CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 21-203

MEDICAL REVIEW(S)

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center For Drug Evaluation and Research

DATE: September 4, 2001

FROM: David G. Orloff, M.D.
Director, Division of Metabolic and Endocrine Drug Products

TO: NDA 21-203
Tricor tablets, 54 mg. and 160 mg
Abbott Laboratories

SUBJECT: NDA review issues and recommended action

Background
This application was originally submitted November 10, 1999 for a new formulation of an approved drug, fenofibrate indicated to reduce elevated TC, LDL-C, TG, Apo B, and to increase HDL-C in patients with Type 2a and 2b hyperlipoproteinemia and to reduce TG in patients with Types 4 and 5 dyslipidemia. The application received an approvable action on September 12, 2000 based on biopharmaceutics deficiencies, specifically that the data submitted did not establish adequately a PK/PD relationship for fenofibrate to permit a conclusion of bioequivalence, that therefore bioequivalence had not been established between the marketed capsule formulation and the proposed tablet formulation, and that the dissolution methodology was inadequate. The sponsor responded to the AE letter on March 2, 2001 with a submission that included new dissolution information as well as the results of a fasting bioavailability study that established bioequivalence between the marketed formulation and the proposed tablets.

Medical
There are no clinical data in the application. Dr. Parks' memos address the labeling issues. Labeling has been finalized and is acceptable to the Division.

Biopharmaceutics
The results of the fasting bioequivalence study comparing the 160 mg tablet to the 200 mg capsule showed that the products are bioequivalent with respect to AUC and that Cmax is higher for the tablet with a point estimate of approximately 30-40% greater than capsule. This is not considered clinically significant for either safety or efficacy.

Pharmacology/Toxicology
There are no new pharm-tox data.

Chemistry/ Microbiology
The chemistry, manufacturing, and controls are satisfactory and the application is approvable. The site inspections were all acceptable. A categorical exclusion from the environmental assessment was claimed by the sponsor and accepted by the Agency.

DSI/Data Integrity
The audits of the BA/BE studies were acceptable.

Financial disclosure
The financial disclosure information is in order. The sponsor has certified that no investigator received outcome payments, that no investigator disclosed a proprietary interest in the product or an equity interest in the company, and that no investigator was the recipient of significant payments of other sorts.

OPDRA/nomenclature
No issues are raised

Other issues
The sponsor does not intend to market the ——— at this time. The approved labeling therefore does not include this dosage strength. At such time that the sponsor wishes to market the ——— , a labeling supplement will be required. This has been conveyed in the action letter.

Recommendation
This application may be approved.

APPEARS THIS WAY
ON ORIGINAL

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

/s/

David Orloff
9/4/01 04:23:30 PM
MEDICAL OFFICER

APPEARS THIS WAY
ON ORIGINAL

MEDICAL TEAM LEADER'S REVIEW OF AMENDMENT TO A PENDING NEW DRUG APPLICATION

NDA#: 21-203, Class 2 response to an approvable action letter issued on September 12, 2000.

Drug Sponsor: Abbott Laboratories

Drug Name: Tricor (fenofibrate tablets)

Purpose of Application: this application seeks to establish bioequivalence between the currently-marketed Tricor capsules (dosages 67, 134, and 200 mg) and the proposed Tricor tablets to be marketed in 54 mg and 160 mg strengths. This application also seeks to add an HDL-raising indication in adult patients with Fredrickson's Type IIa and IIb dyslipidemia.

Date of Submission: March 5, 2001

Date Review Completed: July 23, 2001

INTRODUCTION

The deficiencies of the original application for Tricor tablets were summarized in an approvable letter issued on September 12, 2000 by the Division of Metabolic and Endocrine Drug Products. These deficiencies were primarily clinical pharmacology issues including the inability to establish a PK/PD relationship between plasma fenofibric acid levels (PK measures) and the lipid-altering endpoints (PD measures) as well as bioequivalence between the tablets and capsules. In addition, the dissolution method was considered incomplete.

This submission is a response to the Clinical Pharamcolocy deficiencies. Data from two bioequivalence studies were provided in this submission and will be reviewed by Dr. Wei Qiu from the Office of Clinical Pharmacology and Biopharmaceutics (OCPB).

The original application was reviewed for an HDL-raising indication in the Type IIa and IIb dyslipidemic population and the submitted data were considered sufficient to support language in the CLINICAL PHARMACOLOGY and INDICATIONS AND USAGE sections of the label. However, the approvable letter required that the disclaimer statement on the unknown clinical effects of independently raising HDL-C levels or lowering TG levels remain in the label.

The medical review of this submission will primarily focus only on proposed labeling and recommendations from OCPB. There were no new clinical studies submitted for medical review.

PROPOSED LABELING AND REVIEWER COMMENTS

The majority of the labeling changes were editorial, replacing capsules with tablets and the doses of 67, 134, and 200 mg with 54 and 160 mg. The following sections of the proposed label were relevant to the Clinical Review of this application:

CLINICAL PHARMACOLOGY
The sponsor proposed the following changes:

[redacted]

The independent effect of lowering triglycerides (TG) on the risk of cariovascular morbidity and mortality has not been determined.

[redacted]

[redacted]

Medical Officer's Comments:
The independent effects of HDL-raising or TG-lowering on CV risks have not been established. Clinical trials treating primarily low HDL-C levels, such as VA-HIT, did not demonstrate a clinical benefit solely due to HDL-raising as there was always an accompanying significant reduction in TG levels. The sponsor also proposes to include clinical data from clinical trials involving
Such language is unacceptable as this implies a clinical benefit associated with

The statement, *the independent effect of raising HDL-C or lowering triglycerides (TG) on the risk of cardiovascular morbidity and mortality has not been determined*, should be reinserted and all other proposed statements should be deleted.

INDICATIONS AND USAGE

[redacted]

Medical Officer's Comments:
This indication was reviewed in NDA 19-304/supplement 005. The patient population had elevated LDL-C and total-C levels therefore this statement should be changed to treatment of *elevated* lipoproteins levels.

The above statement should read as follows:
TRICOR is indicated as adjunctive therapy to diet to reduce elevated LDL-C, total-C, TG, and Apo B, and to increase HDL-C in adult patients with primary hypercholesterolemia or mixed dyslipidemia (Fredrickson Types IIa and IIb).

In addition, the sponsor has reference to the NCEP Treatment Guidelines. This table should be updated to reflect the recently revised Adult Treatment Panel III Guidelines.

PRECAUTIONS: Geriatric Use

[redacted]

Medical Officer's Comments:
A response to an AE application cannot include new changes to the label that were not addressed in the original application. The geriatric use data needs to be submitted as a separate efficacy supplement to the NDA.

RECOMMENDATIONS
Pending OCPB's determination that Tricor tablets are bioequivalent to the capsules and labeling negotiations, this application should be approved.

Mary H. Parks, MD
Medical Team Leader
HFD-510

APPEARS THIS WAY
ON ORIGINAL

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/s/

Mary Parks
8/27/01 02:34:58 PM
MEDICAL OFFICER

David Orloff
8/29/01 02:55:44 PM
MEDICAL OFFICER

ADDENDUM TO MEDICAL REVIEW OF NDA 21-203
REVIEW OF FINANCIAL DISCLOSURE

Four clinical trials previously submitted to NDA 19-304 supplement 005 were referenced in NDA 21-203 for support of an HDL-raising indication. Review of financial disclosure information for these studies (CFEN 8104, 8502, 8802, 9116) were previously conducted under NDA 19-304.

Results of two clinical pharmacokinetic studies, M98-961 and M98-962 (see S. Johnson, biopharm review) were submitted with this application. The following financial disclosure summary pertains to these 2 studies.

Outcome Payment (payment dependent upon outcome of study)
none

Proprietary Interest (e.g. patents, trademark, copyright, licensing agreement in the product)
none

Equity Interest (e.g. stock ownership, stock options)
none

Significant Payment of Other Sorts (SPOOS)
none

Conclusions
In accordance with 21 CFR 54 the sponsor has submitted statements disclosing any information regarding financial interests and arrangements of clinical investigators, respective spouses, and dependent children of the investigators. There were no investigators who entered a financial arrangement with Groupe Fournier or Abbott Laboratories which could compromise the integrity of the trial results.

/S/ 9-7-00

Mary H. Parks, MD
Medical Officer
DMEDP (HFD-510)

MEDICAL OFFICER REVIEW

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

Application #: 21-203
Sponsor: Abbott Laboratories
Investigator: Multiple (Not named)
Category: Lipid-altering

Reviewer: Mary H. Parks, MD

Application Type: NDA
Proprietary Name: Tricor
USAN Name: Fenofibrate
Route of Administration: oral

Review Date: August 30, 2000

SUBMISSIONS REVIEWED IN THIS DOCUMENT

Document Date	CDER Stamp Date	Submission Type	Comments
November 10, 1999	November 12, 1999	505(b)(2)	

RELATED APPLICATIONS (If applicable)

Document Date	Application Type	Comments
July 1, 1999	NDA 19-304/S005	

REVIEW SUMMARY: This is a 505(b)(2) NDA for fenofibrate tablets at doses of 54 [redacted] nd 160 mg. The reference listed drug is Tricor micronized capsules at doses of 67, 134, and 200 mg. The sponsor is also seeking an indication for raising HDL-C levels in adult patients with Fredrickson Types IIa and IIb dyslipidemia based on data derived from clinical studies previously reviewed in NDA 19-304/S005 involving the standard and micronized formulations of fenofibrate at doses of 300 mg qd (standard formulation) or the equivalent 200 mg micronized capsules qd.

Four randomized, placebo-controlled, double-blinded, parallel design trials were pooled for efficacy analysis. Types IIa patients with mean baseline HDL-C levels of 58.1 mg/dL and IIb patients with mean baseline HDL-C levels of 46.7 mg/dL had significant elevations in HDL-C from baseline (+7.2 to 12.3%) compared to placebo (+2.3 to 2.6%) after 3 to 6 months daily treatment with fenofibrate. These changes were also accompanied by significant reductions in triglyceride levels (approximately –33% reduction).

Since the increases in HDL-C associated with fenofibrate treatment have only been demonstrated with the standard or micronized capsule formulations, approvability of this application requires demonstration of bioequivalence between the tablets to the listed micronized capsule formulation (see Biopharm Review).

OUTSTANDING ISSUES: none

RECOMMENDED REGULATORY ACTION: N drive location:

New clinical studies _____	Clinical Hold	_____	Study May Proceed
NDA, Efficacy/Label supplement: __x__	Approvable	_____	Not Approvable

SIGNATURES: Medical Reviewer: /S/ Date: 8-30-00
Medical Team Lead /S/ Date: 8-30-00

APPEARS THIS WAY ON ORIGINAL

MEDICAL OFFICER'S REVIEW OF NEW DRUG APPLICATION

NDA #: 21-203

Sponsor: Abbott Laboratories

Drug Name and Formulation: Fenofibrate (Tricor) **tablets**

Dosage Strength: 54 —, and 160 mg

Indication: Treatment of Fredrickson's Type II/IV/V Dyslipidemia

Date of Submission: November 12, 1999

Date Review Completed: August 30, 2000

Medical Officer: Mary H. Parks, MD (HFD-510)

Clinical Pharmacology Reviewer: Stephen B. Johnson, PharmD

TABLE OF CONTENTS	PAGE

INTRODUCTION

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. 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 formulation of 67 mg. 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. More recently, this product was approved 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).

Abbott Laboratories is now submitting a 505 (b) (2) NDA for fenofibrate **tablets** at doses of 54, — and 160 mg to be used in the treatment of Types IIa, IIb, IV, and V dyslipidemia. In this application, the sponsor is also seeking an indication for raising HDL-C levels in adult patients with Fredrickson Types IIa and IIb dyslipidemia based on clinical studies submitted to NDA 19-304/S005. These studies were conducted with the standard and micronized capsule formulations of fenofibrate.

The Office of Clinical Pharmacology and Biopharmaceutics (OCPB) will review the data submitted to establish bioequivalence of the tablets to capsule formulations under therapeutic conditions. The review in DMEDP will determine if the pooled analysis of efficacy involving older fenofibrate formulations demonstrates a significant increase in HDL-C levels. Approval for this indication will rely on the OCPB's determination of comparable plasma concentrations of fenofibric acid levels between the tablet and older approved formulations. An integrated summary safety for fenofibrate was previously reviewed in NDA19-304/S005. No new studies for safety are submitted for review with this application.

HDL-C as a CHD Risk Factor

HDL-C plays an important role in the transport of extrahepatic cholesterol to the liver for excretion into bile as free cholesterol or bile acids formed from cholesterol. This process, known as reverse cholesterol transport, has long been considered an anti-atherogenic process since cholesterol removed from extrahepatic cells and the circulation become less available for oxidation and incorporation into the vascular wall.

Several large cohort studies have demonstrated that low HDL-C level is a risk factor for heart disease independent of other risk factors. For example, the incidence of CHD in a subgroup of the Framingham cohort was greater in individuals with HDL-C levels < 40 mg/dL compared to those with HDL-C levels ≥ 40 mg/dL. This observation was evident even in those individuals with total-C levels below 200 mg/dL.[1]

Transgenic animal models overexpressing the human HDL-C apolipoprotein A1 have provided further evidence for the inverse relationship between HDL-C and atherogenesis. In these animals, the formation of fatty streaks in the proximal aorta is significantly lower than observed in inbred strains of mice lacking this gene.[2]

Contradicting the notion that HDL-C is the "good" cholesterol, however, are familial syndromes involving mutations that result in moderate to markedly elevated HDL-C levels. Notably, genetic mutations of the cholesteryl ester transport protein (CETP), a protein responsible for transferring cholesteryl ester from HDL to apolipoprotein-B-containing lipoproteins (e.g. chylomicron remnants and VLDL), have been identified in several Japanese families. These individuals may have HDL-C levels exceeding 100 mg/dL but have premature coronary artery disease.[3] Such findings raise questions as to which HDL particles contribute to the cardioprotective effect of this lipoprotein and whether an elevated HDL-C level is universally predictive of risk reduction.

Division Approach to HDL-C Raising as an Indication

Further complicating the HDL-C story includes the lack of evidence from clinical trials demonstrating HDL-C increases alone can reduce CHD rates. Several studies, primarily involving the fibric acid derivatives, have directed therapy at increasing HDL-C levels. Although these studies demonstrated that the increase of HDL-C levels by 6-10% was associated with significant risk reductions for cardiac events, the HDL-C increases were also accompanied by significant reductions in triglycerides.[4,5] Nevertheless, low HDL-C levels remain an independent risk factor such that HDL-C levels below 35 mg/dL are considered by the National Cholesterol Education Program (NCEP) a factor in the algorithm for initiating drug therapy.[6] Conversely, HDL-C levels > 60 mg/dL are considered a negative risk factor for heart disease.

Indeed, medical management of dyslipidemia focuses not only on elevated total and LDL-C levels but include counseling on ways to improve HDL-C levels (e.g. smoking cessation, exercise, and moderate alcohol consumption). Consequently, labeling of certain lipid-altering drugs has incorporated the effect of therapy on HDL-C levels for informational purposes only. The independent effects of HDL-raising on clinical outcome are unknown and are summarized in the label to that effect.

EFFECTS OF FENOFIBRATE ON HDL-C LEVELS

Clinical Studies Submitted

Efficacy results of four placebo-controlled trials were pooled to support an indication for HDL-C raising with fenofibrate. These studies were randomized, double-blinded, parallel design trials involving non-diabetic patients with Frederickson Types IIa and IIb dyslipidemia. The following table summarizes these 4 clinical studies previously reviewed in NDA 19-304/S005.

Table 1. Summary of Clinical Studies Submitted to NDA 19-304/S005

Study Number and Study Design	Patients Randomized	Duration	Treatment Groups
Study 8104 DB, PBC, RPT	227	6 month double-blind 6 months open-label	1. fenofibrate 100 mg tid 2. placebo
Study 8502 DB, PBC, RPT	106	3 months	1. fenofibrate 200 mg qam and 100 mg qpm 2. placebo
Study 8802 DB, PBC, RPT	189	3 months	1. fenofibrate 200 mg micronized qd 2. fenofibrate 100 mg tid 3. placebo
Study 9116 DB, PBC, RPT	340	3 months	1. fenofibrate 200 mg micronized qd 2. fenofibrate 267 mg micronized qd 3. fenofibrate 340 mg micronized qd 4. fenofibrate 400 mg micronized qd 5. placebo

DB=double-blind; PBD=placebo-controlled; RPT=randomized, parallel treatment

Available lipid data from only those patients treated with placebo, standard fenofibrate formulation (100 mg tid), or 200 mg micronized formulation were analyzed. A total of 293 placebo-treated and 361 fenofibrate-treated subjects were evaluated.

Patient Baseline Characteristics

Approximately 58% of the pooled cohort were male and the average age was 52 years. Table 2 summarizes the baseline lipid distribution in the evaluated population.

Table 2. Baseline Distribution of Lipid Parameters in Fenofibrate and Placebo Groups by Mean and Percentile Values

Lipid Parameter	All FEN (n=361)	Placebo (n=285)
Total-C (mg/dL)		
mean	304.4	310.0
25th	271.0	277.1
50th	292.0	300.0
75th	322.1	337.6
LDL-C (mg/dL)		
mean	210.1	218.6
25th	182.0	184.8
50th	207.4	212.0
75th	232.0	243.8
HDL-C (mg/dL)		
mean	52.8	51.7
25th	42.0	41.0
50th	51.0	50.0
75th	61.2	61.0
Triglycerides (mg/dL)		
mean	199.5	180.2
25th	94.0	108.0

Lipid Parameter	All FEN (n=361)	Placebo (n=285)
50th	133.6	144.0
75th	197.3	207.1
LDL-C/HDL-C ratio		
mean	4.3	4.7
25th	3.2	3.3
50th	4.1	4.3
75th	5.0	5.6

It is evident from this table that the majority of this cohort had moderate to severe hypercholesterolemia and mild-to-moderate triglyceride elevations. This population was not comprised of individuals with very low HDL-C levels.

Mean % Changes in HDL-C from Baseline by Dyslipidemia
The effects of fenofibrate and placebo in the pooled cohort were evaluated by the following strata:

- Type IIa defined as baseline LDL-C > 160 mg/dL and TG < 150 mg/dL
- Type IIb defined as baseline LDL-C > 160 mg/dL and TG ≥ 150 mg/dL
- Type IV defined as baseline LDL-C < 160 mg/dL and TG ≥ 150 mg/dL

Table 3 summarizes the mean percent changes in HDL-C by Type IIa and IIb dyslipidemia. The number of Type IV patients was inadequate to assess a reliable effect of drug treatment (fenofibrate n=30; placebo n=19).

Table 3. Mean % Change from Baseline in HDL-C and TG in Type IIa/IIb Patients by Treatment Group

Dyslipidemia	HDL-C	TG
Type IIa	mean baseline 58.1mg/dL	mean baseline 101.7 mg/dL
Fenofibrate (n=193)	+9.8%*	-23.5%*
Placebo (n=141)	+2.6%	+11.7%
Type IIb	mean baseline 46.7 mg/dL	mean baseline 231.9 mg/dL
Fenofibrate (n=126)	+14.6%*	-35.9%*
Placebo (n=116)	+2.3%	+0.9%

*p=<0.05 vs. placebo

After 3 to 6 months of treatment with fenofibrate at doses equivalent to 300 mg tid, there were significant mean percent increases in HDL-C levels (+7.2% to 12.3%) from baseline compared to placebo (+2.3 to 2.6%). The percent increase was higher in those patients with lower baseline HDL-C levels as observed in the Type IIb dyslipidemics. Furthermore, the increases in HDL-C levels were associated with significant decreases in triglycerides. The changes observed in this pooled analysis were consistently demonstrated in the individual trials (ref: NDA 19-304, S005).

SPONSOR'S PROPOSED LABELING CHANGES

This review will present only the proposed labeling changes that are relevant to the medical review discipline.

Medical Officer's Comments on Labeling

Clinical Pharmacology Section

The proposed labeling changes under this section are unacceptable for several reasons. First, the statement, *'the independent effect of raising HDL-C or lowering triglycerides (TG) on the risk of cardiovascular morbidity and mortality has not been determined'*, remains a fact. There are currently no clinical data attributing clinical benefits of drug treatment entirely to HDL-C raising.

! implies a clinical benefit associated with fenofibrate, a drug whose effect on cardiovascular morbidity and mortality has not been determined.

Indications and Usage
The proposed change under this section is acceptable.

CONCLUSIONS ON REVIEW OF NDA 21-203

Medical Officer's Recommendations
The clinical studies submitted to this NDA support an indication for HDL-C raising with fenofibrate. These studies, however, were conducted with the standard and micronized formulation of fenofibrate. Therefore, the approvability of this application relies on the demonstrated bioequivalence between the tablet and older formulations of fenofibrate.

In summary, this application is approvable pending the recommended labeling changes to the clinical pharmacology section and OCPB's determination of bioequivalence between the tablet and older fenofibrate formulations.

/S/ 8-30-00
Mary H. Parks, MD
Medical Officer
DMEDP (HFD-510)

concur:

/S/ 8-30-00
David G. Orloff, MD
Medical Team Leader
Deputy Director, DMEDP (HFD-510)

Recommendation code: AE

cc: NDA 21-203
SBJohnson/MASimoneau

REFERENCES

1. Castelli WP et al. Incidence of coronary heart disease and lipoprotein cholesterol levels. The Framingham Study. *JAMA* 1986;256:2835-2838.

2. Rubin EM et al. Inhibition of early atherogenesis in transgenic mice by human apolipoprotein A1. *Nature* 1991;353:265-267.

3. Zhong S et al. Increased coronary heart disease in Japanese-American men with mutations in the cholesteryl ester transfer gene despite increased HDL levels. *J Clin Invest* 1996;97:2917-2923.

4. Frick MH et al. Helsinki Heart Study: primary prevention trial with gemfibrozil in middle-aged men with dyslipidemia. *N Engl J Med* 1987;317:1237-1245.

5. Rubins HB et al. Gemfibrozil for the secondary prevention of coronary heart disease in men with low levels of high-density lipoprotein cholesterol. *N Engl J Med* 1999;341:410-418.

6. Summary of the Second Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel II). *JAMA* 1993;269(23):3015-3023.

THIS SECTION WAS DETERMINED **NOT** TO BE RELEASABLE

draft labeling

58 pages