

CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

Application Number: 20839
Trade Name: Plavix
Generic Name: Clopidogrel bisulfate
Sponsor: Sanofi Pharmaceuticals
Approval Date: November 17, 1997
Indication: Reduction of atherosclerotic events

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION: 20839

CONTENTS

	Included	Pending Completion	Not Prepared	Not Required
Approval Letter	X			
Tentative Approval Letter				X
Approvable Letter	X			
Final Printed Labeling	X			
Medical Review(s)	X			
Chemistry Review(s)	X			
EA/FONSI				X
Pharmacology Review(s)	X			
Statistical Review(s)			X	
Microbiology Review(s)				X
Clinical Pharmacology Biopharmaceutics Review(s)	X			
Bioequivalence Review(s)				X
Administrative Document(s)	X			
Correspondence				

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number: 20839

APPROVAL LETTER

Food and Drug Administration
Rockville MD 20857

NDA 20-839

NOV 17 1997

Sanofi Pharmaceuticals, Inc.
Attention: George Clay, Ph.D.
9 Great Valley Parkway
P.O. Box 3026
Malvern, PA 19355

Dear Dr. Clay:

Please refer to your April 28, 1997 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Plavix (clopidogrel bisulfate) Tablets, 75 mg.

We acknowledge receipt of your submissions dated October 28, 30 and 31, and November 4 and 6, 1997.

This new drug application provides for the use of Plavix for the reduction of atherosclerotic events (myocardial infarction, stroke, and vascular death) in patients with atherosclerosis documented by recent stroke, recent myocardial infarction, or established peripheral arterial disease.

We have completed the review of this application, including the submitted draft labeling, 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 enclosed draft. Accordingly, the application is approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the enclosed draft labeling. 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 20 copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FINAL PRINTED LABELING" for approved NDA 20-839. Approval of this submission by FDA is not required before the labeling is used.

Should additional information relating to the safety and effectiveness of the drug become available, revision of that labeling may be required.

Please note that the approved expiry date for Plavix is 24 months in all containers.

We also note that you have agreed to investigate further possibilities for additional code imprint to the tablet so that it could be more easily identified.

Validation of the regulatory methods has not been completed. At the present time, it is the policy of the Center not to withhold approval because the methods are being validated. Nevertheless, we expect your continued cooperation to resolve any problems that may be identified.

In future morbidity/mortality trials, we recommend that you ensure the following:

Please submit one market package of the drug product 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.

If you have any questions, please contact:

Mr. David Roeder
Regulatory Health Project Manager
(301) 594-5313

Sincerely yours,

Robert Temple, M.D.
Director
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosure

cc:

Original NDA

HFD-110

HF-2/MedWatch (with draft/final labeling)

HFD-002/ORM (with draft/final labeling)

HFD-92/DDM-DIAB (with draft/final labeling)

HFD-101 (with draft/final labeling)

HFD-101/L.Carter

HFD-40/DDMAC (with draft/final labeling)

HFD-613/OGD (with draft/final labeling)

HFD-735/DPE (with draft/final labeling)

HFD-560/OTC (with draft/final labeling - OTC drugs only)

HFD-21/ACS (with draft/final labeling - for drugs discussed at advisory committee meeting)

DISTRICT OFFICE

HFD-810/ONDC Division Director

HFI-20/Press Office (with draft/final labeling)

HFD-110/DRoeder

sb/11/6/97;11/10/97

R/D: RWolters/11/7/97

ADeFelice/11/7/97

JHung/11/7/97

CGanley/11/7/97

NMorgenstern/11/7/97

APPROVAL (AP)

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 20839

APPROVABLE LETTER



Food and Drug Administration
Rockville MD 20857

NDA 20-839

OCT 27 1997

Sanofi Pharmaceuticals, Inc.
Attention: George Clay, Ph.D.
9 Great Valley Parkway
P.O. Box 3026
Malvern, PA 19355

Dear Dr. Clay:

Please refer to your April 28, 1997 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Plavix (clopidogrel bisulfate) 75 mg Tablets.

We acknowledge receipt of your amendments and correspondence dated April 30, May 1, 13, 15, and 22, June 5, 11, 16, 27 and 30, July 2, 14, 23 and 24, August 1, 13, 14, 18, 20 and 28, September 3, 10, 15, 17, 18, 22, 23, 25 (two), and 26 (two), and October 1, 2, 3, 6 (two), 13, 15 and 22, 1997.

We have completed the review of this application as submitted with draft labeling and it is approvable. Before the application may be approved, however, satisfactory resolution is required regarding the issue of documentation of the follow-up of patients who were early permanent discontinuations. To that end, we strongly suggest that you meet with the Division of Cardio-Renal Drug Products to discuss this matter at the earliest mutually convenient time. In addition, it will be necessary for you to submit final printed labeling (FPL) for the drug. The labeling should be identical in content to the enclosed marked-up draft. If additional information relating to the safety or effectiveness of this drug becomes available, revision of the FPL may be required.

Please submit sixteen copies of the printed labels and other labeling, ten of which are individually mounted on heavy weight paper or similar material.

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 Cardio-Renal 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-40
5600 Fishers Lane
Rockville, Maryland 20857

Within 10 days after the date of this letter, you are required to amend the application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. In the absence of such action FDA may take action to withdraw the application.

The drug may not be legally marketed until you have been notified in writing that the application is approved.

Should you have any questions, please contact:

Mr. David Roeder
Regulatory Health Project Manager
Telephone: (301) 594-5313

Sincerely yours,

Robert Temple, M.D.
Director
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosure

cc:

Original NDA

HFD-2/MLumpkin

HFD-92

HFD-101

~~HFD-110~~

HFD-110/Project Manager

HFD-40 (with draft labeling)

HFD-560/DBowen (with draft labeling - OTC drugs only)

DISTRICT OFFICE

HFD-110/KBongiovanni

sb/9/11/97

APPROVABLE

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 20839

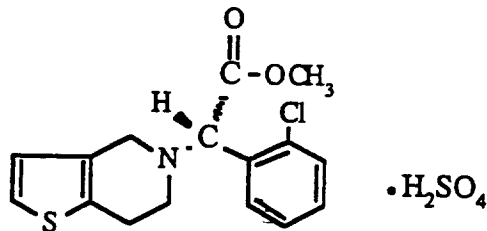
FINAL PRINTED LABELING

PLAVIX®
clopidogrel bisulfate tablets

DESCRIPTION

PLAVIX (clopidogrel bisulfate) is an inhibitor of ADP-induced platelet aggregation acting by direct inhibition of adenosine diphosphate (ADP) binding to its receptor and of the subsequent ADP-mediated activation of the glycoprotein GPIIb/IIIa complex. Chemically it is methyl (+)-(S)- α -(2-chlorophenyl)-6,7-dihydrothieno[3,2-c]pyridine-5(4H)-acetate sulfate (1:1). The empirical formula of clopidogrel bisulfate is $C_{16}H_{16}ClNO_2S \cdot H_2SO_4$ and its molecular weight is 419.9.

The structural formula is as follows:



Clopidogrel bisulfate is a white to off-white powder. It is practically insoluble in water at neutral pH but freely soluble at pH 1. It also dissolves freely in methanol, dissolves sparingly in methylene chloride, and is practically insoluble in ethyl ether. It has a specific optical rotation of about +56°.

PLAVIX for oral administration is provided as pink, round, biconvex, engraved film-coated tablets containing 97.875 mg of clopidogrel bisulfate which is the molar equivalent of 75 mg of clopidogrel base.

Each tablet contains anhydrous lactose, hydrogenated castor oil, microcrystalline cellulose, polyethylene glycol 6000 and pregelatinized starch as inactive ingredients. The pink film coating contains ferric oxide (red), hydroxypropyl methylcellulose 2910, polyethylene glycol 6000 and titanium dioxide. The tablets are polished with Carnauba wax.

CLINICAL PHARMACOLOGY

Mechanism of Action

Clopidogrel is an inhibitor of platelet aggregation. A variety of drugs that inhibit platelet function have been shown to decrease morbid events in people with established atherosclerotic cardiovascular disease as evidenced by stroke or transient ischemic attacks, myocardial infarction, or need for bypass or angioplasty. This indicates that platelets participate in the initiation and/or evolution of these events and that inhibiting them can reduce the event rate.

Pharmacodynamic Properties

Clopidogrel selectively inhibits the binding of adenosine diphosphate (ADP) to its platelet receptor and the subsequent ADP-mediated activation of the glycoprotein GPIIb/IIIa complex, thereby inhibiting platelet aggregation. Biotransformation of clopidogrel is necessary to produce inhibition of platelet aggregation, but an active metabolite responsible for the activity of the drug has not been isolated. Clopidogrel also inhibits platelet aggregation induced by agonists other than ADP by blocking the amplification of platelet activation by released ADP. Clopidogrel does not inhibit phosphodiesterase activity.

Clopidogrel acts by irreversibly modifying the platelet ADP receptor. Consequently, platelets exposed to clopidogrel are affected for the remainder of their lifespan.

Dose dependent inhibition of platelet aggregation can be seen 2 hours after single oral doses of PLAVIX. Repeated doses of 75 mg PLAVIX per day inhibit ADP-induced platelet aggregation on the first day, and inhibition reaches steady state between Day 3 and Day 7. At steady state, the average inhibition level observed with a dose of 75 mg PLAVIX per day was between 40% and 60%. Platelet aggregation and bleeding time gradually return to baseline values after treatment is discontinued, generally in about 5 days.

Pharmacokinetics and Metabolism

After repeated 75-mg oral doses of clopidogrel (base), plasma concentrations of the parent compound, which has no platelet inhibiting effect, are very low and are generally below the quantification limit (0.00025 mg/L) beyond 2 hours after dosing. Clopidogrel is extensively metabolized by the liver. The main circulating metabolite is the carboxylic acid derivative, and it too has no effect on platelet aggregation. It represents about 85% of the circulating drug-related compounds in plasma.

Following an oral dose of ¹⁴C-labeled clopidogrel in humans, approximately 50% was excreted in the urine and approximately 46% in the feces in the 5 days after dosing. The elimination half-life of the main circulating metabolite was 8 hours after single and repeated administration. Covalent binding to platelets accounted for 2% of radiolabel with a half-life of 11 days.

Effect of Food: Administration of PLAVIX with meals did not significantly modify the bioavailability of clopidogrel as assessed by the pharmacokinetics of the main circulating metabolite.

Absorption and Distribution: Clopidogrel is rapidly absorbed after oral administration of repeated doses of 75 mg clopidogrel (base), with peak plasma levels (≈ 3 mg/L) of the main circulating metabolite occurring approximately 1 hour after dosing. The pharmacokinetics of the main circulating metabolite are linear (plasma concentrations increased in proportion to dose) in the dose range of 50 to 150 mg of clopidogrel. Absorption is at least 50% based on urinary excretion of clopidogrel-related metabolites.

Clopidogrel and the main circulating metabolite bind reversibly *in vitro* to human plasma proteins (98% and 94%, respectively). The binding is nonsaturable *in vitro* up to a concentration of 100 μ g/ml.

Metabolism and Elimination: *In vitro* and *in vivo*, clopidogrel undergoes rapid hydrolysis into its carboxylic acid derivative. In plasma and urine, the glucuronide of the carboxylic acid derivative is also observed.

Special Populations

Geriatric Patients: Plasma concentrations of the main circulating metabolite are significantly higher in elderly (≥ 75 years) compared to young healthy volunteers but these higher plasma levels were not associated with differences in platelet aggregation and bleeding time. No dosage adjustment is needed for the elderly.

Renally Impaired Patients: After repeated doses of 75 mg PLAVIX per day, plasma levels of the main circulating metabolite were lower in patients with severe renal impairment (creatinine clearance from 5 to 15 mL/min) compared to subjects with moderate renal impairment (creatinine clearance 30 to 60 mL/min) or healthy subjects. Although inhibition of ADP-induced platelet aggregation was lower (25%) than that observed in healthy volunteers, the prolongation of bleeding time was similar in healthy volunteers receiving 75 mg of PLAVIX per day. No dosage adjustment is needed in renally impaired patients.

Gender: No significant difference was observed in the plasma levels of the main circulating metabolite between males and females. In a small study comparing men and women, less inhibition of ADP-induced platelet aggregation was observed in women, but there was no difference in prolongation of bleeding time. In the large, controlled clinical study (Clpidogrel vs. Aspirin in Patients at Risk of Ischemic Events; CAPRIE), the incidence of clinical outcome events, other adverse clinical events, and abnormal clinical laboratory parameters was similar in men and women.

Race: Pharmacokinetic differences due to race have not been studied.

CLINICAL STUDIES

The clinical evidence for the efficacy of PLAVIX is derived from the CAPRIE (Clopidogrel vs. Aspirin in Patients at Risk of Ischemic Events) trial. This was a 19,185-patient, 304-center, international, randomized, double-blind, parallel-group study comparing PLAVIX (75 mg daily) to aspirin (325 mg daily). The patients randomized had: 1) recent histories of myocardial infarction (within 35 days); 2) recent histories of ischemic stroke (within 6 months) with at least a week of residual neurological signs; or 3) objectively established peripheral arterial disease. Patients received randomized treatment for an average of 1.6 years (maximum of 3 years).

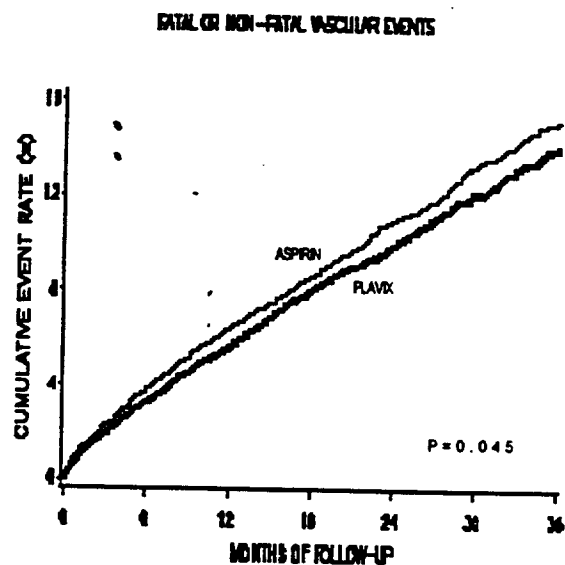
The trial's primary outcome was the time to first occurrence of new ischemic stroke (fatal or not), new myocardial infarction (fatal or not), or other vascular death. Deaths not easily attributable to nonvascular causes were all classified as vascular.

Outcome Events of the Primary Analysis

	<u>PLAVIX</u>	<u>aspirin</u>
Patients	9599	9586
IS (fatal or not)	438 (4.56%)	461 (4.81%)
MI (fatal or not)	275 (2.86%)	333 (3.47%)
Other vascular death	226 (2.35%)	226 (2.36%)
Total	939 (9.78%)	1020 (10.64%)

As shown in the table, PLAVIX was associated with a lower incidence of outcome events of every kind. The overall risk reduction (9.78% vs. 10.64%) was 8.7%, $P=0.045$. Similar results were obtained when all-cause mortality and all-cause strokes were counted instead of vascular mortality and ischemic strokes (risk reduction 6.9%). In patients who survived an on-study stroke or myocardial infarction, the incidence of subsequent events was again lower in the PLAVIX group.

The curves showing the overall event rate are shown in the figure. The event curves separated early and continued to diverge over the 3-year follow-up period.



Although the statistical significance favoring PLAVIX over aspirin was marginal ($P=0.045$), and represents the result of a single trial that has not been replicated, the comparator drug, aspirin, is itself effective (vs. placebo) in reducing cardiovascular events in patients with recent myocardial infarction or stroke. Thus, the difference between PLAVIX and placebo, although not measured directly, is substantial.

The CAPRIE trial included a population that was randomized on the basis of 3 entry criteria. The efficacy of PLAVIX relative to aspirin was heterogeneous across these randomized subgroups ($P=0.043$). It is not clear whether this difference is real or a chance occurrence. Although the CAPRIE trial was not designed to evaluate the relative benefit of PLAVIX over aspirin in the individual patient subgroups, the benefit appeared to be strongest in patients who were enrolled because of peripheral vascular disease (especially those who also had a history of myocardial infarction) and weaker in stroke patients. In patients who were enrolled in the trial on the sole basis of a recent myocardial infarction, PLAVIX was not numerically superior to aspirin.

In the meta-analyses of studies of aspirin vs. placebo in patients similar to those in CAPRIE, aspirin was associated with a reduced incidence of atherothrombotic events. There was a suggestion of heterogeneity in these studies too, with the effect strongest in patients with a history of myocardial infarction, weaker in patients with a history of stroke, and not discernible in patients with a history of peripheral vascular disease. With respect to the inferred comparison of PLAVIX to placebo, there is no indication of heterogeneity.

INDICATIONS AND USAGE

PLAVIX is indicated for the reduction of atherosclerotic events (myocardial infarction, stroke, and vascular death) in patients with atherosclerosis documented by recent stroke, recent myocardial infarction, or established peripheral arterial disease.

CONTRAINDICATIONS

The use of PLAVIX is contraindicated in the following conditions:

- i Hypersensitivity to the drug substance or any component of the product.
- i Active pathological bleeding such as peptic ulcer or intracranial hemorrhage.

WARNINGS

None.

PRECAUTIONS

General

As with other anti-platelet agents, PLAVIX should be used with caution in patients who may be at risk of increased bleeding from trauma, surgery, or other pathological conditions. If a patient is to undergo elective surgery and an antiplatelet effect is not desired, PLAVIX should be discontinued 7 days prior to surgery.

GI Bleeding: PLAVIX prolongs the bleeding time. In CAPRIE, PLAVIX was associated with a rate of gastrointestinal bleeding of 2.0%, vs. 2.7% on aspirin. PLAVIX should be used with caution in patients who have lesions with a propensity to bleed (such as ulcers). Drugs that might induce such lesions (such as aspirin and other nonsteroidal anti-inflammatory drugs [NSAIDs]) should be used with caution in patients taking PLAVIX.

Use in Hepatically Impaired Patients:

Experience is limited in patients with severe hepatic disease, who may have bleeding diatheses. PLAVIX should be used with caution in this population.

Information for Patients

Patients should be told that it may take them longer than usual to stop bleeding when they take PLAVIX, and that they should report any unusual bleeding to their physician. Patients should inform physicians and dentists that they are taking PLAVIX before any surgery is scheduled and before any new drug is taken.

Drug Interactions

Study of specific drug interactions yielded the following results:

Aspirin: Aspirin did not modify the clopidogrel-mediated inhibition of ADP-induced platelet aggregation. Concomitant administration of 500 mg of aspirin twice a day for 1 day did not significantly increase the prolongation of bleeding time induced by PLAVIX. PLAVIX potentiated the effect of aspirin on collagen-induced platelet aggregation. The safety of chronic concomitant administration of aspirin and PLAVIX has not been established.

Heparin: In a study in healthy volunteers, PLAVIX did not necessitate modification of the heparin dose or alter the effect of heparin on coagulation. Coadministration of heparin had no effect on inhibition of platelet aggregation induced by PLAVIX. The safety of this combination has not been established, however, and concomitant use should be undertaken with caution.

Nonsteroidal Anti-Inflammatory Drugs (NSAIDs): In healthy volunteers receiving naproxen, concomitant administration of PLAVIX was associated with increased occult gastrointestinal blood loss. NSAIDs and PLAVIX should be coadministered with caution.

Warfarin: The safety of the coadministration of PLAVIX with warfarin has not been established. Consequently, concomitant administration of these two agents should be undertaken with caution. (See Precautions - General).

Other Concomitant Therapy: No clinically significant pharmacodynamic interactions were observed when PLAVIX was coadministered with atenolol, nifedipine, or both atenolol and nifedipine. The pharmacodynamic activity of PLAVIX was also not significantly influenced by the coadministration of phenobarbital, cimetidine or estrogen.

The pharmacokinetics of digoxin or theophylline were not modified by the coadministration of PLAVIX.

At high concentrations *in vitro*, clopidogrel inhibits P₄₅₀ (2C9). Accordingly, PLAVIX may interfere with the metabolism of phenytoin, tamoxifen, tolbutamide, warfarin, torsemide, fluvastatin, and many non-steroidal anti-inflammatory agents, but there are no data with which to predict the magnitude of these interactions. Caution should be used when any of these drugs is coadministered with PLAVIX.

In addition to the above specific interaction studies, patients entered into CAPRIE received a variety of concomitant medications including diuretics, beta-blocking agents, angiotensin converting enzyme inhibitors, calcium antagonists, cholesterol lowering agents, coronary vasodilators, antidiabetic agents, antiepileptic agents and hormone replacement therapy without evidence of clinically significant adverse interactions.

Drug/Laboratory Test Interactions

None known.

Carcinogenesis, Mutagenesis, Impairment of Fertility

There was no evidence of tumorigenicity when clopidogrel was administered for 78 weeks to mice and 104 weeks to rats at dosages up to 77 mg/kg per day, which afforded plasma exposures >25 times that in humans at the recommended daily dose of 75 mg.

Clopidogrel was not genotoxic in four *in vitro* tests (Ames test, DNA-repair test in rat hepatocytes, gene mutation assay in Chinese hamster fibroblasts, and metaphase chromosome analysis of human lymphocytes) and in one *in vivo* test (micronucleus test by oral route in mice).

Clopidogrel was found to have no effect on fertility of male and female rats at oral doses up to 400 mg/kg per day (52 times the recommended human dose on a mg/m² basis).

Pregnancy

Pregnancy Category B. Reproduction studies performed in rats and rabbits at doses up to 500 and 300 mg/kg/day (respectively, 65 and 78 times the recommended daily human dose on a mg/m² basis), revealed no evidence of impaired fertility or fetotoxicity due to clopidogrel. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of a human response, PLAVIX should be used during pregnancy only if clearly needed.

Nursing Mothers

Studies in rats have shown that clopidogrel and/or its metabolites are excreted in the milk. 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 serious adverse reactions in nursing infants, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the nursing woman.

Pediatric Use

Safety and effectiveness in the pediatric population have not been established.

ADVERSE REACTIONS

PLAVIX has been evaluated for safety in more than 11,300 patients, including over 7,000 patients treated for 1 year or more. The overall tolerability of PLAVIX was similar to that of aspirin regardless of age, gender and race, with an approximately equal incidence (13%) of patients withdrawing from treatment because of adverse reactions. The clinically important adverse events observed in CAPRIE are discussed below.

Hemorrhagic: In patients receiving PLAVIX in CAPRIE, gastrointestinal hemorrhage occurred at a rate of 2.0%, and required hospitalization in 0.7%. In patients receiving aspirin, the corresponding rates were 2.7% and 1.1%, respectively. The incidence of intracranial hemorrhage was 0.4% for PLAVIX compared to 0.5% for aspirin.

Neutropenia/agranulocytosis: Ticlopidine, a drug chemically similar to PLAVIX, is associated with a 0.8% rate of severe neutropenia (less than 450 neutrophils/ μ L). Patients in CAPRIE (see Clinical Trials) were intensively monitored for neutropenia. Severe neutropenia was observed in six patients, four on PLAVIX and two on aspirin. Two of the 9599 patients who received PLAVIX and none of the 9586 patients who received aspirin had neutrophil counts of zero.

One of the four PLAVIX patients was receiving cytotoxic chemotherapy, and another recovered and returned to the trial after only temporarily interrupting treatment with PLAVIX.

Although the risk of myelotoxicity with PLAVIX thus appears to be quite low, this possibility should be considered when a patient receiving PLAVIX demonstrates fever or other sign of infection.

Gastrointestinal: Overall, the incidence of gastrointestinal events (e.g. abdominal pain, dyspepsia, gastritis and constipation) in patients receiving PLAVIX was 27.1%, compared to 29.8% in those receiving aspirin.

The incidence of peptic, gastric or duodenal ulcers was 0.7% for PLAVIX and 1.2% for aspirin.

Cases of diarrhea were reported in 4.5% of patients in the PLAVIX group compared to 3.4% in the aspirin group. However, these were rarely severe (PLAVIX=0.2% and aspirin= 0.1%).

The incidence of patients withdrawing from treatment because of gastrointestinal adverse reactions was 3.2% for PLAVIX and 4.0% for aspirin.

Rash and Other Skin Disorders: The incidence of skin and appendage disorders in patients receiving PLAVIX was 15.8% (0.7% serious); the corresponding rate in aspirin patients was 13.1% (0.5% serious).

The overall incidence of patients withdrawing from treatment because of skin and appendage disorders adverse reactions was 1.5% for PLAVIX and 0.8% for aspirin.

Adverse events occurring in $\geq 2.5\%$ of patients on PLAVIX in the CAPRIE controlled clinical trial are shown below regardless of relationship to PLAVIX. The median duration of therapy was 20 months, with a maximum of 3 years.

Adverse Events Occurring in $\geq 2.5\%$ of PLAVIX Patients

Body System Event	% Incidence (% Discontinuation)	
	PLAVIX [n=9599]	Aspirin [n=9586]
<i>Body as a Whole - general disorders</i>		
Chest Pain	8.3 (0.2)	8.3 (0.3)
Accidental Injury	7.9 (0.1)	7.3 (0.1)
Influenza-like symptoms	7.5 (<0.1)	7.0 (<0.1)
Pain	6.4 (0.1)	6.3 (0.1)
Fatigue	3.3 (0.1)	3.4 (0.1)
<i>Cardiovascular disorders, general</i>		
Edema	4.1 (<0.1)	4.5 (<0.1)
Hypertension	4.3 (<0.1)	5.1 (<0.1)
<i>Central & peripheral nervous system disorders</i>		
Headache	7.6 (0.3)	7.2 (0.2)
Dizziness	6.2 (0.2)	6.7 (0.3)
<i>Gastrointestinal system disorders</i>		
Abdominal pain	5.6 (0.7)	7.1 (1.0)
Dyspepsia	5.2 (0.6)	6.1 (0.7)
Diarrhea	4.5 (0.4)	3.4 (0.3)
Nausea	3.4 (0.5)	3.8 (0.4)
<i>Metabolic & nutritional disorders</i>		
Hypercholesterolemia	4.0 (0)	4.4 (<0.1)
<i>Musculo-skeletal system disorders</i>		
Arthralgia	6.3 (0.1)	6.2 (0.1)
Back Pain	5.8 (0.1)	5.3 (<0.1)
<i>Platelet, bleeding, & clotting disorders</i>		
Purpura	5.3 (0.3)	3.7 (0.1)
Epistaxis	2.9 (0.2)	2.5 (0.1)
<i>Psychiatric disorders</i>		
Depression	3.6 (0.1)	3.9 (0.2)
<i>Respiratory system disorders</i>		
Upper resp tract infection	8.7 (<0.1)	8.3 (<0.1)
Dyspnea	4.5 (0.1)	4.7 (0.1)
Rhinitis	4.2 (0.1)	4.2 (<0.1)
Bronchitis	3.7 (0.1)	3.7 (0)
Coughing	3.1 (<0.1)	2.7 (<0.1)
<i>Skin & appendage disorders</i>		
Rash	4.2(0.5)	3.5 (0.2)
Pruritus	3.3 (0.3)	1.6 (0.1)
<i>Urinary system disorders</i>		
Urinary tract infection	3.1 (0)	3.5 (0.1)

Incidence of discontinuation, regardless of relationship to therapy, is shown in parentheses.

Other adverse experiences of potential importance occurring in 1% to 2.5% of patients receiving PLAVIX in the CAPRIE controlled clinical trial are listed below regardless of relationship to PLAVIX. In general, the incidence of these events was similar in the aspirin-treated group.

Autonomic Nervous System Disorders: Syncope, Palpitation. *Body as a Whole - general disorders:* Asthenia, Hernia. *Cardiovascular disorders:* Cardiac failure. *Central and peripheral nervous system disorders:* Cramps legs, Hypoaesthesia, Neuralgia, Paraesthesia, Vertigo. *Gastro-intestinal system disorders:* Constipation, Vomiting. *Heart rate and rhythm disorders:* Fibrillation atrial. *Liver and biliary system disorders:* Hepatic enzymes increased. *Metabolic and nutritional disorders:* Gout, hyperuricemia, non-protein nitrogen (NPN) increased. *Musculo-skeletal system disorders:* Arthritis, Arthrosis. *Platelet, bleeding & clotting disorders:* GI hemorrhage, hematoma, platelets decreased. *Psychiatric disorders:* Anxiety, Insomnia. *Red blood cell disorders:* Anemia. *Respiratory system disorders:* Pneumonia, Sinusitis. *Skin and appendage disorders:* Eczema, Skin ulceration. *Urinary system disorders:* Cystitis. *Vision disorders:* Cataract, Conjunctivitis.

Other potentially serious adverse events which may be of clinical interest but were rarely reported (<1%) in patients who received PLAVIX are listed below regardless of relationship to PLAVIX. In general, the incidence of these events was similar in the aspirin group.

Body as a whole: Allergic reaction, necrosis ischemic. *Cardiovascular disorders:* Edema generalized. *Gastrointestinal system disorders:* Gastric ulcer perforated, gastritis hemorrhagic, upper GI ulcer hemorrhagic. *Liver and Biliary system disorders:* Bilirubinemia, hepatitis infectious, liver fatty. *Platelet, bleeding and clotting disorders:* hemarthrosis, hematuria, hemoptysis, hemorrhage intracranial, hemorrhage retroperitoneal, hemorrhage of operative wound, ocular hemorrhage, pulmonary hemorrhage, purpura allergic, thrombocytopenia. *Red blood cell disorders:* Anemia aplastic, anemia hypochromic. *Reproductive disorders, female:* Menorrhagia. *Respiratory system disorders:* Hemothorax. *Skin and appendage disorders:* Bullous eruption, rash erythematous, rash maculopapular, urticaria. *White cell and reticuloendothelial system disorders:* Agranulocytosis, granulocytopenia, leukemia, leukopenia, neutrophils decreased.

OVERDOSAGE

One case of deliberate overdose with PLAVIX was reported in the large, controlled clinical study. A 34-year-old woman took a single 1,050-mg dose of PLAVIX (equivalent to 14 standard 75-mg tablets). There were no associated adverse events. No special therapy was instituted, and she recovered without sequelae.

No adverse events were reported after single oral administration of 600 mg (equivalent to 8 standard 75-mg tablets) of PLAVIX in healthy volunteers. The bleeding time was prolonged by a factor of 1.7, which is similar to that typically observed with the therapeutic dose of 75 mg of PLAVIX per day.

A single oral dose of clopidogrel at 1500 or 2000 mg/kg was lethal to mice and to rats and at 3000 mg/kg to baboons. Symptoms of acute toxicity were vomiting (in baboons), prostration, difficult breathing, and gastrointestinal hemorrhage in all species.

Recommendations About Specific Treatment:
Based on biological plausibility, platelet transfusion may be appropriate to reverse the pharmacological effects of PLAVIX if quick reversal is required.

DOSAGE AND ADMINISTRATION

The recommended dose of PLAVIX is 75 mg once daily with or without food.

No dosage adjustment is necessary for elderly patients or patients with renal disease. (See Clinical Pharmacology: Special Populations.)

HOW SUPPLIED

PLAVIX is available as a pink, round, biconvex, film-coated tablet engraved with "75" on one side. Tablets are provided as follows:

NDC 63653-1171-4 bottles of 100
NDC 63653-1171-5 bottles of 500
NDC 63653-1171-3 blisters of 100

Storage

Store at 25°C (77°F); excursions permitted to 15°-30°C (59°-86°F) [see USP Controlled Room Temperature]

Caution: Federal law prohibits dispensing without a prescription.

Manufactured by:
Sanofi Pharmaceuticals, Inc.
New York, NY 10016

Distributed by:
Bristol-Myers Squibb/
Sanofi Pharmaceuticals
Partnership
New York, NY 10016

PLAVIX® is a registered trademark of Sanofi

Date of Labeling Approval

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 20839

MEDICAL REVIEW(S)

Medical Review

NDA #: 20-839/BM
Drug Name: clopidogrel
Type of Document: Response to info request
Date Received: 10/31/97
Medical Reviewer: Charles J. Ganley, M.D.

NDA Volume:
Sponsor: Sanofi
Correspondence Date: 10/30/97
Date Completed: 11/04/97

This submission includes information from the case report forms of 10 patients¹ who were lost to follow-up for the greatest period of time prior to their completion of the trial. The information documents the communication between the investigator/center and the patient. All of the cases appear to adequately document non-fatal and fatal endpoint events with one exception. The notes provided for patient 714-002 are unintelligible.

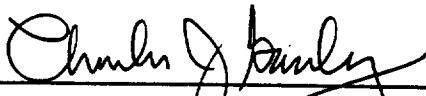
Conclusion

This sample of patients provides some evidence of the adequacy of follow-up. No additional documentation is required for other patients lost to follow-up prior to final communication since it will have little impact on the approvability of the drug.

Other Issues

The CAPRIE Trial did not adhere to the protocol specified termination and follow-up of approximately 944 patients. Of these, 149 had less than one year of follow-up. There is no reason to force the sponsor to go out and find the status of these patients up to the time of their expected termination date because the outcome would have no impact on the approvability of clopidogrel.² In future morbidity/mortality trials, the sponsor should insure the following:

- All patients should have complete follow-up up to their expected termination date. Patients who do not have follow-up to their expected termination date should be classified as lost to follow-up rather than as having completed the study.
- If follow-up is to be performed by any method other than an office visit, there should be full documentation in the case report form of who made the contact, who was contacted, specific questions regarding the endpoint of interest and the method of communication (e.g. phone, letter).
- In many cases, protocol specific issues which were communicated as Bulletins to the investigators should have been submitted to the IND as amendments to the protocol.


Charles J. Ganley, M.D.

cc: orig.
HFD-110
HFD-110 / Project Manager / C. Ganley / R. Fenichel

¹ early permanent discontinuations lost to follow-up for > 1 year prior to final contact

² The labeling does not suggest superiority to aspirin. If it had, then further follow-up might be warranted.

11/3/97
NOV 3 1997

Medical Review

NDA #: 20-839/BM
Drug Name: clopidogrel
Type of Document: Response to info request
Date Received: 10/22/97
Medical Reviewer: Charles J. Ganley, M.D.

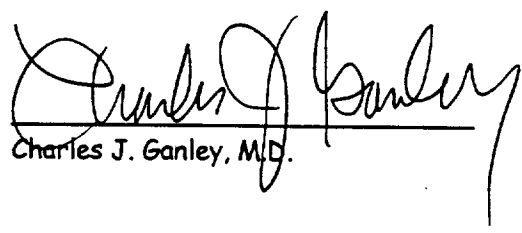
NDA Volume:
Sponsor: Sanofi
Correspondence Date: 10/22/97
Date Completed: 11/3/97

The sponsor, as per FDA request, provides information on the follow-up for 70 clopidogrel and 33 placebo patients who were lost to follow-up for > 1 year prior to their final visit. A listing for these patients is attached.

The majority of contacts were made by phone (85%), by the study coordinator (≈ 75 - 80 %), to the patient (≈ 65%) and specific questions were asked with regard to non-fatal outcomes (80 - 85%).

Regulatory Action

Documentation of follow-up has been requested for the ten clopidogrel patients with the greatest duration of lost to follow-up prior to the final visit.



Charles J. Ganley, M.D.

cc: orig.
HFD-110
HFD-110 / Project Manager / C. Ganley / R. Fenichel

ATTACHMENT 2: CAPRIE
CLOPIDOGREL PATIENTS
THAT WERE EARLY PERMANENT DISCONTINUATIONS,
WHOSE LAST VISIT PREVIOUS TO THE FINAL FOLLOW-UP VISIT WAS > 1 YEAR
AND WHO HAD NO PRIMARY OUTCOME EVENTS RECORDED

Site # (000)	Patient # (0000)	Who made contact?	Type of Contact:	Contact with:	Assessment of Vital Status	Specific Questions Asked About Non- Fatal OE	Assessment of OE From Time of Last Visit until FFV
001	0017	study coord. or nurse	phone	patient	yes	yes	yes
001	0023	study coord. or nurse	phone	patient	yes	yes	yes
001	0035	study coord. or nurse	phone	relative or caregiver	yes	yes	yes
002	0027	study coord. or nurse	phone	patient	yes	uncertain	yes
002	0031	study coord. or nurse	phone	patient	yes	yes	yes
006	0038	study coord. or nurse	written	patient	yes	yes	yes
008	0003	study coord. or nurse	phone	patient	yes	yes	yes
014	0015	study coord. or nurse	phone	patient	yes	yes	yes
020	0012	study coord. or nurse	phone	physician providing care	yes	yes	yes
023	0041	study coord. or nurse	home visit	patient	yes	yes	yes
024	0019	study coord. or nurse	phone	relative or caregiver	yes	yes	yes
024	0033	study coord. or nurse	phone	relative or caregiver	yes	yes	yes
027	0041	study coord. or nurse	written	patient	yes	yes	yes
028	0543	study coord. or nurse	written	patient	yes	yes	yes
032	0099	health professional ¹	phone	patient	yes	yes	yes
037	0011	study coord. or nurse	phone	health professional	yes	no	no ⁹
037	0044	study coord. or nurse	phone	relative or caregiver	yes	no	uncertain
042	0030	study coord. or nurse	phone	patient	yes	yes	yes
046	0004	study coord. or nurse	phone	physician providing care	yes	yes	yes
049	0022	study coord. or nurse	phone	patient	yes	yes	yes
049	0042	study coord. or nurse	phone	patient	yes	yes	yes
049	0055	study coord. or nurse	phone	patient	yes	yes	yes
052	0027	study coord. or nurse	phone	relative or caregiver	yes	uncertain	uncertain
059	0041	study coord. or nurse	phone	relative or caregiver	yes	no	yes
071	0034	study coord. or nurse	phone	relative or caregiver	yes	yes	yes
072	0015	study coord. or nurse	phone	patient	yes	yes	uncertain
078	0029	study coord. or nurse	phone	patient	yes	yes	yes
079	0033	study coord. or nurse	phone	relative or caregiver	yes	yes	yes
081	0005	study coord. or nurse	phone	patient	yes	yes	yes
082	0019	health professional ²	phone	patient	yes	no	no ¹⁰
083	0029	study coord. or nurse	phone	relative or caregiver	yes	yes	yes
084	0004	study coord. or nurse	phone	patient	yes	yes	yes
084	0008	study coord. or nurse	phone	patient	yes	yes	yes
090	0073	study coord. or nurse	other ⁴	health professional	yes	yes	yes
092	0006	study coord. or nurse	phone	patient	yes	yes	yes
101	0012	study coord. or nurse	phone	patient	yes	yes	yes
101	0032	study coord. or nurse	phone	patient	yes	yes	yes
101	0040	study coord. or nurse	phone	patient	yes	yes	yes
104	0010	study coord. or nurse	phone	patient	yes	yes	yes
107	0020	study coord. or nurse	phone	relative or caregiver	yes	yes	yes
112	0026	study coord. or nurse	phone	relative or caregiver	yes	yes	yes
117	0007	study coord. or nurse	phone	patient	yes	yes	yes
118	0013	study coord. or nurse	phone	patient	yes	yes	yes
128	0037	study coord. or nurse	phone	relative or caregiver	yes	yes	yes
128	0038	study coord. or nurse	phone	health professional	yes	yes	yes
129	0003	study coord. or nurse	phone	physician providing care	yes	yes	yes
133	0002	invest or subinvestigator	other ⁵	physician providing care	yes	yes	yes
504	0006	invest or subinvestigator	other ⁶	patient	yes	yes	yes
524	0016	health professional ³	phone	patient	yes	yes	yes
611	0016	study coord. or nurse	phone	patient	yes	yes	yes
612	0086	study coord. or nurse	phone	patient	yes	yes	yes
612	0161	study coord. or nurse	phone	patient	yes	yes	yes
662	0028	invest or subinvestigator	phone	relative or caregiver	yes	yes	yes
663	0015	invest or subinvestigator	phone	patient	yes	yes	yes
663	0021	invest or subinvestigator	phone	patient	yes	yes	yes

ATTACHMENT 2: CAPRIE
CLOPIDOGREL PATIENTS
THAT WERE EARLY PERMANENT DISCONTINUATIONS,
WHOSE LAST VISIT PREVIOUS TO THE FINAL FOLLOW-UP VISIT WAS > 1 YEAR
AND WHO HAD NO PRIMARY OUTCOME EVENTS RECORDED

Site # (000)	Patient # (0000)	Who made contact?	Type of Contact:	Contact with:	Assessment of Vital Status	Specific Questions Asked About Non- Fatal OE	Assessment of OE From Time of Last Visit Until FFV
681	0005	invest or subinvestigator	phone	patient	yes	yes	yes
681	0013	invest or subinvestigator	phone	patient	yes	yes	yes
703	0049	study coord. or nurse	phone	physician providing care	yes	uncertain	uncertain
706	0039	study coord. or nurse	phone	patient	yes	yes	yes
706	0067	study coord. or nurse	phone	patient	yes	yes	yes
706	0199	study coord. or nurse	phone	patient	yes	yes	yes
706	0210	study coord. or nurse	home visit	patient	yes	yes	yes
708	0052	study coord. or nurse	phone	patient	yes	yes	yes
711	0065	study coord. or nurse	phone	patient	yes	uncertain	no
712	0100	study coord. or nurse	other ⁷	patient	yes	uncertain	yes
714	0002	study coord. or nurse	written	physician providing care	yes	uncertain	yes
841	0088	invest or subinvestigator	phone	relative or caregiver	yes	yes	yes
845	0004	invest or subinvestigator	phone	patient	yes	yes	yes
881	0065	invest or subinvestigator	phone	patient	yes	uncertain	yes
881	0081	invest or subinvestigator	other ⁸	patient	yes	uncertain	yes

¹ health professional = M.D. neurologist

² health professional = physician's assistant

³ health professional = physician's medical secretary. In France, there is special training for a medical secretary.

⁴ other = medical chart

⁵ other = investigator's personal visit to the patient's internist

⁶ other = patient's visit to a hospital

⁷ other = patient seen in hospital clinic unrelated to CAPRIE study

⁸ other = medical consultation

⁹ Assessed only for vital status and this was assessed for the entire period from the visit previous to the FFV until the FFV.

¹⁰ Assessed only for vital status and this was assessed for the entire period from the visit previous to the FFV until the FFV.

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ON ORIGINAL

ATTACHMENT 3: CAPRIE
ASPIRIN PATIENTS
THAT WERE EARLY PERMANENT DISCONTINUATIONS,
WHOSE LAST VISIT PREVIOUS TO THE FINAL FOLLOW-UP VISIT WAS >1 YEAR
AND WHO HAD NO PRIMARY OUTCOME EVENTS REPORTED

Site # (000)	Patient # (0000)	Who made contact?	Type of Contact:	Contact with:	Assessment of Vital Status	Specific Questions Asked about Non- fatal OE	Assessment of OE From Time of Last Visit Visit until FFV
001	0011	study coord. or nurse	phone	patient	yes	yes	yes
001	0031	study coord. or nurse	phone	patient	yes	yes	yes
002	0039	study coord. or nurse	phone	patient	yes	yes	yes
037	0002	study coord. or nurse	phone	relative or caregiver	yes	yes	no
037	0042	study coord. or nurse	phone	relative or caregiver	yes	yes	yes
049	0028	study coord. or nurse	phone	patient	yes	yes	yes
049	0035	study coord. or nurse	phone	patient	yes	yes	yes
049	0072	study coord. or nurse	phone	patient	yes	yes	yes
059	0025	study coord. or nurse	phone	physician providing care	yes	no	yes
071	0091	study coord. or nurse	phone	patient	yes	yes	yes
081	0058	study coord. or nurse	phone	patient	yes	yes	yes
082	0036	study coord. or nurse	phone	patient	yes	yes	yes
092	0036	study coord. or nurse	phone	patient	yes	yes	yes
101	0011	study coord. or nurse	phone	relative or caregiver	yes	yes	yes
107	0009	study coord. or nurse	phone	patient	yes	yes	yes
107	0050	study coord. or nurse	phone	relative or caregiver	yes	yes	yes
118	0009	study coord. or nurse	phone	relative or caregiver	yes	yes	yes
128	0002	invest or subinvestigator	phone	health professional	yes	yes	yes
128	0052	invest or subinvestigator	phone	relative or caregiver	yes	uncertain	uncertain
612	0002	study coord. or nurse	phone	physician providing care	yes	yes	yes
612	0056	study coord. or nurse	written	physician providing care	yes	no	yes
662	0009	invest or subinvestigator	phone	patient	yes	yes	yes
663	0051	invest or subinvestigator	phone	patient	yes	yes	yes
706	0002	study coord. or nurse	phone	patient	yes	yes	yes
706	0019	study coord. or nurse	phone	patient	yes	yes	yes
706	0054	study coord. or nurse	phone	patient	yes	yes	yes
706	0059	study coord. or nurse	phone	patient	yes	yes	yes
706	0185	study coord. or nurse	phone	patient	yes	yes	yes
708	0053	study coord. or nurse	other ²	patient	yes	yes	yes
841	0020	other ¹	phone	patient	yes	yes	yes
845	0078	invest or subinvestigator	phone	patient	yes	yes	yes
881	0023	invest or subinvestigator	phone	patient	yes	uncertain	yes
881	0039	invest or subinvestigator	phone	patient	yes	uncertain	yes

¹ other = At this European site, after the patient refused to speak with the investigator, and at the investigator's request, the medical monitor contacted the patient to elicit information.

² other = patient's visit to outpatient clinic

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ON ORIGINAL

D. Rieder

OCT 17 1997

Memo to NDA Record

NDA #: 20-839

Drug Name: clopidogrel

Type of Document: response to information request

Medical Reviewer: Charles J. Ganley, M.D.

NDA Volume:

Sponsor: Sanofi

Correspondence Dates: 9/10, 9/17, 9/23, 9/25, 10/3 and 10/6/97

Date Completed: 10/14/97

The information included in this review was obtained from submissions to the NDA dated 9/10/97, 9/17/97, 9/23/97, 9/25/97, 10/3/97 and 10/6/97. All of these submissions were responses to FDA requests for additional information. This review will deal almost exclusively with validation of the final follow-up visit dates for the patients in the CAPRIE trial.

The termination of patients from CAPRIE differed in some respects from other morbidity and mortality trials previously reviewed by the Cardio-Renal Division¹. The CAPRIE end date is not specified in the protocol but is outlined in Bulletin 10.1 (see attached). The end date for each patient was defined as the final scheduled follow-up visit just prior to the end date for the subgroup² (i.e. Prior MI, Prior Stroke, PAD) or 3 years after the date of randomization, whichever came first. Table 1. lists the study end dates for each subgroup. The end date for a subgroup was 1 year after the enrollment end date for the subgroup. Patient follow-up visits were not supposed to occur after the follow-up end date.

Table 1. Subgroup End Dates

Subgroup	Enrollment End Date*	Follow-up End Date
PAD	10/31/94	10/31/95
MI	12/31/94	1/31/96
Stroke	2/28/95	2/29/96

* no patients randomized into the subgroup after this date

For surviving patients with less than 3 years of follow-up, the Coordinating Methods Center for the CAPRIE study provided each investigator with theoretical final follow-up visit dates for their patients. The theoretical final follow-up visit date should be the patient end date. This date coincided with the scheduled follow-up visit.³ Investigators were requested to perform any follow-up visit within ± 14 days of the scheduled visit date. As such, a patient could be evaluated⁴ up to 14 days prior to their theoretical final follow-up visit date.

Validation of the Minimum One Year Follow-up in Surviving Patients

In the CAPRIE trial, patients were to be followed for a minimum of one year to a maximum of 3 years from their day of randomization. In an analysis of duration of follow-up, 1411 surviving patients had less than 365 days of follow-up. Table 2. lists the frequency distribution of the duration of follow-up for patients with less than 365 days of follow-up.

Table 2. Number of Patients with Less Than 365 Days of Follow-up

Duration of Follow-up (days)	N
358 - 364	1020
351 - 357	243
≤ 350	149

¹ Typically, morbidity/mortality trials have a study end date. The end date may be derived by the date a pre-specified number of endpoints is reached or it may reflect a pre-specified timepoint from the date the last patient was randomized. Generally, on this end date, the status of all randomized patients with regard to morbidity/mortality is known. The exception to this occurs when the duration of follow-up for patients is a set period of time (e.g. 2 years from their randomization date).

² the end date for each subgroup was 1 year from the enrollment end date for the subgroup (see Bulletin 10.1)

³ from the CAPRIE Clinical Center Module page 26 (version 2.0) - All visits should be scheduled in relation to the date of randomization.

⁴ by an office visit or contact by other means (e.g. letter, phone call)

The clinical center module of the Operations Manual⁵ permitted the 4 month visits to occur within a window of ± 14 days. This would have permitted investigators to have a 14 day window around the 1 year follow-up visit date. Consequently, patients could have ≥ 351 days of follow-up and be considered to have fulfilled the one year of follow-up. One hundred and forty nine patients (78 aspirin, 71 clopidogrel; 77 PAD, 33 Prior Stroke, 39 Prior MI) had less than 351 days of follow-up. A complete list of these patients is included in the appendix. All of these patients were considered to have completed the study even though they did not complete 1 year of follow-up. A brief summary outlining the reason four patients (patient numbers: 052-0117, 300-0379, 308-0229, 309-0339) did not complete 365 days of follow-up are provided on appendix page vi. Based on this small sampling of patients, it is clear that follow-up should have been continued. Explanations for the remaining 145 patients has not been requested.

Completion Dates

⁴The sponsor provided the FDA with a SAS program that determined the theoretical final follow-up visit date for each surviving patient with less than 3 years of follow-up. When this date is compared to the actual completion dates for each patient, 1009 patients had their final visit prior to the theoretical final follow-up date. If patients with a primary outcome event are excluded, 944 patients had visits prior to their theoretical final follow-up visit date. Table 2 lists the distribution among subgroups and treatment groups. Investigators in the PAD centers were less likely to adhere to the protocol with regard to evaluating patients on or after their scheduled termination visit.

Table 2. Number Of Patients Who Completed The Trial Prior To Their Scheduled Final Follow-Up Visit Date (excludes patients lost to follow-up and patients with outcome events)

	Stroke Subgroup	MI Subgroup	PAD Subgroup	Total
Clopidogrel	112	105	234	451
Aspirin	125	106	262	493
Total	237	211	495	944

Lost To Follow-Up

In the process of evaluating the completion dates of patients, the sponsor provided a brief summary for patient 020-0012 which outlined the circumstances surrounding the completion of this patient prior to their theoretical final follow-up visit date. Patient 020-0012 was randomized on 3/13/93 and was an early permanent discontinuation on 4/20/93. Subsequent follow-up visits showed that the patient was not contacted until the final follow-up visit of 9/22/95 (see attached follow-up form appendix page vii). The CRF simply documents that the patient was not seen at the center but was contacted by other means (e.g. by letter, by telephone, home visit or other). The sponsor provided information that the investigator contacted the patient's General Practitioner who provided information regarding the patient's status. None of this information is documented in the case report form.

The case of patient 020-0012 raised some concerns because this patient was essentially lost to follow-up for over 2 years until the final follow-up visit. Because the primary endpoint involves the documentation of non-fatal events, questions were raised regarding the adequacy of follow-up⁶ of patients who were early permanent discontinuations. The Steering Committee minutes of 3/24/95 allude to a problem with patients lost to follow-up (see appendix page viii) specifically among those who were early permanent discontinuations. The sponsor was asked to provide information on the number of patients who were early permanent discontinuations and who were lost to follow-up at the visit prior to their final follow-up visit or who had missed the visit prior to their final follow-up visit. Among patients who were early permanent discontinuations, 546 patients (264 aspirin, 282 clopidogrel; 154 stroke, 167 MI, 225 PAD) were lost to follow-up prior to their final follow-up visit and were not evaluated in person at the investigator's center. Table 3 lists the distribution among treatment and subgroups as a function of time lost to follow-up prior to the final visit.

⁵ page 26 of version 2.0

⁶ particularly pertaining to the documentation of non-fatal events

Table 3. Number Of Early Permanent Discontinued Patients Lost To Follow-Up Prior To Their Final Follow-Up Visit.

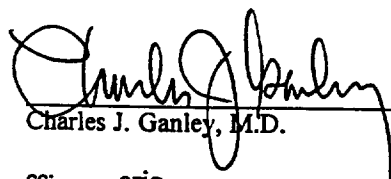
	Treatment	Subgroup			Total
		Stroke	MI	PAD	
< 6 months	Aspirin	26	25	34	85
	Clopidigrel	27	16	34	77
	Total	53	41	68	162
6 - 12 months	Aspirin	19	44	53	116
	Clopidigrel	36	39	60	135
	Total	55	83	113	251
> 12 months	Aspirin	19	21	23	63
	Clopidigrel	27	22	21	70
	Total	46	43	44	133

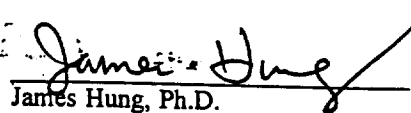
Discussion

Adherence to the protocol, especially with respect to the termination of patients from the trial, is of paramount importance in morbidity/mortality studies. The failure to follow patients to their scheduled end date ultimately raises questions as to whether the early termination was deliberate (e.g. because of deterioration in clinical status or the presence of adverse experiences), by chance (e.g. simply a failure to adhere to the protocol) or a combination of both. The obvious concern is that endpoint events may not be documented. If the early termination of a patient is deliberate, one must determine if it was done with some knowledge of the patient's treatment assignment. Because of the inability of the Agency to adequately validate blinding of a study, it becomes important that the pre-specified procedures in the protocol be followed. When the findings are not robust, as is the case with CAPRIE with a marginally significant p value, a failure to capture a small number of events could have an impact of the statistical significance of the primary endpoint.

More than 5% of the survivors in CAPRIE had their final follow-up visit prior to their theoretical final follow-up visit date. The majority of these patients were from the PAD subgroup (495 of 944) and aspirin treatment group (493 of 944). Of these, 149 had less than the one year minimum follow-up. From the small sample of histories reviewed (see appendix page vi), it is clear that follow-up should have been continued for one year. of 10,000

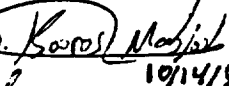
The cohort of patients who were early permanent discontinuations presented additional problem. In this group of patients, an office visit was not required for follow-up. As a consequence, 546 early permanent discontinued patients⁷ were not evaluated in the office on their final visit and were lost to follow-up prior to that visit. Additional information will be required from the sponsor on a subgroup of these patients to document adequate follow-up with regard to the ascertainment of events.

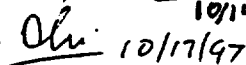

Charles J. Ganley, M.D.


James Hung, Ph.D.

cc: orig.
HFD-110
HFD-110 / cso / ganley / fenichel / fredd
HFD-710 / hung / mahjoob / chi

Concur:

Dr. Mahjoob, Ph.D. 

Dr. Chi, Ph.D. 

appendix

List Of Patients With Less Than 1 Year Of Follow-Up
Bulletin 10.1

Summary of Four Surviving Patients with the Shortest Follow-up

Excerpt From Steering Committee Minutes March 24, 1995

Follow-Up Visit Form For Patient 020-0012

⁷ these patients did not have a primary event

Appendix

Patients with < 351 Days of Follow-up

Patient ID	Dose	Pre-existing Condition	Completion Date	Randomization Date	Duration (days)
01633 300 0379	clopidogrel	MINF	16-Oct-95	30-Jan-95	259
01633 309 0339	clopidogrel	PAD	1-Aug-95	6-Oct-94	299
01633 308 0229	Aspirin	MINF	18-Oct-95	21-Dec-94	301
01633 052 0117	clopidogrel	MINF	15-Nov-95	17-Jan-95	302
01633 706 0310	clopidogrel	PAD	23-Aug-95	14-Oct-94	313
01633 107 0083	Aspirin	MINF	11-Dec-95	30-Jan-95	315
01633 884 0047	Aspirin	MINF	29-Oct-95	15-Dec-94	318
01633 665 0056	Aspirin	PAD	4-Aug-95	20-Sep-94	318
01633 665 0053	Aspirin	PAD	18-Jul-95	2-Sep-94	319
01633 706 0330	Aspirin	PAD	15-Sep-95	31-Oct-94	319
01633 023 0115	Aspirin	PAD	12-Sep-95	26-Oct-94	321
01633 706 0276	clopidogrel	PAD	26-Jul-95	8-Sep-94	321
01633 023 0118	Aspirin	PAD	20-Sep-95	31-Oct-94	324
01633 706 0284	clopidogrel	PAD	4-Aug-95	12-Sep-94	326
01633 300 0631	Aspirin	PAD	21-Jun-95	28-Jul-94	328
01633 612 0277	Aspirin	PAD	21-Sep-95	28-Oct-94	328
01633 069 0053	Aspirin	ISTR	16-Jan-96	21-Feb-95	329
01633 307 0127	Aspirin	ISTR	23-Jan-96	28-Feb-95	329
01633 076 0072	clopidogrel	PAD	30-Aug-95	5-Oct-94	329
01633 706 0314	Aspirin	PAD	8-Sep-95	14-Oct-94	329
01633 517 0052	Aspirin	MINF	2-Nov-95	6-Dec-94	331
01633 681 0034	clopidogrel	PAD	2-Aug-95	5-Sep-94	331
01633 773 0205	clopidogrel	PAD	23-Aug-95	26-Sep-94	331
01633 131 0121	Aspirin	ISTR	19-Jan-96	21-Feb-95	332
01633 612 0275	clopidogrel	PAD	26-Sep-95	28-Oct-94	333
01633 612 0278	Aspirin	PAD	26-Sep-95	28-Oct-94	333
01633 618 0233	clopidogrel	PAD	4-Sep-95	6-Oct-94	333
01633 612 0276	Aspirin	PAD	27-Sep-95	28-Oct-94	334
01633 006 0113	clopidogrel	ISTR	24-Jan-96	22-Feb-95	336
01633 107 0071	clopidogrel	MINF	21-Sep-95	20-Oct-94	336
01633 612 0237	Aspirin	PAD	24-Jul-95	22-Aug-94	336
01633 612 0251	Aspirin	PAD	1-Aug-95	30-Aug-94	336
01633 612 0274	clopidogrel	PAD	28-Sep-95	27-Oct-94	336
01633 703 0068	clopidogrel	PAD	31-Aug-95	29-Sep-94	336
01633 131 0088	clopidogrel	ISTR	4-Oct-95	1-Nov-94	337
01633 612 0240	Aspirin	PAD	25-Jul-95	22-Aug-94	337
01633 684 0064	clopidogrel	PAD	26-Sep-95	24-Oct-94	337
01633 706 0294	Aspirin	PAD	26-Aug-95	23-Sep-94	337
01633 131 0099	Aspirin	ISTR	27-Oct-95	23-Nov-94	338
01633 634 0217	Aspirin	MINF	6-Dec-95	2-Jan-95	338
01633 706 0242	clopidogrel	PAD	27-Jul-95	23-Aug-94	338
01633 024 0079	clopidogrel	MINF	12-Oct-95	7-Nov-94	339
01633 706 0305	Aspirin	PAD	9-Sep-95	5-Oct-94	339
01633 023 0111	Aspirin	PAD	20-Aug-95	14-Sep-94	340
01633 006 0109	Aspirin	ISTR	3-Jan-96	27-Jan-95	341
01633 044 0068	Aspirin	ISTR	6-Nov-95	30-Nov-94	341

Patients with < 351 Days of Follow-up

Patient ID	Dose	Pre-existing Condition	Completion Date	Randomization Date	Duration (days)
01633 131 0107	Aspirin	ISTR	11-Dec-95	3-Jan-95	342
01633 579 0040	Aspirin	ISTR	29-Jan-96	21-Feb-95	342
01633 311 0060	clopidogrel	MINF	8-Jan-96	31-Jan-95	342
01633 788 0042	clopidogrel	MINF	21-Dec-95	13-Jan-95	342
01633 093 0057	clopidogrel	PAD	20-Jun-95	13-Jul-94	342
01633 706 0292	clopidogrel	PAD	27-Aug-95	19-Sep-94	342
01633 511 0023	Aspirin	ISTR	2-Feb-96	24-Feb-95	343
01633 848 0039	clopidogrel	ISTR	29-Jan-96	20-Feb-95	343
01633 034 0024	clopidogrel	MINF	10-Nov-95	2-Dec-94	343
01633 111 0036	Aspirin	MINF	12-Sep-95	4-Oct-94	343
01633 711 0171	Aspirin	MINF	19-Dec-95	10-Jan-95	343
01633 068 0082	clopidogrel	PAD	6-Sep-95	28-Sep-94	343
01633 577 0032	Aspirin	PAD	12-Sep-95	4-Oct-94	343
01633 706 0278	Aspirin	PAD	18-Aug-95	9-Sep-94	343
01633 706 0332	clopidogrel	PAD	9-Oct-95	31-Oct-94	343
01633 708 0119	Aspirin	PAD	18-Jul-95	9-Aug-94	343
01633 773 0236	Aspirin	PAD	5-Oct-95	27-Oct-94	343
01633 051 0066	Aspirin	PAD	7-Sep-95	28-Sep-94	344
01633 044 0075	clopidogrel	ISTR	2-Feb-96	22-Feb-95	345
01633 008 0088	clopidogrel	MINF	11-Jan-96	31-Jan-95	345
01633 115 0035	clopidogrel	MINF	10-Jan-96	30-Jan-95	345
01633 122 0050	clopidogrel	MINF	5-Jan-96	25-Jan-95	345
01633 093 0061	Aspirin	PAD	5-Oct-95	25-Oct-94	345
01633 053 0033	clopidogrel	ISTR	8-Feb-96	27-Feb-95	346
01633 018 0082	Aspirin	MINF	8-Dec-95	27-Dec-94	346
01633 028 0169	Aspirin	MINF	11-Jan-96	30-Jan-95	346
01633 052 0100	Aspirin	MINF	16-Oct-95	4-Nov-94	346
01633 665 0059	clopidogrel	PAD	25-Sep-95	14-Oct-94	346
01633 706 0241	Aspirin	PAD	22-Jul-95	10-Aug-94	346
01633 706 0324	clopidogrel	PAD	9-Oct-95	28-Oct-94	346
01633 023 0119	clopidogrel	ISTR	5-Dec-95	23-Dec-94	347
01633 511 0024	clopidogrel	ISTR	9-Feb-96	27-Feb-95	347
01633 013 0056	clopidogrel	MINF	1-Nov-95	19-Nov-94	347
01633 059 0050	Aspirin	MINF	8-Jan-96	26-Jan-95	347
01633 788 0040	clopidogrel	MINF	18-Dec-95	5-Jan-95	347
01633 773 0232	clopidogrel	PAD	3-Oct-95	21-Oct-94	347
01633 204 0033	Aspirin	ISTR	29-Nov-95	16-Dec-94	348
01633 309 0254	clopidogrel	MINF	4-Oct-95	21-Oct-94	348
01633 929 0013	Aspirin	MINF	2-Oct-95	19-Oct-94	348
01633 612 0269	clopidogrel	PAD	27-Sep-95	14-Oct-94	348
01633 706 0268	Aspirin	PAD	21-Aug-95	7-Sep-94	348
01633 008 0091	Aspirin	ISTR	17-Jan-96	2-Feb-95	349
01633 029 0050	clopidogrel	ISTR	12-Feb-96	28-Feb-95	349
01633 033 0069	Aspirin	ISTR	7-Feb-96	23-Feb-95	349
01633 313 0042	Aspirin	ISTR	8-Feb-96	24-Feb-95	349
01633 508 0045	Aspirin	ISTR	12-Dec-95	28-Dec-94	349
01633 607 0103	clopidogrel	ISTR	8-Feb-96	24-Feb-95	349

Patients with < 351 Days of Follow-up

Patient ID	Dose	Pre-existing Condition	Completion Date	Randomization Date	Duration (days)
01633 609 0162	Aspirin	ISTR	22-Nov-95	8-Dec-94	349
01633 011 0045	clopidogrel	MINF	4-Jan-96	20-Jan-95	349
01633 106 0047	clopidogrel	MINF	25-Sep-95	11-Oct-94	349
01633 200 0027	clopidogrel	MINF	28-Nov-95	14-Dec-94	349
01633 619 0049	Aspirin	MINF	18-Dec-95	3-Jan-95	349
01633 135 0023	clopidogrel	PAD	10-Oct-95	26-Oct-94	349
01633 612 0267	clopidogrel	PAD	28-Sep-95	14-Oct-94	349
01633 612 0268	clopidogrel	PAD	28-Sep-95	14-Oct-94	349
01633 612 0270	Aspirin	PAD	28-Sep-95	14-Oct-94	349
01633 706 0236	Aspirin	PAD	5-Jul-95	21-Jul-94	349
01633 706 0265	clopidogrel	PAD	15-Aug-95	31-Aug-94	349
01633 706 0321	Aspirin	PAD	11-Oct-95	27-Oct-94	349
01633 007 0045	clopidogrel	ISTR	11-Jan-96	26-Jan-95	350
01633 075 0052	Aspirin	ISTR	10-Jan-96	25-Jan-95	350
01633 131 0123	clopidogrel	ISTR	9-Feb-96	24-Feb-95	350
01633 305 0153	clopidogrel	ISTR	21-Dec-95	5-Jan-95	350
01633 604 0050	clopidogrel	ISTR	6-Nov-95	21-Nov-94	350
01633 771 0091	Aspirin	ISTR	12-Feb-96	27-Feb-95	350
01633 771 0092	Aspirin	ISTR	12-Feb-96	27-Feb-95	350
01633 844 0040	Aspirin	ISTR	30-Nov-95	15-Dec-94	350
01633 883 0131	clopidogrel	ISTR	30-Oct-95	14-Nov-94	350
01633 028 0167	Aspirin	MINF	10-Jan-96	25-Jan-95	350
01633 028 0168	Aspirin	MINF	11-Jan-96	26-Jan-95	350
01633 037 0073	Aspirin	MINF	4-Dec-95	19-Dec-94	350
01633 037 0074	clopidogrel	MINF	11-Jan-96	26-Jan-95	350
01633 065 0064	clopidogrel	MINF	15-Jan-96	30-Jan-95	350
01633 119 0038	clopidogrel	MINF	25-Oct-95	9-Nov-94	350
01633 624 0125	clopidogrel	MINF	24-Oct-95	8-Nov-94	350
01633 624 0127	Aspirin	MINF	19-Oct-95	3-Nov-94	350
01633 624 0174	clopidogrel	MINF	16-Jan-96	31-Jan-95	350
01633 624 0175	Aspirin	MINF	16-Jan-96	31-Jan-95	350
01633 049 0080	clopidogrel	PAD	13-Jul-95	28-Jul-94	350
01633 055 0087	Aspirin	PAD	8-Aug-95	23-Aug-94	350
01633 081 0080	Aspirin	PAD	11-Aug-95	26-Aug-94	350
01633 135 0015	clopidogrel	PAD	25-Jul-95	9-Aug-94	350
01633 135 0020	clopidogrel	PAD	10-Oct-95	25-Oct-94	350
01633 528 0207	clopidogrel	PAD	24-Jul-95	8-Aug-94	350
01633 577 0031	clopidogrel	PAD	5-Sep-95	20-Sep-94	350
01633 610 0079	Aspirin	PAD	10-Oct-95	25-Oct-94	350
01633 612 0230	Aspirin	PAD	29-Jun-95	14-Jul-94	350
01633 706 0231	clopidogrel	PAD	4-Jul-95	19-Jul-94	350
01633 706 0232	clopidogrel	PAD	3-Jul-95	18-Jul-94	350
01633 706 0233	Aspirin	PAD	14-Jul-95	29-Jul-94	350
01633 706 0235	Aspirin	PAD	26-Jul-95	10-Aug-94	350
01633 706 0240	Aspirin	PAD	3-Jul-95	18-Jul-94	350
01633 706 0245	Aspirin	PAD	21-Jul-95	5-Aug-94	350
01633 706 0252	Aspirin	PAD	7-Aug-95	22-Aug-94	350

Patients with < 351 Days of Follow-up

Patient ID	Dose	Pre-existing Condition	Completion Date	Randomization Date	Duration (days)
01633 706 0258	Aspirin	PAD	10-Aug-95	25-Aug-94	350
01633 706 0260	Aspirin	PAD	9-Aug-95	24-Aug-94	350
01633 706 0261	clopidogrel	PAD	9-Aug-95	24-Aug-94	350
01633 706 0267	Aspirin	PAD	18-Aug-95	2-Sep-94	350
01633 706 0269	clopidogrel	PAD	16-Aug-95	31-Aug-94	350
01633 706 0270	Aspirin	PAD	17-Aug-95	1-Sep-94	350
01633 706 0272	Aspirin	PAD	16-Aug-95	31-Aug-94	350
01633 706 0328	clopidogrel	PAD	16-Oct-95	31-Oct-94	350
01633 706 0331	clopidogrel	PAD	16-Oct-95	31-Oct-94	350

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CAPRIE BULLETIN

STOPPING OF PATIENT FOLLOW-UP

In Bulletin No. 10 we provided the dates of stopping patient recruitment for each of the three clinical groups and promised to let you know later the corresponding dates for stopping follow-up. The Steering Committee and the Development Decision Committee, a group of senior representatives of the Sponsors, have now agreed that:

There will be no patient follow-up visits beyond:

31 October, 1995 for PAD patients
31 January, 1996 for MI patients
29 February, 1996 for Stroke patients

The Final Visit for each patient will occur at the time of a regularly scheduled visit as per protocol.

Listings of individual patient follow-up schedules are being prepared by the Coordinating and Methods Centre and will be distributed to Clinical Centres shortly. These should facilitate the timely close-out for each patient.

There will be no compassionate drug use following completion of follow-up for individual patients. As indicated in the protocol, open-label Clopidogrel will not be available for patients completing the study since the relative efficacy of Clopidogrel and aspirin will not be established until after the study is completed and analyzed.

When the study data base is finally closed, it is planned to provide each Clinical Investigator with a list of their patients and corresponding allocated treatment and it will be up to each investigator as to whether or not this treatment allocation is made known to individual patients.

Michael Gent

Please Direct Inquiries To:

*CAPRIE Coordinating and Methods Centre
Hamilton Civic Hospitals Research Centre
Henderson General Division
711 Concession Street
Hamilton, Ontario, Canada
LRV 1C3*

*(905) 527-2299, Ext. 2626 (Telephone)
(905) 575-2639 (Facsimile)*

February 27, 1995

Bulletin No. 10.1

Summary of Four Surviving Patients with the Shortest Follow-up

Patient 052-0117 (302 days of follow-up): This patient was randomized on 17 January 1995. The drug was temporarily discontinued due to adverse events (unstable angina and pruritus). Drug was not restarted because the patient withdrew consent secondary. Accordingly, the patient was an early permanent discontinuation (EPD) after only 1 month in the trial. The final contact with the patient was on 15 November 1995 and the CRF contained no information on why this visit was early.

Patient 300-0379 (259 days of follow-up): This patient was randomized on 30 January 1995. The month 6 visit was conducted on 01 June 1995 and the patient was considered an early permanent discontinuation (EPD) due to an adverse event. The month 8 visit for EPD follow-up was conducted on 16 October 1995 and listed as study completion. The patient should have returned for the month 12 visit but apparently, due to a misunderstanding by the study coordinator, the patient did not return for the visit.

Patient 308-0229 (301 days of follow-up): This patient was randomized on 21 December 1994. In August 1995 the patient was hospitalized with chest pain. At that time the patient was advised that if he had further episodes of chest pain he should undergo coronary artery bypass grafting (CABG). The patient experienced further chest pain and underwent CABG. CAPRIE drug was stopped for the surgery but the patient's surgeon did not want the patient to recommence CAPRIE study drug and started the patient on aspirin. The patient withdrew consent to continue in the CAPRIE study in August 1995; however, the investigator was able to get information on the patient's status as of 18 October 1995, and this was considered the last visit.

Patient 309-0339 (299 days of follow-up): The patient was randomized on 06 October 1994. The study coordinator apparently misunderstood when the final visits for PAD patients were to be conducted and performed the final follow-up visit on 01 August 1995. A visit to follow-up an ongoing adverse event occurred on 14 September 1995, however, this was after the patient was considered to have completed the study.

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ON ORIGINAL

Follow-up Visit Form for Patient 020-0012

	Drug No. SR 25990C Protocol No. P1633	Center No. 020	Patient No. 012	Visit No. 11.0	504	Page No in Form 1/1
- Patient Initials -			Date of contact 20 NOV 95 D D M M Y Y 20 11 95			

EARLY PERMANENT DISCONTINUATION FOLLOW-UP

NOTE: This form should only be completed if study drug has been PERMANENTLY DISCONTINUED:

Please continue to follow the patient according to their original study schedule and associated visit numbers.

A) FOLLOW-UP CONTACT

Please tick (✓) one box for each question

Has the patient attended for a scheduled follow-up visit? YES NO

If NO:

Has successful contact been made with the patient (e.g. by letter, by telephone, a home visit, or other)? YES NO

B) OUTCOME EVENTS (See Outcome Events definitions)

Please tick (✓) one box

Has the patient had an outcome event since the last follow-up visit? YES NO DON'T KNOW

NOTE: If YES, please complete: OUTCOME EVENTS FORM.

If event was fatal, also complete: STUDY COMPLETION FORM.

I have reviewed each page of this completed assessment and accept full responsibility for the contents. 6

SIGNATURE [Signature] DATE 04 NOV 95
D D M M Y Y

Excerpt from Steering Committee Minutes of 3/24/95

(6) Patients Lost to Follow-up:

R.S. Roberts presented data on patients for whom the number of days since last known contact was greater than 180 days. These data were of concern given that (1) such patients cannot be taking study drug, and (2) the primary analysis is based on an intention-to-treat. In view of the different methods of early reporting of complete visits among the RDCCs, the CMC and Data Management Group Executive are attempting to assess the reliability of these data. It was recommended that Investigators be advised of the importance of re-establishing contact with potentially lost-to-follow up patients and to re-institute study drug therapy whenever possible. It appeared that the follow-up of EPDSD patients is less diligent than for patients still on study drug. This needs to be investigated further.

APPEARS THIS WAY

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 20839

CHEMISTRY REVIEW(S)

D. Rieder

AUG 6 1997

DIVISION OF CARDIO-RENAL DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

NDA #: 20-839

CHEM.REVIEW #: 1

REVIEW DATE: 1 Aug 97

<u>SUBMISSION</u>	<u>TYPE</u>	<u>DOCUMENT DATE</u>	<u>CDER DATE</u>	<u>ASSIGNED DATE</u>
ORIGINAL		28 Apr 97	28 Apr 97	1 May 97
AMENDMENT		16 Jun 97	17 Jun 97	18 Jun 97

NAME & ADDRESS OF APPLICANT:

Sanofi Pharmaceuticals, Inc.
9 Great Valley Parkway
Malvern, PA 19355

DRUG PRODUCT NAME:

Proprietary:	Plavix
Nonproprietary/USAN:	Clopidogrel (INN, BAN) Clopidogrel Bisulfate (USAN)
Code Name/#:	SR25590C
Chem.Type/Ther.Class:	1 P

PATENT STATUS:

US 4,529,596, Sanofi SA, exp 7/5/03,
Drug, Drug Product, Method of Use
US 4,847,265, Sanofi, exp 2/12/08,
Drug, Drug Product
US 5,576,328, Elf Sanofi, exp 1/31/14,
Method of Use

PHARMACOL.CATEGORY/INDICATION:

Prevention of vascular ischemia

DOSAGE FORM:

TCM

STRENGTHS:

75 mg

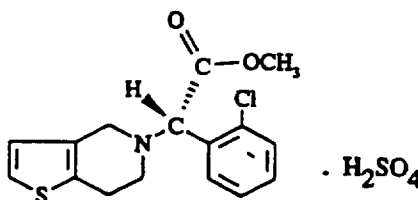
ROUTE OF ADMINISTRATION:

Oral

DISPENSED:

Rx OTC

STRUCTURAL FORMULA, CHEMICAL NAME, MOLECULAR FORMULA, MOLECULAR WEIGHT:



Methyl (+)-(S)- α -(2-Chlorophenyl)-6,7-dihydrothieno(3,2-c)pyridine-5(4H)-acetate
Hydrogen Sulfate

$C_{16}H_{16}ClNO_2 \cdot H_2SO_4$

Base: 321.83

Salt: 419.9

SUPPORTING DOCUMENTS:

RELATED DOCUMENTS (if applicable):

None

CONSULTS:

Environmental Assessment
Division of Biopharmaceutics

REMARKS/COMMENTS:

Most of the CMC information was submitted to IND IC170, on 14 Mar 97. All volume numbers not preceded by "N" refer to this submission (ie. v. 1, p.40). Where additional information was submitted to the NDA, the volume number is preceded by "N," ie. v. N1.3, p. 5.

A Request for Trademark Review, dated 11 Feb 97, was sent to the Labeling and Nomenclature Committee from HFD-530. A response was received from the Committee, dated 27 Mar 97, finding the proposed name unacceptable because of similarities to Flarex, Flavin and Lasix. The amendment of 16 Jun 97 is the applicant's response to the Agency's objections to their proposed Tradename.

CONCLUSIONS & RECOMMENDATIONS:

NOT APPROVABLE

The deficiencies noted during the review of this application are minor and should be easily corrected. None are of such a nature as to impede approval as far as the manufacturing and controls portion of the application is concerned.

cc:

Orig. NDA

HFD-110/Division File

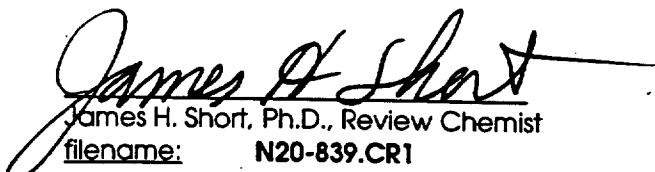
HFD-110/JShort/5/21/97

HFD-110/CSO

District

HFD-810/CHOiberg

R/D Init by: Rwtolters/8/4/97


James H. Short, Ph.D., Review Chemist
filename: N20-839.CR1

DIVISION OF CARDIO-RENAL DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

NDA #: **20-839**

CHEM.REVIEW #: 2

REVIEW DATE: 11 Sep 97

<u>SUBMISSION</u>	<u>TYPE</u>	<u>DOCUMENT DATE</u>	<u>CDER DATE</u>	<u>ASSIGNED DATE</u>
ORIGINAL		28 Apr 97		
AMENDMENT	NC	28 Aug 97	2 Sep 97	4 Sep 97
AMENDMENT	BC	3 Sep 97	5 Sep 97	7 Sep 97

NAME & ADDRESS OF APPLICANT:

Sanofi Pharmaceuticals, Inc.
 9 Great Valley Parkway
 Malvern, PA 19355

DRUG PRODUCT NAME:

Proprietary:	Plavix
Nonproprietary/USAN:	Clopidogrel (INN, BAN) Clopidogrel Bisulfate (USAN)
Code Name/#:	SR25590C
Chem.Type/Ther.Class:	1 P

PATENT STATUS:

US 4,529,596, Sanofi SA, exp 7/5/03,
 Drug, Drug Product, Method of Use
 US 4,847,265, Sanofi, exp 2/12/08,
 Drug, Drug Product
 US 5,576,328, Elf Sanofi, exp 1/31/14,
 Method of Use

PHARMACOL.CATEGORY/INDICATION:

Prevention of vascular ischemia

DOSAGE FORM:

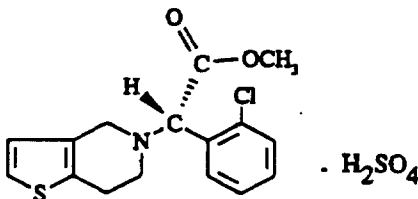
TCM

STRENGTHS:

75 mg

ROUTE OF ADMINISTRATION:

Oral

DISPENSED: Rx OTC**STRUCTURAL FORMULA, CHEMICAL NAME, MOLECULAR FORMULA, MOLECULAR WEIGHT:**

Methyl (+)-(S)- α -(2-Chlorophenyl)-6,7-dihydrothieno[3,2-c]pyridine-5(4H)-acetate Hydrogen Sulfate

C₁₆H₁₆ClNO₂S·H₂SO₄

Base: 321.83

Salt: 419.9

SUPPORTING DOCUMENTS:

RELATED DOCUMENTS (if applicable):

None

CONSULTS:

Division of Biopharmaceutics

REMARKS/COMMENTS:

A Request for Trademark Review, dated 11 Feb 97, was sent to the Labeling and Nomenclature Committee from HFD-530. A response was received from the Committee, dated 27 Mar 97, finding the proposed name unacceptable because of similarities to Flarex, Flavin and Lasix.

Methods Validation will be requested as soon as the dissolution specification is set.

A request was sent to HFD-324 via the EES system on 3 Jun 97 requesting inspection of Sanofi's plant at Sisteron and plant at for manufacture of the drug substance; inspection of Sanofi's plant at Ambares for manufacture of the drug product; and inspection of 7 other facilities for packaging of the drug product. Decisions have not been made on the Mayaguez, PR facility, Sisteron, France facility and Ambares, France facility. The last inspection was scheduled for August 8, 1997.

The correspondence of 28 Aug 97 provides for withdrawal of the Environmental Assessment included in the original submission. The applicant requests a categorical exclusion for clopidogrel bisulfate from preparation of an Environmental Assessment based upon the fifth year marketing estimates and environmental fate data that the quantity of the substance expected to enter the aquatic environment is below The requested categorical is granted, based on the information provided..

The amendment of 3 Sep 97 provides the applicant's responses to the Agency's deficiency letter of 6 Aug 97.

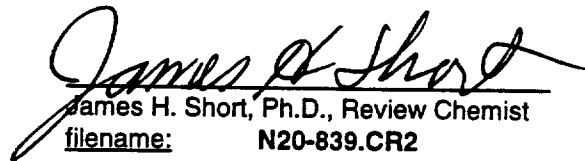
CONCLUSIONS & RECOMMENDATIONS:

NOT APPROVABLE until the impurities specifications for the drug substance are properly aligned, the test is added to the specifications for the drug substance, and labeling issues are resolved.

The deficiencies noted below will be conveyed to the applicant.

APPEARS THIS WAY
ON ORIGINAL

cc:
Orig. NDA
HFD-110/Division File
HFD-110/JShort/9/8/97
HFD-110/CSO
District
HFD-810/CHOiberg
R/D Init by: Rwolters/9/12/97


James H. Short, Ph.D., Review Chemist
filename: N20-839.CR2

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ON ORIGINAL

OCT - 9 1997

DIVISION OF CARDIO-RENAL DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

NDA #: 20-839

CHEM.REVIEW #: 3

REVIEW DATE: 7 Oct 97

<u>SUBMISSION</u>	<u>TYPE</u>	<u>DOCUMENT DATE</u>	<u>CDER DATE</u>	<u>ASSIGNED DATE</u>
ORIGINAL		28 Apr 97		
AMENDMENT	BC	22 Sep 97	23 Sep 97	25 Sep 97
AMENDMENT	BC	26 Sep 97	29 Sep 97	1 Oct 97
AMENDMENT	BC	1 Oct 97	3 Oct 97	7 Oct 97
AMENDMENT	BC	2 Oct 97	3 Oct 97	7 Oct 97
AMENDMENT	BC	6 Oct 97	7 Oct 97	10/9/97

NAME & ADDRESS OF APPLICANT:

Sanofi Pharmaceuticals, Inc.
9 Great Valley Parkway
Malvern, PA 19355

DRUG PRODUCT NAME:

Proprietary:	Plavix
Nonproprietary/USAN:	Clopidogrel (INN, BAN) Clopidogrel Bisulfate (USAN)
Code Name/#:	SR25590C
Chem.Type/Ther.Class:	1 P

PATENT STATUS:

US 4,529,596, Sanofi SA, exp 7/5/03,
Drug, Drug Product, Method of Use
US 4,847,265, Sanofi, exp 2/12/08,
Drug, Drug Product
US 5,576,328, Elf Sanofi, exp 1/31/14,
Method of Use

PHARMACOL.CATEGORY/INDICATION:

Prevention of vascular ischemia

DOSAGE FORM:

TCM

STRENGTHS:

75 mg

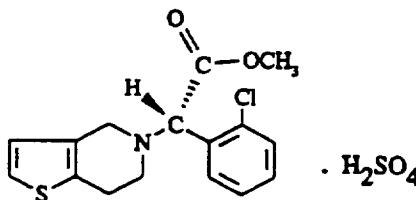
ROUTE OF ADMINISTRATION:

Oral

DISPENSED:

Rx OTC

STRUCTURAL FORMULA. CHEMICAL NAME. MOLECULAR FORMULA. MOLECULAR WEIGHT:



Methyl (+)-(S)- α -(2-Chlorophenyl)-6,7-dihydrothieno[3,2-c]pyridine-5(4H)-acetate Hydrogen Sulfate

C₁₆H₁₆ClNO₂S·H₂SO₄

Base: 321.83

Salt: 419.9

SUPPORTING DOCUMENTS:

RELATED DOCUMENTS (if applicable):

None

CONSULTS:

Division of Biopharmaceutics

REMARKS/COMMENTS:

A Request for Trademark Review, dated 11 Feb 97, was sent to the Labeling and Nomenclature Committee from HFD-530. A response was received from the Committee, dated 27 Mar 97, finding the proposed name unacceptable because of similarities to Flarex, Flavin and Lasix. The Division has decided to accept the proposed trademark.

A request was sent to HFD-324 via the EES system on 3 Jun 97 requesting inspection of Sanofi's plant at Sisteron and plant at for manufacture of the drug substance; inspection of Sanofi's plant at Ambares for manufacture of the drug product; and inspection of 6 other facilities for packaging of the drug product. All facilities have been found acceptable as of 8 Oct 97.

The Division of Biopharmaceutics has recommended a dissolution specification of Q= 20 min at . The applicant has agreed to accept the proposed specification, but is opposed to the paddle speed. They have agreed to carry out feasibility studies (teleconference, 6 Oct 97) to determine if a speed of is practical.

Methods Validation will be requested now that the dissolution specification has been set.

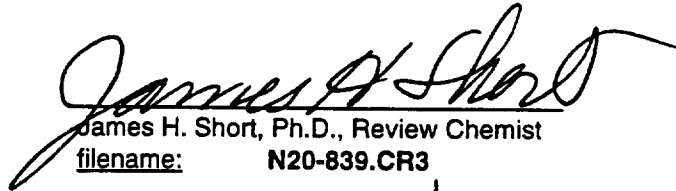
Still unresolved is whether the tablet imprint satisfies 21 CFR 206.10. The applicant has agreed to work with the Agency to resolve this problem, which is not an approvability issue.

CONCLUSIONS & RECOMMENDATIONS:

The application is approvable as far as the CMC section is concerned.

APPEARS THIS WAY
ON ORIGINAL

cc:
Orig. NDA
HFD-110/Division File
HFD-110/JShort/10/1/97
HFD-110/CSO
District
HFD-810/CHOiberg
R/D Init by: Rwolters/10/9/97


James H. Short, Ph.D., Review Chemist
filename: N20-839.CR3

Short
10/9/97

APPEARS THIS WAY
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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 20839

PHARMACOLOGY REVIEW(S)

Koeder

SEP 15 1997

NDA 20-839

OVERVIEW OF PRECLINICAL PHARMACOLOGY AND TOXICOLOGY

Albert DeFelice, Ph.D
September 15, 1997

This consolidates previously reviewed core animal pharmacology and toxicology studies of the anti-thrombotic agent clopidogrel (SR 25990C; Plavix® : Sanofi Pharmaceuticals Inc.). Sponsor's study reports were originally submitted to HFD-180 under IND and reviewed there by Tanveer Ahmad, Ph.D. and team leader Jasti Choudary, Ph.D. For study details and original reviewer evaluations, see Dr. Ahmad's reviews referenced below as: (HFD-180: date of issue).

SYNOPSIS OF OVERVIEW:

Sponsor provided evidence that clopidogrel selectively inhibits binding of ADP to platelets, and, consequently, ADP-mediated activation of a glycoprotein GPIIb-IIIa complex, binding of fibrinogen to that complex, platelet aggregation, and thrombosis. This cascade is initiated by irreversible high-affinity binding of a putative clopidogrel metabolite to platelets.

Results of animal assays, in toto, predicted clinical pharmacology and metabolism : therapeutic potency of clopidogrel (mg/ M² based) was comparable in all species and humans, as was pharmacokinetic estimates based on tracer and major metabolite levels. Full dose - response profiles of anti-platelet aggregating and anti-thrombotic activities were identified in several species and disease models. Both activities occurred over the same dose range. Clopidogrel was tested in a battery of acute, chronic, and system-specific safety assays. Mild reversible hepatic, clinical chemistry, and hemogram changes were the only remarkable findings in protracted (3 and 12 mo.) assays. Depending on whether hemogram or adaptive liver changes was provoked, the threshold toxic dosage in the rat was ca. 35 to 114 times the anti-aggregating ED50% dosage. This therapeutic ratio, based on the same minimal toxicity, was 330 in the baboon. The safety ratio as multiples of anti-thrombotic ED50% dosage in rats and rabbits was ca. 60. Based on the size of these conservative (i.e., minimal toxicity-based) ratios, and the nature of the pathology, the animal data project no clinical safety concerns other than consequent to prolonged bleeding time.

PHARMACOLOGY : Clopidogrel pre-treatment clearly interfered with *ex vivo* ADP binding and ADP-dependent inhibition of adenylate cyclase activity in harvested rat, rabbit, and human platelets. In all species, clopidogrel - at dosages 0.6 to 5 mg/Kg - inhibited ADP-induced platelet aggregation *ex vivo*, as well as thrombus formation *in situ* in several models of arterial and venous thrombosis. Oral and intravenous activity was comparable, long lasting (T 1/2 = 2-3 days), and delayed in onset.

Clopidogrel also suppressed myointimal hyperplasia in vascularly injured rabbits.

Irreversible binding of a putative metabolite(s) to platelets accounts for activities of this pro-drug. Neither the *R*-enantiomer metabolite (< 10%) nor the main circulating metabolite (SR 26334) were active in platelet binding/function studies.

Acute Safety Pharmacology: At up to 125-250 mg/Kg. enteral dosage (> 50 X anti-platelet aggregation dose), clopidogrel did not acutely affect overt CNS (mice, rats), autonomic (dog), cardiovascular (dog), respiratory (dog, guinea pig), gastrointestinal (mice, rat), or renal (rat) function.

It had no anticoagulant or fibrinolytic activity, but did prolong bleeding time in rats and rabbits at therapeutic dosages - a basis for cautious clinical use when lesions predisposed to bleeding exist, e.g. gastric ulcers.

TOXICITY:

a. Acute:

Target organs of single high-dose exposures (LD 50% > 2g/Kg in 3 species) were GI tract (erosions; bleeding), lung (congestion), and kidney (tubulo-interstitial necrosis). These pathologies were not seen in repeat dose studies at up to approx. 400 mg/Kg (>100 X ED50% dosage).

b. Sub-chronic.

Mice tolerated up to 383 mg/Kg/day for 3 months - except for 10-20% change in weight of body and liver at lethal dosages (≥ 766 mg/Kg).

Rats tolerated up to 400 mg/Kg daily (52 x clinical mg/M² dose) for 3 months except for reversible increases in liver wt., plasma cholesterol, and platelet count.

Baboons tolerated, in a 2-week study, up to 250 mg/Kg daily; 500 mg/Kg provoked lethal hemorrhagic GI irritation.

c. Chronic: In a 78 week tumorigenicity study, mice developed no excess tumors when exposed to 27 to 47 times the human AUC. Rats tolerated up to 123 mg/Kg for 1 year except for slightly elevated cholesterol and liver weight, and - in a 2-year tumorigenicity study - exposures of up to 47 times the human AUC with no tumorigenic response. Baboons given up to 200 mg/Kg (approx. 52 x clinical dose as mg/M²) of clopidogrel daily for 1 year revealed (only) slight reversible changes in RBCs, serum albumin, and liver weight.

d. Reproductive:

Clopidogrel was non-fetotoxic in a comprehensive (Segment 1-3) test battery in the rat, and also in a rabbit fetal organogenesis study: In rats given up to maternotoxic dosages (52 x clinical mg/M² dose) clopidogrel had no remarkable effect on a.) fertility and reproductive function of treated dams and their offspring, b.) *in utero* morphology of the F1 and F2 generations, or c.) post-natal development of the F2 generation. It was neither embryotoxic in higher dose rat or rabbit teratology studies at up to maternotoxic dosages of 500 and 300 mg/Kg, respectively (65 and 78 x clinical mg/M² dosages), nor deleterious to peri- and post-natal development of pups delivered of rats that received up to 400 mg/Kg in the 3rd trimester through weaning interval.

d. Genotoxic:

Results of five assays involving adequate drug challenge were uniformly negative. Mutagenicity was not observed, at up to cytotoxic concentrations, in three *in vitro* tests (Salmonella; rat; hamster) with or without rat liver metabolizing enzymes present. No clastogenicity was seen either *in vitro* (human lymphocytes) at up to cytotoxic concentrations, or

in vivo (rat erythrocytes) at up to systemically toxic dosages. Positive controls behaved as expected. An Ames test of clopidogrel's main metabolite (SR26334A) was also negative.

PHARMACOKINETICS: In all species and humans, absorption of radiolabeled clopidogrel was at least 50 - 80% based on excretion balance data. Oral bioavailability of intact clopidogrel was low due to rapid and extensive hydrolysis to SR26334 in the liver (primates) and, also, plasma (rats). The ¹⁴-C label dispersed primarily to organs of metabolism and excretion in all species. Plasma radioactivity elimination T_{1/2} was approx. 7 days, reflecting plasma protein binding. Excretion was mainly biliary and fecal.

Toxicokinetics: Using relative AUC (rodent vs. human) or relative plasma C_{max} (baboon vs. human) values of the major metabolite as the (only feasible) marker of clopidogrel exposure, the dosages tested in the 3 - month baboon, the 1- year rat, and the lifetime rodent tumorigenicity safety assays afforded, respectively, up to 20, 75, and 47 times human steady state clopidogrel burden.

OVERVIEW OF PHARMACOLOGY, TOXICOLOGY, and PHARMACOKINETIC STUDIES:

A. Primary pharmacology:

1. Mechanism of action (HFD-180: 7/16/90;6/28/95).

A hepatic metabolite of clopidogrel specifically inhibits a sequence of thrombotic platelet events initiated by ADP, i.e., platelet ADP binding, glycoprotein activation, binding of fibrinogen to glycoprotein, and aggregation. Oral pre-treatment of rats with at least 1 mg/Kg of the agent dose-dependently antagonized *ex vivo* binding of ADP to specific platelet receptors. Oral dosing at 25 to 50 mg/Kg. also interferes with ADP- dependent inhibition of adenylate cyclase activity in rat and rabbit platelets *ex vivo*. Ability to inhibit ADP receptor-mediated activation of GTP-binding protein in rat platelet membrane is also documented (Thromb. Haemat., 1992,68: 79 -83).

There is evidence that clopidogrel requires hepatic conversion to an unidentified active metabolite to express its effect: rat and human platelets exposed for one hour *in vitro* to up to 10⁻⁴ M clopidogrel respond normally to ADP; the agent had no anti-aggregating effect in rats with a porto-jugular shunt (Sanofi report no. RS 260890324); and its anti-aggregating effect was potentiated or reduced by pre-treatment with, respectively, inducers or inhibitors of CYP 1A (HFD-180:6/9/94).

2. Anti-platelet aggregating activity:

Oral clopidogrel dose-dependently and uniformly inhibited *ex vivo* platelet aggregation provoked by multiple agents in mice, rats, rabbits and

baboons (HFD-180: 7/16/90 ; 8/2/94). After 3 to 5 days oral dosing to rats and baboons, and harvesting of platelets 2 hrs. after the last dose, the ED 50% for blocking ADP, collagen, or thrombin -induced aggregation ranged from 0.6 (baboon) to 4 (rat) mg/Kg daily - values several fold less than seen after a single administration. Maximum activity occurred 2-6 hours after oral dosing in rats and baboons, with multiple daily dosing needed to reach steady state. Duration of anti-aggregating effect was similar to that of platelet life span, which indicated irreversible binding to platelet receptors. As expected of its restricted mechanism of action, clopidogrel did not affect prothrombin time or euglobulin fibrinolytic activity in the rat, or plasma fibrinogen levels in rabbits, but it prolonged bleeding time of rat and rabbits (HFD-180: 7/16/90).

3. Anti-thrombotic activity:

After a single oral administration, clopidogrel demonstrated dose-related prophylactic anti-thrombotic activity in five different rat and rabbit models of thrombosis (foreign body; venous stasis; and electrical.) , with an ED₅₀% range of approx.1.5 to 5 mg/Kg (HFD-180: 7/16/90; Sanofi report RS260890324). After i.v. dosing in female rats, the onset and potency of both the anti-thrombotic and the *ex vivo* anti-aggregating effects were comparable. This suggests that both are closely correlated (HFD-110:6/9/94; Sanofi no. RS260890324/MA1). This agent also reduces frequency and appearance of cyclic flow variations (which are thought to be platelet -aggregate related) in stenosed canine coronary arteries by 50 and 100% at 2.5 and 5 mg/Kg i.v., respectively (Sanofi study no. RS200891213/ML1).

4. Anti-atherogenic activity:

In a rabbit model of atherogenesis provoked by carotid artery de-endothelialization, daily oral administration of clopidogrel at 25 mg/Kg/day for 16 days - beginning 2 hrs. prior to injury - inhibited both sub-endothelial platelet adhesion (after one dose) and myointimal proliferation (examined on day 16) by approximately 40-45% (HFD-180: 7/16/90). Since the agent does not directly inhibit smooth muscle proliferation (HFD-110: 9/4/91; Sanofi report no. RS260901015/MA1), prevention of platelet adhesion may underlie the anti-proliferative effect of clopidogrel on the intima.

5. Potentiation of streptokinase thrombolysis (Sanofi report no. RS260901127/MA).

Neither standard heparin (100 IU / Kg) nor clopidogrel (10 mg/Kg i.v.) had any thrombolytic activity in rabbits with established ¹²⁵Iodine-labeled jugular vein clots, whereas streptokinase increased rate of spontaneous lysis by

ca. 5.5 -fold. However, when given concurrently with streptokinase, these drugs appreciably enhanced lytic activity of the latter by approx. 33% when co-administered individually, and by approx. 60% when heparin and clopidogrel were both administered with the kinase. The dose-response for this heparin-streptokinase and clopidogrel-streptokinase co-operativity was not reported. We can conclude that neither clopidogrel nor heparin revealed any thrombolytic activity but that each agent significantly enhanced that of streptokinase. Sponsor believed, based on analysis of blood vs. clot radioactivity, that the synergistic effect of clopidogrel was due to inhibition of thrombus accretion rather than to any direct dissolution of the clot. Apparently, rate of thrombolysis effected by streptokinase is the net of its lytic activity vs. an opposing thrombotic process of local platelet aggregation.

B. Safety and secondary pharmacology (HFD-180: 7/16/90)

I. Acute Neural Activity

Oral neurobehavioral (CNS), anticonvulsant (vs. pentetrazol), or analgesic (vs. heat; acetic acid) activities were assessed in conscious mice dosed at up to 250 mg/Kg. Activity was uniformly absent except for weak peripheral analgesia and enhanced pentobarbital narcosis at the latter dosage. In the rat, slight EKG, but no behavioral, alterations were observed at 125 and 250 mg/kg.

2. Cardiovascular and respiratory systems

The only acute CV activity reported in dogs that received clopidogrel at up to 250 mg/Kg. i.d. was a decrease in cardiac output (>125 mg/Kg) and a slight respiratory analeptic effect (>62.5 mg/Kg). Except for relief of serotonin - induced bronchospasm, neither basal nor spasmogen - enhanced bronchial tonus were altered in guinea pig dosed at up to 250 mg/Kg.

3. Gastrointestinal system

Neither intestinal motility (mice) nor gastric acid secretion (rat) were affected by oral administration of 250 mg/Kg of clopidogrel. Rat gastric emptying was retarded after oral treatment with 200 mg/Kg of clopidogrel.

4. Urinary

In the rat, a single oral dose of up to 500 mg/kg did not overtly affect renal function.

5. Hemostatic.

In the rat, clopidogrel was devoid of any *ex vivo* anticoagulant or fibrinolytic activities at 10 mg/Kg (Sanofi report no. RS 260890324/MA1) whereas a standard dose of heparin significantly prolonged partial time, prothrombin time, and thrombin time. However, after a single oral dose to female rats of 5 mg/Kg (the approx. ED 50% for anti-aggregating activity), clopidogrel prolonged bleeding time of transected tail by approx. 5-fold (Sanofi report no. RS260890324/MA1). In the rabbit, an effective anti-platelet aggregating dosage of clopidogrel does not appreciably prolong bleeding time, but does significantly potentiate the hemorrhagic effect of streptokinase and enhance the slight increase in bleeding time seen after heparin administration.

C. Toxicology. (HFD-180: 7/16/90)

Toxic affects of clopidogrel were assessed in a standard battery of *in vitro* and *in vivo* studies. Sponsor stated that batches used in the pivotal studies contained all main impurities:

1. Acute (oral; intravenous) . (HFD-180: 7/16/90)

Acute oral LD₅₀% in mice, rats, and baboons exceeded 2000 mg/ Kg.; acute intravenous LD 50% (mice, rats) was 110 to 160 mg/Kg. Target organs of single dose oral toxicity were digestive tract (erosions, hemorrhage), lung (congestion) and kidneys (necrotic tubulopathy); target of intravenous toxicity was cardio-respiratory (rapid death after cyanosis, dyspnea, and apnea). The gastric and renal toxicity was not observed in the repeat dose oral studies, described below, that were performed using up to approx. 400 mg/Kg./day of clopidogrel

2. Sub-chronic: (HFD-180: 7/16/90)

a. Two-week :

Dose-ranging studies were performed in two species:

Rat:

Administration at 125 to 4000 mg/Kg daily (5M/5F/group) provoked an elevated plasma cholesterol and triglycerides, and an increased liver weight; the latter reflected centrilobular hypertrophy and smooth endoplasmic reticulum increase. Drug was lethal at 1000 mg/Kg and above due to an esophagitis, gastritis and/or gastritis also seen with sub-lethal severity at lower dosages. Results were confirmed in a second study performed at up to 1000 mg/Kg daily.

Baboon:

Administration at 500 to 4000 mg/Kg daily (1M/1F/group) provoked prostration, emesis (often hemorrhagic), and death at 500 mg/Kg and above. Autopsy revealed gastric ulceration, renal congestion, and pale livers. Lower doses were tolerable except for slight laryngitis or tracheitis.

b. Three-month :

A total of five 3-month oral toxicity studies were performed in mice (2 dietary studies, one with a 6-week recovery period), rats (1 gavage with 5 -week recovery period; 1 dietary), and baboons (1 gavage with a 5-week recovery period) . Absorption of clopidogrel was confirmed by the presence of it's carboxylic acid derivative (SR26334) in plasma (mice; baboons) or urine (rat):

Mouse:

Two studies, involving 10M/10F/group, were performed using dietary admixtures which afforded up to 306 or 3065 mg/Kg /day, respectively. The first study (Sanofi study # RA860900710/cb1) - performed to allow selection of doses for a carcinogenicity study - revealed no histopathology. However, 10 to 20% increases in liver weight occurred in both sexes at the two high doses (153 and 306 mg/Kg, respectively.). Maximum plasma level of the main metabolite(SR26334) was 40 mg/L at the top dose in both sexes. In the second

study(RS 0006950601/03), excess deaths occurred in males only receiving 766mg/Kg ,or more, daily. At necropsy, dose-related increase in liver weight was observed but no other macroscopic changes. Histology was not performed.

Rat:

Rats gavaged with up to 400 mg/Kg dosage (25M/25F/group) revealed ca. 20% weight loss at the high dose, and - at 100 mg/Kg /day and above - increases in platelet count (up to 20%), liver weight (up to 45%) and plasma cholesterol (up to 20%), and enlarged centrolobular hepatocytes. All changes were reversible within 5-weeks. (HFD-180:7/16/90)

In the 3-month dietary admixture study (RA860900717/JV1), where rats (10M/10F/group) were dosed at up to 306 mg/Kg/day, increases in liver weight and or plasma cholesterol, but no liver histopathology, were observed from the dose level of 153 mg/Kg/day. Drug absorption was confirmed by dose-related urinary presence of the major metabolite. As the mean anti-thrombotic ED 50% is 3.5 mg/Kg in several rat models, the therapeutic ratio based on the reversible hemogram and liver changes at the high dose is 114 in this 3-mo. study (i.e., 400 /3.5).

Baboon:

Young primates gavaged with up to 400 mg/Kg daily (5M/5F/group) presented with vomiting (or gastric erosion at necropsy), a slight leukocytosis , and depressed body weight gain (35-50%) at the high dose. There was no in-life interference with BSP dye clearance at end of treatment phase, although at necropsy enlarged livers (+ 15% vs. control) were present. EKG changes were seen in high-dose group at 1, but not 3, month treatment interval. *Ex vivo* platelet aggregation induced by ADP was inhibited 100% in the 25 mg/Kg group at 2 hrs. post-dosing. After a 5-week recovery period (3M/3F/group), treated and control animals were essentially indistinguishable, indicating reversibility of gastric and body weight effects.

Based on absence of toxicity at 100 mg/Kg and the reversible pathology at high dose, and an anti-platelet aggregating ED 50% of 0.6 mg/Kg, the therapeutic ratio in this 3-mo. study lies between 166 (100/0.6) and 660 (400/0.6). [The 1-year study(see below) identifies 200 mg/Kg as the chronically tolerated dose with minimal toxicity].

3. Chronic

a. One year (HFD-180: 1/12/93):

Two studies were performed: a rat dietary study (20M/20F/group), affording up to 123 mg/Kg of clopidogrel base, and executed concomitantly with the carcinogenicity study; and a dose- by- gavage study in baboons (9M/9F/group) performed at dosages up to 200 mg/Kg daily. Baboon study included a 5-week recovery period, and assessment of immunotoxicity(see below under special tests).

Rat:

There was no excess treatment-related mortality within the 1-year interval. At the end of treatment, plasma cholesterol was elevated up to 19 and 42 % in high-dose males and females, respectively. Liver weight in high-dose groups was also increased by approx. 20%, reflecting the hypertrophy of centrilobular hepatocytes seen at microscopy. Since the mean anti-thrombotic ED_{50%} in the rat models is 3.5 mg/Kg, a conservative therapeutic ratio based on these minor liver and clin. chem. changes in the high-dose group is 35 (i.e., 123/3.5).

Baboon:

There was no excess treatment-related mortality through a dose-range adequate to depress body wt. gain of the young primates by ca. 50-75% at high dose, and to achieve peak and trough SR26334 levels of ca. 100 and 8 mg/L, respectively, over a majority of the treatment interval. The only remarkable effects - other than reduced body weight gain - in a study that involved periodic ophthalmoscopy, electrocardiography, urinalysis, and blood sampling were high-dose reduction in RBC count and hemoglobin (ca. 10%) and urine pH, and ca. 30% increase in liver weight but no gross or histopathology. Bromsulphothalein liver function test was negative. All changes had reversed at the end of a 5-week recovery period.

Since the antiplatelet-aggregating ED_{50%} is 0.6 mg/Kg in the baboon, the therapeutic ratio based on the liver and hemogram changes at 200 mg/Kg is 330 (i.e., 200/0.6)

b. Tumorigenicity assays (HFD-180: 8/2/94):

Standard 18 and 24-month carcinogenicity assays were performed in mice and rats, respectively, at up to 77 mg/Kg base /day i.e., approx. 60 times recommended clinical dose of 75 mg. (1.25 mg/Kg). Tumor incidences were analyzed by sponsor using Peto trend and Fisher's Exact tests. Results of both assays were brought before the Executive CAC primarily to judge adequacy of high-dose exposure in both studies since there were no remarkable differences in mean tumor incidences across cohorts.

A letter from HFD-180 (dated Sept. 8, 1994) indicated that the full package of available toxicology data, including the negative mutagenicity findings, provided adequate information on the carcinogenic potential for clopidogrel hydrogen sulfate, and that both rodent studies were adequate and acceptable.

Mice:

Although the high dose (100 mg/Kg) provoked no excess mortality, chronic histopathology, or body weight change, the CAC Executive Committee agreed with the primary review pharmacologist (Dr. Ahmad) that 100 mg/Kg still provided an adequate high-dose challenge. The basis was a follow-up 1-month study (RS 0005940322/01), showing that that dose afforded 47 (male) and 27 (female) times the SR 26334 AUC level seen in humans taking the maximum

recommended daily dose. [recall that SR26334 is an inactive metabolite of clopidogrel formed in rodents and humans, and necessarily used as a surrogate of clopidogrel exposure in all animal and clinical studies]. These AUC ratios exceed the value(25) established by International Conference on Harmonization (ICH step4.Carcinogenicity : Testing for carcinogenicity of chemicals, recommended for adoption 16 July1997, Brussels).

Regarding autopsy findings, the exec. CAC judged that there was no evidence of excess benign or malignant tumor burden (Exec. CAC final report of 8/23/94) in treated mice of either sex. There was also no decrease in latency of spontaneous tumor appearance based on tumors observed at each 150 day interval in animals which died or were sacrificed prematurely.

Tables of neoplastic lesions provided by the sponsor (IND 34663, amend. 160, 1/24/97, vol. 11), revealed that there was, across all groups: a comparable incidence of animals with tumors (Control vs. treated Males: 28 vs. 32, 30, and 30%, ; C vs. treated Females: 30 vs. 36, 30, and 18 %); a comparable incidence of animals with more than one primary neoplasm (C vs. Treated M: 5 Vs. 2,5, and 4%; C vs. Treated F: 5 vs. 4, 2, and 2%); a comparable number of benign and malignant tumors (C vs. treated M: 15 Vs. 15,15, and 17; C vs. treated F: 13 Vs. 21,16, and 10); and a comparable number of animals with metastases (C vs. treated M: 0 Vs 0, 0, and 0%; C vs. treated F: 3 vs 0, 0, and 0%) .

Rats:

As with the mouse study, the high dose (100 mg/Kg) provoked no excess histopathology or mortality, and no change in body weight. The Exec. CAC Committee again agreed with the primary review pharmacologist that the 100 mg/Kg high dose was acceptable on a pharmacokinetic basis according to current ICH guidelines. In a separate 4-week study(RS 0005931202/01), that dosage afforded large multiples of clinical maximum exposures, i.e., 42 (male) and 28 (female) times steady-state SR 26334 AUC levels in patients receiving clopidogrel daily at the recommended dose.

There were no findings of non-neoplastic histopathology or gross pathology except for a 12% increase in liver weight in high dose males. The Exec CAC concurred with Dr. Ahmad's finding of no evidence of excess benign or malignant tumor burden (Exec. CAC final report of 8/23/94) in treated rats of either sex. Peto analysis (combined prevalence and death rate method) , using standard confidence levels, confirmed absence of any dose-related tumorigenicity, or any decrease in latency of spontaneous tumor appearance (IND , amend. 52, vol. 26).

Dr. Ahmad mentions a 4-6% incidence of adrenocortical adenoma in treated males, but notes that this is within the historical control incidence for this strain (1.4-16.4%; Charles River; February 1992). The Exec. CAC did not acknowledge this as a real finding. In any case, the only adrenocortical *carcinomas* observed resided in 1 control male, 2 control females, and 1 low-dose female.

Tables of neoplastic lesions provided by the sponsor (IND amend. 52, vol. 26), revealed that there was, across all groups: a comparable incidence of animals with neoplasms (Control vs. treated Males: 78 vs. 60, 70, and 68%; C vs. treated Females: 92 vs. 86, 96, and 94 %); a comparable incidence of animals with more than one primary neoplasm (C vs. Treated M: 28 Vs. 22, 26, and 24%; C vs. Treated F: 52 vs. 38, 52, and 54%); and comparable number of benign and malignant tumors (C vs. treated M: 59 Vs. 43, 51, and 49; C vs. treated F: 87 Vs 67, 88, and 87). Clopidogrel had no effect on incidence, latency, or histomorphologic type of spontaneous tumors.

4. Genotoxicity assays: (HFD-180:7/16/90; HFD-180:6/9/94)

Mutagenicity

a. Ames (S. Typhimurium) test.

Genotoxicity tests proper were preceded by toxicity tests to identify cytotoxic and /or insoluble concentrations. Ames tests, each involving 5 strains of S. Typhimurium, were then performed on clopidogrel (2 different batches), its major metabolite (SR26334A), the R-enantiomeric impurity/metabolite (SR 25989C), and the SR24726 impurity of synthesis at up to 2500,5000, 2500, and 2500 micrograms / plate, respectively. Strains used detect frame shift as well as base pair substitution mutations.. Results for clopidogrel were uniformly negative both in the presence and absence of rat hepatic metabolic enzymes (S-9). Dose-related increase in number of revertant colonies (2 or 3-fold depending on bacterial strain) was the criterion for a positive finding. Results for the 2 previously unreviewed impurities were also negative (Sanofi reports: RS0006961015/01; RS0006911219/02). Positive, including metabolically dependent, controls behaved as expected, confirming integrity of rat S-9 metabolic enzyme system.

b. Chinese hamster cells: HPRT locus, *in vitro*

One assay was conducted with , and 2 independent assays were conducted without , a metabolic activation system (rat S9) present. These tested whether clopidogrel could provoke point mutation in lung fibroblasts exposed for 24 hrs. to up to 40 (S9 absent) or 150 (with S9) µg / ml levels of clopidogrel. Positive controls (S9-dependent and independent) were included. At up through cytotoxic concentrations (40µg /ml without S9; 80 µg /ml with S9) and beyond, clopidogrel provoked no increase in mutant frequency. Both positive controls tested positive.

Clastogenicity

a. Metaphase chromosome analysis: lymphocytes

Cultured human cells, stimulated to divide with a mitogen, were exposed to up to cytotoxic levels of clopidogrel with and without S9 metabolic system present.

There was a maximum 1.4% incidence of chromosomal aberrations observed in metaphase-arrested cells that had been exposed to up to 80 µg/ml of clopidogrel vs. 0 or 0.25% incidence in negative control cultures, and 11.5 and 12% incidence in positive controls. Accordingly, clopidogrel clearly was not clastogenic at up to concentrations which markedly suppressed cell division (mitotic index was reduced to 18.4 % of control at the highest clopidogrel concentration).

b. *In vivo* Mouse micronucleus test.

Based on preliminary toxicity testing, where marked clinical signs and mortality occurred at and beyond 2300 mg/Kg, mice were gavaged with up to 2000 mg/Kg. of clopidogrel daily for 3 days. At that dosage (which prostrated the males) there was no evidence of genotoxicity, i.e., incidence of micronucleated polychromatic RBCs was not elevated. Ratio of polychromatic to normochromatic RBCs was also normal which indicates that there was no bone marrow cytotoxicity. Conversely, cyclophosphamide markedly elevated the incidence of micronucleated polychromatic RBCs. Accordingly, there was no evidence of any clastogenic activity for clopidogrel at up to a systemically toxic dose administered for 3 consecutive days.

Other genotoxicity assays

In vitro DNA repair test (Fisher rat hepatocytes in primary culture):

Two assays for unscheduled DNA synthesis were performed. No net increase in nuclear incorporation of tritiated thymidine was seen over a 5-25 µg/ml concentration range in one assay, and 15-40 µg/ml with another batch number, indicating absence of any unscheduled DNA repair. Genotoxicity could not be evaluated at higher concentrations where clopidogrel was cytotoxic (highest tested was 1000 µg/L). Accordingly, clopidogrel was negative in initial and confirmatory assays. Positive controls were genotoxic (mean nuclear grain count > 5), whereas no excess repair was induced by pyrene (negative control). Mixed function oxidative (Cyt p-450) enzymes were functional in these primary culture cells since the metabolically dependent control (2-AAF) was positive.

5. Reproductive toxicity. (HFD-180: 7/16/90 ; 9/4/91)

Effects of clopidogrel on reproductive function and on peri- and post-natal development were comprehensively assessed in four studies in rats and rabbits covering all three reproduction segments - including both male and female fertility, teratogenicity, and any next-generation carry-over effect. The dose range examined in each assay, i.e., up through slight parental toxicity, was

chosen on the basis of maternal or paternal toxicity in preliminary dose-range finding studies and/or results of the 3-month toxicity study. Excretion into milk was also examined.

a. Segment 1. Study: Rat (HFD-180:9/4/91)

Clopidogrel was studied at up to 400 mg/Kg (34M / 34F per group). Males were treated for 71 days prior to pairing and through successful littering of females. Females were dosed for 15 days prior to pairing through to the end of weaning. Uteri and fetuses of 2/3 of the dams were examined at day 20 caesarian section for parameters which included no. of dead and resorbed fetuses, and external or internal malformation; rest of dams were allowed to deliver spontaneously. Growth, reproductive performance, and fertility of the F1 generation, and growth of the F2 generation until weaning, were evaluated. (See HFD-180: 9/4/91 for full details).

Results: *Parental* : Dose-related hypersalivation and, at high dose, depressed parental body weight gain and 2 possibly drug-related male deaths were observed. There were no effects on fertility and mating performance of males or females. *F1 generation* : At 100 mg/Kg and higher, there was a slight retardation of post-natal body weight gain and development, significant at the high dose where 25-day old pup weight was about 90% of control, and times to eye and vaginal opening were slightly delayed. However, this was reversible, since after weaning body weights were similar to control. Moreover, no abnormal effects on fertility or mating performance of F1 generation, or on survival and development of F2 pups up to weaning were seen.

Accordingly, the only remarkable effect observed was a reversible retardation of F1 neonatal growth.

b. Segment 2 (Teratogenicity) .

Rat: (HFD-180: 9/4/91)

This study also included an evaluation of effects of *in utero* exposure on development and reproductive performance of the F1 generation: Groups of 35 gravid rats were treated at up to 500 mg/Kg daily from day 6 to day 17 of gestation, and 23 from each group were sacrificed on gestation day 20 for evaluating embryotoxicity and teratogenicity. Remaining dams (12/gp) gave birth, and F1 pups evaluated for growth and reproductive performance.

Results: High-dose dams experienced rales, hypersalivation, and increased water consumption. F1 pups, at caesarian, revealed no remarkable anomalies. Dams allowed to deliver spontaneously had normal litter size; their F1 progeny had normal post-natal development and reproductive performance at sexual maturity

Accordingly, clopidogrel was not teratogenic at up to 500 mg/Kg, and exposure *in utero* to this parental dosage did not affect F1 development or fertility.

Rabbit: (HFD-180: 7/16/90)

Gravid rabbits (14-15/gp) were dosed at up to 300 mg/Kg daily on days 6 through 18 of gestation. [The highest dose tested was based on a preliminary study in gravid females where clopidogrel was lethal at 400 mg/Kg, and, at 200 mg/Kg, reduced their body wt..] At near term (i.e., day 29), all dams were sacrificed and the uteri and fetuses examined for fetal deaths, resorptions, and external and/or internal anomalies.

Results: Maternal food intake was depressed at the high dose but body weight gain was depressed only in the earlier gestation period. Number of corpora lutea, implants, live fetuses, or dead or resorbed fetuses was unchanged. Fetal and placental weight were also unaffected by clopidogrel. Neither skeletal nor visceral development was affected in these fetuses at up to slightly maternotoxic dosages administered during the stages of major organogenesis i.e., through the second trimester.

c. Segment III. Peri- and post-natal development: rat (HFD-180: 9/4/91)

Dose selection was based on a 3-month toxicity study. Gravid rats were dosed at up to 400 mg/Kg /day from day 15 of gestation through weaning (neonatal day 25). Number of live/dead pups were recorded. Twenty males and 20 females were culled at day 4, their development to sexual maturity was monitored (testis descent, eye opening, vaginal opening, learning ability etc.), and they were paired to yield an F2 generation. Remainder of F1 pups were sacrificed and autopsied for anatomic anomaly. Dams were killed at weaning and the uteri were examined.

Results: Slight reductions in mean numbers of corpora lutea, implantations, and live young at the highest dosage were the only findings. No external, visceral, or skeletal abnormalities were observed in F1 or F2 pups, and - except for ca. 10% lower body weight of weaned high-dose F1 pups. No developmental or reproductive capacity deviations were observed in pups of either generation which were allowed to develop to sexual maturity.

d. Excretion in milk:

Lactating SD rats given a single labeled clopidogrel dose of 5 mg/kg excreted ¹⁴C in milk for more than 48 hours. Peak level occurred 2 hr. after dosing, and was comparable to peak (i.e., 1-hour) maternal plasma level.

6. Special toxicity tests

Immunotoxicity

a. Immunoglobulins and lymphocytes.

Rat: (HFD-180: 9/4/91)

Young SD rats (6M/6F per group) were given up to 100 mg/Kg/ day of clopidogrel for 4 weeks, and blood obtained on days - 7 and 27 for lymphocyte subpopulations, globulins, IgG, and IgM. Splenocytes were harvested for functional testing of lymphoblasts, lymphocytes, and natural killer (NK) cells. No treatment-related effects were seen on clinical signs, clinical chemistries, or at necropsy except for slightly increased liver weight of high-dose females. Hematology revealed, in males, slight dose-related increase in RBC count, HgB level, and PCV. Functional tests on splenocytes were negative for tritiated thymidine incorporation in lymphoblasts (i.e.,DNA turnover), proliferation index in mixed lymphocyte culture, and NK cytotoxicity index.

Baboon: (HFD-180: 6/9/94)

During the 1-year baboon toxicity study (see above: 2.C. Baboon.), blood was drawn at 1, 3, 6, 12, and 15 mo. intervals for monitoring immunoglobulin levels (IgG; IgM), and lymphocyte function at 2 or more time intervals:

There were no treatment-related effects on immunoglobulin levels, or on tritiated thymidine incorporation in lymphoblasts, proliferation index in mixed lymphocyte culture, and NK cytotoxicity index.

b. Antigenicity in guinea pig: (HFD-180: 9/4/91)

Clopidogrel was administered 3 times, at 14-day intervals, to young guinea pigs at up to 50 mg/Kg s.c. to test for anaphylaxis - either systemic (25 mg/Kg i.v. challenge) or passive cutaneous (intradermal injection of serum followed by 25 mg/Kg i.v clopidogrel challenge):

Neither anaphylaxis nor elevated IgG responses were evident. Conversely, 3 of 5 ovalbumin -treated controls died with systemic anaphylaxis, and 5/5 others had marked cutaneous anaphylaxis down to 7241-fold serum dilution.

c. Phototoxicity / Photoallergy in Guinea Pig: (HFD-180: 6/9/94).

Guinea pigs received clopidogrel at 200 mg/Kg. daily for 8 days .They were irradiated with both UVA and UVB one hour after dosing on days 1- 3, and 6-8, and graded for erythema. After a 3-week washout , the same animals and treatment schedule (with a single dose) were used to assess photoallergy to UVA and UVB inflicted separately:

Clopidogrel revealed no phototoxicity potential . However, sponsor did not include a positive control.

Myelotoxicity (HFD-180: 7/16/90)

Male mice were orally treated with up to 500 mg/Kg. of clopidogrel per day for 5 days. Busulfan, at 40 mg/Kg (single dose), was used as the positive control.

Their bone marrow was transplanted to irradiated mice, and 9 days later the number of splenic colonies and the relative number of nucleated and stem (blast) marrow cells was determined at sacrifice:

Clopidogrel did not affect incidence of nucleated bone marrow cells whereas the count was depressed 40% by busulfan. The number of splenic colonies in mice which received marrow implants from clopidogrel-treated was approx. 90 % of the count in negative controls vs. 25% for mice receiving busulfan-treated marrow. Accordingly, there was no evidence of myelotoxicity - at least with respect to *in vivo* colonizing potential of transplanted cells.

[It would have been of interest to perform this study with autologous grafts, i.e., using this sequence: treatment, harvesting of marrow, whole body irradiation, and re-implanting of cells .

D. Biopharmaceutics (HFD-180: 7/16/90; 9/4/01; 6/9/94; 8/2/94; 6/28/95; 6/28/ 95).

Absorption, distribution, and excretion of radioactive clopidogrel was tracked as migration of label (¹⁴C in the pyridine ring). Due to rapid and extensive hepatic hydrolysis of clopidogrel to SR 26334 in the liver (primates) and /or serum(rodents),the latter compound was monitored as a marker of (evanescent) clopidogrel burden. Pharmacokinetics and excretion balance of clopidogrel have been studied in rats and baboons following single intravenous and single / repeated oral administration. Tissue distribution and placental transfer was investigated in rodents (mice; 2 strains of rat) and rabbits, respectively, using radiolabelled clopidogrel. Major metabolites were characterized in plasma (rodents, baboon), urine (rodents, rabbit, baboon), and bile (rat; baboon). Effect of pretreatment with cytochrome P450 modulators on *ex vivo* anti-aggregating activity of clopidogrel was also studied (rat).

Intravenous pharmacokinetics (single dose): (HFD-180: 7/16/90)

Pk parameters were determined after an intravenous dose in rats (25 mg/Kg) and baboon (50 mg/animal): Parent compound had a short elimination T_{1/2} in both species, and large plasma clearances and volumes of distribution. Metabolite SR26334 peaked at approx. 15 min. in both species, and accounted for most of the biotransformation of clopidogrel : SR26334 AUC was approx. 500 (rat) and 50 (baboon) times that of parent compound, and about 80% of clopidogrel was converted in the rat. Conversion after oral dosing is even more extensive (see immediately below).

Absorption:

a. Single oral dose:

Absorption of single oral doses of clopidogrel was studied in rats (both sexes) and male baboons at dosages used in the 3-month toxicity studies, i.e. 25, 100, and 400 mg/Kg. Plasma was assayed for unchanged drug as well as it's major metabolite - the carboxylic acid derivative SR26334 , an S -

enantiomer like its parent. Limits of detectability were 0.002 and 0.050 mg/L for clopidogrel and SR 26334, respectively.

Results: In both species, T_{max} for clopidogrel was 1-2 hrs., and its C_{max} and/or AUC 0-infinity, were much smaller than corresponding values for the major metabolite SR26334. That is, peak plasma levels and AUCs of SR 26334, in both rats and baboons, quickly reached values several thousand -fold those of the parent compound. In the rat, body burden of parent and metabolite was 3 to 10 times greater in females than males (only male baboons were tested), reflecting lower volume of distribution and clearance in females (HFD-180:7/16/90). The AUC for the metabolite was dose-linear in the rat but not the baboon. This metabolite represents about 85% of circulating drug-related compounds in plasma and did not accumulate in repeated dose rat toxicity study.

The very low clopidogrel / major metabolite ratio in venous blood reflects an extensive hepatic first pass effect: Following a single 5 mg/Kg oral dose to a portal vein- catheterized male baboon, the concentration of clopidogrel in portal blood was much higher than in peripheral blood (HFD-180: 6/28/95). Due to the hepatic clearance, bioavailability of clopidogrel in the rat is only several percent, although at least 50 to 70% is absorbed from the rat gut based on regional absorption from ligated GI tracts (HFD-180:6/9/94).

The AUC values for SR26334 obtained at the 400 mg/Kg clopidogrel dosage (namely, ca. 5000 and 1400 mg. h/L for rat and male baboon, respectively) were approx. 175 to 600 times that measured in humans receiving 75 mg/day. The clinical dose affords patients close to peak inhibition (approx. 50%) of platelet response to ADP *ex vivo*. (HFD-180:6/28/95). Accordingly, dosages (up to 400 mg/Kg) tested in such animal toxicity studies afforded body burdens of clopidogrel several orders of magnitude greater than necessary for clinical target pharmacology.

Animal body burdens noted above reflect at least 50% absorption based on urinary excretion of clopidogrel-related metabolites (see Metabolism below).

b. Repeated dose:

Pharmacokinetics of clopidogrel and SR 26334 were studied after repeated administration in rodents and baboon to support interpretation of safety study data. Clopidogrel *per se* was not assayed in rodent plasma samples due to their high esterase activity:

Baboon: (HFD-180: 9/4/91)

1. Sub-acute 14-day study:

Male primates received 5 mg/Kg p.o. of radio-labeled clopidogrel for 14 consecutive days, and blood was sampled on days 1 through 14, and during washout, for parent drug, SR 26334 metabolite, and total plasma radioactivity. Urine and feces were not monitored. Results: Parent drug was not detectable in plasma, and SR26334 represented approx. 50 % of plasma

radioactivity. Half-life of plasma radioactivity decay following drug withdrawal was approx. 7 days.

2. Sub-chronic (3 mo.) and chronic (12- mo.) studies:

Plasma levels of clopidogrel and/or SR26344 were measured at peak and trough i.e., at 2 and 24 hours after gavage, on days 9, 40, and 98 of the 3 month toxicity study (High dose: 400 mg/ Kg/day), and on days 100, 191, 282, and 370 of the 1 year study (High dose: 200 mg/Kg/day): Results: In the 3-mo. study, low plasma levels (<0.015 mg/L) of intact clopidogrel were found, but approx. dose-proportional levels of metabolite SR26334 were seen at peak and trough (125 and 7 mg/L, respectively, at high dose). There was no gender effect. In the 1- year study, peak and trough SR26334 levels at 100 days / 200 mg/Kg were comparable to values in the shorter trial at 3 months / 400 mg/Kg. Peak plasma SR 26334 level during the one year duration of this trial (approx. 175 mg /L) is several orders of magnitude greater than that which obtains at the 75 mg clinical dose.

Rodents:

4-week studies (HFD-180: 8/2/94)

The diet afforded mice and rats dosages up to 100 mg/Kg (and beyond in the rat), matching those tested in the carcinogenicity studies. Blood was sampled on days 27-29, and steady- state drug exposure was determined using 0-22 hr. AUC of the SR26334 S-metabolite as a surrogate. Levels of the R-isomer of SR26334 were also measured to assess for any *in vivo* chiral transformation. Results: In both species, dose-related increases in SR26334 AUCs were observed. AUC values up to 47 times those seen clinically, thereby establishing the acceptability of the exposures achieved in the tumorigenicity bioassays. . There was minimal chiral conversion to the R-enantiomer of SR26334 (approx. 2% in mice; 7% in rat).

Distribution: (HFD-180: 7/16/90; 9/4/91)

Single oral dose:

Tissue distribution, and placental transfer, of ¹⁴C- clopidogrel has been identified in the mouse and rat (2 strains), and pregnant rats and rabbits, by measuring tissue radioactivity and by whole body autoradiography following an oral dose of 5 to 77 mg/Kg. The latter was the mid-dose tested in the teratology study. A total of 6 distribution studies in Sprague-Dawley rats and in mice uniformly indicate rapid (peak concentrations within 15 to 30 min.) and extensive tissue distribution of radioactivity. Gut , liver, and kidney had higher - and brain, heart, muscle, and fat lower - levels than in plasma. In a separate study, whole body autoradiography confirmed this distribution pattern except radioactivity was also associated with melanin in eye, inner ear, pigmented skin, and hair follicles. Three days after dosing of rats, radioactivity was still detectable in liver, kidneys, lung, fat, and skin. Radioactivity in other tissues was less than 0.01% of administered dose.

Repeated oral dose:

In 21-day rat studies, highest levels of radioactivity again occur in the liver, kidney, and lungs from which it departs with half-lives of approx. 1 week (Sanofi report no. RS0005911218/01).

Single intravenous dose:

After i.v. administration to SD rats, uptake of radioactivity by the tissue is rapid, and highest in liver, kidneys, fat, and gut (indicating biliary excretion), and lowest in eyes, brain, and muscle.

Studies in pregnant rats: (HFD-180: 6/9/94)

Clopidogrel and/or its metabolites cross the placenta of rats, is detectable in fetal liver and gut, and is also excreted in the milk of lactating animals: After a single oral dose of labeled clopidogrel at gestation day 11 or 19, maternal ¹⁴C distribution was similar to that in non-gravid animals, and ovary, uterus, and mammary tissue levels were approx. 50% of plasma concentrations. Within 30 min. of dosing, the major fetal organs had 3% (liver) to 50% (brain) of the corresponding maternal ¹⁴C radioactivity. However, approx. 90% of both fetal and maternal tissue radioactivity had cleared within 24 hours based on sacrifice of gravid rats at 0.5, 4, and 24 hr. post administration.

Plasma protein binding: (HFD-180: 6/9/94) At an *in vitro* concentration of 100 mg/ml, approx. 98% of clopidogrel is bound to baboon plasma protein; such binding could not be reliably studied in rats or rabbits where plasma esterases rapidly hydrolyze clopidogrel. The major circulating metabolite binds to human serum protein up to 95%, reaching saturation at *in vitro* incubation concentration of 100 mg/ml.

After single oral dosing with labeled clopidogrel, radioactivity covalently bound to plasma protein has been detected in rodents and baboons. Such binding decays with a T_{1/2} of approx. 8 days. (Sanofi report RS0005951201/06)

Metabolism (HFD-180:7/16/90; 9/4/91; 6/9/94; 6/28/95 :2 reports)

Biotransformation has been identified *in vivo* and *in vitro*, and main metabolites in plasma, urine, and bile characterized by LC-MS. Chiral inversion of clopidogrel - an *S*-enantiomer - has also been assessed. Because metabolism is primarily hepatic in primates, interaction with the Cyt. P₄₅₀ enzymes was also assessed.

Plasma profiles:

Metabolic profiles in plasma have been studied following single (i.v., p.o.) and repeated oral dosing in baboons and rodents. After either route of administration, a stable *S*-carboxylic acid derivative (SR26334) predominates, comprising 45 to 95% of extractable plasma radioactivity across all species and time points. Studies in portal vein-cannulated baboons reveal that this conversion is primarily hepatic in that species; however, *in vitro* studies show that rat and rabbit (but not baboon or human) also have plasma esterases

capable of performing this hydrolysis. . Two other minor metabolites also occur in the plasma of baboons.

Stereo-specific assay of blood collected from baboons for up to 8 hr. after single oral dosing revealed chiral stability of clopidogrel i.e., only the *S*- and not the *R*- metabolite was detected. However, after repeated clopidogrel administration, up to 10% of this carboxylic acid derivative metabolite is the *R*- enantiomer, both in rodents and baboons.

Hepatic metabolism:

Ability of liver to metabolize clopidogrel has been studied in vitro and in vivo, and in the presence of Cyt P450 enzyme inducers and inhibitors. Ability of clopidogrel to modulate those hepatic mixed function oxidases was also assessed.

In vitro: Rat, dog, rabbit, baboon, and human liver microsomal fractions, in the presence of NADPH, are capable of hydrolyzing clopidogrel to SR26334 and oxidizing the thiophenic ring without major species differences.

Interactions with Cyt P450: Studies of livers excised from rats and baboons which had been dosed with up to 100 and 400 mg/Kg of Clopidogrel, respectively, for 3 months show that the drug is able to induce certain Cyt P₄₅₀ oxidases while inhibiting others. In the primate, clopidogrel's effects at 100 mg/Kg dosage were similar to, or less than, those of the structurally related ticlopidine at the same dosage except that clopidogrel did not induce aniline hydroxylation (CYP 2E) activity. Both agents doubled CYP 3A activity, inhibited CYP 1A activity at least 50%, and increased weight of liver and it's Cyt P450 content by 25-50%.

To put these cytochrome P450 results into perspective, it should be noted that enzyme modulation was not observed in the rat or baboon at the end of 3 months dosing at 25 mg/Kg. That regimen afforded rats 10 to 15 times the human clopidogrel body burden (using AUC of main metabolite as a surrogate), and the baboon 7 times the human mg / M² dosage.

Pretreatment of female rats with a variety of selective modulators of Cyt P450 isozymes indicated that clopidogrel was mainly a substrate for Cyt P450 1A (HFD-180: 6/9/94). That is, beta-naphthoflavone and SKF 525A markedly enhanced or completely suppressed, respectively, the anti-aggregating activity of clopidogrel.

Excretion (HFD-180: 9/4/91)

Elimination of [¹⁴-C]-clopidogrel, given orally or intravenously, was tracked in rats, rabbits , and baboons.

Biliary: A dose-dependent biliary metabolite profile was identified in bile duct-cannulated rats and baboons which received labeled clopidogrel enterally. Metabolites included a glutathionyl sulfoxide of clopidogrel (rats), free SR26334 (baboon), and glucuronides of SR26334 (both species). No free clopidogrel was detected.

In rats, approx. 80% of the administered dose (i.e., radioactivity) was excreted in the bile within 48 hours in the context of significant entero-hepatic recirculation of radioactivity.

Excretion Balance:

Within 6 days of i.v. or oral dosing to rats, approx. 70- 80 % of radioactivity was fecally excreted, 10-20% was in the urine, and 1 - 4 % remained in the carcass. In the pregnant rabbit, 85% of the dose was recovered in urine, and 20% in feces after a single oral (100mg/Kg) dose given on gestation day 28. In male baboons repeatedly dosed at 5 mg/Kg /day, approx. 60 and 30 % of the radioactivity was recoverable in the feces and urine, respectively.

Summary:

Safety Evaluations:

Therapeutic Ratios:

Sponsor identified full dose-response profiles for both the anti-thrombotic and the anti platelet- aggregating activities of clopidogrel in multiple species. Anti-atherogenic as well as streptokinase-enhancing effects, at a specific clopidogrel dosage, were also identified in rabbits and rats, respectively. Safety tests conforming to GLP standards were performed up through acutely or chronically toxic dosages. In some cases, efficacy and repeated dose safety assays were performed in the same species, namely rat and baboon. In the latter species, ratios of median effective to threshold toxic dosages were large enough to project no clinical safety concerns in my judgment. Based on reversible gastric irritation and/or slight increase in liver weight, the therapeutic ratios were 35 (rat) and 660 (baboon). Using slight reversible changes in RBCs and/or platelets as toxicity markers, the ratios were 114 (rat) and 330 (baboon). This impression of low risk of serious or irreversible toxicity is reinforced by the consistency of these safety ratios and of other animal observations, namely: a.) the uniform maximum efficacy and potency of this agent across species (ED₅₀'s of 1- 5 mg/Kg) and models of thrombosis; b.) the close correlation of anti-aggregating, anti -thrombotic, and bleeding time-prolonging activities; and c.) the uniform absence across species of any remarkable functional or histologic aberration below 200 mg/Kg/day delivered by gavage (baboon: 1 year) or 400 mg/Kg /day via the diet (rat: 3-month). Furthermore, the slightly aberrant hemograms, clinical chemistries, and liver wt. increases - which were the only remarkable findings in the 12 mo. studies - were uniformly reversible. Lesions of the digestive tract primarily seen at high dose levels (\geq 500 mg/Kg in baboons or \geq 1000 mg/Kg in rats) during the sub-acute studies were not observed in either species in the one-year studies performed at lower doses.

Hematotoxicity:

Potential hematotoxicity was of concern in view of the structural and pharmacological similarity of clopidogrel to ticlopidine. Ticlopidine can cause neutropenia and thrombocytopenia (Moloney, B., : Ticlopidine , Platelets, and Vascular Disease., New York, Spr. Ver. , 1993:117-139.). Only slight, and reversible hemogram changes (platelet/ RBC count) were seen in rats (≥ 400 mg/Kg for 3 months) and baboons (200 mg/Kg for 1 year) and, then, at dosages producing GI irritation and health deterioration. No oral myelotoxicity was seen in mice at up to 500 mg/Kg/day/5 days. However, sponsor, to their credit , reminds us that ticlopidine, a known human myelotoxin, was similarly nontoxic in animal models.

Safety Pharmacology:

Beyond standard assaying for histopathologic or clinical chemistry changes, sponsor also tested for any central or peripheral functional aberrations - including those of the immune system. Based on results of such safety pharmacology studies, where doses at least 30-50 times higher than the anti-aggregating or anti-thrombotic dose produced no remarkable side effects, it could be concluded that the risk of interrupting any vital function at recommended dosages is low. Immunotoxicity was tested in 3 species. Absent were any histologic, immunoglobulin, or lymphocyte function changes in either the 1-year baboon study , executed at 330- fold the therapeutic dosage in that primate, or in 4-week rat studies. Lack of antigenicity or photoallergy in the guinea pig would further reduce the likelihood of eliciting any immunotoxicity or "hypersensitivity" reactions e.g., an autoimmune-based blood dyscrasia.

Noteworthy is the absence of any specific central nervous system toxicity. Potential for CNS toxicity was of concern because the *R* - enantiomer of clopidogrel , which is present in current formulation at up to 1%, provokes CNS toxicity in animals at dose levels greater than 250 mg/Kg.

Effects on Hemostasis:

In rats and rabbits the agent will , as expected , prolong bleeding time of fresh wounds dose-dependently, and in parallel with interference of ADP - induced platelet activation. Accordingly, at therapeutic doses it could promote bleeding of certain lesions e.g., ulcers - as occurred at sites of GI tract lesions in acute high-dose rodent and baboon studies.

Clopidogrel lacks any anticoagulant or profibrinolytic activity both of which are, as I understand, independent of platelet activation. It affects neither prothrombin or thrombin times nor levels of prothrombin or fibrinogen. The experience in the CAPRIE trial - where, according to sponsor, clopidogrel provoked less bleeding than aspirin - would be consistent with the virtual absence of hemorrhages in intact mice, rats, and baboons..

Reproductive function:

Assays of clopidogrel effects on reproductive function and on peri- and post-natal disturbances examined all standard parameters in rats and rabbits. As

reprotox. tests were performed over the same dose ranges as in the subacute toxicity studies, similar parental toxicity was observed at the highest dosages - confirming appropriateness of high dose selection. Although sponsor showed that radiolabelled compound enters rat and rabbit fetuses and rat milk, there was no fetotoxicity, teratogenicity, or irreversible neonatal aberration. The only remarkable finding was a slight delay in physical development of neonates nursing from dams receiving 100 or 400 mg/Kg daily. This effect, which was not observed unless the lactating dams were receiving clopidogrel, was confined to the lactation period and reversed rapidly after weaning.

Genotoxicity /Tumorigenicity:

A comprehensive battery of *in vitro* mutagenicity tests were performed at up to cytotoxic concentrations and with rat S-9 present to compensate for the limited oxidative metabolism capacity of bacteria or cells in culture. Such assays were uniformly negative for genotoxicity vs. unequivocally positive results for the active controls. Ancillary to these findings was the absence of clastogenicity in a mouse micronucleus test performed at up to 26 times the high dose used in the tumorigenicity study.

In lifetime carcinogenicity assays, dosages of clopidogrel which afforded up to 50 times the human clopidogrel body burden (based on relative levels of the major metabolite), were neither lethal nor - according to standard Peto analysis - carcinogenic in rodents. A slight increase in incidence of palpable masses in treated rats was recorded for both the male [3% in control (3/100) Vs 7% in treated (12/ 150)] and female [64% in control (64/100) vs. 74% in female (111/150)]. The raw data show 3 "excess" malignant tumors in mid/high-dose males, and 4 in mid/high-dose females. However, statistical analysis according to Peto et al (1980) revealed no positive trend for any specific tumor type in either sex. Dr. Ahmad and the Exec. CAC agreed that clopidogrel - over an appropriate dose range - provoked no excess tumors in either sex of either species.

Biopharmaceutics:

Pharmacokinetic studies necessary to support pharmacodynamic and toxicity studies characterized ADME of clopidogrel, and confirmed drug exposures in the critical rat and primate studies. Results of the pharmacokinetic studies of [¹⁴C]- clopidogrel are considered to be reliable since radiochemical purity (>99%) was confirmed prior to each investigation, and the low exhalation of radioactive carbon dioxide (0.2%) after single oral administration to rats showed that the ¹⁴C labeling on the pyridine ring was appropriate for the PK studies. The low percentage of SR 26335 (the *R* - enantiomer of major metabolite SR 26334) formed *in vivo* by chiral conversion supported the general use of non-stereospecific methods for assaying SR 26334. Assay of the latter was the only feasible way of tracking clopidogrel's

fleeting exposure. All plasma drug/metabolite assay methods were said to be validated for each animal species used.

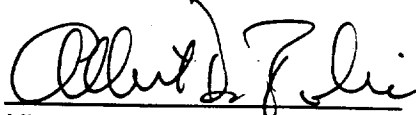
Oral absorption was extensive in all species. In the baboon, sponsor clearly established that the low oral bioavailability of intact clopidogrel reflected rapid hepatic bio-transformation rather than poor absorption. Clopidogrel was primarily hydrolyzed to SR26334 (one of twenty metabolites) which was observed in plasma 0.2 to 0.5 hr. after dosing. This metabolite was approximately 95% protein bound in rats and primates (primarily to albumin in humans), and did not accumulate in the 2 to 4 week safety studies in rodents and baboons. Acute distribution studies in mice, rats (2 strains), and pregnant rats and rabbits at a pharmacologic dose (rats) or dose within range tested in toxicology (mice; rabbits) revealed similarly wide distribution patterns (preponderance of label in gut, liver, and kidney; minimal uptake in eyes, muscle, and CNS), and rapid tissue clearance. In repeat dose rat studies, some accumulation of label did occur, reached steady state in 14 days, and was eliminated from all tissues with half-lives of 4 to 8 days. Label will cross the placenta, and can be detected in fetal liver and gut at low levels, and is excreted in milk. Extensive fecal elimination of intravenously administered label in both rats and baboon showed that biliary excretion was a major route of elimination which, along with the kidney, accounted for the extensive clearing of systemic radioactivity within 48 hr. of dosing.

Because this pro-drug is rapidly and extensively metabolized, its effect on liver mixed function oxidase and interaction with modulators of this system was characterized. Microsomes prepared from animal and human liver homogenates hydrolyzed clopidogrel. Microsomes also oxidized its thiophene ring if NADPH needed for a functional P450 system was present. Livers excised from baboons exposed for 3 months to supra-therapeutic clopidogrel AUC values i.e., a minimum of 10 times that of treated patients - have up to 150% of the weight and total CYT P450 activity of control, and double its Cyp 3A activity. There was no appreciable modulation of liver enzymes at lower clopidogrel exposures in these baboons. This would be consistent with the Sponsor's observation that humans treated for 10 days with clopidogrel metabolized/cleared the P450 substrates antipyrine and 6- β hydroxy cortisol normally. Pretreatment of rats with agents known to modulate CYT 1A, however, markedly enhanced or even abolished anti-aggregating activity of clopidogrel. Since baboons were not tested to see if this interaction extended to primates, the possibility of a drug-clopidogrel interaction in humans cannot be dismissed *a priori*.

LABELING:

Under Carcinogenesis, Mutagenesis, Impairment of Fertility: Add to the third sentence: (52 times the recommended human dose on a mg/ M² basis).

Under Pregnancy: Replace the first sentence with: Reproduction studies performed in rats and rabbits at doses up to 500 and 300 mg/Kg per day , respectively (65 and 78 times the recommended daily human dose on a mg/ M² basis) revealed no evidence of impaired fertility or fetotoxicity due to clopidogrel.



Albert De Felice, Ph.D.

9/12/92

cc: NDA 20-839
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HFD-110/DRoeder

APPEARS THIS WAY
ON ORIGINAL

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