CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-656

PHARMACOLOGY REVIEW

7/13/04

NDA 21-656

Review completed: 4/20/04
Signed off in DFS on 5/27/04

PHARMACOLOGY/TOXICOLOGY COVER SHEET

NDA number: NDA 21-656
Review Number: 1

Sequence number/date/type of submission: October 10, 2003 (original application). It is a It is a 505(b)(1) application. 4/19/04 (B2, response to FDA request on particle size of the drug)
Information to sponsor: Yes ( ) No (X)

Sponsor: Abbott Laboratories, Pharmaceuticals Products Div., Abbott Park, Illinois.

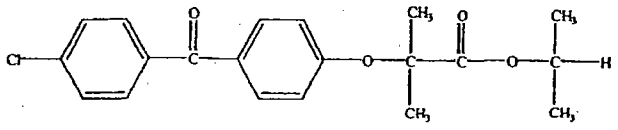
Manufacturer for drug substance: The manufacturer of the drug substance (fenofibrate) will be [redacted] The drug product will be manufactured by Fournier Laboratories Ireland Limited, Ireland.

Reviewer name: Indra Antonipillai, Ph.D. Pharmacology Reviewer.
Division: Division of Metabolic and Endocrine Drug products, **HFD #:** 510
Review completion date: 4/6/2004

Drug:

Trade name: Tricor [redacted] (fenofibrate), tablet strengths are 48 and 145 mg.
Generic name (list alphabetically): Fenofibrate
Code name: Tricor [redacted] procetofen, procetofene
Chemical name: Chemical name: 2-(4-(4-clorobenzoyl)phenoxy)-2-methyl-propanoic acid-1-methylethyl ester.
CAS registry number: 49562-28-9
Mole file number: N/A
Molecular formula/molecular weight: $C_{20}H_{21}O_4Cl$/360.83

Structure:



Relevant INDs/NDAs/DMFs: NDA 19-304 (Tricor capsules, fenofibrate) & NDA 21-203 (Tricor micronized tablets). DMF numbers [redacted] (for the current fenofibrate, from [redacted], and submitted by Abbot laboratories, IL), DMF [redacted] (for silicified microcrystalline celluslose), DMF [redacted] (for [redacted] yellow coating agent), DMF [redacted] (for [redacted] white coating agent).

Drug class: Fenofibrate, a phenoxyisobutyric acid isopropranol ester.

Indication: Treatment of primary hypercholesterolemia, and hypertriglyceridemia (Fredrickson Types IV and V hyperlipidemia).

Clinical formulation: The drug is available in 48 and 145 mg tablet strengths. These contain the active drug and inactive ingredients (see Table on page 6):

Route of administration: Oral

Proposed use: The drug is indicated alone (monotherapy), as an adjunctive therapy to diet for the reduction of elevated LDL-cholesterol, total cholesterol, TG, and Apo B and increase HDL-C in adult patients with primary hypercholestrolemia or mixed dyslipidemia (Fredrickson Types IIa, and IIb) at initial recommended dose of 145 mg/day in adults. It is also indicated in adult hyper-triglyceridemia (Fredrickson Types IV, and V hyperlipidemia), at the initial recommended dose of 48 mg/day, with maximal dose of 145 mg/day

Disclaimer: Tabular and graphical information is from sponsor's submission unless stated otherwise

Studies reviewed in this submission: None

Executive Summary

1. Recommendations

A. **Recommendation on approvability**
Pharmacology recommends approval of this drug for proposed indications

B. **Recommendation for Nonclinical Studies**:
The preclinical studies are adequate to support the recommended doses up to 145 mg/day. No further pre-clinical studies are required

C. **Recommendation on Labeling:** see the labeling section on page 9

II. Summary of Nonclinical Findings:

A. Brief Review of Nonclinical studies
Fenofibrate is an approved drug for oral use in USA as Tricor (NDAs 19-304/21-203). Since extensive nonclinical studies have been conducted with the approved fenofibrate, no additional toxicity studies are considered necessary with the current fenofibrate (Tricor ~) drug product. Tricor ~is a new nanocrystal collidal dispersion formulation of fenofibrate vs Tricor which is micronized formulation with a particle size ~ in the range of ~

B. Pharmacologic activity
Like other fenofibrates, it is a fibric acid derivative, it increases lipolysis and elimination of triglyceride rich particles from plasma by activating lipoprotein lipase.

C. Nonclinical safety issues relevant to clinical use
There are no new nonclincal safety issues relevant to the clinical use with the current drug product.

III. Administrative

A. Reviewer signature: ----------

B. Supervisor signature Concurrence:----------

Non-concurrence: ----------
(see memo attached)

cc: IND Arch
HFD-510
HFD-510/davisbruno/antonipillai/parks/jimenez
Review code: AP
File name: nda21656 (Tricor ~

TABLE OF CONTENTS - PHARMACOLOGY/TOXICOLOGY REVIEW

I. PHARMACOLOGY

Fenofibrate is a fibric acid derivative, and is used as a lipid lowering agent. The underlying mechanisms of its action are not fully established. The major effect of the drug is to enhance triglyceride rich lipoprotein catabolism by increasing lipoprotein lipase activity. It inhibits fatty acid synthesis and stimulates mitochondrial oxidation of fatty acids in rat liver. In addition the drug decreases cholesterol biosynthesis which may in turn enhance LDL clearance by increased LDL receptor activity. The drug may also mobilize cholesterol deposited in peripheral tissues, decrease hyper-aggregability and platelet derived growth factor, and increase esterification of cholesterol in plasma, all of the above actions could contribute to inhibition of atherogenesis.

In vitro in human hepatocyte cultures and in vivo in transgenic mice, fenofibrate activates proxisome proliferator receptor α (PPAR α). It is believed that by this mechanism the drug increases lipolysis and elimination of TG rich particles from plasma by activating lipoprotein lipase and reducing production of apoprotein C-III (an inhibitor of lipoprotein lipase activity).

Fenofibrate is currently a marketed drug in US, as Tricor. Up to 200 mg/day are approved doses. Both micronized and non-micronized formulations are approved, but the micronized drug has increased absorption. The Tricor capsules (67 & 200 mg strengths) and Tricor tablets (54 & 160 mg strengths) have substantial food effects, thus making its absorption still variable/incomplete and dependent on food. The micronized 67 mg ( ) is equivalent to 100 mg of the conventional form.

The current sponsor (Abbott Pharmaceuticals) has come up with the new formulation of the drug, which they claim has bioavailability greater than that of the micronized form. **The current sponsor refers to two previously approved fenofibrates (Tricor capsules (NDA 19-304) and Tricor micronized tablets (NDA 21-203).**

The sponsor states that this new formulation has particle size between the drug substance particle size in the marketed Tricor (NDA 21-203). The dissolution studies on various particle size (ranging from

fractions of fenofibrate drug substance have shown that the rate of solubility increases as the particle size became finer.

With this new formulation the food effect is supposedly eliminated and a dose reduction of approximately 10% is proposed, i.e. tablet strengths of 48 and 145 mg are proposed vs 54 and 160 mg tablet strengths of currently marketed Tricor (NDA 21-203). This new formulation (in NDA 21-656) contains two new excipients, one is silicified microcrystalline cellulose (which is a compression aid, and the other is , which is a white coating agent.

The Clinical formulation contains the active drug and following inactive ingredients:

Table. Composition of Tricor (fenofibrate):

Table 2. Composition of Fenofibrate Tablets, 145 mg

Ingredients	Unit Formula (mg/tablet)	Primary Function	Reference to Standards
Active Substance			
Fenofibrate (micronized)	145.0	Active ingredient	In-house
Excipients			
Hypromellose (2910, 3 cps)			USP
Docusate sodium			USP
Sucrose			NF
Sodium Lauryl Sulfate			NF
Lactose Monohydrate			NF
Silicified Microcrystalline Cellulose			In house
Crospovidone			NF
Magnesium Stearate			NF
			Ph. Eur
			In house
Total	651.6 mg		

* Removed during processing.

The sponsor has also provided the comparison of the marketed tablet formulation vs the current nanocrystal formulation of Tricor

Table 6. Comparison of Current Marketed Tablet Formulation and the New Tablet Formulation

Component	(% w/w)*	
	Marketed Formula	NanoCrystal®
Fenofibrate		
Povidone, USP		
Hypromellose, (2910, 3 cps) USP		
Sodium Lauryl Sulfate, NF		
Docusate Sodium, USP		
Sucrose, NF		
Lactose Monohydrate, NF		
Microcrystalline Cellulose, NF		
Colloidal Silicon Dioxide, NF		
Silicified Microcrystalline Cellulose		
Crospovidone, NF		
Sodium Stearyl Fumarate, NF		
Magnesium Stearate, NF		
TOTAL (core)		

* Values rounded to nearest tenth of one percent.

Most excipients used here have been used at these or higher doses in other approved products (FDA inactive ingredient guide, 1996). The current new formulation contains one new excipient; called silicified microcrystalline cellulose (but it has been used previously in NDA 21-342 (levothyroxine sodium) at doses up to

Since extensive non-clinical studies have been conducted with the approved fenofibrate Tricor (under NDAs 19-304/21-203), no additional non-clinical studies have been considered necessary, and have not been provided for the current drug (Tricor EZ).

X. DETAILED CONCLUSIONS AND RECOMMENDATIONS

Tricor is a new nanocrystal formulation of fenofibrate, vs Tricor which is micronized. It is available in tablets in two strengths, each containing 48, or 145 mg of the drug. Since the particle size is finer in Tricor 10% lower doses are proposed with this drug (i.e. tablet strengths of 48 and 145 mg are proposed vs 54 and 160 mg tablet strengths of currently marketed Tricor, NDA 21-203) and also the food effect is eliminated with Tricor

Fenofibrate is approved (NDA 19-304, Tricor) for oral use in US, Canada, and Europe for the treatment of hypertriglyceridemia, primary hypercholesterolemia or mixed dyslipidemia. Tricor is available in capsules in three strengths, each containing containing 67, 134, or 200 mg of micronized fenofibrate. As per labeling, recommended doses of Tricor capsules are up to 200 mg/day, and of tablets are up to 160 mg/day.

Following pharm/tox studies are summarized from the marketed fenofibrate Tricor:

Pharmacology: Fenofibrate is a prodrug, after absorption it is hydrolyzed in the plasma and tissues to its major metabolite, fenofibric acid (FF) and FF is extensively bound to

plasma albumin. Fenofibrate is absorbed as fenofibric acid which is responsible for the pharmacologic activity of the drug.

Toxicity of Tricor: As per label, the drug fenofibrate (Tricor) does not have a mutagenic potential, but in 24 month rat CAC study the drug produces liver and pancreas carcinomas, pancreatic adenomas, and benign testicular interstitial tumors (in male rats). In mice it produces liver carcinomas. These effects are noted at 0.3-6 times the maximum recommended human dose.

Fenofibrate (Tricor) produces embryocidal and teratogenic effects in rats and embryocidal effects in rabbits at 7-10 times the maximum recommended human dose, and is labeled as category 'C'.

Safety Evaluation: Extensive non-clinical studies have been conducted with the approved fenofibrate Tricor (under NDAs 19-304/21-203). Supportive information for Tricor (fenofibrate) excipients was provided in DMF numbers (for the current fenofibrate, from , and submitted by Abbot laboratories, IL), DMF (for silicified microcrystalline celluslose), DMF (for yellow coating agent), and DMF (for white coating agent).

Fenofibrate contains a new formulation of fenofibrate in two dosage strengths of 48 mg and 145 mg. Sponsor refers to two previously approved fenofibrates, Tricor capsules (NDA 19-304) and Tricor micronized tablets (NDA 21-203). The current fenofibrate is a nanoCrystal tablet formulation, and involves reduction of particle size and has no food effect. Sponsor claims that Its particle size is between the drug substance particle size in the marketed Tricor (NDA 21-203). It also allows a lower strength tablet (145 mg) to provide fenofibric exposure equivalent to that form reference micronized fenofibrate capsule. Thus the new tablet strengths of 48 and 145 mg are proposed (vs 54 and 160 mg tablet strengths of currently marketed Tricor in NDA 21-203). However, the current new formualtion contains one new excipient, called silicified microcrystalline cellulose ( ) , but it has been used previously in NDA 21-342 (levothyroxine sodium) Additionally, DMF has been provided for silicified microcrystalline cellulose

The sponsor is proposing up to 145 mg/day dose of the current drug for primary hyper cholesterolemia or for hypertriglyceridemia. Currently the recommended dose of Tricor is up to 200 mg/day in the label.

The sponsor has demonstrated that bioavailabilty (BA) of one 145 mg of Tricor (or three 48 mg nano crystal fenofibrate tablets) was equivalent to that of one 200 mg of micronized fenofibrate capsule. Thus human PK studies suggest comparable Cmax and AUC exposures with the current drug vs micronized drug.

The sponsor also states that bioavailability of fenofibric acid following administration of one 145 mg of Tricor tablet was equivalent under high fat meal, low fat meal, and under fasting conditions. Thus absence of food effect was documented with the current formulation.

Labeling Review: The preclinical sections of the label for Tricor (fenofibrate) are similar to the approved Tricor label. The following changes in labeling are recommended:

Sponsor's label:

1. Carcinogenesis, Mutagenesis, Impairment of Fertility:

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

Reviewer's recommended changes:

Carcinogenesis and Mutagenesis

Two dietary carcinogenicity studies have been conducted in rats with fenofibrate. In the first 24-month study, rats were dosed with fenofibrate at 10, 45, and 200 mg/kg/day, approximately 0.3, 1, and 6 times the maximum recommended human dose (MRHD, based on mg/meter^2 of surface area). At a dose of 200 mg/kg/day (at 6 times the MRHD), the incidence of liver carcinoma was significantly increased in both sexes. A statistically significant increase in pancreatic carcinomas was observed in males at 1 and 6 times the MRHD; an increase in pancreatic adenomas and benign testicular interstitial cell tumors was observed at 6 times the MRHD in males. In a second 24-month study in a different strain of rats, doses of 10 and 60 mg/kg/day (0.3 and 2 times the MRHD based on mg/meter^2 surface area) produced significant increases in the incidence of pancreatic acinar adenomas in both sexes and increases in testicular interstitial cell tumors in males at 2 times the MRHD (200 mg/kg/day).

A 117-week carcinogenicity study was conducted in rats comparing three drugs: fenofibrate 10 and 70 mg/kg/day (0.3 and 2 times the MRHD), clofibrate (400 mg/kg; 2 times the human dose), and gemfibrozil (250 mg/kg; 2 times the human dose, multiples based on mg/meter^2 surface area). Fenofibrate increased pancreatic acinar adenomas in both sexes. Clofibrate increased hepatocellular carcinoma and pancreatic acinar adenomas in males and hepatic neoplastic nodules in females. Gemfibrozil increased hepatic neoplastic nodules in males and females, while all three drugs increased testicular interstitial cell tumors in males.

In a 21-month study in mice, fenofibrate 10, 45, and 200 mg/kg/day (approximately 0.2, 0.7 and 3 times the MRHD on the basis of mg/meter^2 surface area) significantly increased the liver carcinomas in both sexes at 3 times the MRHD. In a second 18 month study at same doses, fenofibrate significantly increased the liver carcinomas in male mice and liver adenomas in female mice at 3 times the MRHD.

Sponsor's label:

2. Pregnancy Category C:

Reviewer's recommended changes:
Pregnancy : Teratogenic Effects, Pregnancy Category C:

Safety in pregnant woman has not been established. Fenofibrate has been shown to be embryocidal and teratogenic in rats when given in doses 7 to 10 times the maximum recommended human dose *(MRHD)* and embryocidal in rabbits when given at 9 times the *MRHD* (on the basis of mg/meter^2 surface area). There are no adequate and well-controlled studies in pregnant women. Fenofibrate should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

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

Administration of *approximately* 10 times the *MRHD* of fenofibrate to female rats on days 6-15 of gestation caused an increase in gross, visceral and skeletal

findings in fetuses (domed head/hunched shoulders/rounded body/abnormal chest, kyphosis, stunted fetuses, elongated sternal ribs, malformed sternebrae, extra foramen in palatine, misshapen vertebrae, supernumerary ribs).

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

Administration of fenofibrate at 9 to 18 times the *MRHD* to female rabbits caused abortions in 10% to 25% of dams, and death in 7% of fetuses at 18 times the MRHD.

External Recommendation: From the preclinical standpoint, approval of this application is recommended, pending labeling changes.

A. Reviewer signature: Indra Antonipillai

B. Supervisor signature Concurrence:----------

Non-concurrence: ----------
(see memo attached)

cc: IND Arch
HFD-510
HFD-510/davisbruno/antonipillai/parks/jimenez
Review code: AP
File name: nda21656 (Tricor EZ fenofibrate)

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Indra Antonipillai
7/13/04 11:43:02 AM
PHARMACOLOGIST
From the pharm/tox aspect this application is recommended for approval pending labeling changes
This application is recommended for approval pending labeling changes

Karen Davis-Bruno
7/13/04 11:45:43 AM
PHARMACOLOGIST
concur with recommendation

Review completed 11/20/03
Signed off in DFS on 11/25/03

45 Day Meeting Checklist
NONCLINICAL PHARMACOLOGY/TOXICOLOGY

NDA 21-656: This NDA is a 505(b)(1) application.
Submission date: 10/29/03
Sponsor: Abbott Laboratories, Pharmaceuticals Products Div., Abbott Park, Illinois.
Drug: Fenofibrate — tablets.
Introduction: Fenofibrate — contains a new formulation of fenofibrate in two dosage strengths of 48 mg and 145 mg. Sponsor refers to two previously approved fenofibrates, Tricor capsules (NDA 19-304) and Tricor micronized tablets (NDA 21-203). The current fenofibrate — is a nanoCrystal based film-coated tablet formulation, which will supposedly eliminate fed/fasted variable absorption. Its particle size is between — the drug substance particle size in the marketed Tricor (NDA 21-203). With this new formulation not only the food effect will be eliminated, but a dose reduction of approximately 10% is proposed. The new tablet strengths of 48 and 145 mg are proposed (vs 54 and 160 mg tablet strengths of currently marketed Tricor in NDA 21-203). However, the current new formualtion contains one new excipient, called silicified microcrystalline cellulose (— but it has been used previously in NDA 21-342 (levothyroxine sodium) at doses up to —

ITEM: NDA 21-350	**YES**	**NO**	**COMMENT**
1) Does this section of the NDA appear to be organized (according to 21 CFR 314 and current guidelines for format and content) in a manner that would allow a substantive review to be completed?	Yes		
2) Is this section of the NDA indexed and paginated in a manner to enable a timely and substantive review?	Yes		
3) Is this section of the NDA sufficiently legible so that a substantive review can be done? Has the data been presented in an appropriate manner (consider tables, graphs, complete study reports, inclusion of individual animal data, appropriate data analysis, etc.)?	Yes		No new pharm/tox data have been provided. Sponsor refers to two previously marketed fenofibrates NDA 21-203 (tablets) and NDA 19-304 (capsules)

4) Are all necessary and appropriate studies for this agent, including special studies/data requested by the Division during pre-submission communications/discussions, completed and submitted in this NDA? Please itemize the critical studies included and indicate any significant studies that were omitted from the NDA (genotox, reprotox, adequate duration of chronic tox, carcinogenicity)	Yes		Have electronic files of the carcinogenicity studies been submitted for statistical eview? No carcinogenicity or other preclinical studies were conducted with the current drug. This is because non-clinical studies have already been conducted with the approved fenofibrate (Tricor under NDAs 19-304, 21-203), and are not considered necessary for fenofibrate

ITEM	YES	NO	COMMENT
5) Were the studies adequately designed (ie., appropriate number of animals, adequate monitoring consistent with the proposed clinical use, state-of-the art protocols, etc.)?			Not applicable. Since non-clinical studies have already been conducted with the approved fenofibrate Tricor under NDA 19-304
6) If the formulation to be marketed is not identical to the formulation used in the toxicology studies (including the impurity profiles), has the sponsor clearly defined the differences and submitted reviewable supportive data (ie., adequate repeat studies using the marketed product and/or adequate justification for why such repetition would not be necessary)?	Yes		Sponsor has used new nanoCrystal film coated formulation in the current tablet product, and has provided supportive information for fenofibrate excipients. All the excipients have already been used in other approved NDAs (in the FDA inactive ingredient guide, 1996). The only new excipient used here is **silicified microcrystalline cellulose** (**However, this has also been used previously in NDA 21-342 at doses up to** Additionally, DMF has been provided for silicified microcrystalline cellulose.

7) Does the route of administration used in animal studies appear to be the same as the intended human exposure route? If not, has the sponsor submitted supportive data and/or an adequate scientific rationale to justify the alternative route?	Yes		The route of administration is oral in tox studies in NDA (19-304) , which is the intended route in humans
8) Has the proposed draft labeling been submitted? Are the appropriate sections for the product included and generally in accordance with 21 CFR 201.577? Is information available to express human dose multiples in either mg/m2 or comparative serum/plasma AUC levels?	Yes		Yes, the draft labeling submitted in general is similar to the approved Tricor fenofibrate label, and data express human dose multiples in mg/m2.

ITEM	YES	NO	COMMENT
9) From a pharmacology/toxicology perspective, is this NDA fileable? If not, please state in item # 10 below why it is not.	Yes		

10) Reasons for refusal to file: Not applicable

Reviewing Pharmacologist: Indra Antonipillai, HFD-510

Supervisory Pharmacologist: Karen Davis-Bruno

File name: 21656-filing

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Indra Antonipillai
11/25/03 10:59:34 AM
PHARMACOLOGIST
From pharm/tox point of view this application is filable
This application is filable

Karen Davis-Bruno
11/25/03 11:02:47 AM
PHARMACOLOGIST
concur with filing decision