p.o.* fenofibric acid		200,400,800,1600, 2400 mg/kg	75	75	=1200 ± 130 mg/kg
	Mice/Swiss		i.p. fenofibric acid		100,200,300,400, 800 mg/kg	75 (15/sex/dose)	75	=500 ± 40 mg/kg
			*in arabic gum					
	Mice/CRCD		p.o.		0 + 5000 mg/kg	20	20	>5000 mg/kg
	Rats/CRCD		p.o.		0 + 5000 mg/kg	20	20	>5000 mg/kg
	Rats/CRCD		i.p.		0 + 5000 mg/kg	20	20	>5000 mg/kg
	Hamster/ Golden Syrian	7 days	p.o.	One Single Administration	0 + 5000 mg/kg	20	20	>5000 mg/kg
	Hamster/ Golden Syrian		i.p.		0 + 5000 mg/kg	20 (10/sex/dose)	20	>5000 mg/kg
	Dog/Beagle		p.o.		1000,2000 & 4000 mg/kg	3 (1/sex/dose)	3	>4000 mg/kg

APR 13 1989

Return to NV

NDA 19-304

March 28, 1989

Laboratoires Fournier
Dijon, France

Submission: April 29, 1987

Pharmacology Review of NDA

Drug: fenofibrate

Category: lipid altering

Clinical status: The drug is given at a dose of 100 mg t.i.d. (6 mg/kg/day) for the lowering of triglycerides in types IV and V hyperlipidemia.

Previous reviews: December 14, 1981 ( ) and August 31, 1984 (NDA 19-304). These reviews cover Pharmacology, Toxicology, Reproduction, Carcinogenicity, and Mutagenicity.

The first NDA submission was May 30, 1984 as a drug to lower cholesterol which was denied due to lack of efficacy. The current submission is for triglyceride lowering.

New toxicity data in this submission

1) Effects on bone marrow chromosomes of the rat
#86/FOU009/034 November 1985

No effects on chromosome structure were seen after exposure to single doses of 200, 1000, or 5000 mg/kg to CD rats.

Only one time was examined for the two lower doses (24 h post treatment) and the drug effect may not be evident at that time point.

2) Sensitizing potential by topical application to guinea pigs
June 1987.

Application of 0.2 or 0.4 g did not cause any reactions, according to the summary. However, no positive controls were run so we do not know if the study was carried out properly, and it is stated, in French, that erythemas could not be seen because of the color of the drug. The drug was wiped away but the skin was not examined for 6 hours.

(Submitted May 30, 1984 and not previously reviewed)
93-week oral carcinogenicity study in mice (Foreign data)
#493/17. May 1979-February 1981.

Treatment: Six groups of CD-1 mice (50/s/g) were given in the diet 0, 10, 60, or 200 mg/kg/day of fenofibrate (1.7, 10, and 33X HTD) or 0 or 400 mg/kg/day of clofibrate (10X HTD). The clofibrate mice were obtained as a separate batch and may have been a week younger. In week 46, each group was divided into two subgroups "of approximately equal size". One group continued to receive the same diet; the other received a diet with a 10-fold increase in vitamin A via a mixture of retinyl acetate and palmitate (from 3000 I.U./kg to 32,000 I.U./kg of feed). No reason was given for this.
(Doses of 60 mg/kg/day (fenofibrate) and 400 mg/kg/day (clofibrate) are both 10 times the HTD.)

Results
Mortality: no drug effects

Clinical signs: none drug-related but no data presented

Drug concentration in diet: calculated weekly and agrees with expected

Body weight: no drug effects (fenofibrate); females gained (clofibrate)

Food consumption: significantly increased M and HD males and females (fenofibrate)

Hematology (weeks 53 and 94)
No drug effects but large standard deviations makes detection of significant findings unlikely.

Clinical chemistry (GOT, GPT, ALP, cholesterol, TG; weeks 26, 53 and 94):
ALP: increased as a function of dose 2-12 times males (± vit A)
increased HD fenofibrate females (± vit A)
cholesterol: no drug effects
triglycerides: no drug effects
liver transaminases: trend to slight raises (2-fold maximum) in HD males (fenofibrate) and clofibrate males, but S.D. very large

Pathology
Organ weights (as % of body weight):
liver: (males) increased 2-3X M and HD fenofibrate; 1.8X clofibrate
(females) increased 2X HD fenofibrate; 50% clofibrate

Histopathology (non-neoplastic)
Groups= 0, 10, 60, 200 mg/kg/day fenofibrate; 0, 400 mg/kg/day clofibrate

No vitamin A
liver:

basophilic hepatocellular alteration:	4, 4, 3, 37;	15, 16% (males)
Kupffer cell pigmentation	4, 0, 52, 77;	0, 52% (females)
biliary proliferation	0, 0, 0, 15;	0, 0% (females)
	0, 0, 0, 20;	0, 4% (males)
lymph node: hyperplasia	7, 4, 4, 19;	4, 0% (males)

vitamin A (doses as above in 6 groups)
liver:

basophilic hepatocellular alteration	0, 0, 4, 29;	0, 4% (females)
Kupffer cell pigment	0, 0, 10, 22;	0, 25% (males)
	0, 4, 48, 67;	0, 52% (females)
hepatocellular hypertrophy	0, 0, 4, 25;	0, 48% (females)
	0, 0, 5, 22;	0, 13% (males)
lobular dysplasia	0, 0, 0, 43,	0, 4% (males)
	0, 0, 0, 8;	0, 0% (females)

Histopathology (tumor)
no vitamin A
liver:

carcinoma complex	4, 11, 27, 30;	4, 16% (males)
adenoma single	4, 4, 4, 19;	0, 12% (females)

with vitamin A
liver:

carcinoma complex	9, 5, 5, 52;	13, 21% (males)

Evaluation of Mouse Carcinogenicity Study

a) The mouse carcinogenicity has several deficiencies: doses were too low (making it a very insensitive test which would be invalid by today's standards; higher doses might have turned up more target organs and/or carcinogenicity in females) and histopatbology listings were minimal (cyst was the only item under pituitary whereas a mouse carcinogenicity study had 8 categories). The breakup of the 6 major groups to test the effect of vitamin A meant that 12 groups had to be analyzed and group size became too small to obtain statistical significance without pooling data (7-11 males/g and 11-16 females/g at 93 weeks in +/- vitamin A subgroups).

b) Non-neoplastic findings

The liver was clearly the major target organ with the facts as presented:
1) alkaline phosphatase was elevated in M and HD males and HD fenofibrate females
2) liver weight increased 2-3X in M and HD fenofibrate males and HD fenofibrate females (as well as clofibrate males and females)
3) basophilic hepatocellular alteration and hypertrophy, Kupffer cell pigmentation, biliary proliferation, and lobular dysplasia in M and HD fenofibrate and clofibrate treated mice
4) possible increases in serum transaminases (difficult to evaluate due to large standard deviations although says positive)

c) Neoplastic findings

Liver carcinoma increased as a function of dose in fenofibrate males in both +/- vitamin A groups (4, 11, 27, 30% and 9, 5, 5, and 52% -/+ vit A)
Liver adenomas increased in HD females (4, 4, 4, and 19% - vit A).

d) General

There was also an interesting effect on metabolism in that food consumption increased significantly (at 10X and 33X the HTD with fenofibrate) without any increase in body weight. Although no electron microscopy was done in this study, other studies in rats (and in people) have shown changes in mitochondrial morphology implying that there could be an effect on oxidative phosphorylation.

Summary of Significant Neoplastic findings

Mouse Carcinogenicity Studies

Laboratory (strain)	Multiples Tested	% Affected (control/treated)	Organ	Tumor
(CF-1)	0,2X,8X,33X	5,16,6,28 (M)	Liver	Carcinoma
		3, 5,0,17 (F)	Liver	Carcinoma
(CD-1)	0,2X,10X,33X	15,16,32,82 (M)	Liver	Carcinoma
		2, 4, 4,19 (F)	Liver	Adenoma

Rat Carcinogenicity Studies

Laboratory (strain)	Multiples Tested	% Affected (control/treated)	Organ	Tumor
(Wistar)	0,2X,8X,33X	3,0,11,70 (M)	Liver	Carcinoma
		3,1, 1,25 (F)	Liver	Carcinoma
		1,1,13, 8 (M)	Liver	Adenoma
		3,3, 3, 8 (F)	Liver	Adenoma
		0,1, 5,10 (M)	Pancreas	Carcinoma
		0,0, 1, 9 (M)	Pancreas	Adenoma
		0,0, 0, 4 (M)	Testis	Leydig cell
(Sprague-Dawley)	0,2,10X	0, 2, 10 (F)	Liver	Nodules
		0, 2, 14 (M)	Pancreas	Adenoma
		0, 0, 6 (F)	Pancreas	Adenoma
		2, 2, 16 (M)	Testis	Leydig cell
		0, 0, 4 (M)	Brain	Astrocytoma

ADDENDA

A) ____ rat study problems:

1) Inconsistent data Data submitted on frequency of tumors was inconsistent (each submission different) + data on mortality as a function of time (for each tumor type) had missing animals in every case making statistical analyses impossible.

2) Low survival in the females (28%, 32% and 40%; 0, L, HD) at the end of the study at week 117 lowered ability obtain statistical significance for females.

3) Low doses Doses were set too low (1 and 10 X HTD).

B) ____ rat carcinogenicity study results

1) Dose trend

dose trend in males for liver (carcinoma)
pancreas (adenoma and carcinoma)
testis (any tumor)

dose trend in females liver (carcinoma) and mammary (adenoma).

2) Earlier onset of tumors vs clofibrate:

fenofibrate males (10X HTD) tumors were statistically significant at:
week 30 (liver adenoma) vs week 52 for clofibrate
week 41 (liver carcinoma) vs week 78 for clofibrate
week 78 (pancreas adenoma and carcinoma) vs week 94 for clofibrate adenoma

fenofibrate females (33X HTD): tumors were statistically significant at
week 20 (malignancy any organ)
week 52 (liver carcinoma)
week 36 (mammary fibroadenoma)

clofibrate females (10X HTD): week 78 (uterine polyps)

C) No effect levels in rodent carcinogenicity studies

Studies: (W-L) or (HZ)

male rats:
2X HTD for liver adenomas/carcinomas (W-L);
2X HTD for Leydig cell tumors (testis); 8X (W-L)
8X HTD for pancreas adenoma and carcinoma (W-L)
2X HTD for pancreas adenoma (HZ)
2X HTD for brain astrocytoma (HZ)

female rats:
8X HTD for liver adenoma and carcinoma (W-L); 2X for liver nodules (HZ)

male mice:
8-10X HTD for liver carcinoma (W-L and HZ)

female mice:
8X HTD for liver carcinoma (W-L)
10X HTD for liver adenoma (HZ)

Considerations related to toxicity of fenofibrate

I) Pharmacokinetics

A) Long elimination half life

fenofibrate = 20 hours (vs 2 hours for gemfibrozil)

B) High plasma drug levels

1) Human plasma levels

Fenofibrate (5 mg/kg/day) 18 ug/ml (Biopharm Rev.2/2/89)
Gemfibrozil (24 mg/kg/day) 20 ug/ml (Biopharm Rev. 7/15/89)

2) Absorption in humans using 14-C fenofibrate
(Pharmacology Review 12/14/81)

species	dose (mg/kg/day)	plasma level	ratio
rat	25	34	1.4
dog	25	25	1.0
man	5	29	4.8

3-4X higher than dogs or rats which means that potential for toxicity is higher

II) Genotoxicity

Of the seven tests done, none were done by GLP procedures, and all had important deficiencies (analyzed by Dr. Leonard Schectman, HFV-154, with the results conveyed to this reviewer). The result is that one can not draw the conclusion that all were negative, as Fournier has done. The test laboratory conducting the studies concluded that there were several positive findings:

A) "weak clastogenic activity" (chromosomal aberrations)

B) "some activity in inducing high levels of thymidine incorporation in HeLa cells in culture in the presence of rat liver post mitochondrial supernatant"

III) Cytoxicity

(effects of fenofibrate on cultured human liver and skin cells)
(The plasma drug level in humans averages 14 ug/ml; range 6-25 ug/ml)

Fenofibrate added early in culture

A) Cell adhesiveness decreased as a function of dose (at 1 and 10 ug/ml)
B) "Severe" cell alterations increased " " " (" " " ")
C) Cell division delayed at 1 ug/ml
D) Detachment of confluent cells + accumulation of vacuoles, lipid globules, and lysosomes (1 ug/ml and above)

Fenofibrate added later in culture

A) Fenofibrate added after cells cultured 18 or 48 hours: cell division delayed (10 ug/ml) and detached (100 ug/ml)

B) "Severe" delay in cell proliferation when added after "several" weeks of culture: 10 ug/ml requires 18 days to reach confluence vs 6 for control (1st subculture) and 31 days vs 5 days for control (2nd subculture)

The no effect dose level = 0.1 ug/ml

"a cytotoxic action should be considered simply as an additional possible mechanism of carcinogenesis..." Fed. Reg., March 14, 1985, p.23.

"One of the earliest factors identified as associated with teratogenicity is cytoxicity." MHL Snow in "Approaches to Elucidate Mechanisms in Teratogenicity", p. 84, Frank Welsch, ed. (1986)

IV) Carcinogenicity

(direct comparison vs clofibrate by _____, Wistar rats)

A) Tumors appear earlier (statistically significant at similar multiples of HTD)

B) There are more target organs

(direct comparison vs clofibrate and gemfib. by Sprague-Dawley rats)

A) Astrocytomas in males at levels higher than historical and concurrent control (4% vs 1% historical control, biologically significant)

B) Other tumor frequencies same except liver carcinoma higher with clofibrate

V) Toxicity

increases in serum transaminases; decreases in hct (rat/dog/monkey)
cholethiasis/microstones (dog gallbladder)
lithiasis (dog kidney)
steatosis (dog liver)

VI) Maternal and Developmental Toxicity

RAT

Segment I (females): treated 2 weeks before and throughout gestation; doses were 2.5, 13, and 50X HTD; 8X HTD clofibrate; groups for delivery/weaning

DAMS

A) weight gain depression (dams)
5, 14, 33% (L, M, HD); 29% clof. (gestation, term sacrifice subgroup)
4, 4, 64% (L, M, HD); 34% clof. (gestation, deliver and wean subgroup)

	% 0, L, M, HD ; clofibrate
B) % delay in delivery:	10, 29, 21, 100%; 6% clofibrate
C) % post-implantation loss:	8, 15, 10, 68%; 28% clofibrate
D) litter size: decreased (p less than 0.01) M and HD; clofibrate (term sacrifice)	

FETUSES

A) % survival at birth:	97, 94, 97, 37%;	79% clofibrate
B) % survival neonate:	100, 91, 90, 4%;	77% clofibrate
C) % survival at weaning:	98, 93, 81, 0%;	89% clofibrate
D) pup wt decreased, wean. (females)	9, 25%;	10% clofibrate
(males)	8, 25%;	14% clofibrate

pup wt significantly decreased at term, birth, day 4 and weaning for M and HD males and females and clofibrate

p less than 0.01 for HD for all except maternal weight (not calculated)

RAT
Segment II (dosed days 6-15 gestation; doses 0, 2, 20, 60X HTD; 8X clofibrate)
Dams
No mortality or clinical signs
Weight gain dams = 36, 33, 27, -6; -12 grams (days 6-15 of gestation)
Weight gain dams = 154, 153, 150, 118; 110 grams (days 0-21 of gestation)
Food consumption = 21, 21, 20, 18; 15 g/rat/day (days 0-21 ")

Fetuses (individual data only, no litter data available)
Total number of findings (0, L, M, HD; clofibrate)
Gross and visceral: 3, 0, 11, 93; 9 clofibrate
Skeletal: 204, 223, 377, 577, 117 clofibrate

Individual categories (0, L, M, HD; clofibrate; see also Table 1)

Domed head/hunched shoulders/ rounded body/abnormal chest:	0, 0, 0, 2%;	0% clofibrate
Kyphosis:	0, 0, 0.5, 5%;	0% clofibrate
Stunted:	1, 0, 3, 30%;	4% clofibrate
Elongated sternal ribs:	0, 0, 0, 2%;	0% clofibrate
Malformed sternebrae:	0, 0, 0, 2%;	0% clofibrate
Extra foramen in palatine:	3, 2, 14, 10%;	12% clofibrate
Misshapen vertebrae:	13, 4, 19, 41%;	7% clofibrate
Extra ossification C7 extension:	0, 0.7, 0, 3%;	0% clofibrate
Supernumerary ribs:	18, 31, 34, 60%;	23% clofibrate

*Historical control data agrees with concurrent controls in all cases.

Gemfibrozil: no effects on female fertility/teratogenicity up to 10X HTD (maximum tested)

RABBIT (2.5, 25, 50X; clofibrate 5X)
Dams
Weight gains: not a function of dose (LD lost more wt than HD days 0-6)
Abortions/deaths:
HD: 5/20 aborted; 2/20 died (10 additional does added)
MD: 2/20 aborted (fenofibrate); 1/20 died (clofibrate)
LD/control: no effects

Fetuses
Dead fetuses: 0/100, 0/58, 2/82, 5/75 (0, L, M, HD); 2/73 clofibrate
Findings in fetuses: no drug effects due to either drug

Medical Problems (Medical Officer Review, October 30, 1987)
1) No long term human safety data (and patients will use a long time)
2) No substantial benefit over other drugs of this class already available
3) Never tested in the patient population in which it is intended (people at risk of pancreatitis)
4) Numbers of people tested in double blind trials low: 116 treated + 111 placebo for 6 months (type II); 75 treated + 72 placebo for 2 months (type IV) (=NDA indicated group)
5) The higher the TG, the higher the elevation of LDL-C as a result of treatment and the lower the ratio of LDL-C/HDL-C; "adverse and marked"
6) Significant toxicity seen: significant decreases in hematologic parameters and elevation of LFT's in treated groups (also seen in rats, dogs, and monkeys) plus one case of allergic hepatitis
7) If approved, patient population should be "subjects with a previous episode of abdominal pain and/or pancreatitis with a markedly elevated triglyceride level"

Summary and evaluation: Fenofibrate is a member of the "fibrate" family of drugs which, in addition to fenofibrate, includes two approved drugs, clofibrate and gemfibrozil as well as two in the IND stage,
and . Clofibrate was approved February 8, 1967 and gemfibrozil December 21, 1981.

There were 2 rat and 2 mouse carcinogenicity studies for the fenofibrate NDA. Fenofibrate was carcinogenic in all four studies: in 2 strains of each species (in both sexes of rats and mice) and in at least 3 organ systems (liver, pancreas, testis). In addition, there were 2 astrocytomas/50 males at 10X HTD in the rat study (4%) with none in controls, LD, clofibrate or gemfibrozil treated male rats and with a historical control rate in males of 1%.

Although all the fibrates are carcinogens when tested in rats and/or mice in the standard rodent bioassay, much has changed in our way of analyzing and understanding carcinogenicity and mutagenicity data since approval of clofibrate and gemfibrozil:

1) It was thought that 5 or 10 times the human dose was adequate for carcinogencity testing; none of the carcinogenicity studies were done with the "maximum tolerated dose" as is currently required. Under those conditions, when only male rats tested positive, sponsors could say that carcinogenicity was a finding restricted to male rats (Doses used for mouse carcinogenicity studies were the same as those given in rat carcinogenicity studies; mice with higher metabolic rates normally require higher doses to be comparable to rats).

2) It was thought that peroxisomal proliferation seen in rats was specific to that species. It has now been shown that peroxisomal proliferation can be induced by in cats, chickens, pigeons, and 2 species of monkey after exposure for 3-7 weeks. Proliferation was a dose-dependent but not a species-specific phenomenon (Reddy, et al., 1984, Am. J. Path., 171-183). There was no data on electron microscopy of liver in any species in the fenofibrate IND and NDA but it is assumed to behave like the class.

It was thought that these changes did not occur in human liver. However, two studies with clofibrate (1980 and 1983) showed strutural changes in mitochondria (atypical arrangement and proliferation of cristae, paracrystalline inclusions and giant mitochondria), increase in smooth and rough endoplasmic reticulum (SER and RER), as well as increased numbers of mitochondria and peroxisomes. The increase in SER and RER and numbers of mitochondria and peroxisomes "persisted for months" after stopping clofibrate treatment in 3/27 patients (Hanefeld, et al. Atherosclerosis: 36, 159-172 and 46, 239-246). Significant increases in peroxisomes in human liver have also been seen after treatment (IND); changes in morphology have been seen after gemfibrozil treatment (Atherosclerosis, 43, 19-37, 1982).

Fenofibrate was not studied in people with biopsies before and after drug treatment; therefore, nothing can be said about peroxisome numbers. In fact, there does not appear to have been an EM study of rodent liver. However, paracrystalline inclusions were seen in mitochondria, marginal plates in microsomes, as well as dilated ER, in human liver cells in treated patients (Blumcke et al., 1983; de la Iglesia, 1982).

Although it has been widely assumed that peroxisomal proliferation is the mechanism involved in the rodent liver tumors, this has not been proven. Furthermore, liver peroxisomal proliferation does not explain the tumors in pancreas and testis although a careful analysis of these tissues for peroxisomal changes has apparently not been done (these tissues have microperoxisomes which are more difficult to visualize, Novikoff).

3) It was thought that the occurrence of mouse liver tumors had no relevance to man. It has now been shown that tumors induced in B6C3F1 mice by furan and furfural are the result of activation of the H-ras oncogene by point mutations (Reynolds et al., 1987, Science, 237, 1309-1316). This is a general mechanism of carcinogenicity, not something unique to mice.

4) It was thought that negative results in the Ames in vitro mutagenicity test meant that a drug was not carcinogenic. We now know that all peroxisome proliferators are negative in this test in spite of being carcinogenic (Glauert et al., 1986, Cancer Res., 46. 4601-4606). One possible mechanism may involve free radical production by the hydrogen peroxide produced by peroxisomes.

Conclusion: Fenofibrate is carcinogenic in both mice and rats, in two strains each, in both sexes, in four organs (liver, pancreas, and testes as well as brain). It is fetotoxic and teratogenic.

The drug plasma levels are similar to those of gemfibrozil although the HTD dose is only 20% as high on a mg/kg basis; the halftime for fenofibrate is approximately 10 times longer (20 vs 2 hours) meaning that the body burden is significantly higher. Based on a radiolabeled study, man absorbs 3 to 5 times as much fenofibrate as do rats and dogs; thus, we can expect more toxicity and a possibly greater potential for tumors than would be apparent from the carcinogenicity studies. However, because of the long lag time in tumor development, this may not become clear for many years and then only with careful reporting.

Fenofibrate is cytotoxic and possibly genotoxic. Although we lack comparable information on gemfibrozil and clofibrate, we cannot ignore the information that we do have on fenofibrate. Fenofibrate is cytotoxic in human cell lines at drug plasma levels seen in vivo. Cytotoxicity affects fetal development and is one mechanism of carcinogenicity. There is some evidence for direct damage to DNA; however, the data were from flawed studies and, as a result, we are requesting further testing for genotoxicity and cytotoxicity of all three drugs by Fournier.

Fenofibrate causes hepatic toxicity in humans. The clinical and hepatic histological profile resembles "lupoid" autoimmune chronic active hepatitis with anti-organelle antibodies found in patients with drug-induced hepatis. Fenofibrate is listed as one of "the most common culprits" (Sherlock, S., The Spectrum of Hepatotoxicity Due to Drugs in The Lancet, pp. 440-444, August 23, 1986); also Hepatology 5, pp. 904-909 and 722-727, 1985). In the small study submitted with the NDA, there have been elevations of liver enzymes that have never returned to normal even after withdrawing drug (Dr. Ross Pierce Review) and even in the small sample of 43 people, a case of allergic hepatitis (Dr. August Troendle Review).

If it had been shown in clinical trials that fenofibrate could prevent pancreatitis and its use could be restricted to the group of patients that would clearly benefit, then there would be a rationale for approval. However, as Dr. August Troendle observed, the drug was never tested on that group (people with a history of pancreatitis were excluded from the trials) and no one, either on drug or placebo, developed pancrealitis while on the trial. Thus, we have no proven benefit and many risks, both potential (based on animal studies) and observed in humans.

For the reasons explained in the review: carcinogenicity, possible genotoxicity, cytotoxicity, maternal toxicity, fetotoxicity, teratogenicity, liver toxicity, the observed effects on humans (lupoid autoimmune chronic active hepatitis and decreased hematologic parameters) as well as a lack of demonstrated benefit to individuals at risk of pancreatitis, the Pharmacology reviewer can not recommend approval.

Elizabeth Barbehenn

Elizabeth K. Barbehenn, Ph.D.

cc: NDA Arch.
HFD-345
HFD-510 (19-304)
HFD-510/Jordan/Barbehenn/Pierce
HFD-502/Weissinger
Wang #0238r

Excellent Review
I agree completely
A Jordan
4/13/89

Comparison of Carcinogenicity of Fibrates
Mouse Carcinogenicity Studies

Drug (strain)	Multiples Tested	% Affected (control/treated)	Organ	Tumor
Gemfibrozil (CD-1)	0,1X,10X	8,19,14 (M) ~~0,0,0 (F)~~	Liver ~~Liver~~	Carcinoma ~~Carcinoma~~ ?
Clofibrate (CD-1)	0,4X,6X,9X	6,0,4,4 (M) ~~0,0,0,0 (F)~~	Liver ~~Liver~~	Carcinoma ~~Carcinoma~~
Clofibrate (CD-1)	0,10X	15,37 (M) 2,12 (F)	Liver Liver	Carcinoma Adenoma
Clofibrate (NMRI)	0,4X,12X,33X (M) 0,5X,17X,38X (F)	15,27,27,33 3,2,8,57	Liver Liver	Carcinoma Carcinoma
Fenofibrate (CF-1)	0,2X,8X,33X	5,16,6,28 (M) 3,5,0,17 (F)	Liver Liver	Carcinoma Carcinoma
Fenofibrate (CD-1)	0,2X,10X,33X	15,16,32,82 (M) 2,4,4,19 (F)	Liver Liver	Carcinoma Adenoma
(B6C3F1)	0,0.3X,1X,5X	16,6,36,42 (M) 4,8,14,26 (F) 0,0,0,6 (M) 0,0,0,12 (F)	Liver Liver Thyroid Thyroid	Carcinoma Carcinoma Adenoma Adenoma
	0, 3X, 8X, 13X	15,17,30,20 (M) 0,3,2, 5 (F)	Liver Liver	"neoplasm" "

Comparison of Carcinogenicity of Fibrates
Rat Carcinogenicity Studies

Drug (strain)	Multiples Tested	% Affected (control/treated)	Organ	Tumor
Gemfibrozil (CD)	0,1X,10X	6,27,19 (M)	Adrenal	Pheochromocytoma
		2,4,36 (M)	Liver	Adenoma
		0,8,10 (M)	Liver	Carcinoma
		2,16,34 (M)	Testis	Leydig cell
Gemfibrozil (Sprague-Dawley)	0,10X	0,34 (M)	Liver	Nodules
		0,10 (F)	Liver	Nodules
		0,4 (F)	Liver	Carcinoma
		2,10 (M)	Testis	Leydig cell
Clofibrate (Charles River CD)	0,7X	0,40 (M)	Liver	Nodules
Clofibrate (Wistar)	0,5X	1,14 (M)	Liver	Adenoma
		3,36 (M)	Liver	Carcinoma
		0,9 (M)	Pancreas	Adenoma
		7,20 (F)	Uterus	Polyp
Clofibrate (Sprague-Dawley)	0,10X	2,54 (M)	Liver	Carcinoma
		0,20 (F)	Liver	Carcinoma
		2,14 (M)	Testis	Leydig cell
Clofibrate (Sprague-Dawley)	0,3X,7X	11,21,31 (M)	Testis	Leydig cell
		0,10,11 (M)	Liver	Hepatoma
		1,10,25 (F)	Liver	Hepatoma

Comparison of Carcinogenicity of Fibrates
Rat Carcinogenicity Studies
(Unapproved Drugs)

Drug (strain)	Multiples Tested	% Affected (control/treated)	Organ	Tumor
(Fisher 344)	0,0.3X,1X,5X	8,10,40,65 (M)	Liver	Adenoma
		0,2,23,80 (M)	Liver	Carcinoma
		0,22,28,20 (M)	Pancreas	Adenoma
		0,0,0,8 (M)	Stomach	Carcinoma
(Sprague-Dawley) (8 months withdrawal)	0,10X,20X	3,4,8 (M)	Liver	Carcinoma
		1,1,6 (M)	Kidney	Adenoma + Adenocarcin
		5,16,26 (M)	Testis	Leydig cell
(Sprague-Dawley)	0,1X,3X,5X	3,5,4,8 (M)	Testis	Ledig cell
Fenofibrate (Wistar)	0,2X,8X,33X	3,0,11,70 (M)	Liver	Carcinoma
		3,1,1,25 (F)	Liver	Carcinoma
		1,1,13,8 (M)	Liver	Adenoma
		3,3,3,8 (F)	Liver	Adenoma
		0,1,5,10 (M)	Pancreas	Carcinoma
		0,0,1,9 (M)	Pancreas	Adenoma
		0,0,0,4 (M)	Testis	Leydig cell
Fenofibrate (Sprague-Dawley)	0,2X,10X	0,2,14 (M/F)	Pancreas	Adenoma
		0,2,10 (F)	Liver	Nodules
		2,2,16 (M)	Testis	Leydig cell
		0,0,4 (M)	Brain	Astrocytoma

TABLE 1a

SUMMARY OF GROSS AND VISCERAL FINDINGS IN OFFSPRING OF RATS TREATED WITH W13,635 ON DAYS 6-15 OF GESTATION, COMPARED TO THOSE TREATED WITH W5927 OR UNTREATED

Drug	W13,635			W5927	Controls
Group	I 360 mild	II 127 mild	III 14 mild	IV	V
Examined (Litters)	244 (19)	202 (15)	196 (17)	238 [a] (18)	218 (18)
Domed head/hunched shoulders/ Rounded body/abnormal chest	5 [b][c]	0	0	0	0
Encephalocele	1 [c]	0	0	0	0
Depressed skull (brain normal)	1	0	0	0	0
Kyphosis	11	1	0	0	0
Abnormally wide thorax	1	2	0	0	0
Stunted	74	6	0	9	3
Atrophied kidney(s)	0	2 [b]	0	0	0
Ovulation of kidney	1	0	0	0	0
Hydroureter/hydronephrosis	4	14	15	19	1
Discolored viscera	0	0	3 [b]	0	0

[a] = 1 macerated fetus excluded from summary (normal).
[b] = Littermates.
[c] = Same animal.

TABLE I b

SUMMARY OF SKELETAL FINDINGS IN OFFSPRING OF RATS TREATED WITH W13,635 ON DAYS 6-15 OF GESTATION, COMPARED TO THOSE TREATED WITH W5927 OR UNTREATED

Drug	W13,635			W5927	Control
Group	I (HD)	II (MD)	III (LD)	IV clof.	V
# Examined (Litters)	174 (19)	144 (15)	136 (17)	164 ⓐ (18)	155 (18)
Malformations:					
Elongated sternal ribs	4 ⓑ	0	0	0	0
Malformed skull bones	0	0	0	1	0
Malformed vertebrae	1	1	0	0	0
Malformed sternebrae	3 ⓒ	0	0	0	0
Bifid thoracic vertebrae	3	1	1	0	2
Anatomic Variations:					
Extra ossification site-skull	0	1	0	0	0
Extra foramen in palatine	18	20	3	20	4
Misshapen vertebrae	71	28	19	11	20
Misshapen sternebrae	22	26	33	48	27
Extra ossification site-C_7 extension	5	0	1	0	0
Supernumerary ribs	104	49	42	37	28
Ossification Variations:					
Hypoplasia-Generalized	4	2	0	2	0
Skull	11	7	1	5	0
Vertebrae	154	120	101	138	109
Sternebrae	118	26	12	56	8
Phalanges	59	2	3	11	5
Advanced-Calcaneus	0	0	7	1	1

ⓐ = Excludes 1 macerated fetus (normal).

ⓑ = Same animals as described in Table 3a, footnote ⓑ.

ⓒ = Two were littermates.

Comparison of Carcinogenicity of Fibrates
Mouse Carcinogenicity Studies

Drug (strain)	Multiples Tested	% Affected (control/treated)		Organ	Tumor
Gemfibrozil (CD-1)	0,1X,10X	8,19,14	(M)	Liver	Carcinoma
		0,0,0	(F)	Liver	Carcinoma
Clofibrate (CD-1)	0,4X,6X,9X	6,0,4,4	(M)	Liver	Carcinoma
		0,0,0,0	(F)	Liver	Carcinoma
Clofibrate (CD-1)	0,10X	15,37	(M)	Liver	Carcinoma
		2,12	(F)	Liver	Adenoma
Clofibrate (NMRI)	0,4X,12X,33X (M) 0,5X,17X,38X (F)	15,27,27,33 3,2,8,57		Liver Liver	Carcinoma Carcinoma
Fenofibrate (CF-1)	0,2X,8X,33X	5,16,6,28	(M)	Liver	Carcinoma
		3,5,0,17	(F)	Liver	Carcinoma
Fenofibrate (CD-1)	0,2X,10X,33X	15,16,32,82	(M)	Liver	Carcinoma
		2,4,4,19	(F)	Liver	Adenoma
(B6C3F1)	0,0.3X,1X,5X	16,6,30,42	(M)	Liver	Carcinoma
		4,8,14,26	(F)	Liver	Carcinoma
		0,0,0,6	(M)	Thyroid	Adenoma
		0,0,0,12	(F)	Thyroid	Adenoma

Comparison of Carcinogenicity of Fibrates
Rat Carcinogenicity Studies

Drug (strain)	Multiples Tested	% Affected (control/treated)	Organ	Tumor
Gemfibrozil (CD)	0,1X,10X	6,27,19 (M)	Adrenal	Pheochromocytoma
		2,4,36 (M)	Liver	Adenoma
		0,8,10 (M)	Liver	Carcinoma
		2,16,34 (M)	Testis	Leydig cell
Gemfibrozil (Sprague-Dawley)	0,10X	0,34 (M)	Liver	Nodules
		0,10 (F)	Liver	Nodules
		0,4 (F)	Liver	Carcinoma
		2.10 (M)	Testis	Leydig cell
Clofibrate (Charles River CD)	0,7X	0,40 (M)	Liver	Nodules
Clofibrate (Wistar)	0,5X	1,14 (M)	Liver	Adenoma
		3,36 (M)	Liver	Carcinoma
		0,9 (M)	Pancreas	Adenoma
		7,20 (F)	Uterus	Polyp
Clofibrate (Sprague-Dawley)	0,10X	2,54 (M)	Liver	Carcinoma
		0,20 (F)	Liver	Carcinoma
		2,14 (M)	Testis	Leydig cell
Clofibrate (Sprague-Dawley)	0,3X,7X	11,21,31 (M)	Testis	Leydig cell
		0,10,11 (M)	Liver	Hepatoma
		1,10,25 (F)	Liver	Hepatoma

Comparison of Carcinogenicity of Fibrates
Rat Carcinogenicity Studies
(Unapproved Drugs)

Drug (strain)	Multiples Tested	% Affected (control/treated)	Organ	Tumor
_____ (Fisher 344)	0,0.3X,1X,5X	8,10,40,65 (M)	Liver	Adenoma
		0,2,23,80 (M)	Liver	Carcinoma
		0,22,28,20 (M)	Pancreas	Adenoma
		0,0,0,8 (M)	Stomach	Carcinoma
_____ (Sprague-Dawley) (8 months withdrawal)	0,10X,20X	3,4,8 (M)	Liver	Carcinoma
		1,1,6 (M)	Kidney	Adenoma + Adenocarcin
		5,16,26 (M)	Testis	Leydig cell
_____ (Sprague-Dawley)	0,1X,3X,5X	3,5,4,8 (M)	Testis	Ledig cell
Fenofibrate (Wistar)	0,2X,8X,33X	3,0,11,70 (M)	Liver	Carcinoma
		3,1,1,25 (F)	Liver	Carcinoma
		1,1,13,8 (M)	Liver	Adenoma
		3,3,3,8 (F)	Liver	Adenoma
		0,1,5,10 (M)	Pancreas	Carcinoma
		0,0,1,9 (M)	Pancreas	Adenoma
		0,0,0,4 (M)	Testis	Leydig cell
Fenofibrate (Sprague-Dawley)	0,2X,10X	0,2,14 (M/F)	Pancreas	Adenoma
		0,2,10 (F)	Liver	Nodules
		2,2,16 (M)	Testis	Leydig cell
		0,0,4 (M)	Brain	Astrocytoma

TABLE 1a

SUMMARY OF GROSS AND VISCERAL FINDINGS IN OFFSPRING OF RATS TREATED WITH W13,635 ON DAYS 6-15 OF GESTATION, COMPARED TO THOSE TREATED WITH W5927 OR UNTREATED

Treatment	W13,635			W5927	Controls
Group	I 36 mid	II 127 mid	III 14 mid	IV	V
Examined (Litters)	244 (19)	202 (15)	196 (17)	238 ⓐ (18)	218 (18)
Domed head/hunched shoulders/ Rounded body/abnormal chest	5 ⓑⓒ	0	0	0	0
Cephalocele	1 ⓒ	0	0	0	0
Depressed skull (brain normal)	1	0	0	0	0
Kyphosis	11	1	0	0	0
Abnormally wide thorax	1	2	0	0	0
Stunted	74	6	0	9	3
Atrophied kidney(s)	0	2 ⓑ	0	0	0
Dilation of kidney	1	0	0	0	0
Ureter/hydronephrosis	4	14	15	19	1
Discolored viscera	0	0	3 ⓑ	0	0

ⓐ = 1 macerated fetus excluded from summary (normal).
ⓑ = Littermates.
ⓒ = Same animal.

TABLE I b

SUMMARY OF SKELETAL FINDINGS IN OFFSPRING OF RATS TREATED WITH W13,635 ON DAYS 6-15 OF GESTATION, COMPARED TO THOSE TREATED WITH W5927 OR UNTREATED

Drug	W13,635			W5927	Control
Group	I (HD)	II (MD)	III (LD)	IV	V
# Examined (Litters)	174 (19)	144 (15)	136 (17)	164 (a) (21)	155 (18)
Malformations:					
Elongated sternal ribs	4 (b)	0	0	0	0
Malformed skull bones	0	0	0	1	0
Malformed vertebrae	1	1	0	0	0
Malformed sternebrae	3 (c)	0	0	1	0
Bifid thoracic vertebrae	3	1	1	0	2
Anatomic Variations:					
Extra ossification site-skull	0	1	0	1	0
Extra foramen in palatine	18	20	3	20	4
Misshapen vertebrae	71	28	19	11	20
Misshapen sternebrae	22	26	33	48	27
Extra ossification site-C_7 extension	5	0	1	0	0
Supernumerary ribs	104	49	42	37	28
Ossification Variations:					
Hypoplasia-Generalized	4	2	0	2	0
Skull	11	7	1	5	0
Vertebrae	154	120	101	138	109
Sternebrae	118	26	12	56	8
Phalanges	59	2	3	11	5
Advanced-Calcaneus	0	0	7	1	1

(a) = Excludes 1 macerated fetus (normal).

(b) = Same animals as described in Table 3a, footnote (b).

) = Two were littermates.

DEPARTMENT OF HEALTH & HUMAN SERVICES — Public Health Service

Memorandum

Date: June 25, 1990

From: Chief, Genetic Toxicology Branch (HFF-166)

Subject: Review of L5178Y Mouse Lymphoma Mutagenicity Data for Gemfibrozil, Clofibric Acid and Fenofibric Acid

To: Elizabeth K. Barbehenn, Ph.D. (HFD-510)

Fournier Laboratories, Chenove, France sponsored L5178Y mouse lymphoma mutagenicity studies on Gemfibrozil, and Fenofibric Acid. The studies were conducted by and are identified with Study Nos. 10810-0447, 10811-0-447 and 10818-0-447.

The chemicals were identified as 1) Gemfibrozil, lot 18F 0334, a white powder, 2) Clofibric Acid, Lot 105F-3435, an off-white crystalline powder, and 3) Fenofibric Acid, a white crystalline powder. The positive control for the mutagenicity assays without metabolic activation was ethylmethane sulfonate (0.25 µl/ml and 0.40 µl/ml), and with metabolic activation the positive control was 3-methylcholanthrene (2.50 µg/ml and 4.0 µg/ml). The target cells were L5178Y, clone 3.7.2C and were originally obtained from No information is provided in the report about testing for mycoplasma contamination.

Cytotoxicity Testing: Dose range studies to determine the toxicity of the chemicals were carried out prior to the mutagenicity assays. Cells were treated with the compounds both in the presence and absence of aroclor 1254 induced rat liver S9 at a maximum dose of 1.0 mg/ml. Nine lower concentrations at two-fold increments were also tested to give a dose range of 1.95 µg/ml to 1000 µg/ml. After 4 hours exposure, the test compounds were removed and the cells were resuspended in fresh medium. After approximately 24 hours incubation, the density of the cells in each culture was determined and reduction in cell growth relative to the concurrent vehicle controls was determined.

1. Gemfibrozil - In the test without metabolic activation, treatment at the above dose levels resulted in suspension growth of 106.9% at 1.95 µg/ml to 16.3% at 250 µg/ml. At the two higher dose levels (500 µg/ml and 1000 µg/ml) no cell growth was reported. In the test with metabolic activation, suspension growth ranged from 110.6% for 1.95 µg/ml to 9.2% for the 250 µg/ml dose. Again, no growth was reported for the two higher doses.

2. Clofibric Acid - In the cytotoxicity test without

metabolic activation, suspension growth ranged from 89.9% at 1.95 µg/ml to 32.3% at 1000 µg/ml. In the test with metabolic activation, there was more variation in cytotoxicity in relation to dose. At 1.95 µg/ml, the level of suspension growth was 68.1%, at 7.81 µg/ml, 101.9%, at 125 µg/ml, 79.4%, at 250 µg/ml, 101.3%, and finally at 1000 µg/ml it was 33.8%.

3. Fenofibric Acid - In the test without metabolic activation, suspension growth ranged from 102.9% at 1.95 µg/ml to 4.0% at 500 µg. No cell growth was reported for the 1000 µg/ml dose level. In the test with metabolic activation, cytotoxicity ranged from 99.3% at 1.95 µg/ml to 40.1% at 250 µg/ml. No growth was reported at the two higher doses.

Mutagenicity Assays: Based on the data from the cytotoxicity tests, 9 concentration of each compound were tested. Cells (6×10^6) in single tubes were treated with the various concentrations of the test compounds for four hours, and after this exposure period, they were cloned for viable count (200 cells/plate) or in medium containing trifluorothymidine for mutant selection (1×10^6). Six to seven dose levels were cloned in the tests both without S9 and those with S9 for metabolic activation. The same sets of solvent and positive controls were used for three test compounds. The average mutant frequency for the three solvent controls without metabolic was 29.4 X $^{-6}$, and the mutant frequency for the corresponding positive control (EMS) was 411.3×10^{-6}. The average mutant frequency for the solvent controls with metabolic activation was 41.7×10^{-6}, and the positive control (MCA) was 318.6×10^{-6}.

1. Gemfibrozil - In the assay without activation, the test compound induced a dose related increase in mutant frequency, and at the highest dose that could be evaluated (250 µg/ml with 11.9% relative growth), the mutant frequency was 2.2X (66.0×10^{-6}) the solvent control (29.4×10^{-6}). Although the relative cloning efficiency at this dose was only 56.9%, there was an increase in the total number of mutant colonies. This response can be evaluated as weakly positive. However, in order to reach a final conclusion about the activity of this compound, a repeat assay is required.

   In the test with metabolic activation, none of the analyzable dose levels showed a significant increase in mutant frequency. These doses ranged from 5 µg/ml to 200 µg/ml, and the relative growth for these doses ranged from 99.2% to 18.7%.

2. Clofibric Acid - In the test without metabolic activation, there was no increase in mutant frequency at any of the dose levels tested (10 µg/ml to 1000 µg/ml). The relative total growth for these doses ranged from 87.5% to 27.6%.

   No increase in mutant frequency was observed at any dose level (50 µg/ml to 1000 µ/ml) in the test with metabolic activation. The relative total growth for the dose levels used in this test ranged from 90.9% to 28.3%.

3. Fenofibric Acid - There was no increase in mutant frequency in either the test without metabolic activation or the test with metabolic activation. The analyzable doses for the test without metabolic activation ranged from 50 µg/ml to 750 µg/ml and the relative growth for these doses from 94.7% to 17.1%. The analyzabe doses for the test with activation ranged from 50 µg/ml to 350 µg/ml and the relative growth from 90.5% to 27.0%.

This report contains a Quality Assurance Statement indicating that there was an inspection during the dosing phase of the assay and a review of the draft report. It is of interest that no other aspects of the test procedure were monitored, especially since the report covers the testing of three compounds. Considering this is a draft report, I am assuming that the final report also included a detailed protocol as well as copies of the raw data.

In summary, the results contained in this draft report indicate that neither Clofibric Acid or Fenofibric Acid induced a mutagenic response in this assay system either in the presence or absence of S9 for metabolic activation. Gemfibrozil was not mutagenic in the absence of metabolic activation but was possibly weakly mutagenic without activation. Because of the reduced cloning efficiency, a repeat assay is needed to determine what the actual response is.

Virginia C. Dunkel

Virginia C. Dunkel, Ph.D.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

N 11-324

Memorandum

Date July 20, 1990

From Chief, Genetic Toxicology Branch (HFF-166)

Subject Review of Mutagenicity Data for Gemfibrozil, Clofibric Acid and Fenofibric Acid

To Elizabeth K. Barbehenn, Ph.D. (HFD-510)

As you requested, the Genetic Toxicology Branch has reviewed the mutagenicity data on Gemfibrozil, Clofibric Acid and Fenofibric Acid submitted by Fournier Laboratories, Chenove, France. The data for the different assay systems were reviewed by those individuals with the relevant expertise and each of their reviews is attached.

The submission included data for each of the three compounds on induction of 1) mutation in L5178Y mouse lymphoma cells, 2) chromosomal aberrations in Chinese hamster ovary (CHO) cells, 3) sister chromatid exchange in CHO cells and 4) unscheduled DNA synthesis (UDS) in primary rat hepatocytes. The following summarizes the conclusions reached for these studies but each review should be consulted for full details.

Gemfibrozil

1. Mutation in L5178Y mouse lymphoma cells. The response in this assay was evaluated as weakly positive without metabolic activation. Since the cloning efficiency was low at the dose showing the highest increase in mutant frequency, a repeat assay is needed for clarification.

2. Chromosomal aberrations in CHO cells. There was no evidence that Gemfibrozil induced increases in chromosomal aberrations.

3. Sister chromatid exchange in CHO cells. Using criteria designated by the NTP, a positive response was induced in the presence of S9 for metabolic activation.

4. UDS in primary rat hepatocytes. Although the cytoplasmic grain counts were high, the response is sufficiently consistent to consider the response negative.

Since there is useable data for only two mutagenicity assays, no conclusion can be reached about the overall genotoxicity of Gemfibrozil. The reasons for this conclusion are as follows:

1. The test battery for determining genotoxicity is essentially incomplete without results for mutagenicity

testing in Salmonella typhimurium (Ames test). Is there any substantial reason why this compound could not be tested in this assay, or are there any published reports?

2. The SCE test results can not be used in the evaluation, since it is difficult to know what the data from this assay indicate. For example, analysis [Ray et al., Environ. Mol. Mutagen. 11(Suppl. 11):85, 1988] of data for 73 chemicals reported by the National Toxicology Program (NTP) [Tennant et al., Science, 236:933-941, 1987] indicates that responses in the SCE assay were essentially independent of exogenous metabolic activation requirements. In addition, of the 21 reported noncarcinogens tested in this assay, the results for 14 of the chemicals were either positive or equivocal.

3. As indicated above, the L5178Y mouse lymphoma mutagenicity assay needs to be repeated.

Clofibric Acid

1. Mutation in L5178Y mouse lymphoma cells. There was no indication of a mutagenic effect.

2. Chromosomal aberrations in CHO cells. There was no evidence that Clofibric Acid induced increases in chromosomal aberrations.

3. Sister chromatid exchange in CHO cells. Using criteria designated by the NTP, a positive response was observed both in the absence and presence of metabolic activation.

4. UDS in primary rat hepatocytes. Although the cytoplasmic grain counts were high, the response is sufficiently consistent to consider the response negative.

Although there are data for three mutagenicity assays indicating that Clofibric Acid is not genotoxic, no final conclusion can be reached without additional information about the activity of this compound in the Ames test (see comment above).

Fenofibric Acid

1. Mutation in L5178Y mouse lymphoma cells. There was no indication of a mutagenic effect.

2. Chromosomal aberrations in CHO cells. There was no evidence that Fenofibric Acid induced increases in chromosomal

aberrations.

3. Sister chromatid exchange in CHO cells. Using criteria designated by the NTP, a positive response was obtained in the presence of an exogenous metabolic activation system.

4. UDS in primary rat hepatocytes. The response with this compound is questionable and the assay should be repeated.

Since there is useable data for only two mutagenicity assays, no conclusion can be reached about the overall genotoxicity of Fenofibric Acid. The reasons for this conclusion are as follows:

1. The test battery for determining genotoxicity is essentially incomplete without results for mutagenicity testing in Salmonella typhimurium (Ames test). Is there any substantial reason why this compound could not be tested in this assay, or are there any published reports?

2. The SCE test results can not be used in the evaluation, since it is difficult to know what the data from this assay indicate. For example, analysis [Ray et al., Environ. Mol. Mutagen. 11(Suppl. 11):85, 1988] of data for 73 chemicals reported by the National Toxicology Program (NTP) [Tennant et al., Science, 236:933-941, 1987] indicates that responses in the SCE assay were essentially independent of exogenous metabolic activation requirements. In addition, of the 21 reported noncarcinogens tested in this assay, the results for 14 of the chemicals were either positive or equivocal.

3. As indicated above, the UDS assay need to be repeated.

Virginia C. Dunkel

Virginia C. Dunkel, Ph.D.

ORIGINAL

HASSALL

AUG 9 1990

NDA 19-304

August 9, 1990

Fournier Laboratories
Chenove, France

Submission: October 25, 1989

Amended Review of Genotoxicity Data for NDA

Drug: Fenofibrate

Dr. Virginia Dunkel, Chief, Genetic Toxicology Branch (HFF-166) has reviewed the genotoxicity data submitted in the NDA for gemfibrozil, clofibrate, and fenofibrate.

Dr. Dunkel concluded that fenofibrate and clofibrate were negative in three valid tests (mouse lymphoma, chromosomal aberration, and unscheduled DNA synthesis as well as the Ames test; sister chromatid exchange in CHO cells she says is no longer considered a valid test). Gemfibrozil was weakly positive in the mouse lymphoma cell mutation test which Hazleton said it planned to repeat; Dr. Dunkel feels that test should be repeated.

Recommendation: Ask Fournier whether has repeated the test (mutation in L5178Y mouse lymphoma cells, for gemfibrozil) as they indicated they planned to do (p.3 of October 25, 1989 submission).

Elizabeth Barbehenn

Elizabeth K. Barbehenn, Ph.D.

cc: NDA Arch
HFD-510 (19-304)
HFD-510/Jordan/Barbehenn/Pierce

Jordan
8/9

DEPARTMENT OF HEALTH & HUMAN SERVICES — Public Health Service

Memorandum

Date
July 3, 1990

From
Pharmacologist, Ph.D., HFF-166

Subject
Evaluation of In Vitro Sister Chromatid Exchange (SCE) Assay and Chromosomal Aberrations (CA) Assay with Gemfibrozil, Clofibric Acid and Fenofibric Acid

To
Virginia C. Dunkel, Ph.D.
Chief, Genetic Toxicology Branch, HFF-166

The SCE and CA assays were conducted by . from April 21 to July 17, 1989 using Chinese hamster ovary (CHO) cells with and without metabolic activation. The work was sponsored by Laboratories Fournier, and the test chemicals were Gemfibrozil, Clofibric acid and Fenofibric acid.

TEST PROTOCOL

The chemicals were tested up to the toxic level or to the limit of solubility. Negative, solvent and positive controls were tested concurrently with the test chemicals. Single cultures were used in SCE assays for controls and each dose level of test chemical, but duplicate cultures were used in CA assays. The treatment times were 2 and 25 h respectively for SCE assays with and without activation, and 2 and 17 h respectively for CA assays with and without activation. Aroclor-1254 induced rat liver S9 preparations were used as the exogenous activation system.

All slides except those of the positive controls were coded and 50 cells per culture were analyzed for SCE and 100 cells per culture for CA. The data were evaluated statistically, and a set of criteria was used to determine a positive response.

EVALUATION CRITERIA

The following criteria were used for a positive response:

For SCE induction:

(1) approximately a doubling in SCE frequency over the "background" (negative and solvent controls) levels at one or more doses; or
(2) a statistically significant increase in SCE frequency at a minimum of 3 doses and evidence for a positive dose response.

For CA induction:

(1) chromatid and isochromatid gaps were excluded from the evaluation.
(2) The percentage of cells with aberrations and the number of aberrations per cell were analyzed statistically, and test chemical significance was established where p values were less than 0.01.

RESULTS

In all assays, a positive response was induced by the positive control compounds, as expected. The responses induced by the test chemicals were as follows:

GEMFIBROZIL

SCE without activation: the doses evaluated were 2.02, 6.73, 20.0 and 67.3 ug/ml. No significant increase in SCE was observed at the concentrations analyzed (Table 1).

SCE with activation: the doses evaluated were 20.1, 67.0, 201 and 670 ug/ml. A significant increase in SCE was observed at 20.1, 67.0 and 670 ug/ml levels (Table 5).

CA with and without activation: the doses evaluated were 103, 154, 205 and 308 ug/ml without activation (Table 8), and 100, 251, 501 with activation (Table 14). No significant increase in CA was observed at the doses analyzed.

CLOFIBRIC ACID

SCE without activation: the doses evaluated were 19.6, 65.4, 196 and 654 ug/ml. A significant increase in SCE was observed at the highest test dose of 654 ug/ml (Table 2). A significant increase was also observed at 200 and 400 ug/ml levels in a repeat assay using 200, 400 and 600 ug/ml (Table 3).

SCE with activation: the doses evaluated were 66.7, 200, 667 and 2000 ug/ml. A significant increase in SCE was observed at 200 and 667 ug/ml levels (Table 6).

CA with and without activation: the doses evaluated were 807, 1210, 1610 and 2020 ug/ml without activation (Table 10), and 501, 1000, 1500 and 2000 ug/ml with activation (Table 16). No significant increase in CA was observed at the doses analyzed.

FENOFIBRIC ACID

SCE without activation: the doses evaluated were 1.98, 6.59, 19.8 and 65.9 ug/ml. No significant increase in SCE was observed at the dose levels analyzed (Table 4).

SCE with activation: the doses evaluated were 20.1, 66.9, 201 and 669 ug/ml. A significant increase in SCE was observed at 20.1, 66.9 and 201 ug/ml levels (Table 7).

CA with and without activation: the doses evaluated were 150, 300, 450, 600 and 900 ug/ml without activation (Table 12), and 250, 501, 751 and 1000 ug/ml with activation (Table 18). No significant increase in CA was observed at the doses analyzed.

CONCLUSIONS

The authors' conclusions are as follows:

1. All 3 test chemicals were negative for the induction of SCE under nonactivation conditions because (a) Gemfibrozil and Fenofibric acid did not induce statistically significant increases in any of the test doses evaluated and (b) Clofibric acid did induce statistically significant increases in both the initial and repeat assays, but the results failed to meet the requirement of a minimum of 3 significant doses plus a dose response (see criteria). The authors, however, did not rule out the possibility of Clofibric acid as a weak positive.

2. All 3 test compounds were also negative for the induction of SCE under activation conditions because the observed increases for 3 doses of Gemfibrozil, 2 doses of Clofibric acid and 3 doses of Fenofibric acid, although statistically significant upon comparison to the concurrent control values of 7.90 ± 0.35 and 7.14 ± 0.30 (Tables 5, 6 and 7), were insignificant upon comparison to a historical solvent control value of about 8.8 SCE/cell.

3. All 3 test chemicals were negative for the induction of CA under both the activation and nonactivation conditions because a statistically significant increase was not induced at any of the test doses evaluated.

COMMENTS

The reviewer's comments are as follows:

1. Historical solvent control for SCE. The historical solvent control value is stated as about 8.8 in the report (page 19, line 8). In order to assess the adequacy of the concurrent values obtained in the present assays, it is necessary to provide additional information such as the extent of the available data (n value), observed range, and standard

error of the historical value.

2. Evaluation criteria for a positive response in the SCE assay. The criteria used by the authors to consider a test chemical positive for SCE induction are more stringent than those used by the National Toxicology Program (NTP). In the NTP criteria, trials with 2 or more significant doses are taken as a positive response, and emphasis is placed on the number of doses that are positive rather than on the magnitude of the responses or its progression with doses (Environ Mol Mutagen 14: 165-187, 1989). According to the NTP criteria, all 3 test chemicals can be considered positive for the induction of SCE under activation conditions and Clofibric acid also positive for SCE induction under nonactivation conditions.

3. CA induction. I agree with the authors' conclusions that all 3 test chemicals were negative with respect to the induction of CA under the assay conditions.

4. A minor correction on page 19, line 10, the 5th word "positive". I believe the authors meant "solvent".

Ching-ju W. Sheu, Ph.D

NDA 19-304 May 21, 1990

Fournier Laboratories
Chenove, France

Drug: Fenofibrate

Submission: September 13, 1989

Dr. Virginia Dunkel (HFF-166: FBB 1476):

We have data submitted from Fournier of studies conducted by on three fibric acid derivatives: fenofibrate (subject of this NDA), clofibrate, and gemfibrozil. The latter two drugs are approved, and while fenofibrate is not yet approved, it looks like approval will be coming shortly.

All three drugs are carcinogenic in both mice and rats but there has not been a good study on genotoxicity, especially one comparing three drugs of the class.

We have little expertise in evaluating genotoxicity studies and are not sure whether the conclusions reached are valid. Since these drugs are widely used for lowering triglycerides and cholesterol, it is important to interpret these data correctly and use the proper terminology in the labeling.

We would be extrememly grateful for any advice you can provide. If I can be of any assistance, I can be reached at 443-3520.

Elizabeth Barbehenn

Elizabeth K. Barbehenn, Ph.D.

HFD-510
14B-19
5600 Fishers Lane
Rockville, MD 20857

BIO
REVIEW

DIV

FEB 27 1991

FENOFIBRATE
NDA 19-304
Reviewer: M. Daniel Gordin, Ph.D.

FOURNIER
Mamaroneck, NY
Submission Date
September 11, 1990

REVIEW OF DISSOLUTION FEB 27 1991

As requested, the sponsor conducted dissolution for fenofibrate capsule under various test conditions for comparison. In this submission, the firm has submitted the results of those studies for review.

METHOD:

Fenofibrate is a drug substance insoluble in aqueous solvents; therefore, sodium lauryl sulfate (SLS) is used as a surfactant. Dissolution was conducted at 1 L dissolution media at concentrations of 0.1, 0.05, and 0.03 M, paddle speeds of 90 and 120 RPMs on capsules with 1, 3, 5, and , different mixing times and different fenofibrate particle size with the normal formulation.

RESULTS:

The sponsor stated that a speed less than 60 RPM was not conducted because preliminary testing showed large variation in dissolution results. From the attached table, it can be seen that the decrease of rotation speed from 120 RPM to 90 RPM in most cases lead to a slight decrease in percent dissolved for any SLS concentration and the decrease in SLS concentration per rotation speed lead to a decrease in percent dissolved. Based on these results, the sponsor proposed the following dissolution procedure and specification:

1000 ml of 0.05 M aqueous SLS medium
USP apparatus II (paddle) at 120 RPM
Not Less Than at 180 min

However, it appears that 0.1 M SLS concentration at 90 RPM gives slightly better mean results than 0.05 M SLS at 120 RPM. Historically, the Division of Biopharmaceutics usually does not accept RPMs greater than 75 for the paddle method unless circumstances are warranted. Therefore, the sponsor is requested to conduct further dissolution test of bio-lots at 75 RPM and 90 RPM using 0.1 M SLS medium to ascertain the dissolution procedure that may be more desirable than using 120 RPM and 0.05 M SLS.

Additionally, the sponsor provided dissolution profiles on 7 industrial lots of which 4 lots were used in 2 clinical studies using the sponsor's proposed dissolution procedure.

RECOMMENDATION:

The Division of Biopharmaceutics (DB) has reviewed NDA 19-304 which was filed September 11, 1990 for fenofibrate. Based upon the results of the submitted dissolution tests, it is recommended that on an INTERIM BASES, the firm use the following dissolution method and specifications if HFD-510 intends to approve this NDA at this time:

Method: USP Apparatus II (paddle) at 120 RPM
Medium: 1000 mL 0.05 M aqueous SLS medium
Percent Dissolved Specifications: NLT at 180 min

However, the firm is requested to submit within 60 days of NDA approval, dissolution profiles for capsule lots used in bio-studies/clinical studies (if within expiration dates) and any new production size lots using the dissolution paddle method at 75 RPM and 90 RPM in 0.1 M aqueous sodium lauryl sulfate medium utilizing 12 dosage units/lot. If the NDA is to be held up, then the dissolution data should be requested immediately so that it can be reviewed prior to NDA approval.

Please convey the Recommendation as appropriate to the firm.

M. Daniel Gordin, Ph.D.
Pharmacokinetics Evaluation Branch

RD Initialed John P. Hunt February 23, 1991
FT Initialed John P. Hunt JPH 2/26/91

cc: Orig, HFD-510, HFD-426 (Gordin), HFD-344 (Turner), Drug, Chron, and HFD-19 (FOI).

\510\Fenofibr.Dis

DIV

NOV 5 1991

NOV 5 1991

FENOFIBRATE
NDA 19-304
Reviewer: M. Daniel Gordin, Ph.D.

Fournier
Mamaroneck, NY
Submission Date:
August 23, 1991

TYPE OF SUBMISSION: REVIEW OF A PROTOCOL

BACKGROUND:

Fenofibrate is a FAD that is approved in Europe and submitted to this country as a lipid-lowering agent. This study was requested in an Agency letter to the sponsor (Letter Date: April 30, 1990) which requested they conduct a food effect study comparing the bioavailability of the drug when it is given fasting, and with 20% fat, 30% fat, and 40% fat meal. In this protocol, the sponsor intends to compare the bioavailability of fenofibrate when the drug is administered fasting and immediately after meals of approximately 500 kcal with difference fat contents: 20%, 30%, and 40%.

TITLE: A STUDY TO INVESTIGATE THE EFFECT OF FOOD ON THE BIOAVAILABILITY OF FENOFIBRATE ADMINISTERED AS A CAPSULE IN HEALTHY VOLUNTEERS (PROTOCOL NUMBER FOU/C-9101)

INVESTIGATOR:

SUBJECTS:

The inclusion/exclusion criteria is attached. The sponsor intends to enrolled 24 healthy male subjects only who are 18-35 years old with a weight ±15% for their height and body frame and are healthy as determined by a pre-study physical.

DESIGN:

This is a Phase I study which will be randomized, single center, open, 4-way crossover design balanced for carryover effect in a total of 24 male subjects. Following an overnight fast, subjects will receive a single 100 mg of fenofibrate capsule, administered in the AM with 100 ml of water with the following treatments:

Treatment 1	fasting
Treatment 2	immediately after a 20% fat meal
Treatment 3	immediately after a 30% fat meal
Treatment 4	immediately after a 40% fat meal

All 4 meals for that day will be of the same percent fat content. There will a 1 week washout between treatments. Blood for analysis of fenofibrate will be obtained at 0, 1, 2, 3, 4, 5, 6, 8, 10, 12, 24, 48, 72, 96, and 120 hrs post dose.

SAMPLE ASSAY: Not specified

PK ANALYSIS:

STATISTICAL ANALYSIS:

PK parameters will be analyzed by ANOVA for the four period crossover design in which the total sum of squares is divided into subject, period, treatment, and residual. The two-one sided t-test approach and 95% confidence intervals including the Westlake method will be used to determine comparative bioavailability.

COMMENTS TO BE SENT TO THE FIRM:

1. You should include in the study report i) the PK parameters of fenofibrate for each subject i.e AUC (0-T), AUC (0-inf), Cmax, tmax, and half-lives and ii) a complete assay description and assay validation i.e., sensitivity, specificity (cross-reactivity if appropriate), linearity, % accuracy and precision (within and between runs) for the analysis of the drug/metabolite in serum using quality control standards and representative standard curves covering the range of the observed concentrations found in the study. Also drug/metabolite stability data during i) the collection and processing of samples, ii) storage and iii) during assay procedures should be provided.

2. For the capsule being studied, provided should be the batch/lot numbers and information to indicate if the batch(es) is from a full scale production size batch made on production size equipment at the proposed site of manufacture. If the batch(es) is not a full scale production size batch it should ideally represent 10% of the number of dosage units for what a full scale production size batch will be or 100,000 dosage units, whichever is greater.

3. In the statistical analysis of this study, you should include a sequence effect.

4. Following the dose of fenofibrate with the meal, for blood sampling for fenofibrate, the following additional timepoints are suggested: 30 min and 18 hrs post dose.

5. You are encouraged to submit the results of the study as an electronic submission [redacted] to help facilitate its review.

RECOMMENDATION:

The Division of Biopharmaceutics has reviewed Study Protocol FOU/C-9101) submitted to NDA 19-304 on August 23, 1991 and finds it acceptable provided the sponsor includes the above Comments as appropriate . Please convey Comments 1, 2, 3, 4, and 5 to the sponsor.

MAR 11 1992

MAR 11 1992

FENOFIBRATE
100 mg capsule
NDA 19-304
Reviewer: M. Daniel Gordin, Ph.D.

FOURNIER
Mamaroneck, NY
Submission Date
August 23, 1991

TYPE OF REVIEW: DISSOLUTION AND A BIOEQUIVALENCY STUDY

BACKGROUND:

Fenofibrate is indicated for lipid-lowering in patients with Types IV/V hyperlipoproteinemia. It will be marketed as a capsule which contains drug particles which have large variations in particle size distribution. A bioequivalency study conducted in only 9 subjects compared 2 batches which contained particles of different size distribution (Study 13 - original NDA bio-review Review Stamp Date: February 2, 1989). It was concluded that based on the 90% Confidence Intervals (Two One-Sided Tests Procedure), the study failed to demonstrate bioequivalency between the 2 batches. It was recommended that a second bioequivalency study be conducted using a larger number of subjects and to use lots showing the largest particle size distribution. Additionally, the sponsor was requested to submit new dissolution results using the dissolution paddle method at 75 RPM and 90 RPM in 0.1 M aqueous sodium lauryl sulfate medium utilizing 12 dosage units/lot in order to evaluate dissolution at various paddle RPM's. The sponsor has submitted a new bioequivalency study and dissolution which will be reviewed.

TITLE: COMPARATIVE BIOAVAILABILITY STUDY OF TWO DIFFERENT BATCHES OF FENOFIBRATE WITH DISSOLUTION PROFILES (STUDY NO. K 1789101 KH STUDY DATE: April 5, 1991)

INVESTIGATOR:

OBJECTIVE:

To demonstrate bioequivalency of 2 batches of fenofibrate with different particle size distribution profiles.

TREATMENTS:

Treatment 1: 100 mg capsule 1423RG median particle size
Treatment 2: 100 mg capsule 1518RG median particle size

DESIGN:

This was a balanced, randomized, 2 way crossover study involving 24 healthy male subjects who received the above treatments (Table with particle size distribution for both batches is attached) with 100 ml of water after a standard AHA Phase I breakfast of cereal, 1 boiled egg, 1 piece toast, 10 g margarine, 100 ml skim milk, 150 ml tea or coffee with 10 g sugar. After a 7 day washout, subjects were crossed to the alternate treatment. Blood samples were obtained at 0, 1, 2, 3, 4, 5, 6, 7, 8, 10, 12, 24, 48, 72, 96, and 120 hrs post dosing.

ANALYTICAL ANALYSIS:

COMMENT:

1. The assay is acceptable.

RESULTS:

Table 1. The kinetic parameters for fenofibric acid from 2 batches 1423RG and 1518RG (particle size distribution

	1423RG	1518RG	90%CI
AUC∞(ng.h/ml)	61851.97	58506.29	86-103
±SD	25864.45	26784.47	
Cmax (ng/ml)	3723.63	3428.29	81-104
±SD	1184.57	1199.96	
tmax (hr)	4.42	4.67	p>0.3
±SD	1.02	1.09	
half-life (hr)	16.33	17.44	98-115
±SD	5.22	4.87	
T-lag (hr)	0.73	0.46	
±SD	0.87	0.74	
Cl/F (L/h)	1.92	2.01	
±SD	0.91	0.78	

COMMENT:

1. A concern was raised that differences in fenofibrate particle size distribution between batches of finished drug product would lead to variations in the bioavailability of fenofibric acid. Consequently, the sponsor was requested to conduct a bioequivalency study comparing the kinetics of two batches with different particle size distribution. The results of this study demonstrated that based on the 90% Confidence Interval (Two One- Sided Tests Procedure), the 2 batches that differ in particle size distribution of are bioequivalent. However, although this study demonstrated bioequivalency between batches of different particle size distribution, it is not known what effect larger differences could have on the bioavailability of fenofibrate. Therefore, recognizing a need for tighter control over particle size, the sponsor instituted a 4 step particle size quality control specification which will be amended to their qc specifications for industrial fenofibrate as follows:

percentage of particles having a diameter < : 15-35%
percentage of particles having a diameter < : 35-55%
percentage of particles having a diameter < : at least 90%
percentage of particles having a diameter < : at least 99%

The 2 batches used in this study while differing in the median size distribution, passed this quality control check and were shown to be bioequivalent. Therefore, it is anticipated that the introduction of this tighter quality control check over particle size distribution would help insure batch to batch repeatability in terms of the pharmacokinetics/biovailability of fenofibric acid.

2. The relative bioavailability of fenofibric acid from batch 1518RG to batch 1423RG was 97.5% ± 5.0 (±SD).

DISSOLUTION:

As requested, the sponsor conducted dissolution for fenofibrate capsule under various test conditions. In this submission, the firm has submitted the results of those studies for review.

METHOD:

Fenofibrate is insoluble in aqueous solvents; therefore, sodium lauryl sulfate (SLS) is used as a surfactant. The 3 batches, 1554RG, 1423RG, and 1518RG, were used in studies K 1789101KH9102 and FEN8906, and batches 26 and 27 are recent industrial scale production batches for comparison.

DISCUSSION:

Dissolution was performed in USP Apparatus II (paddle) in aqueous solution of 0.1 M and 0.05 M sodium lauryl sulfate (SLS) at 37°C at 75, 90, and 120 RPM's for comparison purposes. Ideally, the Division of Biopharmaceutics (DB) does not accept paddle RPM's to be greater than 75 RPM's; however, since the results showed i) using 75 RPM's did not give greater than dissolution by 3 hrs and ii) comparable fenofibrate capsule percent dissolution in 0.1 M SLS at 90 RPM to 0.05 M SLS at 120 RPM, then the DB will accept the 90 RPM in the 0.1 M SLS concentration. As to dissolution specifications, the sponsor proposed the following 2 step specification to characterize dissolution of fenofibrate capsules:

40 min: A mean of 6 capsules Not Less Than : and Not More Than

180 min: No capsule being less than .

RECOMMENDATION:

The Division of Biopharmaceutics has reviewed NDA 19-304 which was filed August 2[illegible]91 for fenofibrate. Based upon the results of the submitted dissolution tests, the following dissolution method and specifications are recommended for fenofibrate capsule:

Method: USP Apparatus II (paddle) at 90 RPM
Medium: 1000 ml of 0.1 M SLS medium

Percent Dissolved Specifications:
40 min: A mean of 6 capsules Not Less Than and Not More Than
180 min: No capsule being less than

In addition, as the sponsor proposed, institute the following particle size specification for fenofibrate:

percentage of particles having a diameter < : 15-35%
percentage of particles having a diameter < : 35-55%
percentage of particles having a diameter < : at least 90%
percentage of particles having a diameter < : at least 99%

Please convey the Recommendation to the firm.

M Daniel Gordin

M. Daniel Gordin, Ph.D.
Pharmacokinetics Evaluation Branch

RD Initialed Nicholas Fleischer, Ph.D M Dlech 3/4/92
FT Initialed Nicholas Fleischer, Ph.D. N Fleischer 3/4/92

cc: NDA 19-304, HFD-510, HFD-426 (Gordin, Fleischer), Drug, Chron, F (Parekh) and HFD-19 (FOI).

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FENOFIBRATE
100 mg capsule
NDA 19-304
Reviewer: M. Daniel Gordin, Ph.D.

05 NOV 1992

FOURNIER
Mamaroneck, NY
Submission Date
April 24, 1992

DIV

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BACKGROUND:

Fenofibrate is indicated for lipid-lowering in patients with Types IV/V hyperlipoproteinemia. It will be marketed as a 100 mg capsule. The Reviewing Medical Officer requested a consult on the following study in order to confirm or refute the sponsor's claim that based on the results of this study "in patients suffering from moderate renal insufficiency (creatinine clearance of 50 to 90 ml/min) the oral clearance and the oral volume of distribution are increased, compared to healthy adults, but the half-life remained unchanged. These parameters of PK of fenofibric acid led to the conclusion that no adaptation of dosage regimen was required in patients with moderate renal impairment." The review of the study follows:

TITLE: PHARMACOKINETICS OF FENOFIBRATE IN PATIENTS WITH RENAL DISEASE (REPORT K 178 85 03KH8902)

INVESTIGATOR:

OBJECTIVE:

To compare the pharmacokinetics of fenofibrate from renal disease patients to healthy subjects.

DESIGN:

This was a parallel, single dose study in 15 patients with renal disease (ages 16-75, weights 38 to 75 kg, 3 females, 12 males) who received a single 100 mg fenofibrate capsule dose in the AM after a 10 hr overnight fast with a standard high fat breakfast. They were distributed into 3 groups (N=5/group) according to degree of renal impairment as assessed by creatinine clearance:

Group I	50 ml/min < ClCr < 90 ml/min
Group II	10 ml/min < ClCr < 50 ml/min
Group III	hemodialyzed ClCr < 10 ml/min

A group (N=12) from an earlier study was used for comparison as healthy adults. Urine and blood samples were obtained and analyzed for fenofibric acid by a fully validated HPLC procedure.

RESULTS:

Parameters	Group I (mild) n=5	Group II (moderate) n=5	Group III (severe) n=5	Healthy adults (R) n=12	Pairwise comparisons
Cmax (mg/l)	1.856 ± 1.400	1.702 ± 0.656	1.866 ± 1.091	4.8 ± 0.9	I II III R
tmax (h)	8.03 ± 8.98	6.78 ± 2.48	7.80 ± 9.15	4.8 ± 0.8	II I III R
t1/2 (h)	28.76 ± 23.40	50.85 ± 34.17	162.34 ± 203.20	20.8 ± 5.9	III II I R
AUC (mg/l.h)	44.92 ± 14.25	117.83 ± 72.62	367.93 ± 458.03	97.6 ± 54.0	III II R I
Cl/f (l/h)	2.127 ± 0.642	1.047 ± 0.700	0.680 ± 0.684	1.07 ± 0.49	I II III R
Vz/f (l)	94.84 ± 82.52	56.12 ± 34.97	63.08 ± 19.03	30.3 ± 8.5	R II III I
ClR2 (l/h)	0.949 ± 0.869	0.080 ± 0.055	0.063 ± 0.070	0.38 ± 0.23	III II R I
Ae2 (mg)	36.85 ± 28.56	7.71 ± 6.12	4.11 ± 2.81	27.6 ± 12.5	III II I R
Ae2/Ae1	2.79 ± 1.39	2.35 ± 1.74	1.48 ± 0.29	-	
fu	1.76 ± 0.43	1.80 ± 0.41	2.13 ± 0.40	1.00 ± 0.20	
	Ave: 31-63	40-207	43-1166	52-243	

* n = 4

The mean for groups connected by overhead bars are not significantly different ($p > 0.05$).

DISCUSSION:

A journal review article (Cayen, 1985) discussed the effects of kidney disease on clofibrate, a fibrate compound similar to fenofibrate. Kidney disease can result in extensive albumin loss and abnormal albumin molecules with a lower capacity for binding acidic drugs. These 2 conditions can result in different effects on the kinetics of a drug. In patients with nephrotic syndrome (CrCl > 50 ml/min), the half-life of clofibrate was 6-11 hr compared to 17-20 hr in normal subjects; however, the amount of clofibrate and its conjugate excreted in urine from nephrotic patients was similar to controls. In patients with chronic renal failure, there was a decrease in the elimination of clofibrate and conjugate which resulted in higher serum concentrations and longer clofibrate half-lives compared to normals. It was concluded that myopathy experienced by hyperlipidemic uremic patients treated with clofibrate appeared to be due to impaired urinary excretion of free and conjugated clofibrate as well as decreased protein binding which resulted in higher steady-state levels and prolonged half-life which allowed increased amounts of free clofibrate to cross cellular membranes into skeletal muscle.

Specifically for fenofibrate, it is difficult to draw definitive conclusions from this study due to 1) the high degree of variability seen; 2) the use of PK results from 12 subjects from an earlier study (Bianchetti and Duchiev, 1984); 3) the lack of specific PK/PD correlation i.e. what level of fenofibrate is toxic; 4) the use of a single dose as opposed to multiple doses and 5) the use of only 5 patients/renal disease group which results in a low power to detect a true difference. However, the results of this study can be used to detect any trends that may suggest a

difference based on the experience with clofibrate.

Regression analysis was performed on creatinine clearance vs fenofibric acid AUC. The results showed little correlation (r = 0.38); however, the individual results in Group III showed that 1 out of 5 patients with CrCl < 5 had an AUC value of 1167; and in Group II, 2 patients with CrCl of 15 and 12 had fenofibric acid AUC values of 151 and 227, respectively which is compared to a mean AUC of 98 mcg.h/ml in healthy subjects.

The increases in the mean results of fraction unbound (fu) (1.76, 1.80, 2.13), fenofibric acid AUC (44.9, 117.8, 367.9), elimination half-lives (28.7, 50.8, 162.3), and decrease amount excreted (Ae2) (36.8, 7.71, 4.11) suggest that as the severity of the renal disease progresses from Group I to III, there is an increasing impact on the PK of fenofibric acid (the results may have been more pronounced if a multiple dose study was used). Therefore, if the conclusion by Cayen that myopathy in uremic patients treated with clofibrate may be due to impaired free and conjugated clofibrate urinary excretion, increased fraction unbound, and prolonged half-life is valid and if there is a medical concern that patients with "moderate" renal disease may be at a higher risk due to these differences, then the trend seen in the mean data for fenofibric acid suggest that a dosage adjustment may be justified based on these results.

M. Daniel Gordin

M. Daniel Gordin, Ph.D.
Pharmacokinetics Evaluation Branch

RD Initialed Nicholas Fleischer, Ph.D. 11-9-92
FT Initialed Nicholas Fleischer, Ph.D.

cc: NDA 19-304, HFD-510, HFD-510 (Pierce), HFD-426 (Gordin, Fleischer), Drug, Chron, RI and HFD-19 (FOI).

\510\Fenofibr.Con

Cayen M. Disposition, Metabolism, and Pharmacokinetics of Antihyperlipidemic Agents in Laboratory Animals and Man; Pharmac. Ther. Vol 29, 157, 1985

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FENOFIBRATE
100 mg capsule
NDA 19-304
Reviewer: M. Daniel Gordin, Ph.D.

FOURNIER
Mamaroneck, NY
Submission Date
May 8, 1992

Div

BACKGROUND:

Fenofibrate is indicated for lipid-lowering in patients with Types IV/V hyperlipoproteinemia. It will be marketed as a capsule which contains drug particles which were shown to have large variations in particle size distribution. A bioequivalency study conducted in only 9 subjects compared 2 batches which contained particles of different size distribution (Study 13 - original NDA bio-review Review Stamp Date: February 2, 1989) which concluded that the study failed to demonstrate bioequivalency between the 2 batches based on the 90% Confidence Intervals (Two One-Sided Tests Procedure). It was recommended that a second bioequivalency study be conducted using a larger number of subjects and to use lots showing the largest particle size distribution. The sponsor submitted a new bioequivalency study which was reviewed (Review Stamp Date: March 11, 1992) and found to be acceptable. Consequently, the sponsor instituted a particle size specification (Table 1) for fenofibrate which was acceptable and recommended as part of the product specifications.

Table 1. The particle size distribution specifications.

percent particles having a diameter <	: 15-35%
percent particles having a diameter <	: 35-55%
percent particles having a diameter <	: at least 90%
percent particles having a diameter <	: at least 99%

In this submission, the sponsor has summarized all data that was submitted to the Division of Biopharmaceutics which has already been reviewed; therefore, a review of this data is not necessary.

M Daniel Gordin

M. Daniel Gordin, Ph.D.
Pharmacokinetics Evaluation Branch

RD/FT Initialed Nicholas Fleischer, Ph.D. for 9.4.92

cc: NDA 19-304, HFD-510, HFD-426 (Gordin, Fleischer), Drug, Chron, and HFD-19 (FOI).

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DIV FILE

LIPANTHYL^{R}
100 mg capsules
NDA 19-304

Reviewer: Ziad Hussein, Ph.D.
PC
1-D, 13-S

FOURNIER Laboratories
Dijon,France
Laison office
Brookline,MA 02167
Submission Dates:
May 31, 1985
July 10, 1986
April 29, 1987

FEB 2 1989

REVIEW OF A NEW DRUG APPLICATION

BACKGROUND

Fenofibrate is a derivate of isobutyric acid. After oral administration, fenobibrate undergoes rapid and extensive hydrolysis to the major active metabolite, fenofibric acid, which has an antihyperlipidaemic activity. No unchanged fenofibrate was detectable in human plasma and urine after oral administration of ^{14}C-fenofibrate in a capsule during a standardized meal. The recommended dose is 100 mg x 3 times/day with or immediately before meal.

Several studies were submitted under IND and NDA 19-304 (5/31/85 and 7/10/86) for fulfilling the biopharmaceutic requirments for the approval of the product Lipanthyl^{R}. Initial review showed that the submission of NDA 19-304 (5/31/85 and 7/10/86) is not approvable as the studies required by the Division of Biopharmaceutics were deficient or incomplete. Thereafter, the sponsor resubmitted NDA 19-304 with additional BA/PK studies for fulfilling the biopharmaceutic requirments.

In a meeting held on 7/8/1986 it was indicated that fenofibrate capsules will be manufactured by both Fournier Laboratories, France and by Bristol Myers, Enansville, USA.

STUDY -1-
Dissolution Test of Lipanthyl^{R} Capsules

Note: This study was not previously evaluated by Dr. Wang in her bio-review.

TITLE: No title.

REPORTER:

OBJECTIVE: To study the dissolution of fenofibrate from Lipanthyl^{R} capsules and the effect of rotation speed and fenofibrate particle size on the dissolution rate.

FORMULATION: Lipanthyl^{R} capsule with the following composition: 100 mg fenofibrate.

METHODS: Rotating paddles USP XXI, type 2.

Solobility: It was determined at 37° C in the following mediums: warer (A), 0.1 N HCL (B), pH 6.8 buffer ($NaHPO_4$ 0.2 M/ citric acid, C) and 0.025 M, 0.05 M and 0.1 M sodium lauryl sulfate (D, E and F, respectively).
Medium: 1000 ml of 0.1 M sodium laurylsulfate (SLS) at 37°± C.
Rotation Speed: 60, 80, 90, 120 or 150 rpm.
Sampling: 5 ml after 20, 40, 60, 120 and 180 min replaced by 5 ml SLS.
Fenofibrate Assay: 2 ml of each sample were diluted up to 20 ml with SLS. Absorbance of an appropiate calibration curve and samples was measured at 288 ± 2 nm using SLS as the blank. A correction was made by subtracting the absorbance of samples from dissolution of empty capsule. The dissolved amount of fenofibrate was calculted from validated calibration curve.

RESULTS

Solubility: 1.48, 0.91, 0.77, 273, 625 and 1250 mg/L in mediums A, B, C, D, E and F, respecively.
Rotation Speed:: The influence of paddle rotation speed on fenofibrate drug substance dissolution (fenofibrate batch no. 86605) is listed in Table 1.
Dissolution Specification: A specification of the USP type for fenofibrate capsules where Q = in 3 hr.
Dissolution from Different Batches: As listed in Table 2 more than of fenofibrate was dissolved at 3 hr, at 120 rpm, from 5 different batches (2983, 2986, 2993, 3158, 3231).
Dissolution of Granulometric Classes of Fenofibrate: The percentage of fenofibrate dissolved from a batch with different particle size are listed in Table 3. The correlation between the particle size and absorption in rats is listed in Table 4.

CONCLUSION: The dissolution profiles of fenofibrate from different batches of Lipanthyl^R capsules, at rotation speed of 120 rpm, were very similar and exceeded the specification requirement of Q= in 3 hrs. The specification requirement was also exceeded by using lower rotation speed down to 60 rpm, however the dissolution rate was different. Decreasing the particle size of fenofibrate used in the Lipanthyl^R capsules resulted in an increase in the dissolusion rate.

COMMENTS

1. Although more than of fenofibrate was dissolved at 3 hr, at lower rotation speed (60 rpm), the speed used by the sponser in most of the dissolution tests of fenofibrate is higher than that required by the FDA and there is variability between batches. The percentage of fenofibrate dissolved at 3 hr varies from which is significant. This variability could be due to unappropiate dissolution medium and/or rotation speed.
2. The batches used in the dissolution tests are not those used in the bioavailability studies. The sponser is recommended to conduct dissolution tests for the same batches used in the bioavailability studies according and following the required regulations.

3. The sponser stated that "The particle size of fenofibrate is controlled so that at least 90% of the drug particles have a diameter of less than , and at least 99% of the particles have a diameter of less than These dimensions correspond roughly with USSS respectively.". As seen in Tables 3 and 4, the dissolution and the absorption of fenofibrate are affected very much by the distribution of the particle size.

RECOMMENDATIONS: The in vitro dissolution method and specification for fenofibrate 100 mg capsules is not acceptable at the present time. The following information/data are required.

1. Dissolution of fenofibrate from Lipanthyl^{R} capsules in simulated gastric and intestinal fluids provided the sponsor show that the solubility of fenofibrate in these two mediums is very low.

2. The sponsor should identify for the batches used in the dissolution tests whether those are production size batches made on production equipment and the particle size distribution for each batch.

3. The sponsor should provide the batch nos. for the capsules used in the in vitro dissolution studies that compared 60, 80, 90, 120 and 120 rpms along with whether the bathces were a production size batches made on production size equipment and whether it was manufactured in France or the U.S..

4. Based upon the in vitro dissolution profile data provided at 60 rpm, the Division of Biopharmaceutics is not convinced that this rotation speed could not be used as opposed to the sponsor's proposed rotation speed of 120 rpm.

5. The sponsor should provide in vitro dissolution profile data for each batch/lot used in all the bio-studies using a paddle speeds of 60 and 120 rpm. The sponsor should also provide information about the particle size used in the production of each batch as well as whether these were production batches/lots made on production size equipment.

Table 1

% fenofibrate dissolved at time	ROTATION SPEED		
	90 RPM	120 RPM	150 RPM
1 hour			
2 hours			
3 hours			
4 hours			
5 hours			
6 hours			

Time	% fenofibrate dissolved	
	60 RPM	80 RPM
20 min		
40 min		
60 min		
2 hours		
3 hours		

Table 2

% Fenofibrate Dissolved at 3 hours
(results of six individual capsules per batch)

Batch Number

2983	2986	2993	3158	3231

APPENDIX

CORRELATION OF DISSOLUTION AND BIOAVAILIBILITY IN RAT

Dissolution results of granulometric classes of fenofibrate (batch 722) are following :

Particle size in um	% Fenofibrate dissolved (± SD) at sampling times				
	20 min	40 min	1 hour	2 hours	3 hours
	–	–	–	–	–

Pharmakokinetic parameters of fenofibric acid (LF 153), mean metabolite of fenofibrate in plasma in rat of the same granulometric classes of fenofibrate (batch 722) are following :

particle size um	C max (ug/ml)	AUC (ug/hr/ml)	t max (hr)
	58.77	690	4
	17.35	232	4
	11.34	154	6
	12.08	63	4
	6.67	49	4
	6.94	40	4

The logarithms of the AUC were plotted against the percentage of fenofibrate dissolved at 20 and 40 minutes by the method of least squares. Curves and linear regression analysis are hereafter.

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STUDY -3-

CLINICAL PHARMACOKINETIC STUDY OF PROCETOFENE, A NEW HYPOLIPIDEMIC DRUG, IN VOLUNTEERS.

Note: This study was previously evaluated by Dr. Wang in her bio-review.

INVESTIGATOR:

OBJECTIVE: To study the pharmacokinetics of fenofibric acid in volunteers after single and multiple dose administration.

STUDY PROCEDURE:

1- Single-Dose Study:

Subjects: Six healthy male volunteers. Age: 23 to 26 years. Weight: 61 to 74 Kg.

Design: 3 Lipanthyl^{R} capsules (300 mg fenofibrate) were given with 200 ml water after an overnight fast. Breakfast was served 2 hr postdosing.

Blood and Urine Collection: Blood at 0, 2, 4, 6, 8, 10, 12, 26, 50 and 76 hr postdosing. Centrifugation, plasma separation and storage at -20^{0} C until assay. Urine was collected during periods of 0-24, 24-48 and 72-96 hrs and was immediately frozen at -20^{0} C.

2- Multiple-Dose Study:

Subjects: 10 healthy volunteers (6 males and 4 females). Age: 22 to 24 years. Weight: 52 to 79 Kg.

Design: 2 Lipanthyl^{R} capsules (200 mg) at 8 a.m. and one capsule (100 mg) at 8 p.m. for 10 days and 3 capsules (300 mg) at 8 a.m. of day 10.

Blood and Urine Collection: Blood at 0, 24, 48, 72, 96, 120 and 240 hrs after the first administration and 2, 4, 6, 8, 10, 24, 36, 48, 60 and 72 hrs after the last dose at day 10. Centrifugation and plasma separation. Urine was collected from day 9 to 14 at 24 hrs intervals. Plasma and urine were stored at -20^{0} C until analysis.

ANALYTICAL METHODOLOGY:

DATA ANALYSIS: Plasma profiles of fenofibric acid were analyzed by curve fitting with a program based on a multi-exponential equation. $t_{1/2}$ and AUC were determined from the fitting. C_{max} and t_{max} and the urinary excretion ($A_{e,0-96}$) were observed values

RESULTS:

1- Single-Dose Study: The mean parameters are as follows: t_{max}= 5 hr, C_{max}= 6.05 ± 2.3 µg/ml, $t_{1/2}$= 26.6 ± 2.9 hrs, $AUC_{0-\infty}$= 169.9 ± 23 µg.hr/ml and $A_{e,0-96}$= 27.9 ± 5.9%. A large inter-subject variabilities were observed in various parameters.

2- Multiple-Dose Study: The following parameters were obtained: $C_{ss,trough}$= 10 µg/ml reached after 120 hrs, Accumulation factor = 2 after 10 days administration of 300 mg/day, A_e= 31.8% and 30.9% on days 9 and 10, respectively. The following parameters were obtained after the adminstration of 300 mg at day 10: C_{max}= 17.6 ± 2.5 µg/ml, t_{max}= 6 hrs, $t_{1/2}$= 21.7 ± 1.1 hrs (not significantly different from $t_{1/2}$ obtained from the single-dose study) and the bound fraction of finofibric acid was 99.6-99.8%.

CONCLUSION: This study shows that the elimination half-life and the urinary excretion of fenofibric acid do not alter after the multiple-dose regiment.

A trough value of 10 µg/ml for fenofibric acid was acheived after dosing of 300 mg/day for 9 to 10 days with an accumulation factor around 2. The protein binding of fenofibric acid estimated to be 99.6-99.8%.

COMMENTS:

1. In the single dose study an unspecified breakfast was served 2 hr after drug intake, whereas the food schedule was not reported for the multiple-dose study. This was reflected in C_{max} and AUC_{0-96} mean values from the present single dose study where these values were significantly lower than those obtained in Study 8 where the same dose was given with astandardized breakfast.
2. Although the extent of absorption of fenofibric acid is lower in the present study than the other similar study with standardized beakfast (Study 8), the urinary excretion of fenofibric acid obtained from the this study is about twice that in Study 8. The reason could be that in the present study urine samples were incubated for 24 hrs with β-glucuronidase and assyed by method, whereas in Study 8 the urine was incubated for only 30 min and assayed by
3. Steady-state was achieved after 120 hrs compared with 196 hrs in Study 4 and the minimum steady-state concentraion is lower than that achieved in Study 4. Based on the mean half-life of fenofibric acid (about 20 hrs), the steady-state is expected to be reached after 120 hrs.

STUDY -4-

STUDY OF PHARMACOKINETICS OF 100 MG FENOFIBRATE CAPSULES AFTER SINGLE AND REPEATED ADMINISTRATION IN NORMAL HEALTHY VOLUNTEERS

Note: This study was not previously evaluated by Dr. Wang in her bio-review.

INVESTIGATORS:

OBJECTIVE: To evaluate the pharmacokinetics of fenofibrate after single and repeated administrations in healthy volunteers.

Note: This study actually gives the drug according to the recommended dosing regiment in the proposed package insert

SUBJECTS: 18 adult volunteers (9 males and 9 females). Age: 19-31 years. Weight: 47 to 73 Kg. Inclusion/exclusion criteria were adequately described.

DRUG AND DOSAGE SCHEDULE: 100 mg fenofibrate in Lipanthyl^{R} capsule 1(Fournier Laboratories, France), batch no. 551 RG, were administered orally to each subject as follows:

Day1: After 10 hrs overnight fasting, one capsule at 8 a.m. immediately after standardized meal*.
Days 6 to 15: Repeated administration of one capsule t.i.d. (8 a.m., 12 a.m. and 8 p.m.) immediately after standardized breakfast and identical lunch and dinner, respectively. The composition of lunch and dinner is not reported.
Day 16: One capsule at 8 a.m. immediately after standardized breakfast*.
* one egg, 50 g bread, 50 g ham, 25 g cheese, 20 g butter and 100 ml orange juice.

BLOOD COLLECTION:
- 10 ml, into heparnized tubes, at 0, 2, 4, 6, 8, 10, 12, 24, 48, 72, 96, and 120 hrs (days 1 to 6) postdosing on day 1.
- At 8 a.m. on days 11 and 13 (immediately before dosing).
- At 0, 2, 4, 6, 8, 11, 12, 14, 17 and 18 hrs postdosing, at 8 a.m., on day 14.
- At 0, 2, 5, 6, 8, 11, 12, 14, 17 and 18 hrs postdosing, at 8 a.m., on day 15.
- At 0, 2, 4, 6, 8, 10, 12, 24, 48, 72, 96, and 120 hrs postdosing, at 8 a.m., on day 16 (days 16 to 21).

Samples were centrifuged at 3000 rpm (4^{0} C) for 10 min immediately after collection, plasma separation and storage at -20^{0} C until analysis.

ANALYTICAL METHODOLOGY: The assay method used to analyze this study's blood samples is described and evaluated in detail in Study 12. The method is acceptable based upon the assay validation data evaluated for Study 12.

DATA ANALYSIS:
1- Pharmacokinetic Analysis: C_{max} and t_{max} after single-dose and $C_{min,ss}$ after multiple-dose were observed values. The following parameters were obtained from the analysis of plasma profiles of fenofibric acid from the

single-dose study by using interactive pharmacokinetic program PHARM on VICTOR S1 microcomputer: $t_{1/2}$, $AUC_{0-\alpha}$ and the accumulation ratio ($R = AUC_{16-21}/AUC_{1-6}$). AUC_{0-24} at days 14 and 15 were calculated and normalized to 100 mg.

2- Statistical Analysis: $t_{1/2}$ obtained after the first and last dose, was compared by a two-way analysis of variance. $C_{min,ss}$ at days 11, 13, 14, 15 and 16 and $AUC_{0-\alpha}$ on days 14 and 15 were compared using an analysis of variance. Linearity was checked by comparison of $AUC_{0-\alpha}$ after the first dose and AUC_{0-24} on days 14 and 15 normalized to 100 mg dose.

RESULTS: The individual concentrations of fenofibric acid and their mean values obtained during the single and multiple dose studies are listed in Tables I to V. The individual profiles of plasma concentration curves following the administration of the first and last dose are reported in Appendix VI (NDA 19-304, p 868-903). The mean profiles were not submitted as reported by the firm. The individual pharmacokinetic parameters obtained from the single and multiple dose studies are listed in Tables VI to X. Shown below are the mean pharmacokinetic parameters (± S.D.):

Parameter	Day of Study						
	1 - 6	16 - 21	11	13	14	15	16
t_{max} (hr)	6.2±2.0	5.0±2.4	—	—	—	—	—
C_{max} (mg/l)	3.4±1.2	14.6±5.6	—	—	—	—	—
$t_{1/2}$ (hr)	23.0±6.1	23.7±6.5	—	—	—	—	—
$AUC_{0-\alpha}$ (mg.hr/l)	80.5±39.0	449±202	—	—	—	—	—
AUC_{0-24} (mg.hr/l)	———	———	—	—	112.2 ±33.9	112.3 ±35.7	—
$C_{min,ss}$ (mg/l)	———	———	10.7 ±4.4	11.5 ±4.5	13.7 ±6.0	13.5 ±5.2	13.0 ±5.1
$R=\frac{AUC_{16-21}}{AUC_{1-6}}$	———	5.66±1.47	———	———	———	———	———

The summary of statistical analysis is listed in Table XI.

CONCLUSION: Based on $C_{min,ss}$ and AUC_{0-24} values, the steady-state was achieved after the administration of 100 mg of fenofibrate in Lipanthyl^R capsule three times a day with meals (8 a.m., 12 m.d. and 8 p.m.) for eight days (after 192 hrs). According to the mean half-life of fenofibric acid from the single dose study (23.0 hrs) the steady-state was achieved after 8.35 half-lives which is longer than could be predicted theoretically and than observed from Study 3 (after 120 hrs ≈ 6 half-lives).

The normalized area under the curve of fenofibric acid at steady-state (AUC_{0-24}) is significantly higher than the area under the curve from the first single dose study due to higher accumulation than predicted. These findings indicate that the pharmacokinetics of fenofibric acid is not linear. The non-linearity and high accumulation are unlikely to be due to changes in the systemic clearance as the elimination is constant. It might be due to increase in the extent of absorption of fenofibric acid in the multiple dose study particularly when it was administered with large lunch and dinner which probably containing a larger amount of fat the the standardized breakfast and/or due to saturation of tissue binding.

COMMENTS:

1. No urine was collected in any of the studies to compare the urinary excretion of total fenofibric acid from single and multiple dose studies and the urinary excretion in Study 3.

2. Due to unadequate sampling at steady-state, particularly after the morning and evening doses, the calculated AUC at days 14 and 15 is not accurate and, therefore, the assested drug linearity ($AUC_{0-24}/AUC_{0-\omega}$) is not accurate.

LABORATOIRES FOURNIER S.A.

Table I.: Individual concentrations of fenofibric acid ($mg.l^{-1}$) and their mean values (±Sd) after the first oral administration of fenofibrate (100 mg capsule)

SUBJECT	TIMES (Hours) (DAYS 1-5)											
	0	2	4	6	8	10	12	24	48	72	96	120
1												
2												
3												
4												
5												
6												
7												
8												
9												
10												
11												
12												
13												
14												
15												
16												
17												
18												
M	-	0.41	1.85	2.97	2.61	2.59	2.37	1.17	0.47	0.21	0.12	0.07
± Sd	-	0.72	1.25	0.72	1.14	1.07	1.18	0.62	0.32	0.16	0.09	0.06

ND: not detectable

The above values have been individually verified and agree with the raw data

LABORATOIRES FOURNIER S.A.

Table II : Individual minimum concentrations of fenofibric acid (C_{min}) ($mg.l^{-1}$) and their mean values (±Sd), on day 11, 13, 14, 15 and 16 (12 hours after the evening administration)

SUBJECT	TIMES (Days)				
	D11	D13	D14	D15	D16
1					
2					
3					
4					
5					
6					
7					
8					
9					
10					
11					
12					
13					
14					
15					
16					
17					
18					
M	10.70	11.50	13.69	13.50	12.93
± Sd	4.35	4.48	5.97	5.22	5.11

The above values have been individually verified and agree with the raw data

Table III: Individual concentrations of fenofibric acid ($mg.l^{-1}$) and their mean values (±Sd), on day 14

SUBJECT	TIMES (Hours) (DAYS 14)									
	0	2	5	6	8	11	12	14	17	18
1										
2										
3										
4										
5										
6										
7										
8										
9										
10										
11										
12										
13										
14										
15										
16										
17										
18										
M	13.69	12.71	13.77	13.04	13.73	16.39	16.09	14.02	13.87	14.13
± Sd	5.96	5.59	5.06	4.63	4.67	4.73	4.53	4.01	3.63	3.51

The above values have been individually verified and agree with the raw data

Table IV : Individual concentrations of fenofibric acid ($mg.l^{-1}$) and their mean values (±Sd), on day 15

SUBJECT	TIMES (Hours)							(DAYS 15)		
	0	2	5	6	8	11	12	14	17	18
1										
2										
3										
4										
5										
6										
7										
8										
9										
10										
11										
12										
13										
14										
15										
16										
17										
18										
M	13.50	13.08	13.23	12.75	13.89	17.00	16.49	14.67	13.62	14.03
± Sd	5.22	5.08	5.38	4.96	4.65	5.27	5.60	5.05	3.80	3.64

The above values have been individually verified and agree with the raw data

LABORATOIRES FOURNIER S.A.

Table .ψ : Individual concentrations of fenofibric acid ($mg.l^{-1}$) and their mean values (±Sd) after the last oral administration of fenofibrate (100 mg capsule)

SUBJECT	TIMES (Hours) (D16-D20)											
	0	2	4	6	8	10	12	24	48	72	96	120
1												
2												
3												
4												
5												
6												
7												
8												
9												
10												
11												
12												
13												
14												
15												
16												
17												
18												
M	12.99	12.20	14.15	12.94	11.70	11.27	10.31	5.91	2.65	1.31	0.71	0.40
± Sd	5.06	4.90	5.58	5.38	4.54	4.56	4.10	2.60	1.37	0.78	0.50	0.35

ND: not detectable

The above values have been individually verified and agree with the raw data

Table VI : Individual pharmacokinetic parameters of fenofibric acid and their mean values (±Sd) after the first oral administration of fenofibrate (100 mg capsule)

SUBJECT	t max (h)	C max (mg.l-1)	t 1/2 (h)	AUC 0-120 (mg.l-1.h)	AUC ∞ (mg.l-1.h)
1					
2					
3					
4					
5					
6					
7					
8					
9					
10					
11					
12					
13					
14					
15					
16					
17					
18					
M	6.22	3.42	23.02	77.99	80.51
±Sd	2.05	1.18	6.06	37.06	38.99
CV%	33	34	26	48	48

The above values have been individually verified and agree with the raw data

Table ..VII Individual pharmacokinetic parameters of fenofibric acid and their mean values (±Sd), after the last oral administration of fenofibrate (100 mg capsule)

SUBJECT	t max (h)	C max (mg.l-1)	t 1/2 (h)	AUC 0-120 (mg.l-1.h)	AUC ∞ (mg.l-1.h)
1					
2					
3					
4					
5					
6					
7					
8					
9					
10					
11					
12					
13					
14					
15					
16					
17					
18					
M	5.00	14.61	23.70	432.33	448.95
±Sd	2.40	5.55	6.48	189.20	201.85
CV%	48	38	27	44	45

The above values have been individually verified and agree with the raw data

Table V.I I I: Individual maximum plasma concentrations (Cmax) ($mg.l^{-1}$) and their ratio obtained after the first and the last oral administration of fenofibrate (100 mg capsule)

SUBJECT	Cmax D1	Cmax D16	Cmax D16/D1
1			
2			
3			
4			
5			
6			
7			
8			
9			
10			
11			
12			
13			
14			
15			
16			
17			
18			
M	3.42	14.61	4.30
± Sd	1.18	5.55	1.14
CV%	34	38	26

The above values have been individually verified and agree with the raw data

Table · IX : Individual AUC ($mg.l^{-1}.h$) of fenofibric acid and their mean values (± Sd) from 0 to ∞ after the first dose, and from 0 to 24h on day 14 and day 15 (normalized to a 100 mg dose)

SUBJECT	AUC∞ D1	AUC 0-24 D14	AUC 0-24 D15
1			
2			
3			
4			
5			
6			
7			
8			
9			
10			
11			
12			
13			
14			
15			
16			
17			
18			
M	80.51	112.23	112.31
± Sd	38.99	33.88	35.68
CV%	48	30	32

The above values have been individually verified and agree with the raw data

Table XX Individual AUC ($mg.l^{-1}.h$) of fenofibric acid from 0 to 120 h and their ratio (accumulation ratio) obtained after the first and the last oral administration of fenofibrate (100 mg capsule)

SUBJECT	AUC 0-120 (D1-5)	AUC 0-120 (D16-20)	ACCUMULATION RATIO
1			
2			
3			
4			
5			
6			
7			
8			
9			
10			
11			
12			
13			
14			
15			
16			
17			
18			
M	77.99	432.33	5.66
± Sd	37.06	189.20	1.47
CV%	48	44	26

The above values have been individually verified and agree with the raw data

STUDY -5-

EFFECT OF HEMODIALYSIS ON PLASMA KINETICS OF FENOFIBRATE IN CHRONIC RENAL FAILURE

Note: This study was previously evaluated by Dr. Wang in her bio-review.

INVESTIGATOR:

OBJECTIVE: To investigate the pharmacokinetics of fenofibric acid in hemodialysis patients after single and repeated dose studies..

METHODS:

1- Single-Dose Study Without Hemodialysis:

Patients: 9 mild or severe chronic renal failure patients maintained on regular dialysis, 3 times a week.

Study Design and Dosage: The study was carried out during days without hemodialysis and limited to 48 hrs where 3 Lipanthyl^{R} capsules (300 mg) were given orally. No indication to any meals.

Samples Collection: Blood at 0, 0.6, 1, 1.5, 2, 3, 4, 6, 6, 8, 12, 24, 32 and 48 hrs postdosing. A 48-hrs urinary output was collected whenever possible. Routine biological investigation was performed before and at 48 hr postdosing.

2- Single-Dose Study With Hemodialysis:

Patients: 6 patient with end-stage chronic renal failure.

Study Design and Dosage: 3 Lipanthyl^{R} capsules (300 mg) in single oral dose without other drugs. A 4 hrs hemodialysis was started 25 hrs postdosing. Food schedule not reported.

Samples Collection: As reported above and hourly during dialysis.

3- Multiple-Dose Study with Hemodialysis:

Patients: 5 chronic renal failure patients undergoing dialysis 3 times a week.

Study Design and Dosage: 1 Lipanthyl^{R} capsule (100 mg) each day for two weeks without other medication. Food schedule was not reported.

Blood Collection: Each day before drug intake.

4- Analytical Methodology:

RESULTS: The individual pharmacokinetic parameters of fenofibric acid obtained from the above three studies are listed in Tables I-III. The following mean parameters were obtained from the three studies:

Parameter	Study 1 (n=9)	Study 2 (n=6)	Study 3 (n=5)
t_{max} (hr)	17.5 ± 14.0	17.3 ± 11.1	10.4 ± 3.4
C_{48} (µg/ml)	1.6 ± 0.8	0.83 ± 0.54	———— [a]
C_{max}, day 15 (µg/ml)	————	————	7.9 ± 3.0
Cl creatinine (ml/min)	11.5 ± 16.3	0	2.5 ± 3.5

$t_{1/2}$ (hr)	143 ± 100	152 ± 98	———
$A_{e,0-48}$ (mg)	5.4 ± 10.0	———	———
% Bound	———	———	99.4 ± 0.2

—[a] No data

CONCLUSION: There was a dramatic prolongation in the elimination half-life and a decrease in the urinary excretion of fenofibric acid in patients with renal failure without a change in the extent of plasma protein binding in comparison with normal subjects. The pharmacokinetic of fenofibric acid was not affected by hemodialysis.

COMMENTS:

1. The meal schedule, the individuals plasma' concentrations and area under the curve for each study were not reported.
2. Blood samples were collected in the single dose studies until 48 hrs postdosing. The blood collection is not sufficient and therefore the estimation of the half-life is not accurate.
3. Based on the results, the investigator recommended not to use fenofibrate in chronic renal failure.

Table I. 300 mg fenofibrate single dose without hemodialysis (n = 9)

No.	Age, years	Sex	Plasma creatinine mg·dl⁻¹ (μM dl⁻¹)	Creatinine clearance ml·min⁻¹	Elimination half-life h	Peak plasma level μg·ml⁻¹ (nM ml⁻¹)	Time of peak plasma level h	Plasma level 48 h post-drug μg·ml⁻¹ (nM ml⁻¹)	Urinary excretion mg 48 h (μM 48 h)
1									
2									
3									
4									
5									
6									
7									
8									
9									

Table II. 300 mg fenofibrate single dose with hemodialysis (n = 6)

No.	Age, years	Sex	Plasma creatinine mg·dl⁻¹ (μM dl⁻¹)	Creatinine clearance ml·min⁻¹	Elimination half-life h	Peak plasma level μg·ml⁻¹ (nM ml⁻¹)	Time of peak plasma level h	Plasma level 48 h post-drug μg·ml⁻¹ (nM ml⁻¹)	Ultrafiltrate mg ml⁻¹ (nM ml⁻¹)
1									
2									
3									
4									
5									
6									

Table III. 300 mg fenofibrate day during 15 days (n = 5)

No.	Age, years	Sex	Plasma creatinine mg·dl⁻¹ (μM dl⁻¹)	Creatinine clearance ml·min⁻¹	Peak plasma level μg·ml⁻¹ (nM ml⁻¹)	Time of peak plasma level, days	Protein binding %
1							
2							
3							
4							
5							

STUDY -6-
PHARMACOKINETIC AND METABOLIC FATE OF ^{14}C-FENOFIBRATE IN HUMAN PLASMA

Note: These two studies were not previously evaluated by Dr. Wang in her bio-review.

INVESTIGATOR:

STUDY -7-
THE METABOLISM AND DISPOSITION OF ^{14}C-FENOFIBRATE IN RATS AND HUMAN VOLUNTEERS

INVESTIGATOR:

OBJECTIVE: To establish the content of human plasma, urine and faeces radioactivity after oral administration of ^{14}C-fenofibrate during a standardized meal.

SUBJECTS: 4 males and 4 females healthy subjects. Age: 23-33 years. Weight: 54-77 Kg. Inclusion/exclusion criteria were adequately described.

STUDY DESIGN AND DOSAGE: After overnight fast each subject received a dose of 300 mg ^{14}C-fenofibrate (66 µCi) in three capsules during a standardized meal consisting of: 1 egg, 50 g bread, 50 g ham, 25 g cheese, 20 g butter, 100 ml orange juice and 100 ml water.

SAMPLES COLLECTION:
1- Blood: 20 ml predosing and 15 ml at 0.25, 0.5, 1, 2, 3, 4, 5, 6, 7, 8, 12, 14, 48, 72, 96 and 120 hrs postdosing. Immediate centrifugation, plasma separation and storage at -20^0 C until analysis.
2- Urine and Faeces: Urine at 0-4, 4-8, 8-24, 24-48, 48-72, 72-96, 96-120, 120-144 and 144-168 hrs postdosing and stored at -20^0 C until analysis. Faeces were collectd as voided.

ANALYTICAL METHODOLOGY:

DATA ANALYSIS: It was performed for plasma profiles of radioactivity, fenofibric acid and the benzhydrol metabolite for each subject with a multicompartmantal model with PHARM program and the following parameters were determined: t_{max}, C_{max}, $AUC_{0-\alpha}$, K_{abs}, K_m, $t_{1/2}$, Cl/f and V_z/f.

RESULTS:

Plasma: The plasma concentrations versus time of radioactivity, fenofibric acid and benzhydrol metabolite are listed in Tables I and the mean profiles are illustrated in Fig. 1. Individual profiles are illustrated in Volume 1.25 (NDA 19-304, p: E382-E408). The individual parameters are listed in Table II and shown below are the mean parameters of the three measurments:

Parameter	Radioactivity	Fenofibric	Benzhydrol
t_{max}(hr)	6.0 ± 2.9	6.0 ± 2.9	8.9 ± 4.0
C_{max}(mg/l)	9.9 ± 6.2	9.5 ± 5.7	0.27 ± 0.11
K_{abs}(hr^{-1})	0.96 ± 0.46	0.59 ± 0.36	K_m= 0.44 ± 0.13
$t_{1/2}$(hr)	11.6 ± 9.0	20.8 ± 5.1	30.7 ± 8.8
$AUC_{0-\alpha}$(mg.hr/l)	126.4 ± 31.2	144.5 ± 34.2	7.7 ± 2.5
Cl/f (l/hr)	2.5 ± 0.5	1.9 ± 0.4	——[a]
V_z/f (l/Kg)	0.65 ± 0.53	0.89 ± 0.21	——[a]

[a]Not reported.

Urine and Faeces: 79% of the administered dose was excreted in the urine in 7 days with further 25% in the faeces. 56% of the urinary excretion occured in the first 24 hrs and in faeces the higher activity was during the first 48 hrs. 84.1 ± 6.1% of the dose was recovered in urine and faeces in 7 days and ended at that day. Shown below are the detected and identified metabolites of fenofibrate in urine and the percentage of each metabolite from the urinary and faecal excretion collected in the first 24 hrs:

Metabolite	% from first 24 hrs urinary and faecal excretion			
	URINE			FAECES
	Male (n=4)	Female (n=4)	Mean (n=8)	Mean (n=8)
Fenofibrate	——	——	——	86.2±7.0
Fenofibric-acid (FA)	18.8±3.8	13.9±4.4	16.2±4.5	10.5±6.2
Fenofibryl-glucuronide	66.2±3.5	70.2±5.7	68.2±4.9	——
"Reduced FA"	7.7±1.7	7.8±0.8	7.7±1.2	——
"Reduced FA-glucuronide"	5.9±0.9	6.8±0.8	6.4±0.9	——
Unknown polar metabolites	0.2±0.2	0.1±0.1	0.1±0.2	1.4±2.2
Total	98.5±2.1	98.8±1.3	98.6±1.7	98.1

——Not found.

CONCLUSION: The parent drug was not detectable in plasma. Most the radioactivity in plasma was contributed by fenofibric acid and only about 5% by the benzhydrol metabolite. Plasma profiles of the two metabolites (fenofibric acid and benzhydrol metabolite) indicate that both undergo an entero-hepatic recirculation.
Almost 60% of the dose was recovered in the urine in 7 days with further 25% in the faeces. The fact that only 85% of the dose was recovered in urine and faeces might be due to accumulation of fenofibric acid in tissues as it is a highly bound and a lipophylic compound as shown in other studies. Fenofibric acid, its benzhydrol metabolite and their stable glucuronides were excreted in urine, mainly in the first 24 hours, where the major metabolite was the glucuronide of fenofibric acid. No significant difference in the metabolic fate of fenofibrate was found between males and females.
Only the intact fenofibrate and fenofibric acid were recovered in faeces mostly in the first 48 hours. Poor absorption of fenofibrate due to poor solubility could explain the presence of considerable amount of fenofibrate in faeces. An intravenouse study of ^{14}C-fenofibrate in human could clarify this point.

DEFICIENCY: The individual urinary and faecal excretion values of fenofibrate metabolites are not reported except for subject 6.

	0.25	0.5	1	2	3	4		6	7	8	12	14	24	48	72	96	120
1																	
2																	
3																	
4																	
5																	
6																	
7																	
8																	

Table

ND = "not detectable"

Individual plasma concentrations (ng.eq.fenofibric ac./ml) of total radioactivity after oral administration of 300 mg ^{14}C-fenofibrate

Subjects	Time (h)																
	0.25	0.5	1	2	3	4	5	6	7	8	12	14	24	48	72	96	120
1																	
2																	
3																	
4																	
5																	
6																	
7																	
8																	

Table i

ND = "not detectable"

Individual plasma concentration (ng/ml) of fenofibric acid after oral administration of 300 mg ^{14}C-fenofibrate

Subjects	Time (h)																
	0.25	0.5	1	2	3	4	5	6	7	8	12	14	24	48	72	96	120
1																	
2																	
3																	
4																	
5																	
6																	
7																	
8																	

ND = "not detectable"

Individual plasma concentrations (ng/ml) of benzhydrol metabolite after oral administration of 300 mg ^{14}C-fenofibrate

Parameters	Subjects								M±Sd
	1	2	3	4	5	6	7	8	
tmax (h)									
^{14}C									
II									
III									
Cmax(mg/l)									
^{14}C									
II									
III									
$t_{\frac{1}{2}}$ (h)									
^{14}C									
II									
III									
AUC ($mg.h.l^{-1}$)									
^{14}C									
II									
III									

Table I

Individual values of main kinetic parameters of total radioactivity (^{14}C), fenofibric acid (II) and benzhydrol metabolite (III) estimated by using only plasma samples in which radioactivity can be measured

STUDY -8-

STUDY OF THE KINETICS OF FENOFIBRATE ADMINISTERED ORALLY AT INCREASING DOSES

Note: This study was not previously evaluated by Dr. Wang in her bio-review.

INVESTIGATORS:

ADDITIONAL STATISTICAL ANALYSIS OF FENOFIBRATE DOSE PROPORTIONALITY DATA

INVESTIGATOR:

OBJECTIVE: To examine the linearity of the kinetics of fenofibric acid and LF 433 following oral adminstration as a single dose of the marketed form of fenofibrate (Lipanthul^{R}) at four increasing doses: 100, 200, 300 and 500 mg, with a standard meal.

SUBJECTS: 12 male subjects. Age 20 to 40 years. Homogeneous body weight and height. Inclusion/exclusion criteria were adequatly described.

FORMULATION: Lipanthyl^{R} capsules, 100 mg, Laboratories Fournier (Dijon, France), Batch No. 2767.

STUDY DESIGN AND DOSING: Each subject will receive each of the following 4 treatments with 8-days washout period between treatments. The first 3 treatment were allocated according to a randomization schedule and treatment D was added at the end of the study. Each treatment was administered in the mornining, after overnight fasting, with a standardized breakfast*. All subjects received the same standard lunch and dinner.

Treatment	Formulation and Dosage
A	1x100 mg Lipanthyl^{R}
B	2x100 mg Lipanthyl^{R}
C	3x100 mg Lipanthyl^{R}
D	5x100 mg Lipanthyl^{R}

*1 egg, 50 g ham, 25 g cheese, 50 g bread, 20 g butter, 100 ml orange juice and 100 ml of water.

SAMPLES COLLECTION:
Blood: Immediately before dosing and 2, 3, 4, 5, 6, 7, 8, 12, 14, 24, 48, 72 and 96 hr postdosing. Immediate centrifugation and plasma separation and storage at -20^{0} C until analysis.
Urine: Immediately before dosing and during periods 0-12, 12-24, 24-48, 48-72 and 72-96 hr postdosing where the bladder was emptied completely. Urine pH and volume were controlled and sample were stored at -20^{0} C until analysis.

ANALYTICAL METHODOLOGY:

RESULTS

Plasma and Urine Data of Fenofibric Acid: The mean plasma concentration of fenofibric acid (±S.D.) obtained in 12 subjects after the administration of 100, 200, 300 and 500 mg fenofibrate in capsules and the mean parameters (±S.D.) and the percentage of dose excreted in urine are listed in Tables I and II, respectively. The mean normalized concentration-time curves for the four treatments (for 100 mg dose) are illustrated in Fig. 1. The individual plasma concentrations and pharmacokinetic parameters of LF 153 are reported in Volume 1.25 of NDA No. 19-304.

The coefficient of variation (C.V.) for t_{max}, C_{max}, $t_{1/2,abs}$, $t_{1/2,dis}$, $t_{1/2,elim}$, AUC and MRT range from 16 to 27%, 19 to 27.9%, 56 to 66%, 22 to 54%, 20 to 32%, 31 to 62% and 26 to 41%, respectively. This indicates to some inter-subject variability particularly in AUC.

Statistical Analysis of Pharmacokinetic Parameters of Fenofibric Acid: The

analysis showed that t_{max}, $t_{1/2}$ and MRT were dose-independent.
C_{max}, AUC: The 90% confidence interval of the dose-normalized C_{max} and AUC, in which 100, 200 and 300 mg were used, showed that the mean dose-normalized C_{max} and AUC values at the 100 mg dose level were significantly greater than the values observed at the 200 and 300 mg dose levels (Tables III AND IV). This indicate that the increase in the C_{max} and AUC is not proportional to the increase in the dose.
A_e: Statisical analysis were not performed for urinary excretion of fenofibric acid.
Plasma and Urine Data of LF 433: The mean plasma concenntration of the metabolite LF 433 (±S.D.) obtained in 12 subjects after the adminstration of 100, 200, 300 and 500 mg fenofibrate in capsules and the mean pharmaco-kinetic parameters and the percentage excreted in urine (±S.D.) are listed in Tables V and VI, respectively. The sponsor did not provide figures of the mean concentration-time curves for any of the treatments. The individual plasma concentrations and pharmacokinetic parameters are reported in Volume 1.25 of NDA No. 19-304. The coefficient of variation (C.V.) for t_{max}, C_{max} and AUC ranged from 51 to 73%, 25 to 55% and 36 to 57%, respectively.
Statistical Analysis of LF 433 Pharmacokinetic Parameters: The sponsor reported that the increase in C_{max} and AUC with the dose seems to be linear but not proportional with the dose. No statistical analysis was carried out to compare the various pharmacokinetic parameters between treatments and to support the above statment.

CONCLUSION: Pharmacokinetic analysis of the mean metabolite, fenofibric acid, showed that the parameters t_{max}, $t_{1/2}$ and MRT are dose-indepedent. However, the increase in C_{max} and AUC is somehow linear but it is not proportional to the increase in the administered dose. It could be that the poor absorption after increasing the dose is due to a limitation in solubility of fenofibrate in the G.I. tract, as fenofibrate has poor solubility.

COMMENTS

1. The analytical methodology used

2. The analytical methodology used to

3. The sponser did not conduct statistical analysis to compare t_{max}, C_{max}, AUC and percentage ecxreted in urine of LF 433 between different doses of fenofibrate.

Table I: Mean plasma concentrations of fenofibric acid observed in 12 subjects after single oral administration of 100, 200, 300 and 500 mg fenofibrate in capsules during standardized meal.

Time (hr)	Plasma Concentration ±S.D. (ng/ml)			
	1x100 mg	2x100 mg	3x100 mg	5x100 mg
2	1113±333	2048±620	5175±1054	4062±1460
3	2540±453	4331±765	8057±1405	9170±1358
4	3575±388	5988±814	10050+1170	11724±1465
5	4682±300	7569±715	11196±994	11985±1382
6	4142±256	7747±724	10137±820	10260±1110
7	3453±229	6466±724	8822±596	8730±865
8	3279±300	5675±635	7856±517	7985±757
12	2630±336	4418±668	5629±406	49[illegible]±501
14	2256±360	3500±635	4613±380	4497±[illegible]
24	1265±229	1942±431	2219±360	2723±2[illegible]
48	543±126	848±271	1002±280	1217±186
72	261±83	429±162	486±167	618±129
96	144±50	243±104	261±106	357±92

Table II: Mean values of the pharmacokinetic parameter of fenofibric acid obtained after single oral administration of 100, 200, 300 and 500 mg fenofibrate in capsules to 12 subjects, during standarized meal.

Dose (mg)	t_{max} (hr)	C_{max} (ng/ml)	$t_{1/2,abs}$ (hr)	$t_{1/2,elim}$ (hr)	$AUC_{0-\infty}$ (mg.hr/l)	MRT (hr)	$A_{e,0-96}$ (% Dose)
1x100	4.8	4801	0.9	20.8	97.6	26.2	27.6
	±0.8	±912	±0.6	±5.9	±46.0	±8.4	±3.6
2x100	5.2	8641	0.7	22.5	160.0	25.6	15.9
	±1.2	±2413	±0.4	±4.6	±109.4	±8.3	±1.0
3x100	5.2	12697	0.9	21.0	221.2	23.6	17.6
	±1.4	±3367	±0.6	±5.2	±69.4	±9.6	±2.5
5x100	4.5	15039	0.8	23.6	228.0	28.8	10.9
	±1.2	±3479	±0.5	±7.5	±80.9	±11.1	±1.4

Table V: Mean plasma concentrations of LF 433 observed in 12 subjects after single oral adminstration of 100, 200, 300 and 500 mg fenofibrate in capsules during standarized meal.

Time (hr)	Plasma Concentration±S.D. (ng/ml)			
	1x100 mg	2x100 mg	3x100 mg	5x100 mg
2	27.5±4.5	19.9±7.5	67.0±13.6	79.3±24.9
3	47.8±7.6	64.3±13.0	124.0±20.0	125.7±20.9
4	50.3±7.4	86.9±10.8	157.7±19.0	153.7±21.7
5	80.8±7.4	119.8±11.9	190.9±21.0	173.5±24.2
6	85.0±7.3	139.3±11.3	211.4±15.4	198.9±28.2
7	79.9±7.4	137.2±19.9	200.6±12.1	186.5±17.6
8	90.1±15.1	124.8±12.3	199.8±14.4	185.3±24.3
12	107.0±16.5	160.0±16.3	193.2±16.9	243.0±44.7
14	117.4±15.5	175.1±27.9	198.7±22.0	259.3±57.9
24	146.1±25.0	182.2±30.0	176.3±29.4	205.1±31.3
48	101.3±24.7	97.2±25.7	93.9±22.0	102.6±22.7
72	57.3±13.5	56.1±14.3	61.0±12.6	51.5±13.2
96	37.9±5.7	70.8±17.6	39.0±6.7	36.7±7.5

Table VI: Mean values of the pharmacokinetic parameters of LF 433 obtained after single oral administration of 100, 200, 300 and 500 mg fenofibrate in capsules to 12 subjects, during standarized meal.

Dose (mg)	t_{max} (hr)	C_{max} (ng/ml)	AUC_{0-96} (mg.hr/ml)	$A_{e,0-96}$ (% Dose)
1x100	20.9	164	8.2	27.6
	±10.7	±90	±4.4	±12.5
2x100	11.1	172	9.8	15.9
	±8.1	±77	±5.6	±3.5
3x100	8.9	261	10.3	17.6
	±6.2	±65	±3.7	±8.6
5x100	9.4	310	10.9	10.9
	±6.4	±134	±5.5	±5.0

TABLE 9.1

Fenofibrate Dose Pro[illegible]lity Study
Analysis of Varian[illegible] Full Model
Dose Normalized AUC

DEPENDENT VARIABLE: NAUC

SOURCE	DF	SUM OF SQUARES	MEAN SQUARE	F VALUE	PR > F	R-SQUARE	C.V.
MODEL	17	90031.57952778	5295.97526634	30.86	0.0001	0.945905	17.9057
ERROR	30	5148.76890185	171.62563006		ROOT MSE		NAUC MEAN
CORRECTED TOTAL	47	95180.34842963			13.10059655		73.16444444

SOURCE	DF	ANOVA SS	F VALUE	PR > F
SEQ	5	28542.84814907	33.26	0.0001
SUBJ(SEQ)	6	31511.55878056	30.60	0.0001
PER	3	12937.88822037	25.13	0.0001
DOSE	3	17039.28437778	33.09	0.0001

TESTS OF HYPOTHESES USING THE ANOVA MS FOR SUBJ(SEQ) AS AN ERROR TERM

SOURCE	DF	ANOVA SS	F VALUE	PR > F
SEQ	5	28542.84814907	1.09	0.4524

DUNCAN'S MULTIPLE RANGE TEST FOR VARIABLE: NAUC
NOTE: THIS TEST CONTROLS THE TYPE I COMPARISONWISE ERROR RATE,
NOT THE EXPERIMENTWISE ERROR RATE.

ALPHA=0.05 DF=30 MSE=171.626

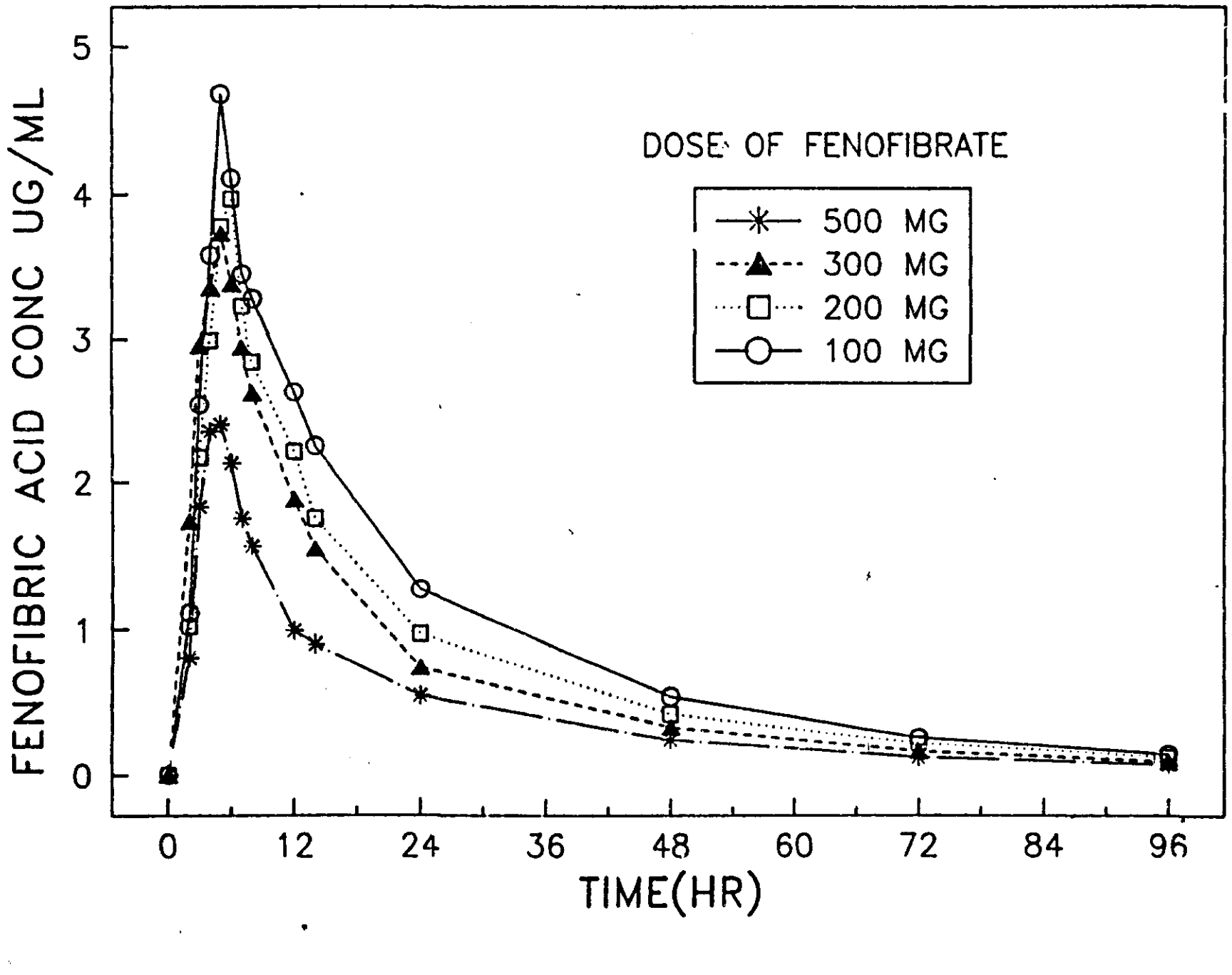
MEANS WITH THE SAME LETTER ARE NOT SIGNIFICANTLY DIFFERENT.

DUNCAN GROUPING	MEAN	N	DOSE
A	97.650	12	100
B	80.000	12	200
B			
B	69.403	12	300
C	45.605	12	500

994

FIGURE 1

MEAN PLASMA CONCENTRATIONS OF FENOFIBRIC ACID
ADJUSTED FOR DOSE OF FENOFIBRATE



Fenofibrate Dose Pr[illegible]ality Study
Analysis of Var[illegible]ull Model
Dose Normalized Cmax

DEPENDENT VARIABLE: NCM

SOURCE	DF	SUM OF SQUARES	MEAN SQUARE	F VALUE	PR > F	R-SQUARE	C.V.
MODEL	17	61545752.40928333	3620338.37701667	6.72	0.0001	0.791976	18.1509
ERROR	30	16165879.71069390	538862.65702313		ROOT MSE		NCM MEAN
CORRECTED TOTAL	47	77711632.11997723			734.07265105		4044.27152778

SOURCE	DF	ANOVA SS	F VALUE	PR > F
SEQ	5	5181598.79344940	1.92	0.1199
SUBJ([illegible])	6	4085900.49902773	1.26	0.3034
PER	3	25206621.32229197	15.59	0.0001
DOSE	3	27071631.79451424	16.75	0.0001

TESTS OF HYPOTHESES USING THE ANOVA MS FOR SUBJ(SEQ) AS AN ERROR TERM

SOURCE	DF	ANOVA SS	F VALUE	PR > F
SEQ	5	5181598.79344940	1.52	0.3098

DUNCAN'S MULTIPLE RANGE TEST FOR VARIABLE: NCM
NOTE: THIS TEST CONTROLS [illegible]E TYPE I COMPARISONWISE ERROR RATE,
NOT THE EXPERIMENTWISE ERROR RATE.

ALPHA=0.05 DF=30 MSE=538863

MEANS WITH THE SAME LETTER ARE NOT SIGNIFICANTLY DIFFERENT.

DUNCAN GROUPING	MEAN	N	DOSE
A	4801.1	12	100
A A	4320.5	12	200
A A	4260.3	12	300
B	2795.2	12	500

STUDY -9-

PHARMACOKINETIC INVESTIGATION OF LIPANTHYL CAP

Note: This study was previously evaluated by Dr. Wang in

INVESTIGATOR:

OBJECTIVE: To determine the bioavailability of single capsules (100 mg) administered with and without food in reference suspension of fenofibrate.

SUBJECTS: 12 healthy subjects (7 males+5 females). 18 to Weght: 50 and 85 Kg. Inclusion/exclusion criteria were adeq

STUDY PREPARATIONS

1- Lipanthyl^{R} Capsules, 100 mg
Batch No. 2134
Laboratories Fournier
Dijon, France

2- Fenofibrate Susp
300 mg/100 ml
Batch No. 560
Laboratories Fou
Dijon, France

DOSAGE AND ADMINISTRATION: Each subject received each of the treatments after overnight fasting until at least 4 hr after (except treatment A). Wash-out period of 2-weeks between treatments.

Treatment	Formulation & Dosage	Administ
A	3 capsules of Lipanthyl^{R}, 300 mg	with
B	3 capsules of Lipanthyl^{R}, 300 mg	witho
C	Fenofibrate suspension, 300 mg/100 ml of wate	with

*1 egg, 50g ham, 25g cheese, 50g bread, 20g butter, 100 ml
100 ml water.

BLOOD COLLECTION: 5 ml at 0, 0.5, 1, 2, 3, 4, 6, 10, 12, 24,
96 hr postdosing.

ANALYTICAL METHODOLOGY:

STATISTICAL ANALYSIS: No statistical analysis was

sponsor.

RESULTS

Analytical Method: The following results were obtained without using internal standard and without validation of the assay:
Linearity: At the range 100-5000 ng/ml, $r \geq 0.999$.
Precision: 6.6% at 100 ng/ml, 3.4% at 1000 ng/ml, 2.1% at 5000 ng/ml.
Accuracy: ± 4.25%. *Recovery*: 60% at 100 ng/ml. *Sensitivity*: 100 ng/ml.
Data Analysis: The mean serum concentrations of fenofibric acid, obtained after the administration of the three treatments to 12 subjects, are listed in Tables I and illusrated in Fig. 1. The individual serum concentrations and pharmacokinetic parameters are reported in Volume 4.7 of NDA 19-304.

The following mean pharmacokinetic parameters were obtained from the measured serum profiles without curve fitting:

Treatment	C_{max} (µg/ml)	t_{max}(hr)	$AUC_{0-\infty}$(µg.hr/ml)
A	9.86±3.58	5.83±1.80	159.07±90.66
B	1.77±2.04	10.58±12.30	52.75±28.27
C	1.56±0.93	5.58±3.09	56.04±35.72

The coefficient of variation (C.V.) for these parameters were found to be between 30% and 116%, indicating large inter-subject variabilities. As seen from the above table the administraion of fenofibrate with the specific meal increased the extent of absorption by factor of 3.

The following mean pharmacokinetic parameters of fenofibric acid were obtained from curve fitting of the serum concentration profiles after treatment A: C_{max}: 10.58 ± 3.92 µg/ml, t_{max}: 5.99 ± 1.69 hr, $AUC_{0-\infty}$: 155.19 ± 94.37 µg.hr/ml and $t_{1/2}$: 16.5 ± 8.0 hr. Apparently, the AUC, C_{max} and t_{max} values obtained from curve fitting were not different from those obtained without fitting.

The individual pharmacokinetic parameters obtained from fitting are reported in Volume 4.7 of NDA 19-304.

CONCLUSION: There are considerable inter and intra-subject variabilities in the absorption rate and extent. There was increase of three folds in the absorption of fenofibrate after its administration with the specific standardized meal (fatty) compared with under fasting condition.
The study is considered to be a supportive study. Study coded no. 12 is considered to be more important in assesing the bioavailabilty of the capsule compared to suspension because a single dose unit was evaluated there.

DIFICIENCES

1. The analytical methodology used

2. The sponsor did not conduct statistical analysis to compare the pharmacokinetic parameters of fenofibric acid obtained after the administration of the different treatments.

COMMENTS

1. The present study and other studies indicate a significant increase in the relative bioavailability of fenofibrate from capsules when is administered with meal. The Medical Officers of the Agency are recommended to ascertain that all the clinical efficacy and safety

studies have been conducted with fenofibrate capsules taken with or immediately before meals.

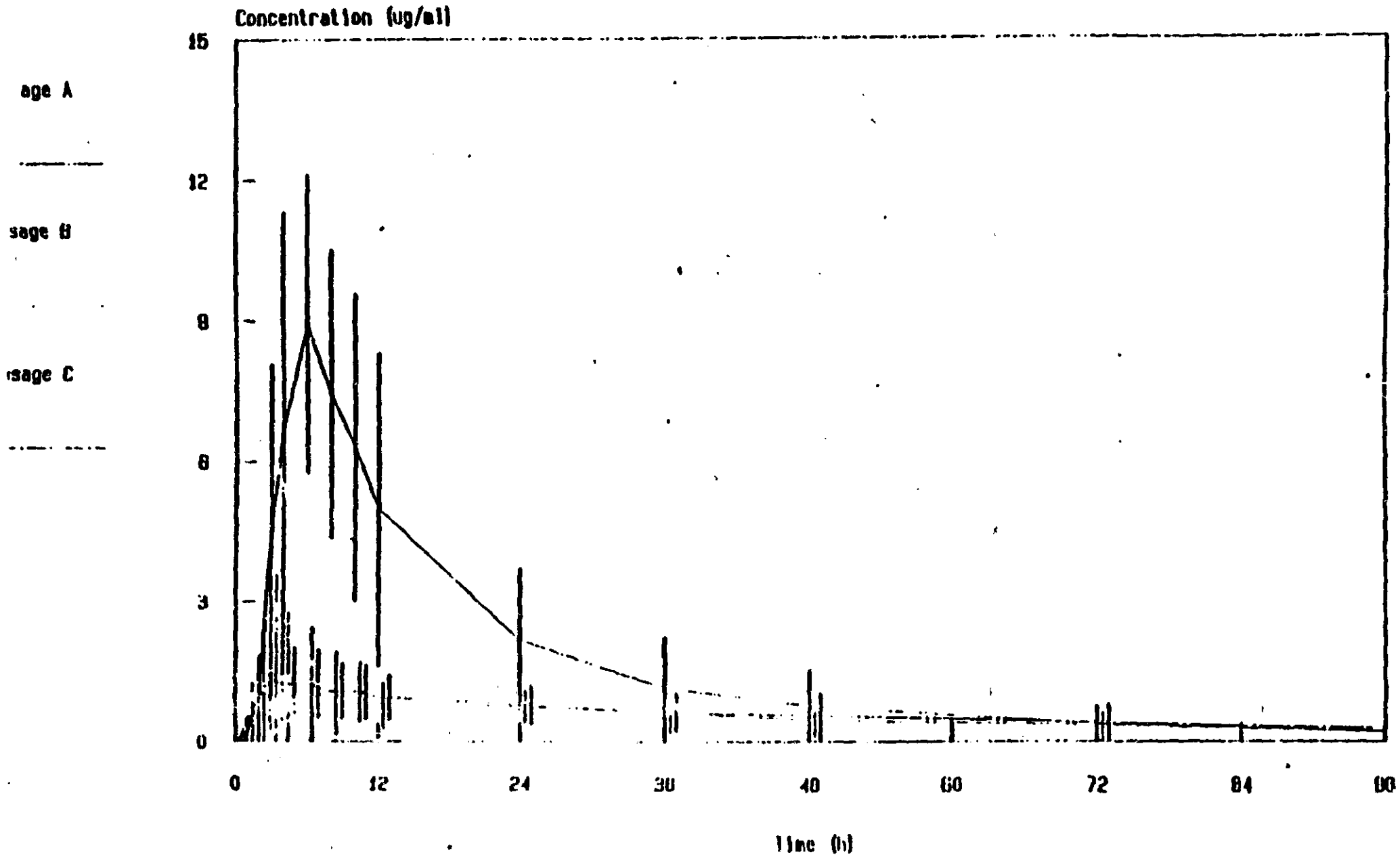
2. The present study and following studies used a standardized meal with high fat content, which increased the relative bioavailability by almost 3 fold. Fenofibrate is used to reduce elevated serum cholestrol and triglyceride in blood, therefore, it is not reasonable that such a patients will have such a meal. It is desirable to determine whether the relative bioavailability of fenofibrate capsules taken with a low fat or non fat meal would be different from that obtained after a high fat meal.

Table I: Mean serum concentrations (±S.D.)of fenofibric acid obtained after the administration of the three treatments.

Time (hr)	Fenofibric acid serum conc. (µg/ml) A		B		C	
0	0	(0)	0	(0)	0	(0)
0.5	0.05	(0.11)	0.10	(0.15)	0.20	(0.15)
1	0.21	(0.23)	0.42	(0.85)	0.52	(0.38)
2	0.94	(0.93)	0.94	(1.67)	0.99	(0.80)
3	4.53	(3.55)	1.44	(2.14)	1.28	(0.95)
4	6.73	(4.60)	1.27	(1.61)	1.20	(0.82)
6	8.94	(3.18)	1.24	(1.23)	1.22	(0.75)
8	7.44	(3.07)	1.05	(1.10)	1.09	(0.66)
10	6.29	(3.27)	1.10	(0.67)	1.06	(0.58)
12	4.97	(3.35)	0.80	(0.52)	0.95	(0.49)
24	2.17	(1.52)	0.74	(0.38)	0.78	(0.41)
36	1.14	(1.08)	0.62	(0.44)	0.60	(0.40)
48	0.75	(0.78)	0.45	(0.35)	0.54	(0.47)
72	0.38	(0.38)	0.35	(0.30)	0.40	(0.38)
96	0.21	(0.21)	0.21	(0.26)	0.29	(0.34)

Serumlevels of LF 153

mean over subjects



STUDY -10-

PHARMACOKINETICS OF FENOFIBRATE IN THE ELDERLY

Note: This study was not previously evaluated by Dr. Wang in her bio-review.

INVESTIGATORS:

OBJECTIVE: To investigate the pharmacokinetics of fenofibrate in elderly subjects.

SUBJECTS: Five subjects (3 females and 2 males). Age: 77 to 87 years. Weight: 45 to 70 Kg. Inclusion/exclusion criteria were adequatly described.

DOSAGE AND ADMINISTRATION: After overnight fasting, one capsule of Lipanthyl^{R}, batch no. 3158, containing 100 mg fenofibrate was administered to each subject during a standardized meal. No food was allowed until 4 hr after administration.

SAMPLE COLLECTION

Blood: 5 ml at 0, 0.25, 0.5, 1, 2, 3, 4, 5, 6, 7, 8, 12, 14, 24, 36, 48, 72, 96 and 120 hrs postdosing. Immediate centrifugation (15 min x 1000 g), plasma separation and storage at -20^{0} C.

Urine: During 3 hr predosing and for periods: 0-4, 4-8, 8-12, 12-24, 24-48, 48-72, 72-96 and 96-120 hr. Volume and pH of each collection were recorded and an aliquot of 30 ml was frozen immediatly.

ANALYTICAL METHODOLOGY: Described in details in Study 12.

DATA ANALYSIS: For each subject, the plasma concentrations of fenofibric acid obtained after each treatment were analyzed by using the interactive pharmacokinetic program PHARM (Gomeni).

The following parameters were determined from the observed data : t_{max}, C_{max}, $AUC_{0-\alpha}$, the apparent total body clearance (Cl/f) and the total amount (free+conjugate) of fenofibric acid excreted into urine (A_e) and the following parameters were obtained from the fitting of three exponentials model to the plasma concentration-time profile: $AUC_{0-\alpha}$, elimination half-life ($t_{1/2}$) and the apparent volume of distribution (V_z/f).

STATISTICAL ANALYSIS: Individual values of the kinetic parameters t_{max}, C_{max}, $t_{1/2}$, $AUC_{0-\alpha}$, Cl/f and V_z/f obtained in elderly during this study were compared to the values of the same parameters obtained in adult volunteers from Study 13. The statistical analysis was performed by analysis of variance except for t_{max} where U test of Mann-Whitney was used.

RESULTS: The individuals and mean plasma concentrations of fenofibric acid, obtained after the administration of 100 mg fenofibrate in Lipanthyl^{R} capsule are listed in Table I.

The mean plasma concentration-time profile of fenofibric acid is illustrated in Fig. 1. The individual figures are illustrated in Volume 4.7 of NDA No. 19-304 (p E1061-E1065).

The individual and the mean calculated pharmacokinetic parameters are listed in Table II.

The urinary excretion of fenofibric acid (free+conjugate) is listed in

Table III.
The pharmacokinetic parameters of fenofibric acid obtained in adult healthy subjects (12) from another study, where the same dose was administered under the same conditions, are listed in Table IV.
Shown below are the mean pharmacokinetic parameters of fenofibric acid in adults and elderly obtained after the administration of Lipanthyl[R] with standardized meal

Parameter	Range		Mean±S.D.		$F_{15,1}$	P	Sign.
	E	A	E	A			
t_{max} (hr)/	3-7	3-6	4.4±1.6	4.8±0.8	$U_{12,5}=7$	>0.05	N.S.
C_{max} (mg/l)	1.30-6.46	3.69-6.74	2.96±2.03	4.80±0.91	7.0	>0.025 <0.01	S
$t_{1/2}$ (hr)	14.9-46.0	13.1-32.5	31.7±13.0	20.8±5.9	5.87	>0.05 <0.025	S
$AUC_{0-\infty}$ (mg.hr/l)	38.9-112.6	46.6-243.0	83.2±30.4	97.6±54.0	0.309	>0.05	N.S.
Cl/f (l/hr)	0.78-2.27	0.36-1.90	1.23±0.62	1.09±0.44	0.295	>0.05	N.S.
V_z/f (l)	20.6-73.8	16.9-46.6	52.3±20.2	30.3±8.1	10.45	>0.01 <0.001	S
A_e (mg)	2.6-24.6[a]	13.9-46.4[b]	12.8±9.7	27.6±12.5	———		c

a- amount excreted in urine during 120 hr.
b- amount excreted in urine during 96 hr.
c- no statistical analysis was performed.
E- elderly.
A- adults.

CONCLUSION: The rate (t_{max}) and extent (AUC) of the absorption of fenofibrate in adults and elderly subjects were not significantly different. However, the elimination half-life and the apparent volume of distribution were significantly higher in elderly than in adults and C_{max} was lower for the elderly.
The predicted maximum plasma concentration at steady-state ($C_{max,ss}$) in elderly and adults were 16.13 ± 6.05 mg/l and 20.92 ± 7.89 mg/l, respectively, at dosing interval of 100 mg every 8 hours. However, it will take longer to reach steady-state in elderly than in adults because of longer half-life.

COMMENTS: The elderly subjects who participated in the present study have been under other medications. The sponser did not mention or report if there is any interaction between fenofibric acid and the co-administered medications.

Subject	TIME (h) 0.25	0.5	1	2	3	4	5	6	7	8	12	16	24	36	48	72	96	120
M	0.09	0.22	0.24	1.10	2.00	2.34	2.72	2.63	2.55	2.26	1.91	1.41	1.01	0.67	0.55	0.31	0.24	0.22
Sd	-	0.11	0.18	0.70	1.08	1.68	2.13	2.03	1.80	1.48	0.36	0.61	0.31	0.30	0.29	0.21	0.16	0.09

N.D. = not detectable

Individual plasma concentrations ($mg.l^{-1}$) of fenofibric acid after oral administration of 100 mg fenofibrate to the elderly.

Table 1

EP 0 203 4

TABLE II

SUJECTS	tmax (h)	Cmax ($mg.l^{-1}$)	$t_{\frac{1}{2}}$ (h)	AUC ($mg.l^{-1}.h$)	Cl/f ($l.h^{-1}$)	Vz/f (l)
M	4.4	2.96	31.7	83.2	1.23	52.3
Sd	1.6	2.03	13.0	30.4	0.62	20.2

Fenofibric acid individual pharmacokinetic parameters obtained in elderly after single oral administration of 100 mg fenofibrate (88.4 mg fenofibric acid).

TABLE III

Urinary excretion of fenofibric acid (free + conjugated)

							M ± Sd
U							-
U1 0-4 H	conc. (µg.ml^{-1}) volume (ml) amount (µg)						703 ± 283.5
U2 4-8 H	Conc. (µg.ml^{-1} volume (ml) amount (µg)						749.4 ± 1049.8
U3 8-12 H	conc. (µg.ml^{-1}) volume (ml) amount (µg)						2762 ± 2320.2
U4 12-24 H	conc. (µg.ml^{-1}) volume (ml) amount (µg)						3657.7 ± 3940.3
U5 24-48 H	conc. (µg.ml^{-1}) volume (ml) amount (µg)						3701.3 ± 2814.3
U6 48-72 H	conc. (µg.ml^{-1}) volume (ml) amount (µg)						1833.7 ± 1755.2
U7 72-96 H	conc. (µg.ml^{-1}) volume (ml) amount (µg)						904.3 ± 250.9
U8 96-120 H	conc. (µg.ml^{-1}) volume (ml) amount (µg)						640.2 ± 644.2
Ae (ug)		10649	24627	5128	2644	21171	12843.8 ± 9702.7

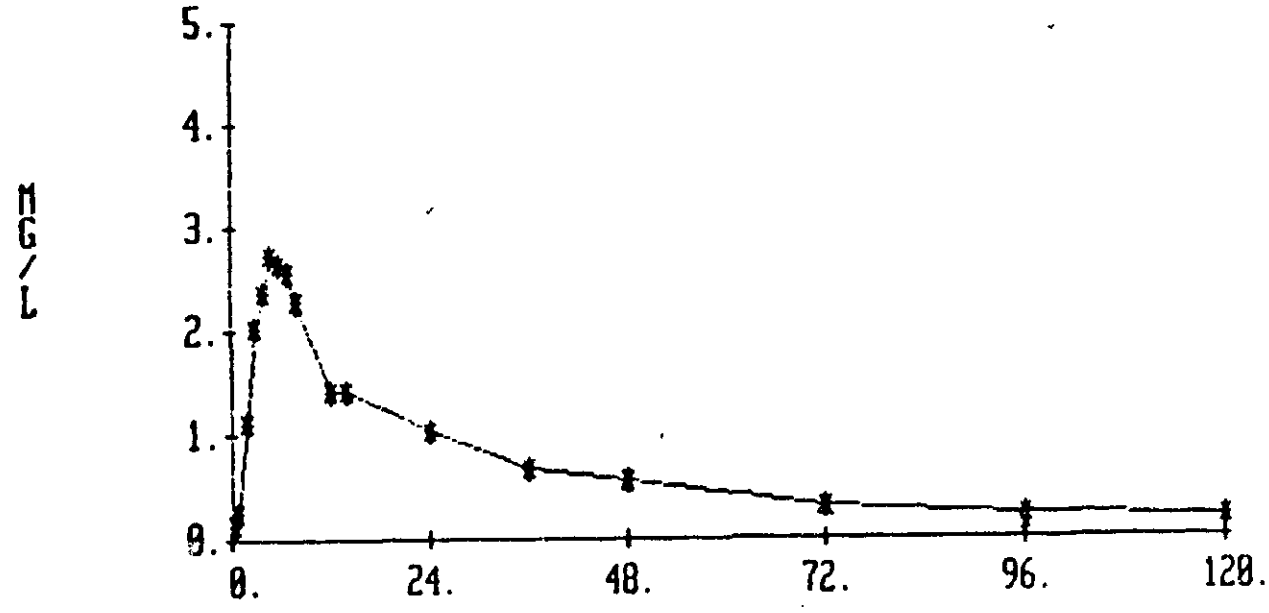
UL = urine lost

TABLE IV

SUJECTS	tmax (h)	Cmax ($mg.l^{-1}$)	$t_{\frac{1}{2}}$ (h)	AUC ($mg.l^{-1}.h$)	Cl/f ($l.h^{-1}$)	Vz/f (l)
1						
2						
3						
4						
5						
6						
7						
8						
9						
10						
11						
12						
M	4.8	4.80	20.8	97.6	1.09	30.3
Sd	0.8	0.91	5.9	54.0	0.44	8.5

Fenofibric acid individual pharmacokinetic parameters obtained in adult after single oral administration of 100 mg fenofibrate (88.4 mg fenofibric acid) (Bianchetti, Duchier, 1984)

MEAN



STUDY -11-

SERUM BINDING AND INTERACTIONS OF CHLOROPHENOXYISOBUTYRIC ACID, ITANOXONE AND FENOFIBRIC ACID ACCORDING TO THEIR DIFFERENT HSA BINDING SITES

Note: This study was previously evaluated by Dr. Wang in her Bio-review.

INVESTIGATORS:

OBJECTIVE: To study the binding characteristics of fenofibric acid (FA), chlorphenoxy-isobutyric acid (CIA) and itanoxane (ITX), their HSA binding sites and their serum interactions either with other drugs or else in different pathological states including hyperlipidemia, mild and severe hepatic failure.

METHODS

RESULTS

Binding of Fenofibric Acid (FA) to Human Serum and to HSA

1- Normal subjects: At fenofibric acid concentration of 28 and 83 μM, 99% of FA is bound to serum proteins (HSA 580-750 μM).

2- Patients with hyperlipidemia or mild cholestasis: Binding of FA to serum is unaffected.

3- Patients with severe cholestasis: Significant decrease in binding to 95.5% ($p < 0.001$).

4- Binding to HSA: At 15 μM of HSA, the binding of FA decreased from 91% to 14% by increasing FA concentration from 3 μM to 5540 μM.

5- Binding parameters: $n_1=4.7\pm0.5$ $K_1=125200\pm31200\ M^{-1}$

$n_2=6.2\pm0.3$ $K_2=1250\pm230\ M^{-1}$

Serum Protein Binding Interactions

1- Palmitic acid (PA): Addition of PA to pooled normal serum (HSA=580 μM) with fenofibric acid concentrations of 28 or 83 μM decreased significantly ($p < 0.01$) the binding of the latter. The percentage of the decrease in binding is not reported.

2-Acid drugs: FA (83.3 μM) was displaced from proteins by phenylbutazone and vise versa ($p < 0.001$) but no effect on or by salicylic acid, indomethacin, warfarin and sulfamethoxazole.

CONCLUSION: Fenofibric acid is extensively bound (99%) to serum proteins at its steady-state therapeutic range. The fraction unbound of FA is unaffected in patients with mild cholestasis or hyperlipidemia, but it is 5 times higher in patients with severe colestasis (bilirubin > 200μM). Free fatty acids decrease the protein binding of FA, however the extent in the decrease is not reported. A significant interaction ($p < 0.001$) occurs between FA and phenylbutazone where the latter was displaced by about 0.6% from serum proteins by FA. No significant interaction between FA and other acidic drugs used in this study.

COMMENTS

1. The interactions between fenofibric acid and other compounds as free fatty acids and phenylbutazone should be indicated in the labelling.

2. The Medical Officer of the Agency is recommended to decide if a dosing regiment adjustment is needed in patients with severe cholestasis, where the fraction unbound (which has pharmacological activity) is 5 times higher than in normal subjects.

STUDY -12-

COMPARATIVE BIOAVAILABILITY STUDY OF FENOFIBRATE ORALLY ADMINISTERED IN 100 MG CAPSULES OR IN SUSPENTION IN WATER

Note: This study was not previously evaluated by Dr. Wang in her Bio-review.

INVESTIGATORS:

OBJECTIVES: To compare the bioavailability of fenofibric acid after the administration of 100 mg fenofibrate in Lipanthyl^{R} capsule and in water suspension and to investigate the influence of food on the bioavailability of fenofibric acid.

SUBJECTS: 12 healthy male volunteers. Age: 20 to 45 years. Body weight: 65 to 95 Kg. Inclusion/exclusion criteria were adequatly described.

DOSAGE AND DOSAGE SCHEDULE: 100 mg fenofibrate (batch no. 913036) in Lipanthyl^{R} capsule (batch no. 3465) as test preparation or 100 mg/100 ml water suspension as reference preparation. Each subject received the following four treatments in a four-way balanced cross-over design where 7 days elapsed between each administration:

Treatment	Preparation & Dosage	Administration
A	Lipanthyl^{R}, 100 mg	Fasting
B	Lipanthyl^{R}, 100 mg	With standardized meal*
C	Suspension, 100 mg	Fasting
D	Suspension, 100 mg	With standardized meal

*1 egg, 50 g ham, 50 g bread, 25 g cheese, 20 g butter, 100 ml orange juice and 100 ml water.
Food and drink were allowed only at 4 and 12 hours after administration.

SAMPLES COLLECTION

Blood: 10 ml predosing and 5 ml at: 0.5, 1, 2, 3, 4, 5, 6, 8, 10, 12, 24, 48, 72, 96 and 120 hrs postdosing. Centrifugation, separation of plasma and storage at -20^{0} C until analysis.
Urine: The bladder was emptied before each administration and 20 ml were stored. samples were collected during periods:0-4, 4-8, 8-24, 24-48, 48-72, 72-96 and 96-120 hr. Volume and pH were recorded and 10 ml were stored at -20^{0} C until analysis.

ANALYTICAL METHOD

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Data and Statistical Analysis: The plasma concentrations of fenofibric acid and pharmacokinetic parameters obtained after the administration of the four treatments are listed in Tables I-VIII. The mean plasma profiles are illustrated in Fig. 1. Shown below are the mean ± S.D. results of the pharmacokinetic parameters and following this are the 90% confidence interval values:

Treatment	t_{max} (hr)	C_{max} (mg/l)	$AUC_{0-\infty}$ (mg.hr/l)	$t_{1/2}$ (hr)	A_e (mg)
A	6.24±2.34	1.06±0.88	37.45±24.30	24.80±6.89	9.6±8.6
B	7.25±3.14	3.67±1.35	95.19±34.85	19.72±5.70	25.7±11.3
C	7.66±5.29	0.82±0.71	36.26±31.67	29.73±6.70	6.2±3.4
D	7.47±2.51	3.97±0.87	98.88±35.07	23.26±4.61	28.3±11.4

The results of the 90% confidence interval testing performed on t_{max}, C_{max} and $AUC_{0-\infty}$ values using two one-sided tests, showed the following feature:

Parameter	Power		90% C.I.		Conclusion	
	A/C	B/D	A/C	B/D	A/C	B/D
t_{max} (hr)	23.8	23.2	55.6-107.3	75.0-127.4	Fail	Fail
C_{max} (mg/l)	7.2	59.9	58.1-202.0	77.7-107.2	Fail	Fail
$AUC_{0-\infty}$ (mg.hr/l)	13.0	64.0	64.8-141.8	82.1-110.4	Fail	Pass
$t_{1/2}$ (hr)	72.5	54.5	70.6-96.2	68.4-101.2	Fail	Fail

It is clear from the statistical analysis that under fasting conditions Lipanthyl^R capsules which is 'to be marketed' fails to be bioequivalent to the reference suspension, whereas during a standardized meal the extent but not the rate of the absorption are bioequivelant after the administration of the two formulations. Furthermore, the results show 3-fold increases in the extent of absorption when the suspension and the capsules were administered during standardized fatty meal.

CONCLUSION: The 'to be marketed' Lipanthyl^R capsule and the reference suspension are not bioequivelant neither with nor without meal.

COMMENTS: Hyperlipidemic patients are ristricted to eat highly fat meals like the standardized breakfast used in most of the studies in the present NDA. Therefore, a pharmacokinetic study should be conducted by the sponsor to investigate the effect of different meals on the extent of fenofibrate absorption from Lipanthyl^R capsules.

Table

Individual plasma concentrations (mg.l^{-1}) of fenofibric acid after oral administration of fenofibrate (100 mg capsule) under fasting conditions (Treatment A).

Subject	0.5	1	2	3	4	5	6	8	10	12	24	48	72	96	120
M	ND	0.132	0.509	0.690	0.780	0.981	0.791	0.895	0.772	0.578	0.607	0.248	0.128	0.083	0.054
± Sd	-	±0.143	±0.869	±0.841	±0.803	±0.791	±0.591	±0.645	±0.563	±0.284	±0.556	±0.098	±0.063	±0.024	±0.017
CV %	-	94.185	170.916	121.838	102.912	80.605	74.647	72.123	72.966	49.205	91.650	40.234	48.947	29.185	31.333

ND = not detectable

I, II, III, IV = periods

Table

Individual plasma concentrations ($mg.l^{-1}$) of fenofibric acid after oral administration of fenofibrate (100 mg capsule) during a standardized meal (Treatment B).

Subject	0.5	1	2	3	4	5	6	8	10	12	24	48	72	96	144
$\bar{M}$	ND	0.240	1.179	1.631	2.049	2.489	2.827	2.906	2.894	2.653	1.501	0.550	0.247	0.159	0.138
±Sd	-	±0.313	±0.980	±1.672	±1.802	±1.477	±1.103	±1.027	±0.979	±1.047	±0.747	±0.313	±0.172	±0.116	±0.109
CV %	-	130.218	83.080	102.540	87.976	59.320	39.025	35.343	33.826	39.470	49.740	56.969	69.806	73.458	78.858

ND = not detectable

I, II, III, IV = periods

Table

Individual plasma concentrations (mg.l-1) of fenofibric acid after oral administration of fenofibrate (100 mg suspension in water) under fasting conditions (Treatment C).

Subject	0.5	1	2	3	4	5	6	8	10	12	24	48	72	96	120
M	0.351	0.190	0.346	0.487	0.592	0.713	0.762	0.700	0.640	0.600	0.400	0.290	0.172	0.125	0.093
±Sd	±0.519	±0.186	±0.383	±0.475	±0.507	±0.556	±0.681	±0.620	±0.537	±0.491	±0.393	±0.296	±0.188	±0.125	±0.072
CV %	147.93	98.052	110.944	97.464	85.634	77.964	78.223	88.554	74.310	81.782	98.332	101.985	109.533	99.961	75.563

ND = not detectable

I, II, III, IV = periods

Table

Individual plasma concentrations ($mg.l^{-1}$) of fenofibric acid after oral administration of fenofibrate (100 mg suspension in water) during a standardized meal (Treatment D).

Subject	0.5	1	2	3	4	5	6	8	10	12	24	48	72	96	120
M	0.(..)	0.339	0.989	1.568	2.179	2.870	3.047	3.466	3.179	2.659	1.440	0.569	0.288	0.164	0.094
±Sd	±0.05	±0.362	±1.010	±1.278	±1.378	±1.330	±1.006	±1.082	±0.992	±0.879	±0.616	±0.305	±0.213	±0.135	±0.067
CV %	50.478	106.697	102.148	81.501	63.261	46.337	33.013	31.228	31.201	33.074	42.778	53.707	73.996	82.417	71.208

ND : not determinable

I, II, III, IV : periods.

Table . .

Fenofibric acid individual kinetic parameters and their mean values, obtained after administration under fasting conditions of one 100 mg fenofibrate capsule of LIPANTHYL^{R} (Treatment A)

Subjects	tmax (h)	Cmax ($mg.l^{-1}$)	$t_{\frac{1}{2}}$ (h)	AUC_{0-t} ($mg.l^{-1}.h$)	AUC ($mg.l^{-1}.h$)
$\bar{M}$	6.24	1.061	24.80	35.17	37.45
Sd	± 2.34	± 0.877	± 6.89	± 24.28	± 24.39
CV	37.5	82.7	27.7	69.0	64.9

Table

Fenofibric acid individual kinetic parameters and their mean values, obtained after administration during a standardized meal of one 100 mg fenofibrate capsule of LIPANTHYL^{R} (Treatment B)

Subjects	tmax (h)	Cmax (mg.l^{-1})	$t_{\frac{1}{2}}$ (h)	AUC_{0-t} (mg.l^{-1}.h)	AUC (mg.l^{-1}.h)
$\bar{M}$	7.25	3.67	19.72	91.84	95.19
Sd	± 3.14	± 1.350	± 5.70	± 32.78	± 34.85
CV	43.3	36.8	28.9	35.7	36.6

Table

Fenofibric acid individual kinetic parameters and their mean values, obtained after administration under fasting conditions of 100 mg fenofibrate in water suspension (Treatment C)

Subjects	tmax (h)	Cmax (mg.l^{-1})	$t_{\frac{1}{2}}$ (h)	AUC_{0-t} (mg.l^{-1}.h)	AUC (mg.l^{-1}.h)
$\bar{M}$	7.66	0.816	29.73	30.30	36.26
Sd	± 5.29	± 0.712	± 8.70	± 28.23	± 31.67
CV	69.1	87.3	29.3	93.2	87.3

* Abnormal value not used for calculations

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Table

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Fenofibric acid individual kinetic parameters and their mean values, obtained after administration during a standardized meal of 100 mg fenofibrate in water suspension (Treatment D)

Subjects	tmax (h)	Cmax ($mg.l^{-1}$)	$t_{\frac{1}{2}}$ (h)	AUC_{0-t} ($mg.l^{-1}.h$)	AUC ($mg.l^{-1}.h$)
$\bar{M}$	7.57	3.97	23.26	95.66	98.88
Sd	± 2.51	± 0.87	± 4.61	± 32.51	± 35.07
CV	33.2	21.9	19.8	34.0	35.5

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STUDY -13-
COMPARATIVE BIOAVAILABILITY OF TWO COMMERCIAL BATCHES OF LIPANTHYL^R

Note: This study was not previously evaluated by Dr. Wang in her bio-review.

INVESTIGATORS:

OBJECTIVE: To compare the bioavailabilty of fenofibric acid from two different batches of Lipanthyl^R capsules prepared with different batches of fenofibrate.

SUBJECTS: 10 male subjects. Age: 21 to 27 yeas. Weight: 60 to 78 Kg. Inclusion/exclution criteria were adequately described.

STUDY DESIGN AND DOSING: Each subject received the following two treatments in a balanced cross-over design, immediately after a standardized meal*, where one week elapsed between each administration:
Treatment A: One Lipanthyl^R capsule (100 mg) batch no. 2965 (fenofibrate batch no. 824).
Treatment B: One Lipanthyl^R capsule (100 mg) batch no. 2583 (fenofibrate batch no. 648).
Lunch and dinner, with identical composition, were taken at 4 and 12 hours after the administration.
The particle size distribution of the two batches of fenofibrate used in the production of the two batches of capsules are listed in Table V.
*As described in previous studies.

BLOOD COLLECTION: 10 ml predosing and 5 ml at 2, 3, 4, 5, 6, 8, 12, 24, 48, 72 and 96 hr postdosing. Immediate centrifugation, plasma separation and storage at -20^0 C until analysis.

ANALYTICAL METHODOLOGY: As described in Study 8.

DATA ANALYSIS
1- Pharmacokinetic Parameters: The following parameters were determined for each subject from the plasma profiles of fenofibric acid obtained after the
adminstration of the two treatments: t_{max}, C_{max}, $t_{1/2}$ and $AUC_{0-\alpha}$.
2- Statistical Analysis: The 90% confidence interval testing and the power analysis were performed on t_{max}, C_{max} and $AUC_{0-\alpha}$, using two one-sided t-test. Treatment A was compared to treatment B.

RESULTS: Plasma concentrations of fenofibric acid obtained after treatments A and B are listed in Tables I and II, respectively. The mean plasma profiles are illustrated in Fig. 1. The individual pharmacokinetic parameters obtained after treatments A and B are listed in Tables III and IV. Shown below are the mean ± S.D. results of the pharmacokinetic parameters and following the 90% C.I. and power analysis values.

Parameter	A-Lipanthyl^R batch no. 2965	B-Lipanthyl^R batch no 2853
t_{max} (hr)	6.7±2.1	7.5±3.0
C_{max} (mg/l)	4.01±1.35	3.53±1.16
$AUC_{0-\alpha}$(mg.hr/l)	78.4±13.7	75.3±25.0

The results of 90% C.I. and power analysis showed the following features:

Parameter	Power	90% C.I.	Conclusion
t_{max}(hr)	23.8	65.3-113.4	Fail
C_{max}(mg/l)	19.8	86.9-140.2	Fail
$AUC_{0-\alpha}$ (mg.hr/l)	44.0	86.8-121.4	Fail

The statistical analysis shows that the extent and rate of absorption of fenofibric acid obtained after the administration of the two formulations, immediately after the standardized meal, are not bioequivelant. The dissolution studies (study 1) showed that the dissolution rate from Lipanthyl^R capsules increased significantly with a decrease in the fenofibrate particle size which could occur in the G.I. tract and will be reflected in the absorption rate and extent.

CONCLUSION: The two batches of Lipanthyl^R capsules which were prepared from two different batches of fenofibrate are not bioequivelant when they were administered immediately after fatty meal.

COMMENTS: The present study shows that differences in particle size distribution do modify the bioavailability of fenofibrate administered in capsules immediately after fatty meal. Similar finding was observed in rats. It seems that more subjects are needed to the present study, otherwise the sponsor should take into consideration to select only fenofibrate batches with the same particle size distribution in preparing Iipanthyl^R capsules.

Table I

Subject	Time (h)											
	2	3	4	5	6	8	10	12	24	48	72	96
1												
2												
3												
4												
5												
6												
7												
8												
9												
10												
Mean	1.033	1.475	2.024	3.749	3.777	3.069	2.892	2.573	1.171	0.373	0.142	0.06
Sd	0.989	0.791	0.997	1.445	1.212	0.679	0.412	0.254	0.198	0.085	0.948	0.024

+ = no sample ; ND = not detectable

Individual plasma concentrations ($mg.l^{-1}$) of fenofibric acid after oral administration of 100 mg fenofibrate capsule batch 2965 (treatment A)

E 2965

Table II

Subject	Time (h)											
	2	3	4	5	6	8	10	12	24	48	72	96
1												
2												
3												
4												
5												
6												
7												
8												
9												
10												
Mean	1.006	1.277	1.769	2.918	2.866	2.683	2.609	2.499	1.187	0.395	0.15	0.097
Sd	0.784	0.755	1.037	1.087	0.797	1.034	0.782	1.138	0.433	0.197	0.080	0,044

ND = not detectable

Individual plasma concentrations ($mg.l^{-1}$) of fenofibric acid after oral administration of 100 mg-fenofibrate capsule batch 2583 (treatment B)

Table III

Subjects	tmax (h)	Cmax (mg.l-1)	t½ (h)	AUC0-t (mg.l-1.h)	AUC (mg.l-1.h)
1					
2					
3					
4					
5					
6					
7					
8					
9					
10					
$\bar{M}$	6.7	4.01	16.1	76.7	78.4
Sd	2.1	1.35	2.2	13.4	13.7

Fenofibric acid individual pharmacokinetic parameters and mean values obtained after oral administration of one 100 mg fenofibrate capsule batch n° 2963 (treatment A)

Table IV

Subjects	tmax (h)	Cmax (mg.l-1)	t½ (h)	AUC0-t (mg.l-1.h)	AUC (mg.l-1.h)
1					
2					
3					
4					
5					
6					
7					
8					
9					
10					
$\bar{M}$	7.5	3.53	16.3	73.1	75.3
Sd	3	1.16	2.4	24.3	25.0

Fenofibric acid individual pharmacokinetic parameters and mean values obtained after oral administration of one 100 mg fenofibrate capsule batch n° 2583 (treatment B)

Table V

Fenofibrate batches	Particle size (um)						
A 648	3.3	14.80	30.65	31.30	13.10	4.15	2.80
B 824	0.6	6.9	28.45	32.80	21.15	7.65	2.45

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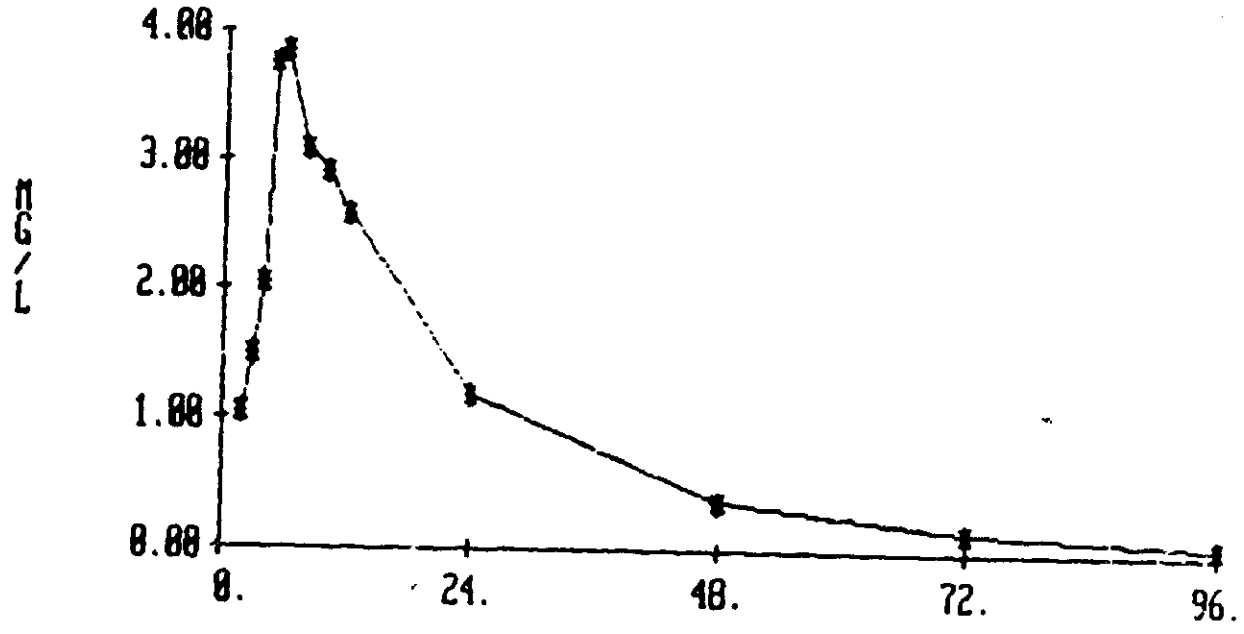
Particle size analysis of fenofibrate batches used in the study expressed in % of total weight (w/w)

E 820

GRANULO LIPANTHYL
MEAN A



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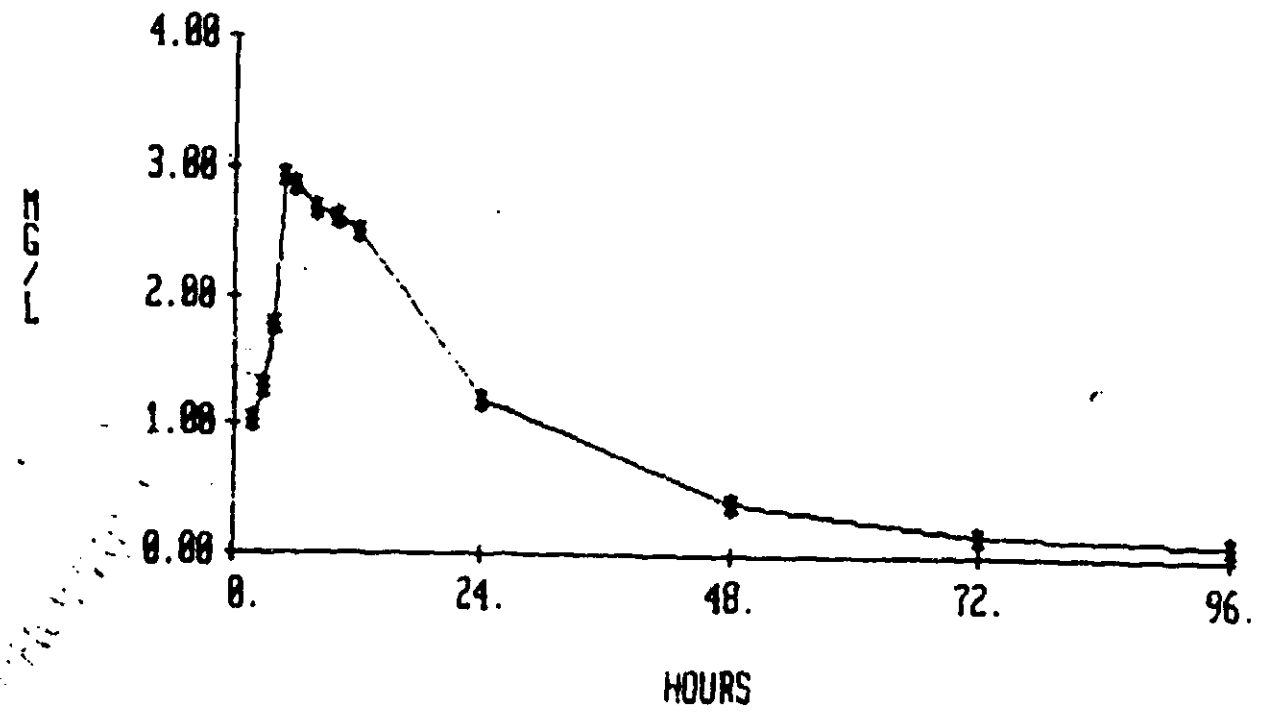
MEAN B



STUDY -14-
LACK OF PHARMACOKINETIC INTERACTION OF COLESTIPOL AND FENOFIBRATE IN VOLUNTEERS

Note: This study was previously evaluated by Dr. Wang in her bio-review.

INVESTIGATOR:

OBJECTIVE: To investigate the possibility of pharmacokinetic interaction between the two hypolipidemic drugs colestipol and fenofibrate in healthy volunteers.

SUBJECTS: 6 healthy male volunteers. Age: 22-24 yeas. Weight: 60-85 Kg. Physical examination and biochemical test were carried out to all subjects.

FORMULATIONS: Lipanthyl^{R} capsule (100 mg fenofibrate) and colestipol.

STUDY PROTOCOLS

1- Fenofibrate Single Dose Study (Days 1 to 3): After overnight fasting, each subject received three Lipanthyl^{R} capsules with 200 ml water. Blood was collected at: 0, 2, 4, 6, 8, 10, 26, 50 and 74 hrs post-dosing. Urine was collected at: 0-26, 26-50 and 50-74 hr. Storage of plasma and urine samples at -20^{O} C until analysis.

2- Fenofibrate Multiple Dose Study (Days 4 to 9): During a 5-day period, 2 Lipanthyl^{R} capsules were given at 8 a.m. and one capsule (1x100 mg) at 8 p.m.. Blood was collected before the morning dose on days 8 and 9.

3- Fenofibrate-Colestipol Multiple Dose Study (Days 9 to 15): During a 6-day period, two Lipanthyl^{R} capsules along with 10 g of colestipol suspended in 200 ml orange juice at 8 a.m. and one capsule in the same way at 8 p.m. with5 g colestipol. Blood was collected just before the 8 a.m. dosing on days 10, 11, 12, and 15 and the 24-hr urine was collected on days 13 and 14.

4- Fenofibrate-Colestipol Single Dose Study (Days 15 to 18): 3 Lipanthyl^{R} capsules and 15 g colestipol were given in the morning of day 15. Blood was collected at 2, 4, 6, 8, 10, 25, 48 and 72 hrs post-dosing. Urine was collected as 24-hrs fractions at days 15 to 18.

PHARMACODYNAMIC MEASURMENTS: Total cholestrol, HDL-cholestrol, phospho-lipids, triglycerides and plasam uric acid levels were determined on days 1, 8 and 16.

ANALYTICAL METHODOLOGY:

RESULTS: The plasma concentration of FA achieved during the 4-phases of the study are illustrated in Fig. 1 and the pharmacokinetic parameters of FA are listed in Table I. The urinary excretion of total FA on typical days of the study is depicted in Fig. 2. Shown below are the mean pharmacokinetic and pharmacodynamic parameters obtained from the four studies:

Parameter	Days				
	1 - 3	8,9	9-12 & 15	13,14	15 - 18
t_{max}(hr)	6.3±0.8	———	———	———	5.0±1.1
C_{max}(µg/ml)	8.9±1.6	———	———	———	15.8±1.5
C_{min}(µg/ml)	———	9.4±0.3	10.5±0.9	———	———
$t_{1/2}$(hr)	19.6±1.1	———	———	———	18.4±0.6
$A_{e,0-74}$(%)	37.6±4.5	———	———	———	37.4±7.2
$A_{e,0-24}$(%)	———	———	———	45.3± 10.5	———
uric acid (mg/dl)	6.03±0.13	3.89±0.23	———	———	3.89±0.23
T.G.[a] (mg/dl)	99±13	85±6	———	———	62±5
T.C.[b] (mg/l)	199±16	182±16	———	———	125±8

[a]Trigglycerides. [b]Total colesterol.

CONCLUSION: The pharmacokinetic of fenofibrate in plasma and urine was not affected by colestipol neither in single dose study nor in multiple dose study.

COMMENTS: The mean urinary excretion (0-74 hr) of fenofibric acid from the present single dose study (300 mg) is 37.6 ± 4.5% where breakfast was taken 2 hr after dosing, whereas in study 8 it was 17.6 ± 4.5% (collection 0-96 hr) after the administration of the same dose with standardized meal. The reason for the discrepency in the urinary excretion could be due to the difference in the incubation period of urine with β-glucuronidase and the use of different assay method in the two studies.

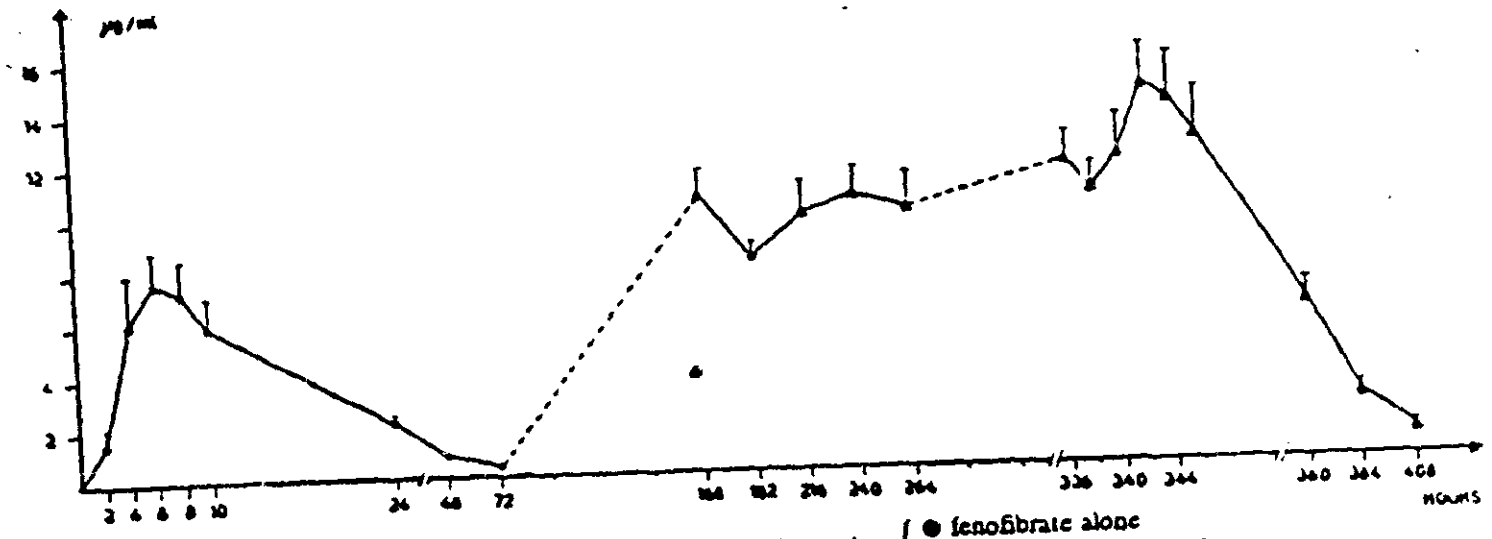


Fig. 1 Plasma fenofibric acid levels during the different stages of the study { ● fenofibrate alone ▲ fenofibrate + colestipol

Table 1. Pharmacokinetic data

Vol.	Fenofibrate mg/kg body wt/day	Mean fasting plasma f. a. (µg/ml ± SE)		β Half-life (h) of f. a.			Time of peak plasma f. a. (h)		Peak plasma f. a. level (µg/ml)		Mean concentration of plasma f. a. (µg/ml)	Mean pool size (mg)
		A	B	I	II	III	I	II	I	II	I	I
1	4.41	9.45 ± 1.81	7.58 ± 0.55	20.4	18.9	18.6	8	8	5.43	20.26	3.44	122.8
2	3.53	10.43 ± 3.07	11.11 ± 1.10	18.5	18.0	18.5	4	6	7.83	12.2	2.56	111.5
3	5.00	8.29 ± 1.26	9.31 ± 0.77	20.0	17.5	16.1	4	6	14.36	17.97	3.45	119.9
4	4.61	9.99 ± 2.34	8.84 ± 0.84	23.7	19.6	16.4	6	2	5.97	10.84	2.73	142.6
5	4.17	9.20 ± 0.76	13.36 ± 0.92	19.4	20.1	22.6	8	6	13.33	16.14	5.26	116.35
6	3.75	8.72 ± 2.12	12.65 ± 1.08	15.4	16.5	17.4	8	4	6.49	17.14	2.86	93.04
Mean ± SE	4.25 ± 0.22	9.35 ± 0.32	10.48 ± 0.93	19.6 ± 1.1	18.4 ± 0.6	18.3 ± 1.0	6.3 ± 0.8	5 ± 1.1	8.9 ± 1.6	15.76 ± 1.46	3.38 ± 0.40	117.7 ± 6.6

A = fenofibrate alone 300 mg/d (Days 8 & 9)
B = fenofibrate 300 mg/d plus Colestipol 15 g/d Days 10, 11, 12, 15
I = Days 1 to 3 single 300 mg dose of fenofibrate
II = Days 15 to 18 300 mg dose of fenofibrate and 15 g Colestipol together after steady state
III = Estimate for the steady state alone (Days 15 to 18)
Mean concentration of plasma fenofibric acid = integrated area of plasma fenofibric acid curve/time (h)
Mean pool size = volume of distribution × mean concentration of plasma fenofibric acid
f. a. = fenofibric acid

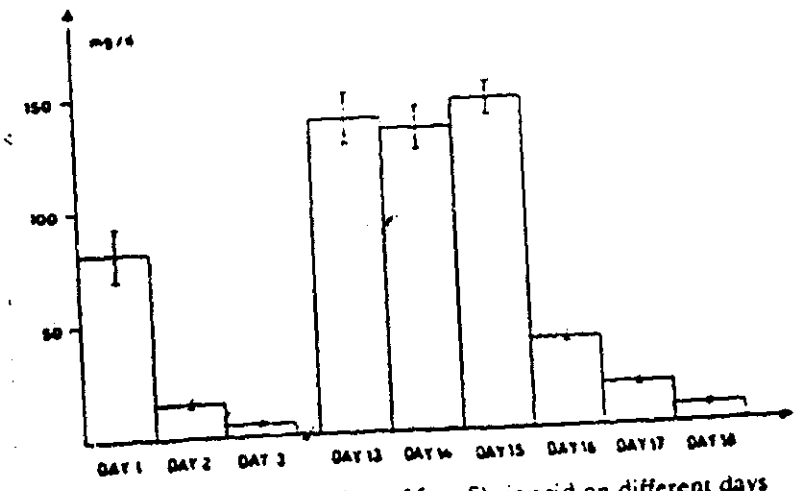


Fig. 2 Daily urinary excretion of fenofibric acid on different days during the study

Overall Deficencies (Total information below to be communicated to the firm)

Note:

Deficency Nos. 1 to 8 that follow relate to the studies listed below. The following studies filed under NDA 19-304 are considered pivotal for helping to meet the Agency's bio-regulations (21 CFR 320) and/or for supporting the package insert's labelling. The outstanding deficencies as related to these studies, etc. that are covered below need to be addressed as appropriate.

Assigned Study No.	Title of Study (Investigators)	Type of Study
3	Clinical Pharmacokinetic Study of Procetofene, A New Hypolipidemic Drug in Volunteers	Single Dose plus Mult. Dose Study
4	Study of Pharmacokinetics of 100 mg Fenfibrate Capsules After Single and Repeated Administration in Normal Healthy Volunteers	Single Dose plus Mult. Dose Study
5	Effect of Hemodialysis on Plasma Kinetics of Fenofibrate in Chronic Renal Failure	Chronic Renal Disease
7	The Metabolism and Disposition in Rats and Human Volunteers	^{14}C-Fenofibrate
8	Study of the Kinetics of Fenofibrate Administered Orally at Increasing Doses	Dose Proportionality Study
10	Pharmacokinetics of Fenofibrate in the Elderly	
12	Comparative Bioavailability Study of Fenofibrate Orally Administered in 100 mg Capsules or in Suspension in Water	Bioavailability and Food Effect Study
13	Comparative Bioavailability of Two Commercial Batches of Lipanthyl	Batch to Batch Bioequivalence
14	Lack of Pharmacokinetic Interaction of Colestipol and Fenofibrate in Volunteers	Drug-Drug Interaction

1. For the studies coded Nos. 3, 5, 8(urine), and 14, provided should be additional assay validation data, as appropriate (i.e., linearity, specificity, precision, accuracy, recovery data as was provided for the study coded No. 12). Provided also for all the different assay methods used to assay fenofibric acid in plasma/serum in the different bio-studies should be evidence that there is no degradation of possible circulating fenofibric acid glucuronide as a result of sample handling and processing unless data can be provided to indicate that there is no circulating fenofribric acid glucuronide.

2. The sponsor allows in the package insert fenofibrate to be given as 300 mg daily in divided doses. Pharmacokinetic studies have been conducted where drug was given as 2X100 mg caps. at 8 am and 1X100 mg cap. at 8 pm as well as 1X100 mg at 8 am, 12 am, and 8 pm. In the study coded No. 8 the mean data suggests there is reduced bioavailability of fenofibrate for a 200 mg dose compared to a 100 mg dose. The sponsor should therefore provide:

   a) Ratio analyses for each study subject where nonnormalized AUC and C_{max} ratios are determined for the 200 mg dose compared to the 100 mg dose.

   b) 90% Confidence Interval Analyses for dose normalized AUC and C_{max} for the 100 mg and 200 mg doses.

   c) The sponsor should provide information as to which dosing regimens were used in their pivotal safety and efficacy studies (e.g., 100 mg at 8 am, 12 am and 8 pm vs 200 mg at 8 am and 100 mg at 8 pm) for the different indications they are trying to get approval for.

3. For the study coded No. 13, the bioavailability of two different production batches (?) of market (?) Lipanthyl 100 mg capsules made in France (?), which had different particle size distribution characteristics per batch, was not equivalent in terms of rate and extent of absorption using the 90% Confidence Interval Approach. Since it is our understanding that Bristol Myers will be manufacturing fenofibrate here in the U.S., a bioequivalence study is required to evaluate batch-to-batch bio-variability for the U.S. site as well as to compare fenofibrate capsules made here and in France.

4. For the study coded No. 7, provided were only the individual urinary and faecal excretion values for subject No. 6. The same information should be provided for the remaining 7 subjects.

5. Demonstrated has been a significant food effect on the absorption of fenofibrate using a high fat meal (i.e., 3 fold increase). In order to help us better understand the different pharmacokinetic study findings as related to labelling as related to clinical safety and efficacy studies that were conducted to support this drug's different indications, provided should be information for the studies coded Nos. 3, 4, 5 and for the pivotal clinical safety and efficacy studies as to the content of meals (e.g., high or low fat meals) and when drug was given in relation to meals for those studies. Depending on this information an additional food effect study to assess this drug's pharmacokinetis may be required (e.g., low fat meal).

6. In the study coded No. 5 there was a significant effect of severe disease on the fenofibrates pharmacokinetics (i.e. t1/2 increased or greater). Little or no pharmacokinetic information was provided patients with less than severe renal disease. Since the proposed insert contraindicates only severe renal dysfunction, an additional (ies) in patients with lesser degrees of renal dysfunction is req

7. For the bio-studies coded Nos. 3, 4, 5, 8, 10, 12, 13, and 14, for capsule batch tested in each respective study, provided should be following: batch size, site of manufacture, fenofibrate particle distribution, in vitro dissolution profile data using USP 30 1000 ml 0.05 and 0.1 M sodium lauryl sulfate at 37^0 C at 60 For each capsule batch it should be identified if it is the U.S. market formulation and whether it is made on production equipment. Additionally particle size distribution informati batches used in the pivotal clinical safety/efficacy studies provided.

8. The proposed package insert will require updating pending the the new/additional information that is provided.

Overall Recommendation

The Division of Biopharmaceutics has reviewed the biopharmaceu pharmacokinetic information that has been filed on 5/31/85, 7/10/86 for NDA 19-304. Based upon the review of that information the Di Biopharmaceutics is currently of the opinion that the NDA is not accep meeting the bio-regulations (21 CFR 320) until such time that the spo provide acceptable responses and/or data to resolve the outstanding bi his recommendation as well as Overall Deficency Nos. 1 to 8 of this should be communicated to the firm.

Ziad Hussein, Ph.D.
Pharmacokinetics Evaluation Branch

RD Initialed by John P. Hunt 2/1/89
FD Initialed by C.T. Viswanathan, Ph.D. 2/2/89

cc: NDA 190-304 (IND 19-056) Orig., HFD-510, HFD-426 (Hussein), HFD-344 (Turner), Drug, Chron, and FOI files.

ZH/PC/12-20-88

Fenofibrate
Lipantil^{R}
100 mg capsule
NDA 19-304
(IND)
Reviewer: Laurene Wang, Ph.D.
Wang #3124X
8-S, 1-0

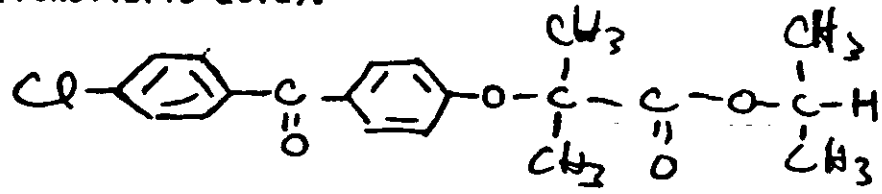
Laboratories Fournier
Dijon, France
Liaison Office
Brookline, MA 02167
Submission Dates:
May 31, 1985
July 10, 1986
RS 4.29.87

FEB 6 1989

Review of A New Drug Application

Background:

Fenofibrate (Isopropryl 2-[p-(chlorobenzoyl) phenoxy]-2-methyl-propionate) as shown below is catergorized as a lipid altering agent of the clofibrate class. The major pharmacologically active component is the hydrolyzed free acid metabolite (fenofibric acid).



The proposed indication of fenofibrate is to reduce elevated serum cholesterol and triglycerides which may be of benefit in the treatment of severe hyperlipoproteinemias. The recommended dosing regimen in the draft labelling was initial dose of Lipantil^{R} 300 mg/day, taken in divided doses and with or immediately before food. The following studies were submitted under IND and NDA 19-304 (5/31/85 and 7/10/86) for fulfilling the requirement of bioavailability/pharmacokinetic (BA/PK) data for product approval. The initial submission of NDA 19-304 (5/31/85) was considered to be incomplete with regard to clinical studies by HFN-810 (Now HFD-510). As shown in the following review, several studies required as pivotal studies by the Division of Biopharmaceutics were also deficient or incomplete. The sponsor resubmitted NDA 19-304 on 4/29/87 and included additional BA/PK studies for fulfilling the Biopharmaceutics requirement. Thus, the approvalability of the product Lipantil^{R} 100 mg from the Biopharmaceutics point of view will be based on the review of NDA 19-304 resubmitted on 4/29/87. Several studies included in the 5/31/85 NDA 19-304 submission were also resubmitted on 4/29/87. Thorough review of the 5/31/85 NDA submission was close to completion before the resubmission NDA 19-304 was resubmitted on 4/29/87. Thus, the following review of 5/31/85 & 7/10/86 submissions are provided for reference purpose and for facilitating the review of the resubmission (4/29/87) of NDA 19-304.

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A. Pivotal Studies

1. Bioavailability/Pharmacokinetic Study
Title: Report of Pharmacokinetic Investigation (NDA 19-304, 1.23/12.0400)

2. Dose Proportionality/Bioavailability Study
Title: Not reported (ref. INFOSTAT FR/001/84/001, Indicated in 7/10/86 submission)

B. Supportive Studies

1. Metabolic Fate and Disposition study (C^{14}-Fenofibrate)
Title: The Metabolic Fate of ^{14}C-LF-178, Isopropryl 2-[4'-(p-chlorbenz [^{14}C]-oyl)-phenoxy] Isobutyrate in Man and Rats (IND)

2. Single-Dose Disposition Study (Unlabelled Fenofibrate)
Title: Pharmacokinetic Study of Fenofibrate after Oral Administration of One 100 mg capsule of Lipanthyl with a Standard Meal (Report submitted on 7/10/86)

3. Multiple-Dose Pharmacokinetics Studies
Title: Serum Concentrations in Patients on Continuous Medication (IND)
Title: Clinical Pharmacokinetic Study of Procetofene, a New Hypolipidemic Drug, in Volunteers (IND)

4. Protein Binding Study
Title: Serum Binding and Interactions of Chlorophenoxy-isobutyric Acid, Itanoxone and Fenofibric Acid According to Their Different HSA Binding Sites (NDA 19-304/1.23/12.0391)

5. Pharmacokinetic Studies in Renal Impaired Patients
Title: Kinetics of Fenofibrate in Renal Disease (IND 19,056/1.20/724)
Title: Effect of Hemodialysis on Plasma Kinetics of Fenofibrate in Chronic Renal Failure (NDA 19,304/1.22/12.0200)

6. Drug Interaction Study
Title: Lack of Pharmacokinetic Interaction of Colestipol and Fenofibrate in Volunteers (IND)

A. PIVOTAL STUDIES

A.1. Bioavailability/Pharmacokinetic Study

Title: Report of Pharmacokinetic Investigation

Investigator and Site:

Study Objective and Plan:

A 3-way randomized, crossover study was carried out to determine the bioavailability of single dose Lipanthyl® capsules (100 mg) administered with and without food in comparison with a reference suspension of fenofibrate.

Subjects:

Twelve (7 male, 5 female) normal healthy volunteers between 18 and 50 years of age and with body weights between 50 and 85 kg (10% deviation from normal weight) participated the study. All subjects had normal medical history, normal physical, laboratory and EEG screenings. Smokers and excessive alcohol drinkers were excluded. Women using contraceptives pills and lactating women or women with positive pregnancy tests were excluded. No medication was allowed 2 weeks and no other research drug was allowed 2 months prior to the study.

Study Preparations:

(1) Lipanthyl capsules, 100 mg, Laboratories Fournier (Dijon, France), Batch No. 2134

(2) Suspension of Fenofibrate, 300 mg/100 ml water, Laboratories Fournier (Dijon, France), Batch No. 560

Dosage and Administration:

Each subject will receive each of the following 3 treatments with 2-week wash-out periods between treatments. Subjects fasted from last supper until at least 4 hours after drug intake (except in treatment A). Subjects were free to drink any non-alcoholic and non-caffeinated beverages during the studies.

Treatment	Formulation and Dosage	Administration (Single Dose)
A	3 capsules of Lipanthyl, 100 mg	with standardized meal*
B	3 capsules of Lipanthyl, 100 mg	without meal
C	Suspension of Fenofibrate, 300 mg/100 ml	without meal

*Standardized Meal:
1 egg, 50g of ham, 25g of cheese, 50g of bread, 20g of butter, 100 ml of orange juice and 100 ml of water.

Sample Collection:

Blood samples were collected in clean glass tubes before drug intake and at 0.5, 1, 2, 3, 4, 6, 8, 10, 12, 24, 36, 48, 72 and 96 hr after dosing.

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Data Analysis:

The following pharmacokinetic parameters of fenofibric acid were determined from the fenofibric acid plasma concentration vs. time curves obtained after the 3 treatments.

Cmax = peak concentration
Tmax = peak time
AUC = area under serum conc. vs. time curves

Cmax and Tmax were directly obtained from measured data by observation. The sponsor did not mention whether the AUC represents the area under the curve from 0 to 96 hr (the last sampling time) or from 0 to infinity. It was reported that AUC was calculated from 0 to the last sampling time with measurable serum fenofibric acid concentration. Serum profiles of fenofibric acid obtained after treatment A were also analyzed using "Bateman" curve fitting method based on a two compartment model with zero order absorption. Cmax, Tmax and AUC (0-∞) were obtained from the calculated serum concentrations generated by the model following curve fitting. With this model, the terminal half life (t1/2, B) was estimated for treatment A. No statistical analysis was carried out to compare the various pharmacokinetic parameters between treatments.

Results:

Table 1 lists the serum fenofibric acid concentration-time profiles of the 12 subjects obtained after the three treatments with fenofibrate formulations. The mean (+ S.D.) concentration-time curves for the 3 treatments are depicted in Figure 1. Pharmacokinetic parameters of fenofibric acid in the 12 subjects are listed in Table 2 for the 3 treatments. These parameters were obtained from the measured serum profiles without curve fitting. The terminal half-life of fenofibric acid was not estimated in this case. The Cmax's were 9.86 ± 3.58, 1.77 ± 2.04 and 1.56 ± 0.93 ug/ml respectively for treatments A, B and C. The Tmax's were 5.83 ± 1.80, 10.58 ± 12.30 and 5.58 ± 3.09 hrs respectively and the AUC's were 159.07 ± 90.66, 52.75 ± 28.27 and 56.04 ± 35.72 ug xh/ml respectively for treatments A, B and C. The coefficients of variation (C.V.) for these measurements are also listed in Table 2 and were found to be between 31% and 118%, indicating large inter-subject variabilities in the measurements of various pharmacokinetic parameters. Intra-subject variabilities in AUC and Cmax are shown in Table 3 by determining the ratios of these parameters between treatments within the same subject. The ratios in

AUC and Cmax between treatments as shown are generally much greater than one. This indicates that there are differences between treatments or differences in the same subjects for the absorption of fenofibrate from different formulations between days. However, statistical analyses were not performed to show significance in treatment effects among these subjects with considerable inter-subject variations. Statistical analyses are required to confirm the effect of food on the bioavailability of fenofibrate and to determine the relative bioavailability of fenofibrate capsules as compared to a suspension formulation of fenofibrate.

Table 4 shows the pharmacokinetic parameter of fenofibric acid obtained from curve fitting of the plasma concentration profiles after treatment A. The terminal half-life of fenofibric acid was estimated to be 16.5 + 8.0 hours. Apparently, the AUC, Cmax and Tmax measurements obtained from fitted plasma concentration vs. time curves were not different from those obtained without curve fitting.

Conclusion:

This study reported various pharmacokinetic parameters (Cmax, Tmax, AUC and t1/2) of fenofibric acid following oral administration of 300 mg fenofibrate in different formulations (suspension or capsules) and regimens (with or without meals). The data clearly indicate that there are considerable inter-and intra-subject variabilities in the pharmacokinetic parameters for fenofibric acid. Thus, statistical analyses are necessary for the comparison of these parameters between treatments. The relative bioavailability of fenofibrate in capsule formulation as compared to fenofibrate in suspension formulation appeared to be greater than 90% when the dosage form were taken without meals. Food appeared to increase the relative bioavailability of fenofibrate in capsule formulation by almost 3 fold.

Deficiencies:

1. The analytical methodology used

2. The sponsor did not conduct statistical analyses to compare AUC and Cmax of fenofibric acid between different treatments with fenofibrate formulations. Analysis of variance with appropriate design is required to confirm the effect of food on the bioavailability of fenofibrate and to correctly determine the relative bioavailability of fenofibrate capsules as compared to a suspension formulation.

Comments:

1. In vitro degradation of the major metabolite of fenofibric acid may occur during the collection, storage and processing of serum samples. This phenomenon has been documented for clofibric acid (structually very similar to fenofibric acid) glucuronide and many other acyl glucuronides (Zomespirac glucuronide, bilirubin glucuronide, tolmetin glucuronide, etc). If degradation of fenofibric glucuronide (formed in vivo) to its free acid, fenofibric acid, occurs after sample collection and before analysis by , the assay results would not accurately indicate the serum concentrations of fenofibric acid but the combined concentrations of fenofibric acid and the degraded glucuronide conjugate. Depending on the conditions, a varying degree of degradation may occur which would result in variable and inaccurate determinations of in vivo serum concentrations of fenofibric acid (the active form). Therefore, it is essential to determine the stability of fenofibric acid glucuronide in serum during processing and storage to assess whether the glucuronide conjugate would interfere with the determination of in vivo serum concentrations of fenofibric acid. The stability testing should be done by using serum samples collected from volunteers administered with fenofibrate and by assaying the concentrations of fenofibric acid at different time and under different conditions of processing and storage. If in vitro degradation does occur, special precautions and procedures should be taken to prevent such degradation and to control the degree of degradation.

2. Since food appeared to increase the relative bioavailability of fenofibrate and the labelling requires the drug be taken with or immediately before food, the Medical Officers of the Agency are recommended to ascertain whether the clinical efficacy and safety studies have been conducted with fenofibrate capsules taken with or immediately before food.

3. The present study used a standardized meal with high fat content, which increased the relative bioavailability apparently by almost 3 fold. It is desirable to determine whether the relative bioavailability of fenofibrate capsules taken with a low fat or non fat meal would be different from that obtained after a high fat meal.

B. SUPPORTIVE STUDIES

B. 1. Metabolite Fate and Disposition Study (^{14}C-Fenofibrate)

Title: The Metabolic Fate of ^{14}C-LF-178, Isopropryl-2-[4'-p-chlorbenz[^{14}C]-oyl]phenoxy] Isobutyrate in Man and Rats

Investigator and Site:

Objective:

To determine the urinary metabolites of fenofibrate in man.

Subjects:

Two healthy adult male subjects aged 45 (HVI) and 36 (HVZ) years were studied. The outwardly healthy status of the subjects were confirmed by clinical serum chemistry and urinalysis perform 1 wk prior to the study. Clinical serum chemistry and urinalysis were again performed at 1 wk following the study. Subjects were refrained from consuming any other pharmaceutical products during the course of study.

Study Preparation:

Unlabelled fenofibrate (LF-178) and ^{14}C-labelled fenofibrate were supplied by Laboratories Fournier, France. The specific activity of ^{14}C-fenofibate was 15uCi/mg. Portions of ^{14}C fenofibrate (8.8 mg) and unlabelled fenofibrate (739.8 mg) were ground together and dissolved in sunflower oil (15 ml). The theoretical specific activity of the test solution was determined by assaying 50 ul of the sample before and after dosing. The dose administered to each subject was:

HV 1: 6 ml (5.839 g) solution containing 309 mg fenofibrate and 55 uCi of ^{14}C-fenofibrate)

HV 2: 6 ml (5.773 g) solution containing 306 mg fenofibrate and 54.4 uCi of ^{14}C-fenofibrate)

Drug Administration and Sample Collection:

The subjects were requested to fast overnight prior to dosing. Each subject was given a gelatin capsule containing the study preparation as described above, followed by 100 ml water. Urine samples were collected at 24 hour intervals over the 96 hours following dosing. The urine samples were stored at -20°C prior to analysis.

Analytical Method:

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Conclusion:

Following a single oral dose of fenofibrate, the majority (~88%) of the dose can be recovered in the urine within 48 hours. Fenofibrate is extensively metabolized with less than 3% of the dose excreted unchanged in the urine. Three major metabolites were found in the urine. Fenofibrate is hydrolyzed *in vivo* to form fenofibric acid ~ 9% of the dose in urine which is then metabolized to its glucuronide conjugate (~60% the dose). The glucuronide conjugate of fenofibric acid is heat and acid labile. Heat and acid may cause breakdown of fenofibric acid glucuronide to form either fenofibric acid or some other compounds that can not be extracted or identified by . Acid may also cause the breakdown of the free fenofibric acid.

Comments:

1. This study is considered as preliminary in characterizing the disposition of fenofibrate in 2 human volunteers. The study shows that fenofibrate is extensively metabolized and fenofibric acid conjugate is the major metabolite in urine. Thus, control of the stability of the glucuronide conjugate of fenofibric acid during sample collection, storage and analysis is essential for the determination of the concentrations of the free fenofibric acid and its conjugate in biological samples. The present study indicated that fenofibric acid conjugate is heat and acid labile. Acid may cause the breakdown of both fenofibric acid and its conjugate. Therefore, a well-controlled analytical procedure is indispensible for the determination of serum and urine concentrations of fenofibric acid and its glucuronide in any pharmacokinetic/bioavailability studies of fenofibrate. The sponsor again is requested to provide stability data on fenofibric acid and its glucuronide in both serum and urine samples. A validated analytic procedure (including samples processing and storage) which controls for the stability of fenofibric acid and its glucuronide should be reported and used for all pharmacokinetic studies.

B. 2. **Single-Dose Disposition Study (Unlabelled Fenofibrate)**

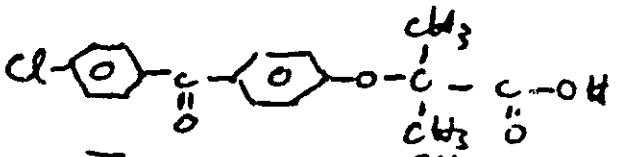
Title: Pharmacokinetic Study of Fenofibrate after Oral Administration of One 100 mg capsule of Lipanthyl with a Standard Meal

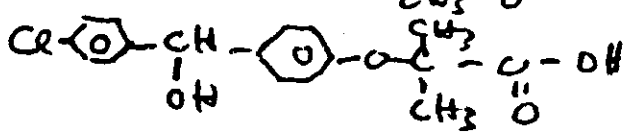
Investigator and Site:

Objective:

1. To determine the pharmacokinetic parameters of fenofibric acid (LF 153) and LF 433, metabolites of fenofibrate*, after oral administration of one 100 mg capsule of Lipanthyl with a standard meal.

2. To study the urine excretion of LF 153 and LF 433.

LF 153  (major circulation active metabolite of fenofibrate)

LF 433  (inactive, minor metabolite)

(*Note: Fenofibrate is metabolized very rapidly and is not detectable in blood following oral administration.)

Subjects:

Twelve male normal healthy volunteers aged between 21 and 26 (mean ± S.D. = 23 ± 2) years with body weight of 63.8 ± 3.4 kg and height of 174.9 ± 6.0 cm participated in the study. All subjects had normal medical history, healthy physical, clinical and biological parameters.

Study Preparation:

Lipanthyl 100 mg Capsules (Batch No. 2767), Lab. Fournier.

Study Procedure:

The study was an open trial. All subjects received the drug after an overnight fast (22 hrs). The drug was given as a 100 mg Lipanthyl capsule with standard meal consisting of 1 egg, 50 g of ham, 25 g of cheese, 50 g of bread, 20 g of butter, 100 ml of orange juice and 100 ml of water. Four and Twelve hours after dosing, the subjects received lunch and dinner respectively. These two meals were standard and identical for all subjects. No alcohol or caffeine containing beverages were allowed during the first 24 hours of the trial. Blood samples were collected at prior to dosing and at 2, 3, 4, 5, 6, 7, 8, 12, 14, 24, 48, 72 and 96 hours post-dosing. Plasma samples were obtained and stored immediately at -20°C until assayed. Urine samples were taken immediately before dosing and during periods of 0-12, 12-24, 24-48, 48-72 and 72-96 hrs following drug treatment. The urine volume and pH were determined and urine samples were stored frozen until assayed.

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Results:

Table 5 lists the individual and mean plasma concentrations of fenofibric acid (LF 153) in the 12 subjects after oral administration of one 100 mg Lipanthyl capsule with a standard meal. No plasma concentration vs time plots were shown in the report. The individual and mean values of the various pharmacokinetic parameters for fenofibric acid obtained with or without curve fitting are listed in Table 6. The maximum concentration of LF 153 in plasma was reached at 4.8 ± 0.2 hrs (ranging from 3 to 6 hrs). The Cmax of LF 153 was 4801 ± 263 ng/ml (between 3685 and 6743 ng/ml). The absorption t1/2 and the terminal elimination t1/2 for LF 153 were 0.9 ± 0.2 (0.4-2.3) hours and 22.8 ± 3.7 (13.1 - 32.5) hours respectively. The AUC_{0-96} and $AUC_{0-\infty}$ for LF153 were 96.9 ± 13.3 (49.6 - 213.7) mcg. hr/ml and 97.6 ± 54.0 (46.6-243.0) mcg. hr/ml respectively. The

inter-subject variation especially in t 1/2 and AUC values.

The individual and mean plasma concentrations of LF 433 in the 12 subjects following dosing of 100 mg Lipanthyl capsule are listed in Table 7. The individual and mean values of the pharmacokinetic parameters of LF 433 are listed in Table 8. A mean peak concentration of 164 ± 90 (95 - 356) ng/ml was reached at 20.9 ± 10.7 (5 - 48) hours post-dosing. The AUC_{0-96} was 8.2 ± 4.4 (.45 - 17.6) mcg.hr/ml for LF 433. There was a considerable inter-subject variability in all parameters for LF 433.

The total (free + conjugated forms) urinary excretion data for LF 153 and LF 433 are presented in Tables 9 and 10 respectively. Over the period of 96 hours, the cumulative values of urinary excretion of LF 153 varied between 13.9 and 46.4% (27.6 ± 3.6%) of the fenofibrate dose administered. The cumulative urinary excretion of LF 433 from 0 to 48 hours was 3.9 ± 0.3 (2.5-6)% of the fenofibrate dose administered.

Conclusion:

If the assay method is validated,

Comments:

1. The assay method for the determination of urine concentrations of LF 153 and LF 433 was not validated for its linearity, accuracy and precision. The assay procedure for the plasma samples was not validated for its accuracy and within day precision. In addition, the stability of LF 153 and LF 433 as well as their glucuronides in plasma and urine during sample collection, storage and processing was not determined. The precision of the assay methods should be assessed using samples containing both the free and conjugated forms of LF 153 and LF 433, that is real samples but not spiked samples used for the validation procedure. The importance for assessing the stability of these compounds, especially the glucuronide conjugates, in plasma and urine has been elucidated in the previous comments.

2. The Cmax and AUC values obtained in this study following dosing of 100 mg fenofibrate were approximately half of the respective values obtained in the previous study when 300 mg fenofibrate was administered (Study B.1). Although such a between study comparison may not be valid due to the large inter-subject variability, this preliminary comparison could indicate that plasma concentrations of fenofibric acid may not be linearity proportional to the dose of fenofibrate administered. Thus, a dose proportionality study which compares the AUC's and Cmax's between various doses of fenofibrate within the dosing range proposed in the labelling should be conducted.

3. The urinary excretion data for fenofibric acid and its glucuronide conjugates were not consistent between this study and the metabolic fate study of fenofibrate presented previously (Study B.1.). In Study B.1. where 300 mg of ^{14}C-labelled fenofibrate was administered, the total urinary excretion of fenofibric acid and its glucuronide accounted for approximately 70% of the fenofibrate dose given. However, the present study reported that the total urinary excretion of fenofibric acid and its glucuronide accounted for only 27.6% of the fenofibrate dose given. This discrepancy could be due to incomplete absorption of fenofibrate in this study or due to an inaccurate assay procedure used in this study. However, comparison of the AUC data for fenofibric acid between this study and previous studies indicate that incomplete absorption of fenofibrate is unlikely. Thus, it is very likely that the assay procedure used in this study for the determination of urine concentrations of fenofibric acid and its glucuronide is not accurate. Again, this could be due to the instability of both fenofibric acid and its glucuronide with degradation occurring during sample storage and processing. Consequently, to better characterize the pharmacokinetics of fenofibric acid following fenofibrate administration, one must determine the stability profiles for fenofibric acid and its glucuronide in both plasma and urine samples.

B. 3. Multiple-Dose Pharmacokinetic Studies

Study 1

Title: Serum Concentrations in Patients on Continuous Medication

Investigator and Site:

Objective:

To determine the circulating concentrations of fenofibric acid in hyperlipidemic subjects under continuous medication of fenofibrate.

Subjects:

Forty hyperlipidemic patients of either sex (26 M, 14 F), aged between 13 and 65 (48 + 12) years, under continuous medication of fenofibrate partcipated in the study. The type of hyperlipidemia in these patients was determined by electrophoresis (23 IIa, 16 IIb, 1 IV). None of the patients had been on Lipanthyl prior to the start of the study.

Study Preparation:

Lipanthyl 100 mg capsules. (Batch No. unknown)

Drug Administration and Sample Collection:

The daily dose of fenofibrate ranged from 100 to 400 mg. The frequency and the way of dosing were not described. The treatment duration was apparently 12 months. In some patients, the daily dose was either reduced or increased after several months of treatment. Blood samples were collected at 1, 4, 5, 6, 7, 8, 9, 10, 11 or 12 months after dosing. However, the time at which the sample was collected following dosing was not mentioned. Serum samples were obtained and assayed.

Analytical Method:

Results:

The sponsor reported a mean serum level of fenofibric acid of 14 ug/ml (ranging from 10 to 40 ug/ml) at 1 month after fenofibrate treatment. Serum concentrations of fenofibric acid at the several months after fenofibrate treatment were within the range found at 1 mouth following treatment.

Recommendations

5. This study is considered to be a preliminary pilot type study. The quality of the study and study report is poor. In addition to the lack of information on the sampling time and the exact study procedure, the assay method for fenofibric acid is poor and unvalidated. Thus, one can not conclude whether significant accumulation of fenofibric acid could occur following long term treatment with fenofibrate.

B. 3. Multiple-Dose Pharmacokinetic Studies

Study II

Title: Clinical Pharmacokinetic Study of Procetofene, a New Hypolipidemic Drug, in Volunteers

Investigator and Site:

Objective:

To characterize the pharmacokinetics of fenofibric acid in volunteers taking single and repeated therapeutic doses of fenofibrate

Study Procedures:

(1) Single-Dose Study:

Six male normal volunteers with age between 23 to 26 years and body weight between 61 to 74 kg participated in the study. All subjects underwent physical and biochemical examinations prior to the study. Fenofibrate (Lipanthyl) was given, after an overnight fast, as 3 x 100 mg capsules with 200 ml water. The subjects were allowed a light breakfast 2 hrs after drug intake. Blood samples were collected at 0, 2, 4, 6, 8, 10, 12, 26, 50 and 76 hrs following dosing. After centrifugation, plasma was stored at -20°C until assayed. Urine samples were collected during the periods of 0-24, 24-48, 48-72 and 72-96 hours and then immediately frozen at -20°C.

(2) Multiple-Dose Study:

Ten normal volunteers (6 M, 4 F) with age between 22 to 24 years and body weight between 52 to 79 kg participated in the study. Fenofibrate (Lipanthyl) was administered to the subjects daily as 2 x 100 mg capsules at 8 a.m. and 1 x 100 mg at 8 p.m. for 10 days. Blood samples were collected at 0, 24, 48, 72, 96, 120 and 240 hours after the first drug administration. At 240 hrs (day 10) following the first dosing, a last dose of 300mg Lipanthyl was given once and blood samples were obtained at 2, 4, 6, 8, 10, 24, 36, 48, 60 and 72 hrs after the last dose. Plasma samples were stored at -20°C until analyzed. A 6-day urinary output was collected at 24-hr intervals from day 9 to day 14 and stored at -20°C.

Assay Method:

Results:

(1). Single-Dose Study:

In the six subjects given 300 mg fenofibrate, a peak concentration of 6.05 ± 2.3 mcg/ml for fenofibric acid was obtained at 4 hrs post dosing. The terminal elimination t1/2 of fenofibric acid was 26.58 ± 2.85 hrs and the AUC_0 value was 169.9 ± 23 mcg. hr/ml. Large inter-subject variabilities in the various parameters were observed. The 96-hr urinary excretion of fenofibric acid and its glucuronide accounted for 27.9 ± 5.9% of the fenofibrate dose given.

(2). Multiple-Dose Study:

The plasma profiles of fenofibric acid obtained after 300 mg daily dose of fenofibrate during a 10-day period is shown in Figure 2 (middle panel). Apparently, a plateau phase around 10 ug/ml (Trough) of fenofibric acid in plasma was reached after 120 hours. An accumulation factor of approximately 2 was estimated for fenofibric acid after 10 days administration of 300 mg fenofibrate. The mean urinary excretion of fenofibric acid and its glucuronide accounted for 31.8% and 30.9% of the dose given on day 9 and day 10 respectively. Plasma concentration-time profiles of fenofibric acid following the last dose (given at 240 hr) are also shown in Figure 2 (right panel). Apparently, a peak plasma level of 17.6 ± 2.5 mcg/ml for fenofibric acid was obtained at 6 hrs after dosing of 300 mg fenofibrate during steady-state. The terminal t1/2 was estimated to be 21.73 ± 1.07 hrs which was not significantly different from that obtained in the single-dose study. The plasma protein binding of fenofibric acid was estimated for 5 samples to be between 99.6 and 99.8%.

Conclusion:

Assuming that the assay method in this study is validated.

Comments:

1. Without a validated assay method, the present study results are only preliminary and not conclusive.

2. The food schedule in the mulitple dose study was not specified. Since the labelling requires that fenofibrate capsules be administered with or immediately before food, the dosing and food schedule in the multiple dose studies should be planned as stated in the labelling.

B. 4. Protein Binding Study

Title: Serum Binding and Interactions of Chlorophenoxy-isobutyric Acid, Itanoxone and Fenofibric Acid According to Their Different HSA Binding Sites

Investigator and Site:

Objective:

To study the binding characteristics of fenofibric acid (FA), chlorphenoxy-isobutyric acid (CIA) and itanoxone (ITX), their HSA binding sites and their serum protein binding interactions with other drugs and in different pathological states including hyperlipidemia, mild and severe hepatic failure.

Methods:

1 page
purged

Conclusion:

Fenofibric acid (FA) is shown to be extensively bound (99%) to serum proteins in normal serum at FA concentrations of 8.9 or 26.4 mcg/ml. The FA serum concentration of 8.9 mcg/ml is within the range of the maximum serum concentration of FA observed following oral administration of 300 mfg of fenofibrate with meal. The free fraction of FA in serum is unaffected in patients with mild cholestasis (bilirubin ~ 25 uM) or hyperlipidemia; but is significantly increased (from 1% to 5%) in patients with severe cholestasis (bilirubin $>$200 uM). Free fatty acid such as palmitic acid appeared to decrease the binding of FA to serum proteins; however the extent of reduction was not reported. The serum protein binding interactions between FA and various compounds (salcyclic acid, sulfamethoxazole, phenylbutazone, indomethacin, warfarin) were studied. The interaction between FA and salicylic acid or sulfamethoxazole was not clearly demonstrated by the sponsor. FA appeared to displace phenylbutazone (by about 0.6%) but not indomethacin or warfarin from serum protein binding sites.

Comments:

The fact that fenofibric acid is extensively (99%) bound to plasma proteins should be reported in the labelling.

B. 5. Pharmacokinetic Studies in Renal Impairment Patients

Report I

Title: Kinetics of Fenofibrate in Renal Disease

Report II

Effect of Hemodialysis on Plasma Kinetics of Fenofibrate in Chronic Renal Failure

Note:

Reports I and II are essentially derived from the same study (same investigators and sites, same subjects, same protocols and same results).

Investigators and Sites:

Objective:

To determine whether the pharmacokinetics of fenofibric acid, the major metabolite fenofibrate, is altered in patients with severe or terminal renal diseases and to determine the effect of hemodialysis on pharmacokinetics of fenofibric acid in these patients.

1 page
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Conclusion:

If the assay method for is validated,

Comments

1. The meal schedule around the dosing of fenofibrate in this study should be reported. In addition, the bioavailability of fenofibrate in renal failure patients should be assessed and be compared to normal subjects. Raw data of plasma concentrations of FA in these patients should be provided

2. The assay method used for

3. Raw data of FA plasma concentrations in each of the 5 patients given multiple doses of fenofibrate (100 mg/day for 15 days) should be provided in order to determine the accumulation of FA in renal failure patients following multiple dosing. The meal schedule around the dosing of the drug should also be reported.

4. This study only addressed patients with chronic renal failure. The consequences of mild to moderate decreased renal function is unknown.

B. 6. Drug Interaction Study

Title:

Lack of Pharmacokinetic Interaction of Colestipal and Fenofibrate in Volunteers.

Investigator and Site:

Objective:

To investigate the possibility of pharmacokinetic interaction between two hypolipidemic drugs, colestipol, an ion exchange resin and fenofibrate in healthy volunteers.

Subjects:

Six normalipemic and normouricemic male volunteers, aged between 22 and 24 yrs and weighed between 60 and 85 kg, were studied. All subjects underwent physical examination and biochemical investigations (blood, liver, kidney and plasma lipids) prior to the study.

Study Protocols

(1). Fenofibrate Single Dose Study (Days 1 to 3)

After an overnight fast, fenofibrate (Lipanthyl) 3 x 100 mg capsules were given with 200 ml water. Breakfast was given 2 hrs later. Blood samples were collected at 0, 2, 4, 6, 8, 10, 26, 50 and 74 hrs post-dosing. Urine was collected in 3 periods: 0-26, 26-50 and 50-74 hr. Plasma and urine samples were stored at -20°C until assayed.

(2). Fenofibrate Multiple Dose Study (Days 4 to Morning of Day 9)

During a 5-day period, fenofibrate was given as 2 x 100 mg capsules at 8 a.m. and 1 x 100 mg at 8 p.m. (300 mg/day). Blood samples were collected before the morning dose on Days 8 and 9.

(3). Fenofibrate-Colestipol Multiple Dose Study (Day 9 to Morning of Day 15)

Dosing a 6-day period, fenofibrate was administered as 2 x 100 mg capsules along with 10 g of colestipol suspended in 200 ml orange juice at 8 a.m., and in the same way at 8 p.m., as 1 x 100 mg fenofibrate with 5 g colestipol. Blood samples were collected just before the morning dose on days 10, 11, 12 and 15 and the 24-h urine was collected on Days 13 and 14.

(4). Fenobibrate-Colestipol Single Dose Study (Days 15 to 18)

A last single dose of 300 mg fenofibrate and 15 g colestipol was given in the morning of Day 15. Blood samples were collected at 2, 4, 6, 8, 10, 25, 48 and 72 hr post-dosing. Urine was collected as 24-h fractions from Days 15 to 18.

Pharmacodynamic Measurements:

Total cholesterol, HDL-cholesterol, phospholipids, triglyceride and plasma urine acid levels were determined on Days 1, 8 and 16.

Analytical Methods:

Conclusion:

If the assay method for

Comments:

1. The method for

2. The Cmax and Tmax values of FA obtained in this study after a 300 mg single dose of fenofibrate alone on Day 1 or after 300 mg fenofibrate along with colestipol at steady state was given were similar to those found in Study A. 1. after a single dose of 300 mg fenofibrate was administered with a high fat meal. However, in this study food (contents not reported) was ingested at 2 hrs post-dosing. It appears that food given upto 2 hrs post-dosing of fenofibrate may satisfy the need of administering fenofibrate "immediately" before meal as stated in the labelling.

Overall Evaluation:

From the Biopharmaceutics point of view, this NDA application has some deficiencies that do not allow us at this time to conclude that the sponsor has met the requirements. The deficiencies are clearly stated in the different "Deficiencies" and "Comments" part of this review and are summarized as follows

1) All anlytical methods used in the BA/PK studies submitted for determining plasma (serum) concentrations of fenofibric acid and urine concentrations of fenofibric acid and its conjugate were not validated.

2) No dose proportional study was submitted.

3) Food appears to increase the bioavailability (rate and extent) of fenofibrate and the labelling requires that fenofibrate capsules be given with or immediately before food. However, in several of the pharmacokinetic studies, the food schedule and contents were not controlled or specified. These studies included Study B. 1. (metabolic rate and disposition study), B. 3. (Multiple Dose Study), B. 5. (Studies in renal failure with and without hemodialysis) and B. 6. (drug interaction studies in single and multiple doses).

4) Discrepancy in the percent of fenofibrate dose excreted in the urine as FA and its conjugate was found between studies (Study B. 1 and Study B. 2). This discrepancy is very likely due to the different and unvalidated assay methods used. However, the values for the percent dose excreted in the urine as FA and its conjugate were similar between Studies B. 2, B. 3. II. and B. 6, although different and unvalidated assay methods were applied between studies. From the analytical methodology point of view, assay method used in Study B. 1. where radiolabelled fenofibrate was administered may present more accurate assessment of the percent ofdose excreted in urine.

5) A well-controlled multiple dose study showing the accumulation characteristics of plasma levels of FA following repeated dosing of

TABLE 1: Serum concentration-time profiles of fenofibric acid in the 12 subjects after three treatments with fenofibrate formulations.

TREATMENT A.

dosage A): Lipanthyl and standardized meal, 3 caps. of 100 mg Batch: 2134

time in h
concentration in ug/ml

time	0	0.5	1	2	3	4	5	8	10	12	24	36	48	72	96
subject															
1															
2															
3															
4															
5															
6															
7															
8															
9															
10															
11															
12															
mean	0.000	0.049	0.209	0.933	4.526	5.727	8.939	7.436	5.292	4.973	2.169	1.144	0.753	0.382	0.214
sdev	0.000	0.110	0.234	0.931	3.553	4.598	3.180	3.066	3.255	3.349	1.517	1.084	0.777	0.376	0.206
sem	0.000	0.033	0.068	0.291	1.026	1.386	0.918	0.885	0.942	0.967	0.457	0.313	0.246	0.119	0.060

mean: mean value
sdev: standard deviation
sem: standard error of the mean

< = value below detection limit, - = sample lost or destroyed
N = value not measurable, * = value not reliable

TABLE 1. Serum Concentration-time profiles of fenofibric acid in 12 subjects.

TREATMENT B

dosage B : Lipanthyl 3 caps. of 100 mg Batch: 2134

time in h
concentration in ug/ml

time	0	0.5	1	2	3	4	6	8	10	12	24	36	48	72	96
subject															
1															
2															
3															
4															
5															
6															
7															
8															
9															
10															
11															
12															
mean	0.000	0.096	0.420	0.937	1.441	1.272	1.236	1.054	1.096	0.905	0.740	0.624	0.449	0.350	0.287
sdev	0.000	0.146	0.845	1.672	2.143	1.609	1.225	0.901	0.671	0.519	0.381	0.440	0.348	0.297	0.254
sem	0.000	0.044	0.244	0.483	0.619	0.464	0.354	0.260	0.202	0.150	0.110	0.127	0.100	0.086	0.073

mean: mean value
sdev: standard deviation
sem: standard error of the mean

(= value below detection limit, - = sample lost or destroyed
x = value not measurable, * = value not reliable

TABLE 1. Serum Concentration-time Profiles of fenofibric acid in 12 subjects

TREATMENT C

dosage C : Suspension of 300 mg Fenofibrate in 100 ml water Batch: 560

time in h
concentration in ug/ml

time	0	0.5	1	2	3	4	6	8	10	12	24	36	48	72	96
subject															
1															
2															
3															
4															
5															
6															
7															
8															
9															
10															
11															
12															
mean	0.000	0.198	0.519	0.991	1.279	1.198	1.217	1.090	1.063	0.949	0.776	0.601	0.540	0.398	0.288
sdev	0.000	0.154	0.380	0.798	0.953	0.818	0.751	0.561	0.576	0.488	0.411	0.395	0.473	0.381	0.337
sem	0.000	0.044	0.114	0.230	0.275	0.236	0.217	0.191	0.166	0.141	0.119	0.114	0.137	0.115	0.097

mean: mean value
sdev: standard deviation
sem: standard error of the mean

(= value below detection limit, - = sample lost or destroyed
x = value not measurable, * = value not reliable

Figure 1: Mean (± SD) Concentration-time Curves of fenofibric acid following the three Treatments.

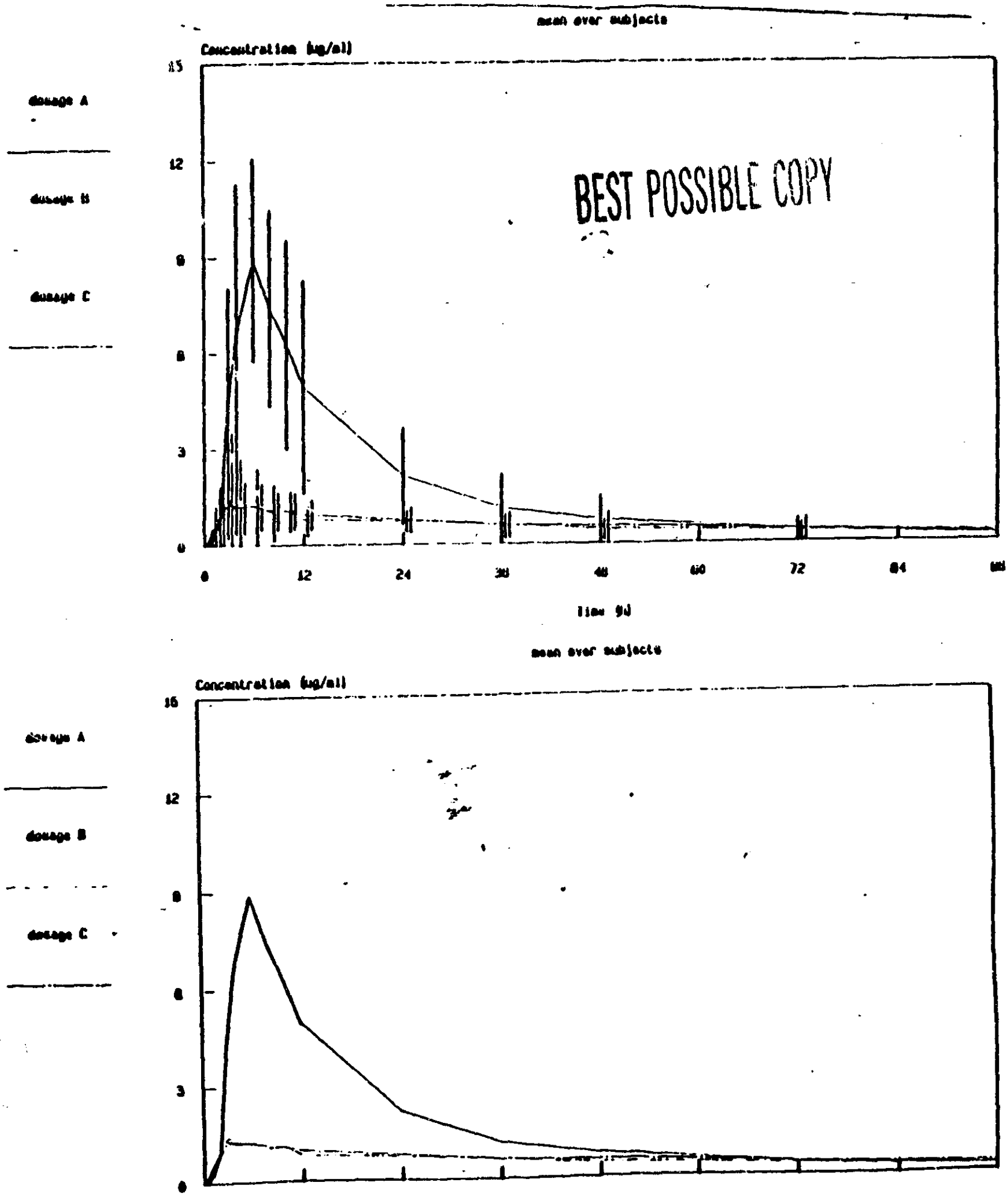


TABLE 2. Pharmacokinetic Parameters of Fenofibric Acid in the 12 Subjects following 3 treatments
(calculated from serum levels of fenofibric acid)

	TREATMENT A.			TREATMENT B			TREATMENT C		
subject	AUC	Cmax	Tmax	subject	AUC	Cmax	Tmax	subject	AUC	Cmax	Tmax
1				1				1			
2				2				2			
3				3				3			
4				4				4			
5				5				5			
6				6				6			
7				7				7			
8				8				8			
9				9				9			
10				10				10			
11				11				11			
12				12				12			
Mean	159.07	9.8636	5.8333		52.754	1.7699	10.583		56.044	1.5392	5.5833
Stdev	90.663	3.5828	1.8007		28.271	2.0406	12.295		35.724	0.93489	3.0883
Sem	26.172	1.0343	0.51981		8.1612	0.58907	3.5493		10.312	0.26988	0.89153
C.V. (%)	57%	36%	31%		54%	115%	116%		64%	60%	55%
Units:	hrug/ml	ug/ml	h		hrug/ml	ug/ml	h		hrug/ml	ug/ml	h

TABLE 3: Ratio Analysis FOR AUC and Cmax of Fenofibric Acid between Treatments

	1	2	3	4	5	6	7
1	Subject	AUC	AUC	AUC	AUC	AUC	AUC
2	No.	A	B	C	A/C	B/C	A/B
3	1						
4	2						
5	3						
6	4						
7	5						
8	6						
9	7						
10	8						
11	9						
12	10						
13	11						
14	12						
15							
16	Mean				3.55	1.30	3.41
17	S.D.				2.04	1.07	1.68
18	C.V.				57%	82%	49%
19							

	8	9	10	11	12	13	14
1	Subject	Cmax	Cmax	Cmax	Cmax	Cmax	Cmax
2	No.	A	B	C	A/C	B/C	A/B
3	1						
4	2						
5	3						
6	4						
7	5						
8	6						
9	7						
10	8						
11	9						
12	10						
13	11						
14	12						
15							
16	Mean				9.84	2.02	9.32
17	S.D.				8.97	3.62	5.46
18	C.V.				91%	179%	59%
19							

TABLE 4: Pharmacokinetic Parameters of Fenofibric Acid For Treatment A (Obtained from Curve Fitting)

A: Lipanthyl and standardized meal, 3 caps. of 100 mg, Batch: 2134

Subj.	model	AUC (hxug/ml)	Cmax (ug/ml)	Tmax (h)	t1/2β (h)
1					
2					
3					
4					
5					
6					
7					
8					
9					
10					
11					
12					
					16.512
mean		155.19	10.850	5.993	7.964
stdev		94.37	3.920	1.688	2.299
sem		27.24	1.132	0.487	

TABLE 5:

Individual plasma concentrations (ng/ml) and mean values of LF 153, calculated in the 12 study subjects after oral administration of one 100 mg capsule of Lipanthyl, with a standard meal.

(LF 153 : Fenofibric Acid)

cts	Time 2.000	3.000	4.000	5.000	6.000	7.000	8.000	12.000	16.000	24.000	48.000	72.000	Time 96.000
	1112.2500	2939.5835	3575.8000	4483.4478	4192.4170	3492.6665	3278.4335	2629.0315	2256.2500	1265.8667	962.6666	761.3333	143.8333
	337.5767	452.5782	388.2958	299.8242	255.6850	224.7118	188.6778	136.5537	148.2681	229.2622	124.2172	82.7108	

ay unit : mg; time unit : hr; concentration unit : ng/ml)

TABLE 6 : Individual kinetic parameters and mean values of LF 153, after oral administration of one 100 mg capsule of Lipanthyl, with a standard meal.

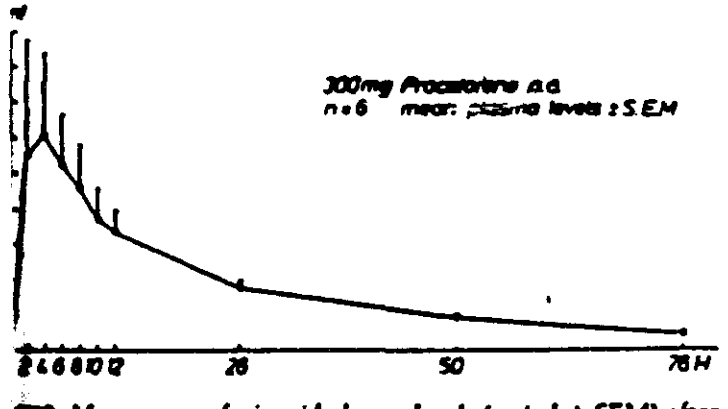
Subject	tmax (hr)	Cmax (ng/ml)	t1/2 a (hr)	t1/2 (hr)	$AUC_{0 \rightarrow 96}$ (mcg/ml.hr)	$AUC_{0 \rightarrow \infty}$ (mcg/ml.hr)
1						
2						
3						
4						
5						
6						
7						
8						
9						
10						
11						
12						
Mean	4.8	4801	0.9	20.8	90.9	97.6
S.D.	0.8	912	0.6	5.9	46.0	54.0
S D.M.	0.2	263	0.2	1.7	13.3	15.6
CV %	16	19	66	28	50	55

TABLE 7: Individual plasma concentrations (ng/ml) and mean values of LF 433, calculated in the 12 study subjects after oral administration of one 100 mg capsule of Lipanthyl, with a standard meal.

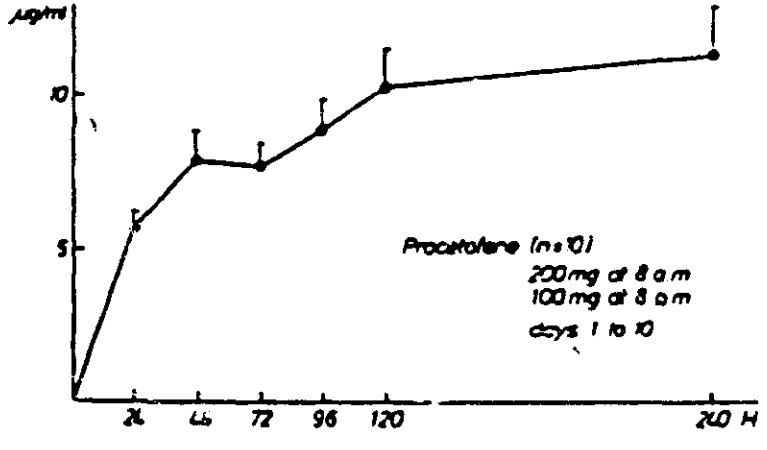
	Time											
Objects	2.000	3.000	4.000	5.000	6.000	7.000	8.000	12.000	14.000	24.000	48.000	72.000	Time 96.000
01-A													
02-A													
03-A													
04-A													
05-A													
06-A													
07-A													
08-A													
09-A													
010-A													
011-A													
012-A													
Mean	27.5833	47.0167	58.3333	68.0000	64.0833	72.7167	78.1333	107.6667	117.9167	144.6500	101.3636	57.3333	37.9167
S.D.	4.5360	7.6358	7.4165	7.4000	7.3034	7.0769	15.1497	16.5132	15.5767	25.8763	24.1241	11.5074	5.7386

(Assay unit : mg; time unit : hr; concentration unit : ng/ml)

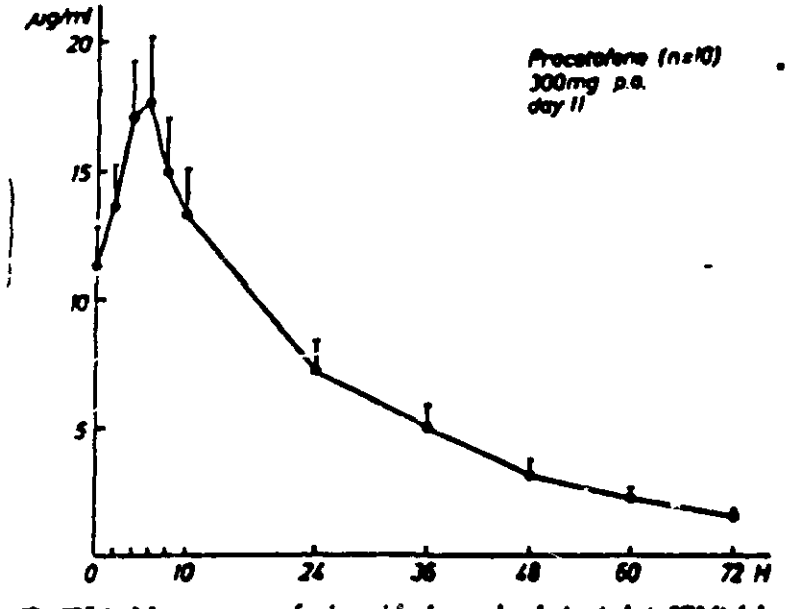
FIGURE 2



Mean procetofenic acid plasma levels (μg/ml ± SEM) after administration of a single 300 mg dose of procetofene (Lipanthyl®) to 6 normolipemic volunteers.



Mean plasma levels of procetofenic acid (μg/ml ± SEM) measured in 10 normolipemic volunteers after repeated and divided administration of a daily dose of 300 mg procetofene (Lipanthyl®) during 10 days.



Mean procetofenic acid plasma levels (μg/ml ± SEM) following administration on day 11 of a single 300 mg dose of procetofene (Lipanthyl®) to 10 normolipemic volunteers already participating in a 10-day repeated-doses study.

TABLE 8: Individual kinetic parameters and mean values of LF 433, after oral administration of one 100 mg capsule of Lipanthyl, with a standard meal.

Subject	t_{max} (hr)	Cmax (ng/ml)	$AUC_{0 \rightarrow 96}$ (ng/ml.hr)
1			
2			
3			
4			
5			
6			
7			
8			
9			
10			
11			
12			
Mean	20.9	164	8.2
S.D.	10.7	90	4.4
S.D.M.	3.1	26	1.2
CV %	51	55	54

TABLE 9: Total urinary excretions (in free + conjugate forms) of LF 153, calculated in the 12 study subjects after oral administration of one 100 mg capsule of Lipanthyl, with a standard meal.

Subject	0-12hrs		12-24hrs		24-48hrs		48-72hrs		72-96hrs		cumulative mg or % of the dose
	Vol. (ml)	mg excreted	Vol. (ml)	mg excreted	Vol. (ml)	mg excreted	Vol. (ml)	mg excreted	Vol. (ml)	mg excreted	
1											
2											
3											
4											
5											
6											
7											
8											
9											
10											
11											
12											
Mean											27.6
S.D.											12.5
S.D.M.											3.6
CV %											45

TABLE 10: Total urinary excretions (in free + conjugate forms) of LF 433, calculated in the 12 study subjects after oral administration of one 100 mg capsule of Lipanthyl, with a standard meal.

Subject	0-12hrs		12-24hrs		24-48hrs		48-72hrs		72-96hrs		cumulative mg or % of the dose
	Vol (ml)	mg excreted	Vol (ml)	mg excreted	Vol (ml)	mg excreted	Vol (ml)	mg excreted	Vol (ml)	mg excreted	
1											
2											
3											
4											
5											
6											
7											
8											
9											
10											
11											
12											
Mean											3.9
S.D.											1.1
S.D.M.											0.3
CV %											28

* Values not calculated because of chromatographic interferences. These values are, however, below 50 ng/ml

TABLE 11:

[redacted] 300 mg fenofibrate single dose without hemodialysis (n = 9)

No.	Age, years	Sex	Plasma creatinine mg·dl^{-1} (μM dl^{-1})	Creatinine clearance ml·min^{-1}	Elimination half-life h	Peak plasma level μg·ml^{-1} (nM ml^{-1})	Time of peak plasma level h	Plasma level 48 h postdrug μg·ml^{-1} (nM ml^{-1})	Urinary excretion mg/48 h (μM/48 h)
1									
2									
3									
4									
5									
6									

TABLE 12:

[redacted] 300 mg fenofibrate single dose with hemodialysis (n = 6)

No.	Age, years	Sex	Plasma creatinine mg·dl^{-1} (μM dl^{-1})	Creatinine clearance ml·min^{-1}	Elimination half-life h	Peak plasma level μg·ml^{-1} (nM ml^{-1})	Time of peak plasma level h	Plasma level 48 h postdrug μg·ml^{-1} (nM ml^{-1})	Ultra-filtrate ng·ml^{-1} (nM ml^{-1})
1									
2									
3									
4									
5									
6									

TABLE 13:

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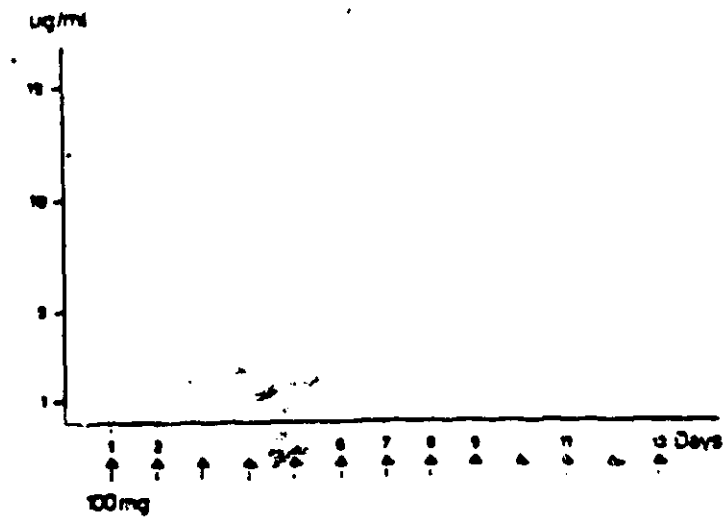
[redacted] 100 mg fenofibrate/day during 15 days (n = 5)

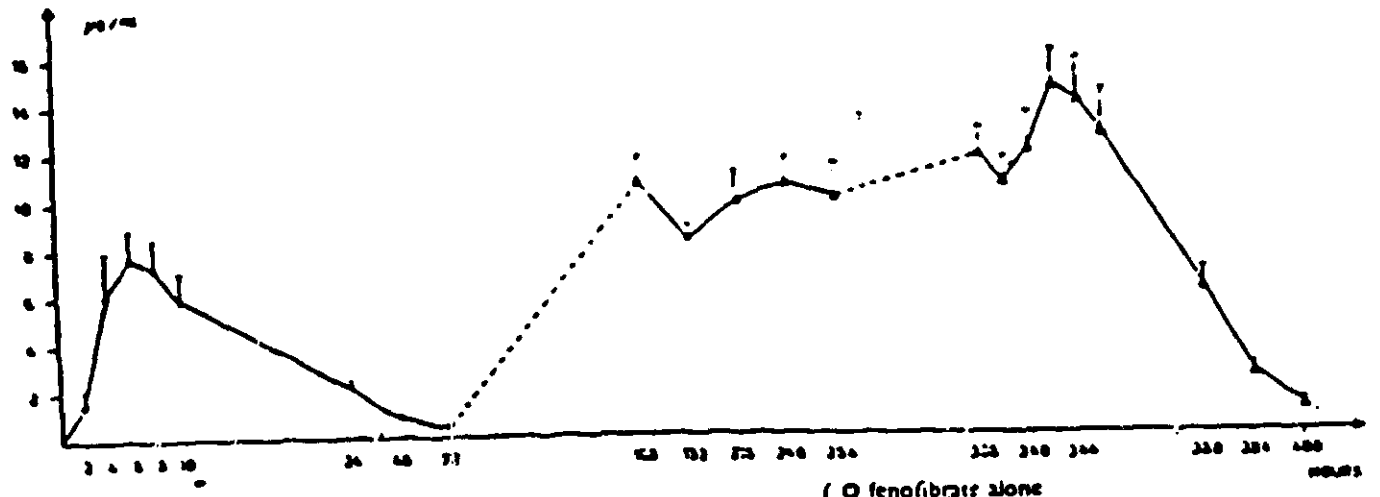
No.	Age, years	Sex	Plasma creatinine $mg \cdot dl^{-1}$ ($\mu M\ dl^{-1}$)	Creatinine clearance $ml \cdot min^{-1}$	Peak plasma level $\mu g \cdot ml^{-1}$ ($n M \cdot ml^{-1}$)	Time of peak plasma level, days	Protein binding, %
1							
2							
3							
4							
5							

FIGURE 3:



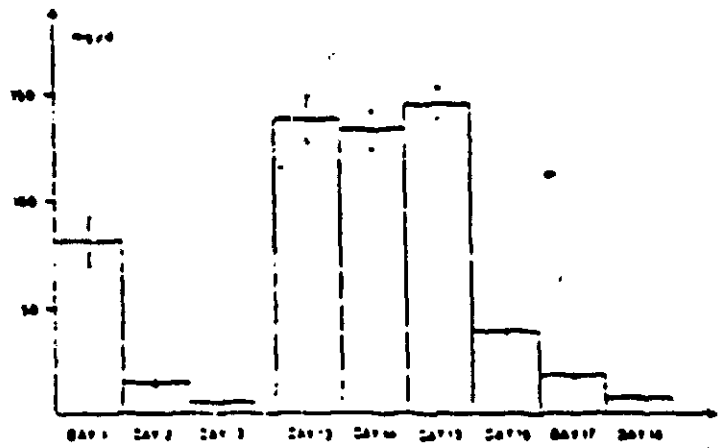
[redacted] Fenofibric acid plasma levels in patient 2, undergoing hemodialysis three times a week, after regular intake of 100 mg fenofibrate daily.

FIGURE 4:



[redacted] Plasma fenofibric acid levels during the different stages of the study { ○ fenofibrate alone ▲ fenofibrate – colestipol

FIGURE 5:



[redacted] Daily urinary excretion of fenofibric a. · on different days during the study

TABLE 14:

[redacted] Pharmacokinetic data

Vol.	Fenofibrate mg/kg body weight/day	Mean fasting plasma f. a. (μg/ml ± SE)		β Half-life (h) of f. a.			Time of peak plasma f. a. (h)		Peak plasma f. a. level (μg/ml)		Mean concentration of plasma f. a. (μg/ml)	Mean pool size (mg)
		A	B	I	II	III	I	II	I	II	I	I
1												
2												
3												
4												
Mean	4.25	9.35	10.48	19.6	18.4	18.3	6.3	5	8.9	15.76	3.38	11.
± SE	0.22	0.32	0.93	1.1	0.6	1.0	0.8	1.1	1.6	1.46	0.40	6.6

A = fenofibrate alone 300 mg/d (Days 8 & 9)
B = fenofibrate 300 mg/d plus Colestipol 15 g/d Days 10, 11, 12, 13
I = Days 1 to 3 single 300 mg dose of fenofibrate
II = Days 15 to 18 300 mg dose of fenofibrate and 15 g Colestipol together after steady state
III = Estimate for the steady state alone (Days 15 to 18)

6) Pharmacokinetics of fenofibrate in renal failure patients was not adequately characterized. Deficiencies include unvalidated assay method, no raw data on plasma levels of fenofibric acid, lack of information on food schedule and accumulation of fenofibric acid and its conjugate following repeated dosing. A Phase IV study is required to support labelling information on pharmacokinetics of fenofibrate in renal failure.

7) Pharmacokinetics of fenofibrate in patients with liver dysfunction, cholestasis and hyperlipidemia was not reported to support the labelling information. Phase IV studies of fenofibrate disposition in these patients are required from the BA/PK point of view.

8) No <u>in vitro</u> dissolution data on fenofibrate capsules were included in the Biopharmaceutics submission.

9) A better planned food effect study may be needed to determine if the contents and the schedule of the meals (time difference between meal and dosing of fenofibrate) could affect the bioavailability of fenofibrate.

<u>Overall Review Comments:</u>

Since NDA 19-304 was resubmitted on 4/29/87, the approvability of the product Lipantil^{R} 100 mg from the biopharmaceutics/pharmacokinetics point of view will be based on the review of NDA 19-304 resubmitted on 4/29/87. The studies filed 5/13/85 and 7/10/86 and evaluated in this bio-review are covered, as appropriate, in a bio-review prepared by Dr. Hussein. In Dr. Hussein's bio-review, the studies covered in this review as well as new studies filed 4/29/87 are assessed as related to meeting the Agency's bio-regulations for product approval.

Laurene Wang, Ph.D.
Pharmacokinetics Evaluation Branch

RD Initialed John P. Hunt 2/1/89
FT Initialed C.T. Viswanathan, Ph.D. 2/6/89

cc: NDA 19-304 (IND 19-056) Orig., HFN-810, HFN-226(Hunt, Zang), HFN-344(Turner), Drug, Chron and FOI files

LW:lyt:3124X:1-15-88