CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE for:

APPLICATION NUMBER: 018631/S030

TRADE NAME: Trental Tablets

GENERIC NAME: Pentoxifylline

SPONSOR: Hoescht Marion Roussel

APPROVAL DATE: 04/29/97

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 18-631/S-030

APR 29 1997

Hoechst Marion Roussel
Attention: J. Michael Nicholas, Ph.D.
P.O. Box 9627
Kansas City, MO 64134-0627

Dear Dr. Nicholas:

Please refer to your April 3, 1997 supplemental new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Trental (pentoxifylline) Tablets.

The supplemental application provides for addition of the following text after the first sentence of the last paragraph of the **CLINICAL PHARMACOLOGY** section, **Pharmacokinetics and Metabolism** subsection of the labeling:

> Coadministration of Trental Tablets with meals resulted in an increase in mean C-max and AUC by about 28% and 13% for pentoxifylline, respectively. C-max for metabolite M^1 also increased by about 20%.

We have completed the review of this supplemental application and have concluded that adequate information has been presented to demonstrate that the drug is safe and effective for use as recommended in the final printed labeling included in the April 3, 1997 submission. Accordingly, the supplemental application is approved effective on the date of this letter.

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. Gary Buehler
Regulatory Health Project Manager
(301) 594-5332

Sincerely yours,

a l 4/29/97

Raymond J. Lipicky, M.D.
Director
Division of Cardio-Renal Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

cc:
Original NDA
HF-2/MedWatch (with draft/final labeling)
HFD-92 (with draft/final labeling)
HFD-110
HFD-40 (with draft/final labeling)
HFD-613 (with draft/final labeling)
HFD-735 (with draft/final labeling)
DISTRICT OFFICE
HFD-810/New Drug Chemistry Division Director
HFD-110/GBuehler/4/22/97;4/23/97
sb/4/22/97;4/28/97
R/D: DCunningham/4/24/97
RWolters/4/24/97
AParekh/4/24/97
NMorgenstern/4/25/97

Approval Date: 8/30/84

APPROVAL

4/29/97

Labeling: ORIGINAL
NDA No: 18-631 Rec'd. 4-4-9
Reviewed by:

APPROVED
APR 29 1997

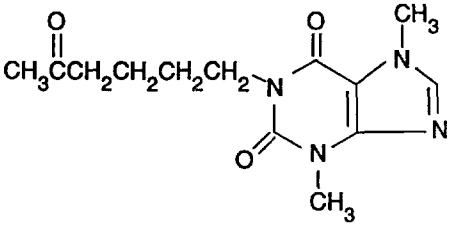
Prescribing Information as of April 1997

TRENTAL®
(pentoxifylline)*
Tablets, 400 mg

DESCRIPTION

TRENTAL® (pentoxifylline) tablets for oral administration contain 400 mg of the active drug and the following inactive ingredients: benzyl alcohol NF, D&C Red No. 27 Aluminum Lake or FD&C Red No. 3, hydroxypropyl methylcellulose USP, magnesium stearate NF, polyethylene glycol NF, povidone USP, talc USP, titanium dioxide USP, and other ingredients in a controlled-release formulation. TRENTAL is a tri-substituted xanthine derivative designated chemically as 1-(5-oxohexyl)-3, 7-dimethylxanthine that, unlike theophylline, is a hemorrheologic agent, i.e. an agent that affects blood viscosity. Pentoxifylline is soluble in water and ethanol, and sparingly soluble in toluene. The CAS Registry Number is 6493-05-6.

The chemical structure is:



CLINICAL PHARMACOLOGY

Mode of Action

Pentoxifylline and its metabolites improve the flow properties of blood by decreasing its viscosity. In patients with chronic peripheral arterial disease, this increases blood flow to the affected microcirculation and enhances tissue oxygenation. The precise mode of action of pentoxifylline and the sequence of events leading to clinical improvement are still to be defined. Pentoxifylline administration has been shown to produce dose-related hemorrheologic effects, lowering blood viscosity, and improving erythrocyte flexibility. Leukocyte properties of hemorrheologic importance have been modified in animal and *in vitro* human studies. Pentoxifylline has been shown to increase leukocyte deformability and to inhibit neutrophil adhesion and activation. Tissue oxygen levels have been shown to be significantly increased by therapeutic doses of pentoxifylline in patients with peripheral arterial disease.

Pharmacokinetics and Metabolism

After oral administration in aqueous solution pentoxifylline is almost completely absorbed. It undergoes a first-pass effect and the various metabolites appear in plasma very soon after dosing. Peak plasma levels of the parent compound and its metabolites are reached within 1 hour. The major metabolites are Metabolite I (1-[5-hydroxyhexyl]-3,7-dimethylxanthine) and Metabolite V (1-[3-carboxypropyl]-3,7-dimethylxanthine), and plasma levels of these metabolites are 5 and 8 times greater, respectively, than pentoxifylline.

Following oral administration of aqueous solutions containing 100 to 400 mg of pentoxifylline, the pharmacokinetics of the parent compound and Metabolite I are dose-related and not proportional (non-linear), with half-life and area under the blood-level time curve (AUC) increasing with dose. The elimination kinetics of Metabolite V are not dose-dependent. The apparent plasma half-life of pentoxifylline varies from 0.4 to 0.8 hours and the apparent plasma half-lives of its metabolites vary from 1 to 1.6 hours. There is no evidence of accumulation or enzyme induction (Cytochrome P450) following multiple oral doses.

Excretion is almost totally urinary; the main biotransformation product is Metabolite V. Essentially no parent drug is found in the urine. Despite large variations in plasma levels of parent compound and its metabolites, the urinary recovery of Metabolite V is consistent and shows dose proportionality. Less than 4% of the administered dose is recovered in feces. Food intake shortly before dosing delays absorption of an immediate-release dosage form but does not affect total absorption. The pharmacokinetics and metabolism of TRENTAL have not been studied in patients with renal and/or hepatic dysfunction, but AUC was increased and elimination rate decreased in an older population (60-68 years) compared to younger individuals (22-30 years).

After administration of the 400 mg controlled-release TRENTAL tablet, plasma levels of the parent compound and its metabolites reach their maximum within 2 to 4 hours and remain constant over an extended period of time. Coadministration of TRENTAL tablets with meals resulted in an increase in mean C_{max} and AUC by about 28% and 13% for pentoxifylline, respectively. C_{max} for metabolite M^1 also increased by about 20%. The controlled release of pentoxifylline from the tablet eliminates peaks and troughs in plasma levels for improved gastrointestinal tolerance.

INDICATIONS AND USAGE

TRENTAL is indicated for the treatment of patients with intermittent claudication on the basis of chronic occlusive arterial disease of the limbs. TRENTAL can improve function and symptoms but is not intended to replace more definitive therapy, such as surgical bypass, or removal of arterial obstructions when treating peripheral vascular disease.

CONTRAINDICATIONS

TRENTAL should not be used in patients with recent cerebral and/or retinal hemorrhage or in patients who have previously exhibited intolerance to this product or methylxanthines such as caffeine, theophylline, and theobromine.

PRECAUTIONS

General

Patients with chronic occlusive arterial disease of the limbs frequently show other manifestations of arteriosclerotic disease. TRENTAL has been used safely for treatment of peripheral arterial disease in patients with concurrent coronary artery and cerebrovascular diseases, but there have been occasional reports of angina, hypotension, and arrhythmia. Controlled trials do not show that TRENTAL causes such adverse effects more often than placebo, but, as it is a methylxanthine derivative, it is possible some individuals will experience such responses. Patients on Warfarin should have more frequent monitoring of prothrombin times, while patients with other risk factors complicated by hemorrhage (e.g., recent surgery, peptic ulceration, cerebral and/or retinal bleeding) should have periodic examinations for bleeding including, hematocrit and/or hemoglobin.

Drug Interactions

Although a causal relationship has not been established, there have been reports of bleeding and/or prolonged prothrombin time in patients treated with TRENTAL with and without anticoagulants or platelet aggregation inhibitors. Patients on Warfarin should have more frequent monitoring of prothrombin times, while patients with other risk factors complicated by hemorrhage (e.g., recent surgery, peptic ulceration) should have periodic examinations for bleeding including hematocrit and/or hemoglobin. Concomitant administration of TRENTAL and theophylline-containing drugs leads to increased theophylline levels and theophylline toxicity in some individuals. Such patients should be closely monitored for signs of toxicity and have their theophylline dosage adjusted as necessary. TRENTAL has been used concurrently with antihypertensive drugs, beta blockers, digitalis, diuretics, antidiabetic agents, and antiarrhythmics, without observed problems. Small decreases in blood pressure have been observed in some patients treated with TRENTAL; periodic systemic blood pressure monitoring is recommended for patients receiving concomitant antihypertensive therapy. If indicated, dosage of the antihypertensive agents should be reduced.

Carcinogenesis, Mutagenesis and Impairment of Fertility

Long-term studies of the carcinogenic potential of pentoxifylline were conducted in mice and rats by dietary administration of the drug at doses up to 450 mg/kg (approximately 19 times the maximum recommended human daily dose (MRHD) in both species when based on body weight; 1.5 times the MRHD in the mouse and 3.3 times the MRHD in the rat when based on body surface area). In mice, the drug was administered for 18 months, whereas in rats, the drug was administered for 18 months followed by an additional 6 months without drug exposure. In the rat study, there was a statistically significant increase in benign mammary fibroadenomas in females of the 450 mg/kg group. The relevance of this finding to human use is uncertain. Pentoxifylline was devoid of mutagenic activity in various strains of *Salmonella* (Ames test) and in cultured mammalian cells (unscheduled DNA synthesis test) when tested in the presence and absence of metabolic activation. It was also negative in the in vivo mouse micronucleus test.

Pregnancy

Category C. Teratogenicity studies have been performed in rats and

rabbits using oral doses up to 576 and 264 mg/kg, respectively. On a weight basis, these doses are 24 and 11 times the maximum recommended human daily dose (MRHD); on a body-surface-area basis, they are 4.2 and 3.5 times the MRHD. No evidence of fetal malformation was observed. Increased resorption was seen in rats of the 576 mg/kg group. There are no adequate and well controlled studies in pregnant women. TRENTAL (pentoxifylline) should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers

Pentoxifylline and its metabolites are excreted in human milk. Because of the potential for tumorigenicity shown for pentoxifylline in rats, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

ADVERSE REACTIONS

Clinical trials were conducted using either controlled-release TRENTAL tablets for up to 60 weeks or immediate-release TRENTAL capsules for up to 24 weeks. Dosage ranges in the tablet studies were 400 mg bid to tid and in the capsule studies, 200-400 mg tid. The table summarizes the incidence (in percent) of adverse reactions considered drug related, as well as the numbers of patients who received controlled-release TRENTAL tablets, immediate-release TRENTAL capsules, or the corresponding placebos. The incidence of adverse reactions was higher in the capsule studies (where dose related increases were seen in digestive and nervous system side effects) than in the tablet studies. Studies with the capsule include domestic experience, whereas studies with the controlled-release tablets were conducted outside the U.S. The table indicates that in the tablet studies few patients discontinued because of adverse effects.

INCIDENCE (%) OF SIDE EFFECTS

	Controlled-Release Tablets		Immediate-Release Capsules	
	Commercially Available		Used only for Controlled Clinical Trials	
	TRENTAL	**Placebo**	**TRENTAL**	**Placebo**
(Numbers of Patients at Risk)	(321)	(128)	(177)	(138)
Discontinued for Side Effect	3.1	0	9.6	7.2
CARDIOVASCULAR SYSTEM				
Angina/Chest Pain	0.3	-	1.1	2.2
Arrhythmia/Palpitation	-	-	1.7	0.7
Flushing	-	-	2.3	0.7
DIGESTIVE SYSTEM				
Abdominal Discomfort	-	-	4.0	1.4
Belching/Flatus/Bloating	0.6	-	9.0	3.6
Diarrhea	-	-	3.4	2.9
Dyspepsia	2.8	4.7	9.6	2.9
Nausea	2.2	0.8	28.8	8.7
Vomiting	1.2	-	4.5	0.7
NERVOUS SYSTEM				
Agitation/Nervousness	-	-	1.7	0.7
Dizziness	1.9	3.1	11.9	4.3
Drowsiness	-	-	1.1	5.8
Headache	1.2	1.6	6.2	5.8
Insomnia	-	-	2.3	2.2
Tremor	0.3	0.8	-	-
Blurred Vision	-	-	2.3	1.4

TRENTAL has been marketed in Europe and elsewhere since 1972. In addition to the above symptoms, the following have been reported spontaneously since marketing or occurred in other clinical trials with an incidence of less than 1%; the causal relationship was uncertain:

Cardiovascular - dyspnea, edema, hypotension.
Digestive - anorexia, cholecystitis, constipation, dry mouth/thirst.
Nervous - anxiety, confusion, depression, seizures.
Respiratory - epistaxis, flu-like symptoms, laryngitis, nasal congestion.
Skin and Appendages - brittle fingernails, pruritus, rash, urticaria.

angioedema.
Special Senses - blurred vision, conjunctivitis, earache, scotoma.
Miscellaneous - bad taste, excessive salivation, leukopenia, malaise, sore throat/swollen neck glands, weight change.

A few rare events have been reported spontaneously worldwide since marketing in 1972. Although they occurred under circumstances in which a causal relationship with pentoxifylline could not be established, they are listed to serve as information for physicians. "Cardiovascular – angina, arrhythmia, tachycardia, anaphylactoid reactions." Digestive – hepatitis, jaundice, increased liver enzymes; and Hemic and Lymphatic – decreased serum fibrinogen, pancytopenia, aplastic anemia, leukemia, purpura, thrombocytopenia.

OVERDOSAGE

Overdosage with TRENTAL has been reported in pediatric patients and adults. Symptoms appear to be dose related. A report from a poison control center on 44 patients taking overdoses of enteric-coated pentoxifylline tablets noted that symptoms usually occurred 4-5 hours after ingestion and lasted about 12 hours. The highest amount ingested was 80 mg/kg; flushing, hypotension, convulsions, somnolence, loss of consciousness, fever, and agitation occurred. All patients recovered. In addition to symptomatic treatment and gastric lavage, special attention must be given to supporting respiration, maintaining systemic blood pressure, and controlling convulsions. Activated charcoal has been used to absorb pentoxifylline in patients who have overdosed.

DOSAGE AND ADMINISTRATION

The usual dosage of TRENTAL in controlled-release tablet form is one tablet (400 mg) three times a day with meals.
While the effect of TRENTAL may be seen within 2 to 4 weeks, it is recommended that treatment be continued for at least 8 weeks. Efficacy has been demonstrated in double-blind clinical studies of 6 months duration.
Digestive and central nervous system side effects are dose related. If patients develop these effects it is recommended that the dosage be lowered to one tablet twice a day (800 mg/day). If side effects persist at this lower dosage, the administration of TRENTAL should be discontinued.

HOW SUPPLIED

TRENTAL is available for oral administration as 400 mg pink film-coated oblong tablets imprinted Trental®; supplied in bottles of 100 (NDC 0039-0078-10), Bulk Pack 5000 (NDC 0039-0078-80, and Unit Dose Packs of 100 (NDC 0039-0078-11).

Store between 59 and 86° F (15 and 30° C).

Dispense in well-closed, light-resistant containers.

Protect blisters from light.

Prescribing Information as of April 1997

*US Patents 3,737,433 & 4,189,469
US Patent 3,737,433 patent term has been extended.

Hoechst-Roussel Pharmaceuticals
Division of Hoechst Marion Roussel, Inc.
Kansas City, MO 64137 USA

trep0497

4/6.1

APR 8 1997

	1. ORGANIZATION HFD-110	2. NDA Number 18-631
3. Name and Address of Applicant (City & State) Hoechst Marion Roussel, Inc. Route 202-206 P.O. Box 6800 Bridgewater, NJ 088		4. Supplement(s) Number(s) Date(s) S-030 4/3/97 (LR)
5. Drug Name Trental	6. Nonproprietary Name Pentoxifylline	8. Amendments & Other (reports, etc) - Dates
7. Supplement Provides For: Response to the letter of March 12, 1997 - labeling changes.		
9. Pharmacological Category Hemorrheologic agent	10. How Dispensed ☒ Rx ☐ OTC	11. Related IND(s)/ NDA(s)/DMF(s)
12. Dosage Form(s) Tablets, CR, Film coated	13. Potency(ies) 400 mg	
14. Chemical Name and Structure		15. Records/Reports Current ☐ Yes ☐ No Reviewed ☐ Yes ☐ No

16. Comments:

CHANGES BEING EFFECTED SUPPLEMENT

Prescribing information as of April 1997 is satisfactory for DESCRIPTION and HOW SUPPLIED sections.

17. Conclusions and Recommendations:

Satisfactory for DESCRIPTION and HOW SUPPLIED sections.

18. REVIEWER		
Name Danute G. Cunningham	Signature Danute G. Cunningham	Date Completed April 8, 1997

Distribution:

☒ Original Jacket ☐ Reviewer ☐ Division File ☐ CSO ☐ District

18631S30.SUP

4/8/97

APR 29 1997

CSO REVIEW OF LABELING

NDA 18-631/S-030 Trental (pentoxifylline) TAblets

Sponsor: Hoechst Marion Roussel
10256 Marion Park Drive
Kansas City, MO 64134-0627

Date of Submission: April 3, 1997

BACKGROUND

A food-effect study was performed by Hoechst Marion Roussel and submitted to their annual report on December 3, 1996. Because of an issue relating to a generic application for pentoxifylline, the Office of Generic Drugs requested that this study be reviewed. The study was reviewed by Dr. Parekh (date of review 2/24/97), and labeling recommendations were made. On March 12, 1997, a supplement request letter was sent to Hoechst Marion Roussel. This letter requested that a statement regarding the effect of food administration on the absorption of Trental be added to the labeling. The text and placement were also specified in the letter. The text employed by the firm and it location in the labeling were exactly as specified in the supplement request letter.

REVIEW

The supplemental application was submitted as "Changes Being Effected" and provided for the addition of the following after the first sentence of the last paragraph of the **CLINICAL PHARMACOLOGY** section, **Pharmacokinetics and Metabolism** subsection of the labeling:

> Coadministration of Trental tablets with meals resulted in an increase in mean C-max and AUC by about 28% and 13% for pentoxifylline, respectively. C-max for metabolite M-1 also increased by about 20%.

The labeling was reviewed and found to be acceptable. An approval letter will be drafted for Dr. Lipicky's signature.

Gary Buehler
RHPM

Orig NDA
HFD-110
HFD-110 GBuehler
HFD-110 SBenton
HF-2/MedWatch