

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-350

MEDICAL REVIEW

MEDICAL TEAM LEADER'S MEMO OF NDA SUBMISSION

NDA #: 21-350

Sponsor: RTP Pharma, Inc.

Drug Product: fenofibrate (IDD-P)

Dosage Strength: 50 and 160 mg tablets

Indications: Fredrickson Types IV and V dyslipidemia

BACKGROUND

Fenofibrate, a fibric acid derivative, was approved by the FDA in 1993 for the treatment of hypertriglyceridemia due to increases in very low-density lipoprotein cholesterol (VLDL-C) alone or in conjunction with increased chylomicrons (Fredrickson Types IV and V) based on studies using the standard formulation of fenofibrate 100 mg administered three times daily. Although marketed widely throughout Europe and Canada for this indication, this formulation was never marketed in the United States. In 1998, a supplemental new drug application (NDA 19-304/S001) was approved, establishing bioequivalence between the standard formulation of 100 mg to a micronized capsule formulation of 67 mg. The micronized formulation was marketed in the U.S. under the tradename, Tricor® (Abbott Laboratories). This was followed by the approval of another supplemental NDA (NDA 19-304/S003) establishing bioequivalence between the daily dosing of micronized formulations of 200 mg to three 67 mg capsules. Tricor was approved in a subsequent application for the treatment of elevated low-density lipoprotein cholesterol (LDL-C), total-C, triglycerides, and apolipoprotein B in adults with primary hypercholesterolemia or mixed dyslipidemia (Fredrickson Types IIa and IIb) based on the review of the integrated efficacy data from 4 placebo-controlled trials involving daily doses of fenofibrate 300 mg (standard formulation) or the bioequivalent 200 mg micronized formulation (Tricor) of fenofibrate (NDA 19-304/S005). In July 2001, a more bioavailable tablet formulation of Tricor was approved at 54 and 160 mg dosage strengths. These tablets were equivalent under fed conditions to the 67 and 200 mg capsules, respectively.

Fenofibrate at daily doses equivalent to 160 mg Tricor can achieve mean reductions in TG levels of -46 to -55% in patients with Types IV/V dyslipidemia with greater reductions achieved in those individuals whose baseline TGs levels are higher.¹ Tricor should be taken with meals as the absorption of fenofibrate in Tricor formulations is increased by 35% in the fed state (w/ low-fat meal) compared to fasting conditions.

RTP Pharma Incorporated has submitted a new drug application (NDA) under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for a new fenofibrate formulation, IDD-P (insoluble drug delivery microparticle) fenofibrate. The proposed dosage strengths for IDD-P fenofibrate are 50 and 160 mg. The sponsor asserts that the different formulation of this product allows for increased bioavailability relative to the reference listed product, Tricor micronized capsules, 67 and 200 mg strengths (*note: Tricor 54 and 160 mg tablets had not been approved during clinical development of IDD-P fenofibrate*). Furthermore, the sponsor purports that the absorption of IDD-P fenofibrate is not extensively affected by food and therefore, administration of this formulation can be with or without food.

¹ from Tricor® package insert based on studies published in *Clinical Therapeutics*, 11, pp 69-83, 1989.

The increased bioavailability of IDD-P fenofibrate may be an advantage over Tricor micronized capsules as less amount of active ingredient is required to achieve bioequivalent plasma levels for the two products. However, with the approval of Tricor 54 and 160 mg tablets which are bioequivalent to the 67 and 200 mg capsules, respectively, under fed states, the availability of IDD-P fenofibrate at 50 and 160 mg does not offer a significant advantage to the currently marketed fenofibrate product. The demonstration of no food effect by IDD-P fenofibrate will, however, be an advantage over Tricor fenofibrate formulations as this product can be taken regardless of meals.

The studies conducted in support of approval for IDD-P fenofibrate include only food effect studies, comparative bioavailability trials, and dose equivalence studies reviewed by the Office of Clinical Pharmacology and Biopharmaceutics. No clinical studies for safety and efficacy were conducted with this product as the approval of this product relies on the bridging studies of IDD-P fenofibrate to Tricor micronized capsules and the reliance on the safety and efficacy findings of Tricor®. The approval of IDD-P fenofibrate will also be limited by any patent and/or exclusivity remaining for Tricor®. A paragraph IV certification letter was submitted with this NDA stating that this product had no infringement on Tricor's patent. However, this product can only be approved for Type IV and V dyslipidemia as the treatment for hypercholesterolemia (Types IIa and IIb) is still under exclusivity protection until April 24, 2003.

DESCRIPTION OF STUDIES SUBMITTED

Food Effect Studies

A pilot (FEN100-C03 Part 1) and pivotal (FEN100-C05) food effect study was conducted by RTP-Pharma Inc. These are summarized as follows:

FEN100-C03 Part 1: Pilot study of the food effect on the bioavailability of IDD-P fenofibrate in healthy subjects. This study was conducted under fasting vs. high-fat fed conditions as a 2-period crossover study.

FEN100-C05: Comparative bioavailability of IDD-P fenofibrate tablet 160 mg under fasting, low-fat, fed and high-fat fed conditions in healthy subjects. This was a 3-period crossover study of IDD-P fenofibrate tablet 160 mg evaluating the effect of fasting, low-fat fed conditions, and high-fat fed conditions on BA.

Comparative Bioavailability Studies

A pilot (FEN100-C03 Part 2) and 2 pivotal (FEN100-C06 and FEN100-C07) comparative bioavailability studies were conducted by RTP-Pharma Inc. These are summarized as follows:

FEN100-C03 Part 2: Pilot study of the food effect on the bioavailability of IDD-P fenofibrate in healthy subjects and comparison with micronized fenofibrate under low-fat fed conditions.

FEN100-C06: Comparative bioavailability of IDD-P fenofibrate tablet 160 mg with micronized fenofibrate capsule 200 mg in healthy fed subjects. This was a 2-period crossover study designed to establish comparative BA of IDD-P fenofibrate tablet 160 mg and Tricor capsule 200 mg.

CONCLUSIONS

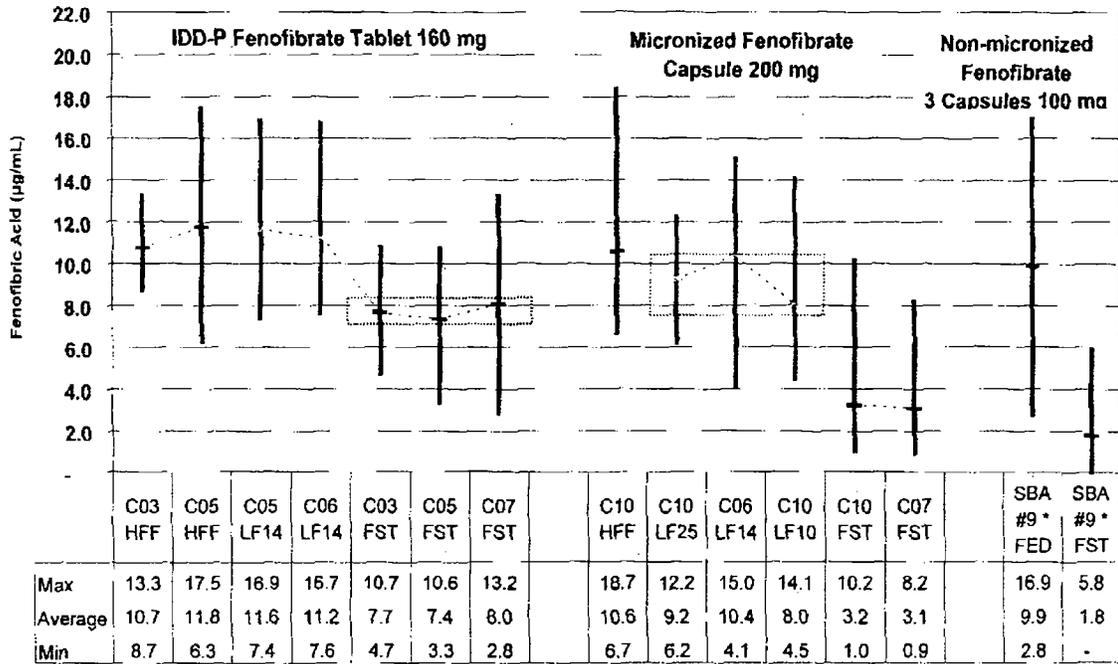
As a 505(b)(2) submission the sponsor was required to demonstrate relative bioequivalence to another FDA-approved product (reference listed product) such that the efficacy and safety data established with the reference listed product can be relied upon without requiring the 505(b)(2) applicant to conduct additional clinical studies. Approval of this 505(b)(2) product is also limited by patent and exclusivity remaining on the reference listed product.

For this submission, RTP-Pharma conducted only biopharm studies to bridge its product to the reference listed product, Tricor micronized capsules 200 mg. Based on Dr. Qiu's review from the Office of Clinical Pharmacology and Biopharmaceutics, IDD-P fenofibrate 160 mg tablets administered under low-fat fed conditions does result in comparable fenofibrate blood levels to that of Tricor 200 mg capsules thereby establishing comparable bioavailability between the two products. Since there was dosage form equivalence established for three 50 mg IDD-P fenofibrate tablets to the 160 mg dose, a biowaiver was granted and a relative BE study was not required for IDD-P fenofibrate 50 mg to Tricor 67 mg capsules. Based on these results this product can be approved without conducting clinical trials to establish safety and efficacy.

This application also proposes that IDD-P fenofibrate be taken with or without meals as the food effect studies did not demonstrate significant effects of food on drug absorption. Although the AUC data for IDD-P fenofibrate do fall within the confidence intervals of 80 to 125% in the food effect studies, there is still a food effect as evidenced by a 60% increase in C_{max} under fed conditions relative to fasting conditions. The effect of this difference in C_{max} is unlikely to affect the safety of this product as the higher C_{max} values under fed states are within the range of values observed with the reference listed product. Similarly, the lower C_{max} of IDD-P fenofibrate under fasting conditions is unlikely to affect efficacy as the values are similar to those observed with the reference listed product under fed states. The following diagram obtained provided by the sponsor compares, across multiple pK studies, the range of fenofibric acid levels detected with IDD-P fenofibrate, micronized fenofibrate 200 mg capsules, and non-micronized fenofibrate three-100 mg capsules.

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Figure 1: Range (min-max) and average rate of absorption (C_{max}) with IDD-P, micronized and nonmicronized fenofibrate, under various fed or fasting conditions (HFF: High-fat fed, LF: Low-fat fed [25, 14, 10 gram of fat in test meal], FST: Fasting)



* for Study 9, SBA #19,304 Min & Max are approximations calculated as average +/- 1.98 standard deviation (2.04 µg/mL).

Although this diagram shows overlap between drug concentration levels of IDD-P fenofibrate under fed and fasted states and Tricor under fed states, there are no clinical data to claim that efficacy of IDD-P fenofibrate will remain the same if the product is taken with or without meals. IDD-P fenofibrate has demonstrated comparable bioavailability to Tricor capsules 200 mg under fed conditions; however, the efficacy of Tricor was not established with the micronized capsule formulation but rather with the nonmicronized formulation administered as 100 mg tid. These efficacy data were from a study in which the nonmicronized formulation was administered with meals. Indeed, no clinical studies have been conducted with any formulation of Tricor administered with and without meals to examine differences in efficacy. To the extent that IDD-P fenofibrate has no comparative bioavailability data to the nonmicronized formulation of fenofibrate nor does it have data to support similar efficacy of its product under fed and fasted states, the label for IDD-P fenofibrate should not have a section under DOSAGE and ADMINISTRATION stating that the drug could be taken regardless of meals thereby implying no difference in clinical efficacy.

In order for the sponsor to make a claim under the DOSAGE AND ADMINISTRATION section that IDD-P fenofibrate can be taken regardless of meals, clinical evidence of similar efficacy will need to be demonstrated for this product.

RECOMMENDATIONS

Labeling Recommendations

The labeling recommendations across all disciplines reviewing this application were submitted to the sponsor on March 13, 2002. These changes were subsequently discussed during a teleconference on March 18, 2002 and most of the proposed changes were accepted by the sponsor with exception for 2 significant areas in the label. In a counter-proposal submitted to the FDA on March 25, 2002 the sponsor recommends the following changes (highlighted sections) under CLINICAL PHARMACOLOGY: Pharmacokinetics; Effect on Food Absorption and DOSAGE AND ADMINISTRATION sections:

CLINICAL PHARMACOLOGY; Pharmacokinetic subsection

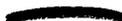
Effect of Food on Absorption

Fenofibrate is insoluble in water and its bioavailability is optimized when taken with meals.



DOSAGE AND ADMINISTRATION

Patients should be placed on an appropriate lipid-lowering diet before receiving IDD-P™ fenofibrate and should continue on this diet during treatment with 

For adult patients with hypertriglyceridemia, the initial dose is 50 mg to 160 mg 

Dosage should be individualized according to patient response, and should be adjusted if necessary following repeat lipid determinations at 4 to 8 week intervals.

The maximum dose is 160 mg per day.

Treatment with  should be initiated at a dose of 50 mg/day in patients with impaired renal function, and increased only after evaluation of the effects on renal function and lipid levels at this dose.

In the elderly, the initial dose should likewise be limited to 50 mg/day.

Lipid levels should be monitored periodically and consideration should be given to reducing the dosage of  if lipid levels fall significantly below the targeted range.



[REDACTED]

The DOSAGE and ADMINISTRATION section should state the following:
For adult patients with hypertriglyceridemia, the initial dose is 50 mg to 160 mg
once daily.

[REDACTED] Dosage should be
individualized according to patient response, and should be adjusted if necessary
following repeat lipid determinations at 4 to 8 week intervals.

[REDACTED]

Recommendation on Approvability of Application

Given the deficiencies outlined in the Chemistry review, this application is approvable at this time. However, comments on labeling discussed in the preceding section should be conveyed to the sponsor as part of the action letter.

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/s/

Mary Parks
4/3/02 10:21:21 AM
MEDICAL OFFICER

David Orloff
4/4/02 03:16:51 PM
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MEDICAL OFFICER REVIEW

Division of Metabolic and Endocrine Drug Products (HFD-510)

Application #: 21-350	Application Type: NDA
Sponsor: RTP Pharma Inc. ■	Proprietary Name: IDD-P tm fenofibrate
	USAN Name: fenofibrate
Investigator: Multiple (Not named)	
Category: Lipid Lowering Drug	Route of Administration: oral
Reviewer: S.W. Shen, M.D.	Review Date 3/12/02:

SUBMISSIONS REVIEWED IN THIS DOCUMENT

Document Date	CDER Stamp Date	Submission Type	Comments
06/22/01	06/25/01	3S	

OUTSTANDING ISSUES:

None

RECOMMENDED REGULATORY ACTION:

: Approvable

SIGNATURES:	Medical Reviewer:	Date 3/12/02
	Medical Team Leader	Date

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List of Abbreviations used in this review:

AE	Adverse Events
Alk. Phos.	Alkaline phosphatase
ALT	Alanine aminotransferase (formerly SGPT)
AST	Aspartate aminotransferase (formerly SGOT)
Apo A1	Apolipoprotein A1
Apo B	Apolipoprotein B
CHD	Coronary Artery Disease
CK	Creatine kinase
D/C	Discontinued
D/T	Due To
GI	Gastrointestinal
GRAS	Generally Regarded As Safe
Hb	Hemoglobin
HDL-C	High-density lipoprotein-cholesterol
HLP	Hyperlipoproteinemia
LDL-C	Low-density lipoprotein-cholesterol
Lp (a)	Lipoprotein a
MCE	Major Coronary Event
MI	Myocardial Infarction
PTS	Patients
TOTAL-C	Total-cholesterol
TSH	Thyroid stimulating hormone
TG	Triglycerides
VLDL-C	Very-low-density-lipoprotein-cholesterol
ULN	Upper limit of normal
WBC	White Blood Count

The Executive Summary of the Primary Clinical Review

1. RECOMMENDATIONS

IDD-P™ fenofibrate is approvable as adjunctive therapy to diet for treatment of adult patients with hypertriglyceridemia (Fredrickson Types IV and V hyperlipidemia).

Based on PK/Bioavailability studies, it is anticipated that therapy with IDD-P™ fenofibrate will:

- a. Reduce TC, TG and VLDL.
- b. The effect of fenofibrate on blood HDL-C levels are variable, but in most studies an increase in HDL-C will be observed.
- c. LDL-C will increase during therapy.

No clinical efficacy and safety trials in patients with hyperlipidemia had been performed with IDD-P™ fenofibrate. Since it has comparable bioavailability (equivalent in extent and rate of absorption under low-fat fed state), efficacy and safety for the new IDD-P™ fenofibrate formulation is expected to be the same as for the approved micronized fenofibrate formulation.

It should be noted that 160 mg of IDD-P™ fenofibrate is bioequivalent to 200 mg capsule of Tricor fenofibrate, the RLD.

2. SUMMARY OF CLINICAL FINDINGS

2.1. Brief Overview of Clinical Program

No clinical trials of safety and efficacy were performed. There were 7 RTP Pharma-Sponsored Comparative PK/Bioavailability Studies on IDD-P™ fenofibrate. One hundred thirty-eight healthy subjects were exposed to either single-dose of 50 mg or 160 mg IDD-P™ fenofibrate in these studies.

2.2. Efficacy

In Type IV patients, from the published European clinical trials, in the comparative studies which were conducted with fenofibrate in comparison with placebo or active control, TG ↓ 53%; TC ↓ 14%; LDL-C ↑ 6% (↓9%-↑45%); and HDL-C ↑ 14-15%.

From the US placebo-controlled double-blind studies, 100 mg of Tricor fenofibrate TID reduced TG by 46-55%, Total-C by 9-14%; increased HDL-C by 20-23% and increased LDL-C by 15-45 %.

On the basis of demonstrated bioequivalence to RLD (Tricor fenofibrate) under low-fat fed state, it is anticipated that therapy with 160 mg of IDD-P™ fenofibrate will result in similar efficacy results as 200 mg capsule of Tricor.

2.3 Safety

- 1). Since it was marketed in Europe in 1975, the sponsor estimates that more than ██████ patients have been administered fenofibrate. From published European clinical trials, the following Adverse Events have been reported as probably related to fenofibrate treatment: hepatitis, cholelithiasis, hepatomegaly, myalgia, myasthenia, rhabdomyolysis, photosensitivity, eczema and allergic pulmonary alveolitis.
- 2). The incidence of AEs ranged from 6% in short-term studies to 10% in long-term studies. In long-term studies, gastrointestinal effects (mild constipation and diarrhea) occurred most frequently (5%), with headache and muscle pain in 1% of the patients, neurologic 1.9%, dermatological 0.3%.
- 3). Adverse Events specific for IDD-P™ fenofibrate are difficult to evaluate since only single-dose PK/BE studies were performed.

2.4 Dosing, Regimen, and Administration

For adult patients, the initial dose is 50 mg to 160 mg per day and the maximum dose is 160 mg per day.

2.5 Drug-Drug Interactions

No drug-drug interaction studies had been performed with IDD-P™ fenofibrate. However, fenofibrate had been shown to interact with the following non-lipid lowering drugs: anticoagulants, estrogens, cyclosporine, Doneperil, Ketoprofen, sulfonylureas and insulin. In addition, fenofibrate had been shown to interact with other lipid-lowering agents: statins and bile acid sequestrants.

2.6 Special Populations

No clinical trials had been performed to address the issues of gender, racial, ethnic differences with IDD-P™ fenofibrate. No gender differences had been reported with fenofibrate in general. Similarly no racial differences had been recorded. No clinical studies had been conducted in patients with hepatic impairment. In patients with history of hepatic disorder, fenofibrate should either not be used or used with extreme caution. In

patients with severe renal insufficiency, the dosage should be adjusted downward.

In type 2 diabetes, use of fenofibrate had not resulted in changes in glucose tolerance or adverse events different from those seen as the non-diabetic patients.

Clinical trials had been conducted only in adult patients. The effects in the elderly had not been fully studied although very limited data suggested there were minor changes in PK parameters. Pediatric Waiver had been requested and granted.

Fenofibrate had not been studied in pregnant women and it is not known whether or not fenofibrate passes into human breast milk.

Clinical Review

1. Introduction and Background:

1.1. Established and Proposed Trade Name of Drug, Drug Class, Sponsor's Proposed Indications(s). Dose, Regimens, Age Groups

- a. IDD-PTM fenofibrate is to be replaced by the approved Proprietary/Trade Name. IDD-PTM fenofibrate is a new formulation of the U.S-approved reference listed drug, Tricor, and submitted as a 505(b)(2) NDA.
- b. Drug Class: Lipid lowering.
- c. Sponsor's Proposed Indication: IDD-PTM fenofibrate is indicated as adjunctive therapy for treatment of adult patients with hypertriglyceridemia (Fredrickson Types IV and V hyperlipidemia).
- d. For adult patients, the initial dose is 50 mg to 160 mg per day. Dosage should be individualized and adjusted at 4 to 8 week intervals according to patient response.

1.2 State of Armamentarium for Indications (s):

Elevated levels of total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), triglycerides (TG), and decreased level of high-density lipoprotein cholesterol (HDL-C), are known risk factors for atherosclerotic vascular disease. Clinical trials have demonstrated the beneficial effects on cardiovascular mortality and morbidity by modifying these risk factors. However, the independent effect of raising HDL-C or of lowering TG had not been demonstrated.

Fenofibric acid, the active metabolite of fenofibrate, has been shown to decrease plasma levels of TC and TG in healthy subjects and in patients with hyperlipidemia. The major pharmacological effects are thought to be due to the enhanced catabolism of very-low-density lipoprotein (VLDL). Hepatic synthesis of TG may also be decreased. Thus, plasma TG and VLDL-TG are greatly lowered.

1.3. Important Milestones in Product Development

Fenofibrate was first approved in France in 1975 and has since been approved in over 80 countries worldwide (including US, Canada, and countries in Europe, Africa, Asia, Caribbean, Central America, and south America). Fenofibrate has been in clinical use for more than 25 years.

The IDD-P™ fenofibrate formulation has not been marketed or withdrawn from investigation in any country.

Pre-IND meeting between the Agency and RTP Pharma on 2/10/2000.

Pre-IND Biopharmaceutics' Follow-up Teleconference on 8/14/2000.

NDA Filing Meeting on 8/9/2001 in which Biopharmaceutics recommended that the sponsor conduct either a bioequivalence study to compare the 50 mg IDD-P™ fenofibrate with the 67 mg Tricor capsule or a dosage form equivalence study to compare one 160 mg tablet with three of the 50 mg tablets.

2. Significant Findings from Chemistry, Animal Pharmacology and Toxicology:

Each IDD-P™ tablet contains 50 mg or 160 mg of microparticle fenofibrate. The chemical name for fenofibrate is 2-[4-(4-chlorobenzoyl)phenoxy]-2-methylpropanoic acid, 1-methyl ester.

Each tablet also contains egg lecithin, monobasic sodium phosphate, magnesium stearate, and colloidal dioxide. IDD-P™ fenofibrate uses the proprietary technology to increase drug absorption. However, it does not “decrease the effects of food on absorption” as the sponsor claims..

According to Pharmacology/Toxicology Review, these ingredients are GRAS (in particular, egg lecithins are of no safety concern).

For details, please see Chemistry and Pharmacology/Toxicology Reviews.

3. Human Pharmacokinetics and Pharmacodynamics

Please see Pharmacology/Biopharmacology Reviews for detailed evaluation of PK parameters, and comparative bioavailability of IDD-P™ fenofibrate tablets. No PD studies were performed.

The PK/BE studies were the “bridging studies” between RLD Tricor fenofibrate and IDD-P™. The efficacy and safety of IDD-P™ are based on the demonstrated bioequivalence of the two formulations. Of particular importance is the bioequivalence between 160 mg of IDD-P™ fenofibrate tablets and Tricor 200-mg capsule under low-fat fed condition since in clinical use patients will be on low-fat diet. In addition, the lack of food effect had not been demonstrated. IDD-P™ fenofibrate should be taken with meals to optimize its effect.

4. Description of Clinical Data and Sources:

4.1 Sources of Clinical Data

This NDA submission contained product/literature information on nonmicronized fenofibrate and micronized Tricor fenofibrate. It also contained data from RTP Pharma sponsored studies in PK/BE studies on IDD-P™ fenofibrate..

4.2. Overview of Clinical Trials.

No clinical safety or efficacy trials in patients with hyperlipidemia have been performed with IDD-P™ fenofibrate.

4.3. Postmarketing Experience.

No postmarketing data were formally submitted in support of this NDA.

4.4 Literature Review

A total of 74 references of published European clinical trials on fenofibrate were submitted and selectively reviewed.

5. Clinical Review Methods

5.1. Describe How Review was Conducted

No clinical trials of the safety and efficacy were conducted with IDD-P™ fenofibrate. Literature review was therefore largely relied upon to support safety and efficacy. However, the sponsor did perform and submitted 7 PK/BE studies, which were reviewed to supplement the literature review.

5.2 Overview of Materials Consulted in Review

According to the sponsor, there are 52 noncomparative studies with >3000 patients and 25 comparative studies with >1000 patients exposed to fenofibrate. Individual studies were not reviewed for the following reasons: (1). Most of the studies were performed on Types IIa/IIb patients not Types IV/V. Therefore, only those studies including Types IV/V patients were reviewed; (2). Some of the studies had been submitted and reviewed by the Agency to support previous Tricor NDAs.

The data comprised of three sources: **1.** Efficacy and safety data from published European clinical trials of fenofibrate in patients with Types II and IV; **2.** Efficacy and safety data from US Placebo-controlled Studies (RLD--Tricor); **3.** The PK parameters obtained from the PK/BE studies on IDD-P™ fenofibrate and the relevant safety data.

5.3 Overview of Methods Used to Evaluate Data Quality and Integrity

No methods were used to attempt to evaluate the quality and integrity of the data other than to rely on the fact that the articles were published in reputable, referred journals.

5.4 Evaluation of Financial Disclosure

Of the investigators involved in the PK/BE studies, the sponsor stated:

1. “that have not entered into any financial arrangement with the listed clinical investigators whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2 (a).“
2. “that each listed clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in this product or significant equity in the sponsor as defined in 21 CFR 54.2(b) did not disclose any such interests.
3. “that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).”

Therefore, the submitted data are valid and not biased.

6. Integrated Summary of Efficacy

6.1. Brief Statement of Conclusions

The extent of absorption of IDD-P™ fenofibrate tablet and Tricor micronized fenofibrate capsule were bioequivalent when administered following low-fat meal. IDD-P™ fenofibrate tablet at 160 mg will result in comparable efficacy results as Tricor micronized fenofibrate capsule 200 mg.

6.2 General Approach to Review of the Efficacy of the Drug

Since no clinical trials were performed in patients with hyperlipidemia with IDD-PTM, the efficacy data comprised of three sources: 1. Efficacy data from published European clinical trials of fenofibrate in patients with Types II and IV ; 2. Efficacy data from US Placebo-controlled Studies (RLD--Tricor); 3. The PK parameters obtained from the PK/BE studies on IDD-PTM.

6.3. Detailed Review of Trials

6.3.1. Efficacy data from published European clinical trials of fenofibrate in patients with Types II and IV:

There were 13 relevant clinical trials which included patients with Type IV/V in addition to Type IIa/IIb. They were summarized by Guay (1) and shown in **Table 6.3. 1**):

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Table 6.3.1: Noncomparative Clinical Trials of Fenofibrate in Hyperlipidemia: (If responses were segregated by types, type-specific results are indicated)

Reference	N (breakdown by HLP Type)	Regimen	Study design	Results
Sirtori et al 1985	11 (n=6, IIa/IIb, n=5, IV)	Fenofibrate 100mg tid x 6 weeks and Fenofibrate SR 250 mg for 6 wks.	Random. Crossover	II: TG ↓ 41%, VLDL-C ↓ 39%, VLDL-TG ↓ 34%; LDL-C ↓ 12%; HDL-C ↑ 8% IV: TG ↓ 56%; VLDL-C ↓ 53%; LDL-C ↑ 23%; HDL-C ↑ 23%.
Sommariva et al, 1984	25 (n=16, IV, n=9, IIb)	Fenofibrate 100 mg tid for 4 mos.	Open Label	IIb: TG ↓ 36%; TC ↓ 17%; LDL-C ↓ 8%; IV: TG ↓ 50%, VLDL-C ↓ 47%, LDL-C ↑ 38%; HDL-C ↑ 16%
McPherson et al; 1996	13 with ↑ TG	Fenofibrate 100 mg tid for 12 wks.	Open Label	TC ↓ 19%, TG ↓ 48%, VLDL-C ↓ 70%, HDL-C ↑ 28%.
Rouffy et al 1976	191 (n=95, IIa, n=88, IIb; n=8, IV)	Fenofibrate 200-400 mg for 1-18 months.	Open Label	IIa/IIb: TC ↓ 24/25%; TG ↓ 26/40% IV: TL ↓ 25%; TG ↓ 52%
Wulfert et al, 1976	393 (n=152, IIa, n=189, IIb, n=52, IV)	Fenofibrate 200 –400 mg qd for 1-12 mos.	Open Label	IIa/IIb: TC ↓ 24/23%; TG ↓ 17/42% IV: TL ↓ 30%, TC ↓ 16%, TG ↓ 61%.
Lehtonen et al, 1981	33 (n=16, II2a; n=72 IIb; n=10, IV)	Fenofibrate 100 mg tid for 6 mos (dose increase in 52% pts).	Open Label	IIa/IIb: TC ↓ 20/28%; LDL-C ↓ 25/29% TG ↓ 34/67%, HDL-C ↑ 15%, IV: TG ↓ 46%; LDL-C ↓ 9%; HDL-C ↑ 12%
Komitzer et al, 1994	1334 (IIa/b IV).	Micro Fenofibrate 200 mg for 6 mos.	Open Label	Overall: TC ↓ 20%, TG ↓ 37%, LDL-C ↓ 20%, HDL-C ↑ 15%,
Franceschini et al, 1985	26 (n=13 IIa; n=13 IV)	Fenofibrate 100 mg tid for 9 wks.	Open Label	IIa: TC ↓ 20%; TG ↓ 44%, VLDL-C ↓ 51%, VLDL-TG ↓ 52%, LDL-C ↓ 13%, IV: TG ↓ 55%, HDL-C ↑ 14%; LDL-C ↑ 8%.
Harvengt et al 1980	19 (n=5, IIa; n=2, IIb; n=6, IV, n=6, V)	Fenofibrate 200mg qam+100mg qpm for 12 mos.	Open Label	Graphic data only; significant ↓ for TC, TG at end of therapy for types IIa, IV/V.
Avogaro et al 1983	28 (n=8, IIa; n=12, IIb; n=8, IV)	Fenofibrate 100mg tid for 2 mos.	Open Label	IIa: TC ↓ 25%, TG ↓ 22%; IV: TG ↓ 47%; HDL-C ↑ 23%
Daubresse, 1980	45 (n=14, IIa; n=15, IIb; n=16, IV)	Fenofibrate 300mg for 2-10 mos. (mean 5.4 mos)	Open Label	Pooled TC ↓ 25%, TG ↓ 48%
Otto et al 1996	23 (n=15, IIa, n=8, FHTG)	Fenofibrate 250mg for 8 weeks	Open Label	FHTG (familial hypertriglyceridemia): TC ↓ 3%, HDL-C ↑ 21%, LDL-C ↑ 36%, TG ↓ 42%, VLDL-C ↓ 41%, VLDL-TG ↓ 22%.
Luley et al 1980	41 (n=21 IIa; n=11, IIb; n=9, IV).	Fenofibrate 100 mg tid for 24 wks.	Open Label	IIa/IIb: TC ↓ 20/15%, TG ↓ 30/41%. IV: TC ↓ 20%; TG ↓ 48%

1. The effects of fenofibrate were different in Types IIa/IIb patients compared to Type IV patients:

- a. In Types IIa/IIb patients: TG ↓ (17-42%); TC ↓ (17-28%); LDL-C ↓ (8-29%); and HDL-C ↑ (8-15%).

- b. In Type IV patients, TG ↓ (48-61%); TC ↓ (3-20%); LDL-C (↓ 9%- ↑23%); and HDL-C ↑ (12-28%).

6.3.2. Efficacy Information from US Placebo-Controlled Studies:

Goldberg et al (8) reported a randomized, double-blind, placebo-controlled clinical trial in patients with types IV/V. After 6-12 weeks dietary stabilization and 4-week placebo period, 147 patients were assigned to Group A (baseline TG of 350-499 mg/dL) or to Group B (baseline TG of 500-1500 mg/dL). Patients in both groups were randomly assigned to treatment with placebo or fenofibrate 100 mg TID for 8 weeks. The details of the study had been submitted to support the Tricor NDA. The relevant efficacy results [reproduced from Goldberg et al (8)] are shown below:

Table 6.3.2: Mean (±SE) cholesterol & TG levels in group A and group B:

	Fenofibrate 100 mg TID			Placebo Treatment			P*	P**
	Baseline	Endpoint	Mean % change	Baseline	Endpoint	Mean % change		
Group A	N=27			N=28				
Total-C	251.8±5.3	227.4±6.7	↓9.1	255.1±8.4	261.4±9.2	↑2.8	<0.001	0.012
VLDL-C	92.1±6.8	45.8±4.5	↓44.7	99.3±8.5	99.3±10.0	↑5.8	<0.001	<0.001
LDL-C	128.4±7.1	136.7±5.3	↑14.5	119.6±8.4	128.5±7.5	↑12.9	0.8570	0.772
HDL-C	33.7±1.1	40.3±1.9	↑19.6	35.1±1.2	36.0±1.1	↑4.0	0.0014	0.004
Total TG	437.0±19.1	223.4±13.9	↓46.2	449.0±17.2	449.6±37.4	↓0.5	<0.001	<0.001
VLDL-TG	349.8±34.3	177.8±24.6	↓44.1	367.0±35.9	349.7±42.3	↑2.7	<0.001	<0.001
Group B	N=48			N=44				
Total-C	261.0±6.7	223.3±6.6	↓13.8	271.7±8.6	271.2±10.0	↑0.4	0.0001	<0.001
VLDL-C	126.2±7.0	53.7±3.4	↓49.4	136.6±9.5	141.5±11.4	↑11.0	0.0001	<0.001
LDL-C	103.3±6.8	131.0±6.0	↑45.0	100.3±7.1	90.3±6.8	↓4.2	0.0002	<0.001
HDL-C	29.6±1.3	36.0±1.8	↑22.9	27.4±0.9	28.4±1.0	↑5.0	0.0029	<0.001
Total TG	725.6±37.4	308.0±19.9	↓54.5	710.0±30.6	750.2±50.2	↑7.2	0.0001	<0.001
VLDL-TG	543.3±50.8	204.7±23.0	↓50.6	536.7±58.9	571.3±62.9	↑18.7	0.0001	<0.001

*= two-way analysis of variance

**=van Elteren's test (nonparametric test), a statistically significant difference in efficacy was determined to occur at P<0.05..

1. Group A had baseline TG values of 350-499 mg /dL while group B had TG in the range of 500-1500 mg/dL. The responses were similar in both groups as can be seen from above. In both groups, the endpoint values for TC, VLDL-C, HDL-C, TG and VLDL-TG were statistically significantly different between the treatment groups.

2. LDL-C levels increased in both groups (\uparrow by 14.5% in group A and by 45% in group B). Thus in group B, the difference of LDL-C was statistically significant between the treatment groups. According to Grundy et al (9), “Many patients with markedly elevated TGs have reduced LDL-C levels because of a derangement in the normal composition of LDL. This derangement produces a TG-rich, and cholesterol-depleted LDL. When TG are reduced with therapy, the composition of LDL normalizes; this can elevate LDL-C levels.” It is of interest to note that group B patients had higher percent of LDL-C increases (45%) compared to group A patients (14.5%) because of more derangement in their LDL composition due to greatly elevated TG.

6.3.3. Efficacy information from IDD-PTM fenofibrate studies:

No clinical efficacy trials were performed in patients with hyperlipidemia with IDD-PTM fenofibrate. Efficacy of IDD-PTM fenofibrate (160 mg) is based on the comparable bioavailability to marketed Tricor fenofibrate. Comparisons of blood levels in healthy subjects following single oral administration of 160 mg of IDD-PTM fenofibrate and 200 mg of micronized fenofibrate are shown below:

Table 6.3.3: PK parameters (mean \pm SD) following single oral dose of fenofibrate in normal subjects: (reproduced from sponsor’s submission):

Study #	Drug product	Dose	C _{max} mg/L	T _{max} h	T _{1/2} h	AUC _{0-t} mg.h/L	AUC _{0-∞} mg.h/L	K _{el} h ⁻¹	F _{rel} %
FEN 100-C06	IDD-P TM Fenofibrate	160 mg	11.2 \pm 2.5	3.2 \pm 1.1	15.7 \pm 5.5	137.6 \pm 48.2	140.1 \pm 49.4	0.05	94
	Micronized fenofibrate	200 mg	10.4 \pm 3.0	4.8 \pm 0.9	17.8 \pm 6.5	149.3 \pm 58.6	152.6 \pm 60.5	0.05	100

AUC_{0-t} = area under the concentration-time curve from time zero to time t.

AUC_{0-∞} = area under the plasma concentration curve from time zero to infinity.

K_{el} = elimination rate constant

F_{rel} = relative bioavailability

These PK parameters are comparable. (Please see Pharmacology & Biopharmaceutics Review for detailed analysis/evaluation). Dr. Wei Qiu, of the Clinical Pharmacology and Biopharmaceutics, concluded that:

“The rate and extent of absorption of IDD-PTM fenofibrate tablet 160 mg and micronized Tricor fenofibrate capsule 200 mg are equivalent when administered under low-fat fed conditions.”

“The rate and extent of absorption of IDD-P™ fenofibrate tablet 160 mg are higher than micronized Tricor fenofibrate capsule 200 mg under fasting condition.”

Please see Biopharmacology Review for further discussion regarding food effect.

6.3.4. Reviewer’s Evaluation and Conclusions on Efficacy:

- 1). Efficacy data from published European clinical trials of fenofibrate in patients with Types II and IV and efficacy data from US placebo-controlled studies (RLD--Tricor) can be summarized as follows:
 - a. All the fenofibrate formulations, nonmicronized and micronized, reduced TC, TG and VLDL.
 - b. The effects of fenofibrate on blood HDL-C levels were variable, but in most studies an increase in HDL-C was observed.
 - c. In patients with Type IIa/IIb hyperlipidemia, LDL-C was decreased during therapy.
 - d. In Type IV/V hyperlipidemia, LDL-C was increased. In the US placebo-controlled study, according to Goldberg et al, “the final mean of LDL-C level was below the 50th percentile value for women and men aged 45 to 74 years, some patients in group B had LDL-C levels above 160 mg/dL.” This is of concern, particularly in light of the most recent NCEP Treatment Guidelines. Even in patients with 0-1 risk factor, additional therapy maybe indicated.
- 2). Efficacy data according to Clinical Pharmacology and Biopharmaceutical review:
 - a. “The studies showed that the rate and extent of absorption of IDD-P™ fenofibrate 160 mg tablet and Tricor micronized fenofibrate 200 mg capsule were bioequivalent when administered following low-fat meal.”
 - b. IDD-P™ fenofibrate tablet at 160 mg will result in comparable efficacy results as Tricor micronized fenofibrate capsule 200 mg.

7. Integrated Review of Safety:

7.1. Brief Statement of Findings

The adverse events and laboratory abnormalities of fenofibrate and the RLD (Tricor) are well known from published literature and post marketing surveillance reports. The safety issues specific for IDD-P™ fenofibrate as documented from the PK/BA studies are difficult to evaluate because these were single-dose studies.

The overall safety profile of IDD-P™ fenofibrate is expected to be similar to that of the RLD, Tricor fenofibrate.

7.2. Materials Utilized in the Review

Since no clinical trials were performed in patients with hyperlipidemia with IDD-P™, the safety data comprised of three sources: **1.** adverse events data from published European clinical trials of fenofibrate in patients with Types II and IV ; **2.** Safety information from US Placebo-controlled Studies (RLD—Tricor fenofibrate); **3.** PK/BA studies performed with IDD-P™ fenofibrate by the sponsor.

7.3. Description of Patient Exposure

According to the sponsor, there were 52 noncomparative studies with >3000 patients and 25 comparative studies with >1000 patients were exposed to fenofibrate.

One hundred thirty-eight healthy subjects were exposed to either single-dose of 50 mg or 160 mg IDD-P™ fenofibrate in these studies.

7.4. Safety Findings from Clinical Studies

7.4.1. Adverse Events from published European clinical trials of fenofibrate which included Type IV patients:

There were 20 relevant clinical trials summarized by Guay (1), ten of the 20 trials did not provide safety data. The remainder of the trials are summarized below in **table 7.4.1:**

Table 7.4.1 Clinical Trials with Micronized Fenofibrate:

Reference	N (breakdown by HLP Type)	Regimen	Study design	Adverse Events (no. pts)
Wulfert et al 1976	393 (n=152, IIa; n=189, IIb, n=51, IV)	Fenofibrate 200-400 mg/d 1-≥12 mo.	Open label	None reported.
Lehtonen & Viikari, 1981	33 (n=16, IIa; n=7, IIb; n=10, IV).	Fenofibrate 100 mg tid for 6 mos.	Open	AST transiently increased (5); no other AE data provided
Komitzer et al 1994	1334 IIa/b; IV	Micro fenofibrate 200 mg qd for 6 mos	Open	Lab. AE in 13 (1%); serious AE possibly drug-related (4); epistaxis (1); hepatitis (1); pancreatitis (1); recurrence of pancreatitis (1).
Franceschini et al, 1985	26 (n=13, IIb; n=13, IV)	Fenofibrate 100 mg tid for 9 wks.	Open	Skin rash (1).
Boissonnat et al, 1994	43 (TC>270mg/dL and /or TG>252 mg/dL)	Micro fenofibrate 200 mg qd for 12 mos.	Open	4 withdrew d/t AE (diarrhea 2; steatorrhea & biliary colic in 1 pt each); rash (1); 14 pts withdrew d/t increased creatinine & 2 d/t increased CPK. Increases in creatinine in 18%; AST 35%; & CPK in 63%.
Avogam et al, 1983	28 (n=8, II2a; n=12 IIb; n=8, IV)	Fenofibrate 100 mg tid for 2 mos.	Open	GI discomfort (6 pts)---premature d/c.
Harvengt et al, 1980	19 (n=5, IIa; n=2 IIb; n=6 IV; n=6, V).	Fenofibrate 200 mg qAM+100 mg QPM for 12 mos.	Open	Moderate, transient increase CPK (4, myalgias, 3); sl. Increase/transient in AST/ALT (3); oral anticoagulant dose had to decrease 30%.
Luley et al, 1980	41 (n=21 IIa; n=11 IIb; n=9, IV)	Fenofibrate 100 mg tid for 24 wks.	Open	Gastric discomfort (4); headache (3); nausea (2); creatinine increase 0.02 mg/dL overall
Daubresse, 1980	45 (n=14, IIa; n=15 IIb; n=16, IV)	Fenofibrate 200 mg/day for 2-10 mos (mean 5.4 mos.	Open	Digestive intolerance (2)—1 premature d/c; rash (1); sl increase ALT (3); transient increase BUN/creatinine
Canzler & Bojanonski, 1980	32 (n=12 IIa; n=7 IIb; n=5 III; n=5 IV; n=3 other).	Fenofibrate 300 mg/day for 26 wks.	Open	2 pts prematurely d/c (nausea); muscle pain increase CPK (1); dizziness, angina (1).

1. The listed AEs above were derived from different doses of fenofibrate (200-400 mg per day) and the study design was open label, not randomized, double-blind and placebo controlled. In a review article by Balfour (2), which included several large placebo-controlled studies, he stated that "the incidence of AEs ranged from 6% in short-term and medium-term studies to 11% in long-term studies (duration > 6 months). In long-term studies, gastrointestinal effects occurred most frequently (5%) with headache and muscle pain each occurring in about 1% of patients. Dermatological reactions occurred in a significantly greater proportion in patients treated with fenofibrate compared to patients taking placebo in short-term studies."
2. In the same review article by Balfour et al (2), isolated cases of hepatitis, with increases in transaminases up to 70 times normal values were recorded. He cited

two studies that were performed to evaluate the possible hepatocellular toxicity. In one study, liver biopsies from 38 patients (28 patients were treated with fenofibrate for 2 years and 10 patients treated with dietary therapy) showed no differences between the groups. In another study, no morphological differences, in terms of precancerous liver pathology or peroxisome proliferation, in liver biopsies from patients treated with fenofibrate up to two years.

3. Fenofibrate may increase cholesterol excretion into bile and may result in cholestasis. According to Guay (1), “a significant mean decrease in biliary bile acids of 16% and significant mean increases in phospholipids and cholesterol saturation of 45% and 21 % respectively.” However, in a 3-year, double-blind, placebo-controlled study in 418 patients with type 2 diabetes, there were no differences in gallbladder symptoms and/or cholecystectomy rates (4). It should be pointed that diabetic patients have increased incidence of gallbladder disease. No comparable study had been performed in non-diabetic patients.
4. According to Kirchgassler et al (5), postmarketing surveillance of 9884 patients treated with daily dose of 200 mg micronized fenofibrate for 3 months showed that <1% of patients developed abnormal lab. parameters. In the long-term study (6 months) listed in **Table 7.4.1** above, Komitzer et al (6), reported increases in AST and ALT values > 3X ULN in less than 1% and 2% respectively of the 1334 patients studied. Plasma creatinine values >2.0 mg/dL during treatment was observed in 5 patients (2/5 had an elevated baseline values).

7.4.2. Safety Information from US Placebo-Controlled Studies: Two multi-center clinical studies were submitted in the Tricor NDA. These studies were performed in patients with IIa/IIb and IV/V treated with 300 mg nonmicronized fenofibrate daily for 6 months and 8 weeks, respectively [Brown et al (7) & Goldberg et al (8)]. Adverse events of these two studies are reproduced in **Table 7.4.2.**

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Table 7.4.2. Reported Adverse Events in Patients with Type II & IV/V treated with fenofibrate or placebo:(IDD-Ptm fenofibrate. (Reproduced from Brown et al (7) & Goldberg et al (8)].

Adverse Events	Type IIa/IIb		Type IV/V	
	Fenofibrate (n=116)	Placebo (n=111)	Fenofibrate (n=75)	Placebo (n=72)
	Number of patients		Number of patients	
Gastrointestinal	15	17	13	8
Musculoskeletal	2	3	4	2
Neurologic	7	6	4	4
Dermatologic	13	1	3	0
Genitourinary	3	2	3	0
Cardiovascular	2	0	1	1
Ear-nose-throat	1	0	1	1
Other	Not reported	Not reported	1	0
Number of patients with AEs	30	22	16	11
% of patients with AEs	26%	20%	21%	15%

The difference between the number of patients with AEs treated with fenofibrate or placebo was not statistically significant. However, as noted in Lipidil Micro^R Monograph (3), AEs were likely to occur in the longer term, 6-month trial in patients with Type II.

7.4.2.1. Clinical Laboratory Evaluations [From Lipidil Micro^R Monograph (3)]:

7.4.2.1.1. Elevation of ALT > 2X ULN were observed in 6.8% of the patients treated with fenofibrate vs. 1.6% in patients treated with placebo. Some were transient elevations which usually returned to normal without discontinuation of therapy. Persistent elevations of transaminases > 2X ULN occurred on some patients and returned to normal upon discontinuation of therapy. This appeared to be a dose-dependent finding. In an 8-week dose-ranging study, the incidence of ALT or AST elevation > 3X ULN was 0% in placebo treated patients or patients receiving 34 mg-67 mg micronized fenofibrate/day. And it increased to 3% in patients receiving 34 mg-200 mg micronized fenofibrate /day.

7.4.2.1.2. Moderate increases in urea, CPK, and creatine kinase levels had also been observed as well as decrease in alkaline phosphatase levels.

7.4.2.1.3. Mild decreases in hemoglobin, hematocrit, and white blood cell counts had been observed.

7.4.3 Safety Information from Comparative PK/Bioavailability Studies Performed by RTP Pharma Inc.:

There were 7 RTP Pharma-Sponsored Studies on IDD-Ptm fenofibrate. They were single-center, randomized (R), open-label (O), two-treatment (IDD-Ptm and Tricor/ or other fenofibrate), 2 or 3-periods (P)[each period refers to dietary condition i.e. fasting, low-fat or high-fat];. crossover (CO), studies as shown below in Table 7.4.3.1

Table 7.4.3.1. Summary Table of PK/Comparative BA Studies:

Study ID, country # of subjects	Design	Dose, Drugs	Condition	Adverse events
FEN100-C03, UK N=12	Single-dose R, O, 2p CO	160 mg IDD-P tm Tricor 200 mg	Fasting Low-fat	Itching (1), headache (4), nausea (1), backache (1), phlebitis (1)
FEN100-C04A, Canada, N=16	Single-dose R, O, 4p CO	160 mg IDD-p tm 160/200 mg Lipidil Micro	Low-fat	Abd. Pain (1), dizziness (1), flatulence (1), headache (2), CPK increase (1), somnolence (1), back pain (1).
FEN100-C05, Canada, N=24	Single-dose R, O, 39 CO	160 mg IDD-P tm	Fasting Lo/hi- fat	D/c d/t nausea & syncope (1), asthenia (1), headache (4), myalgia (3), dizziness (1), nausea (2), dyspepsia (1), CPK increase (1), back pain (2), glucose increase (1).
FEN100-CO6, Canada, N=28	Single-dose R, O, 2p, CO	160 mg IDD-p tm 200 mg Tricor	Low- fat	Abd. Pain (1), headache (8), pruritis (2), diarrhea (1), flatulence (2), leukopenia (1), polyuria (2).
FEN100-C07, Canada, N=24	Single-dose R, O, 2p CO	160 mg IDD-P tm 200 mg Tricor	Fasting	Chest pain (1), flatulence (4), headache (4), nausea (1), rhinitis (3), hematuria (2), hypochromic anemia (1).
FEN100-CO8, Canada, N=12	Single-dose R, O, 2p CO	50 mg IDD-P tm 3 different forms	Fasting	Dizziness (2), pain back (2), headache (1), somnolence (1)
FEN100-C12, Canada, N=24	Single-dose R, O, 2p CO	160 mg IDD-P tm 50 mgx3 IDD-p TM	Low-fat	Asthenia (2), abd. Pain (1), CPK increase (2), headache (4), SGOT/SGPT increase (1 each), albuminuria (2).

These Adverse Events were observed with IDD-PTM fenofibrate, in contrast to the previously listed Adverse Events, which were observed with other formulations of fenofibrate.

7.3.4.2. Hematuria: In FEN100-CO7 study, microscopic hematuria were noted in 2 subjects. The clinical significance, if any, is unknown.

- a). Subject # 8 had RBCs (3-8 /hpf) 4 days post-dosing and returned to normal after 28 days post-dosing.
- b). Subject #24 had RBCs in urine (3-8/hpf) 4 days post-dosing and returned to normal 21 days post-dosing.

7.3.4.3 CPK elevations: There were 4 cases of CPK elevations:

- a). In FEN100-C04 study there was one case of CPK elevation of unknown magnitude.
- b). In FEN 100-C05 study, subject #10 had CPK of 536 U/L approximately 11 days after Period 3 drug administration. Repeat test approximately 19 days later showed a value of 353 U/L. This elevation was considered not to be clinically significant.

7.3.4.4. AST/ALT elevations.

- a). In FEN 100-C07 study, subject # 9, had glucose of 9.5 mmol/L, AST 67 U/L, ALT 48 U/L, and creatine kinase 1459 U/L approximately 9 days after Period 2 drug administration. Repeat test 13 days after, showed normal results: glucose 4.5 mmol/L, AST 17 U/L, ALT 17 U/L and creatine kinase 86 U/L
Subject #17, had creatine kinase of 411 U/L approximately 9 days after Period 2 drug administration. Repeat test 8 days later showed a result of 239 U/L that was not considered to be clinically significant.
- b). In FEN100-C012 study, subject # 9 had increased AST and ALT which returned to normal upon repeat testing (see above under CPK increases).

7.3.4.5. Hematological changes:

- a). In FEN100-C07 study, subject #19 had hemoglobin of 11.0 g/L approximately 4 days after Period 2 drug administration. Repeat test done 28 days later showed to be 11.3 g/L.
- b). In FEN100-CO6 study, subject #18 a baseline WBC count of $3.1 \times 10^9/L$ and post-study, decreased to $2.4 \times 10^9/L$ which was considered to be clinically significant. However, repeat testing 39 days later, the WBC count had returned to baseline of $3.0 \times 10^9/L$.

7.3.4.6. Glucose Changes:

In FEN100-C05 study, subject # 3 had glucose value of 12.4 mmol/L approximately 11 days after Period 3 drug administration. The test was repeated 12 days later and showed a normal value (5.0 mmol/L).

7.4. Safety Findings from Clinical Studies

No clinical studies on safety had been performed.

7.5 Miscellaneous Studies: NA.

7.6 Literature Review for Safety: See literature review for fenofibrate in general.

7.8. Safety Update

7.8.1 First Safety Update: Four Months After Initial NDA Submission:

This was submitted on Oct. 2001. One study, FEN100-C08: an exploratory, single-dose PK study of two IDD-Ptm fenofibrate dosage forms) had been completed during this Safety Update reporting period. This report was included in this submission and reviewed above.

7.8.2. Second Safety Update: Eight Months After Initial NDA Submission:

This was submitted on 2.14.02. It contained essentially the same information/data as the previous update.

There were no new clinical safety information that requires changes to the original NDA submission.

7.9. Drug Withdrawal, Abuse, and Overdose Experience

Fenofibrate has not been withdrawn from any market during the past 25 years of use. The IDD-Ptm fenofibrate formulation has not been marketed or withdrawn from investigation in any country.

7.10 Adequacy of Safety Testing.

The adverse events and laboratory abnormalities of fenofibrate and the RLD (Tricor) are well-known from published literature and post marketing surveillance reports. Relevant data were reviewed in detail above. The safety issues specific for IDD-Ptm fenofibrate as documented from the PK/BE studies are difficult to evaluate because these were single-dose studies. The occurrence of adverse events and abnormal laboratory parameters after only a single-dose is of concern. However, because it was a single-dose study, it cannot be ascertained if they were drug-related. On the other hand, microscopic hematuria had not been reported with other fenofibrate formulation. This finding of hematuria could be drug-induced, and it is possible that with continued therapy, it could change from microscopic hematuria to gross hematuria. Unfortunately, with the limited data, the clinical significance, if any, cannot be determined at present. The other findings of mild decreases in hemoglobin, hematocrit, and white blood cell counts had been observed with other fenofibrate formulations in clinical use. However, these changes stabilized during long-term administration. Therefore, the clinical significance of above finding in single-dose administration is unknown. No glaringly/singularly serious adverse event or laboratory abnormality was observed and some of the abnormalities returned to baseline/normal levels upon repeat testing.

The overall safety profile of IDD-Ptm fenofibrate is similar to that of the RLD, Tricor fenofibrate.

7.11. Labeling Safety Issues and Postmarketing Commitments

None.

8.0 Dosing, Regimen, and Administrative Issues

The recommended initial dose is 50 mg to 160 mg per day and the maximum dose is 160 mg per day. Both these dose regimens are reasonable and supported by the submitted data.

9.0 Use in Special Populations

9.1. No clinical study of IDD-PTM fenofibrate had been performed. In studies performed with RLD (Tricor fenofibrate), no significant differences in PK had been observed between males and females or in the elderly (77-87 years of age). The effect of race had not been studied.

9.2 No clinical or PK studies of IDD-PTM fenofibrate or Tricor fenofibrate had been performed with hepatic compromised patients. Fenofibrate's clearance had been shown to be reduced in patients with creatinine clearance <50 ml/min. The dosage of Tricor and of IDD-PTM fenofibrate should be adjusted accordingly.

There were no adequate and well-controlled studies of Tricor or IDD-PTM fenofibrate use in pregnant women.

9.3 Pediatric waiver had been requested and granted.

10. Conclusions Recommendations, and Labeling

10.1 Conclusions Regarding Safety and Efficacy

No clinical efficacy and safety trials in patients with hyperlipidemia have been performed with IDD-PTM fenofibrate. Since it has comparable bioavailability (equivalent in extent of and rate of absorption under low-fat fed-state), efficacy and safety for the new IDD-PTM fenofibrate formulation are expected to be the same as for the approved micronized Tricor fenofibrate formulation.

10.2 Recommendation on Approvability

IDD-PTM fenofibrate is approvable as adjunctive therapy to diet for treatment of adult patients with hypertriglyceridemia (Fredrickson Types IV and V hyperlipidemia).

10.3 Labeling Review

12 Page(s) Withheld

 Trade Secret / Confidential

✓ Draft Labeling

 Deliberative Process

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/s/

Shiao Shen
3/14/02 12:57:13 PM
MEDICAL OFFICER

Mary Parks
4/3/02 10:25:30 AM
MEDICAL OFFICER
Please see Team Leader's Memo regarding labeling comments and
approvability of application

Note to File

NDA 21-350 (IND-60,743)
Sponsor: RTP Pharma Inc./CATO Research
Drug: IDD-Ptm fenofibrate tablets

Submitted: 7/13/01
Received: 7/17/01
Reviewed: 1/15/02

I. Resume:

“ NDA 21-350 was submitted 22 June 2001 by RTP Pharma Inc. for Insoluble Drug Delivery-Microparticle (IDD-Ptm) fenofibrate tablets for the treatment of hyperlipidemia. The NDA application cover letter indicates that the NDA contains no pediatric use information or exclusivity claims and the pre-NDA document (IND SN: 003) indicates that a full waiver of the pediatric rule is requested.” This formal Request for Waiver of Pediatric Study Requirement for IDD-Ptm fenofibrate tablets 160 mg, 50 mg, was submitted.

II. Reviewer's Evaluation:

IDD-Ptm fenofibrate is a new formulation of the reference listed drug (RLD), Tricor, and submitted as 505(b)(2) NDA. Tricor (NDA 19-304) and supplement approvals was granted waiver of the pediatric study requirement according to 21 CFR 314.55 (c)(2)(i) (“The drug product does not represent a meaningful benefit over existing treatments for pediatric patients and is not likely to be used in a substantial number of pediatric patients”). The waiver of the pediatric study requirement applied to the RLD Tricor should be applicable to IDD-Ptm fenofibrate.

III. Recommendation:

The Request for Waiver of Pediatric Study Requirement is granted.

S.W.Shen, M.D.

Medical Officer-510

CC:
Original NDA
HFD-510-Files
HFD-510-SWSHEN
HFD-510-MPARKS
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