

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

**APPLICATION NUMBER: 19-304/S005**

**CORRESPONDENCE**

Marlou Reed  
D-491, AP6B-1  
100 Abbott Park Road  
Abbott Park, IL 60064-3600  
(847) 937-6844  
fax - (847) 937-8002

**Abbott Laboratories**

# Fax

## BEST POSSIBLE COPY

**To:** Margaret Simoneau

**From:** Marlou Reed

**Fax:** (301) 443-8282

**Pages:** 3

**Phone:** (301) 827-8418

**Date:** April 4, 2000

**Re:** Draft Labeling

**CC:**

Urgent     For Review     Please Comment     Please Reply     Please Recycle

**Comments:**

Dear Margaret,

Attached is the revised draft labeling that was the subject of the voice mail I left you this morning. I believe these p values were inadvertently left out of the FDA revised table and would like to put them back in. I have also included the table showing the p-values.

Please let me know if we can make this change without holding up the approval process. I can send you revised draft labeling today if the change can be made.

Thanks,

Marlou

**APPEARS THIS WAY  
ON ORIGINAL**

2 Page(s) Redacted

Draft

Labeling

ActimPeg

Marlou Reed  
D-491, AP6B-1  
100 Abbott Park Road  
Abbott Park, IL 60064-3500  
(847) 937-6844  
fax - (847) 937-8002

**Abbott Laboratories**

# Fax

**To:** Margaret Simoneau **From:** Marlou Reed

---

**Fax:** (301) 443-9282 **Pages:** 2

---

**Phone:** (301) 827-6418 **Date:** April 3, 2000

---

**Re:** Patent Information - NDA 18-304/S-005 **CC:**

Urgent     For Review     Please Comment     Please Reply     Please Recycle

**Comments:**

Dear Margaret,

Attached is the patent information you requested. Please let me know if you need more information.

Thanks,

Marlou

**APPEARS THIS WAY  
ON ORIGINAL**



**ABBOTT**

**Pharmaceutical Products Division**

Abbott Laboratories  
10 Abbott Park Road  
D 191 AP08 1SW  
Abbott Park, Illinois 60064-0108

April 3, 2000

Dr. John Jenkins  
Acting Director, Division of Metabolism & Endocrine  
Drug Products  
Food and Drug Administration, HFD-510  
ATTN: Document Control Room 14B-19  
5600 Fishers Lane  
Rockville, MD 20857

RE: **TRICOR™, (fenofibrate capsules), micronized-**  
**NDA 19-304/S-005**

**RESPONSE TO FDA REQUEST  
FOR INFORMATION  
Patent Information**

Dear Dr. Jenkins,

Reference is made to our approved New Drug Application 19-304 for Tricor™ (fenofibrate capsules), micronized, to our pending Supplement 005 which provides for an additional indication for Type II hyperlipidemia and to a request from Ms. Margaret Simoneau of your Division to provide patent information regarding this pending Supplement. We are herewith responding to that request.

All patent information regarding Supplement 005 to NDA 19-304 is cross-referred to the existing patent information contained in the currently approved application. There is no new patent information pertaining to Supplement 005.

Should you have any questions concerning this information, please do not hesitate to contact me directly.

Sincerely,  
ABBOTT LABORATORIES

Marijou Reed  
Associate Director, Regulatory Affairs  
(847) 937-8844, fax (847) 937-8002

**APPEARS THIS-WAY  
ON ORIGINAL**



**ABBOTT**

NDA SUPPLEMENT  
5E1-005-0L

**Pharmaceutical Products Division**

Abbott Laboratories  
100 Abbott Park Road  
D-491, AP6B-1SW  
Abbott Park, Illinois 60064-6108

March 24, 2000

**DUPLICATE**



Dr. John Jenkins  
Acting Director, Division of Metabolism & Endocrine  
Drug Products  
Food and Drug Administration, HFD-510  
ATTN: Document Control Room 14B-19  
5600 Fishers Lane  
Rockville, MD 20857

RE: **TRICOR™, (fenofibrate capsules), micronized**  
**NDA 19-304/S-005**

**RESPONSE TO FDA REQUEST FOR  
INFORMATION**  
Draft Labeling

Dear Dr. Jenkins,

Reference is made to our approved New Drug Application 19-304 for Tricor™ (fenofibrate capsules), micronized and to our pending Supplement 005 which provides for an additional indication for Type II hyperlipidemia and to a telefax dated March 23, 2000 which provided comments on the draft labeling from the Biopharmaceutics reviewers and to a telefax received today March 24, 2000 with further minor changes. Reference is also made to two telephone conversations between Abbott representatives and representatives of your Division and the Division of Biopharmaceutics during which labeling changes were discussed.

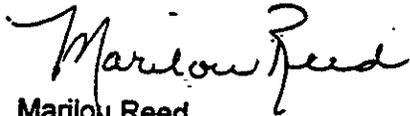
In the telephone conversation between Dr. Parks and I it was agreed that the last sentence in the third paragraph under "Dosage and Administration" could be changed to read "The maximum dose is 200 mg per day."

In the telephone conversation between Margaret Simoneau, Dr. Hae Young Ahn, and Dr. Steve Johnson and Abbott representatives Dr. Jim Ferraro and I it was discussed whether the term mild-to-moderate was accurate in describing the in vitro CYP2C9 results and whether additional studies using S-warfarin should be completed. Changes have been made in the draft labeling conforming to the requested by the Agency as received in a telefax on March 24, 2000 and it is understood no further drug interaction studies will be required:

Appended is the final draft labeling with all changes made in accordance with the latest telefax and the further agreements in the telephone conversations since the last submission dated March 17, 2000. One copy has all changes from the original draft labeling highlighted for ease of review and the other copy is a clean copy of the final text.

Should you have any questions concerning this information, please do not hesitate to contact me directly.

Sincerely,  
ABBOTT LABORATORIES



Mariou Reed  
Associate Director, Regulatory Affairs  
(847) 937-6844, fax (847) 937-8002

APPEARS THIS WAY  
ON ORIGINAL



**ABBOTT**

ORIGINAL

NDA SUPP AMEND

SEI-005 BL

**Pharmaceutical Products Division**

Abbott Laboratories  
100 Abbott Park Road  
D-491, AP6B-1SW  
Abbott Park, Illinois 60064-6108

March 17, 2000



Dr. Solomon Sobel  
Director, Division of Metabolism & Endocrine  
Drug Products  
Food and Drug Administration, HFD-510  
ATTN: Document Control Room 14B-19  
5600 Fishers Lane  
Rockville, MD 20857

RE: **TRICOR™, (fenofibrate capsules), micronized  
NDA 19-304/S-005**

**RESPONSE TO FDA REQUEST  
FOR INFORMATION  
Draft Labeling**

Dear Dr. Sobel,

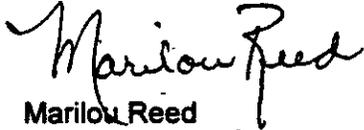
Reference is made to our approved New Drug Application 19-304 for Tricor™ (fenofibrate capsules), micronized and to our pending Supplement 005 which provides for an additional indication for Type II hyperlipidemia. Reference is also made to a telephone conversation between Dr. David Orloff, Dr. Mary Parks and Margaret Simoneau and Abbott Representatives today regarding the proposed changes to the labeling. We are herewith providing revised draft labeling in accordance with that telephone conversation.

Appended are two copies of the revised draft labeling. One copy has the highlighted changes in accordance with our discussions and the other copy is a clean text. Under the "Clinical Trials" section we have calculated the mean baseline lipid values using all 646 ISE patients. The changes from the FDA text using this patient population are highlighted in this section.

Subsequent to our discussions this morning, we noted under "Dosage and Administration" under the third paragraph the text reads "The maximum dose is three 67 mg capsules or one 200 mg capsule." We believe that statement is left over from the approval of our additional dosage forms 134 mg and 200 mg capsules. We believe the sentence should read "The maximum dose is 200 mg " and would like to make that change on the next revision.

Should you have any questions concerning this information, please do not hesitate to contact me directly.

Sincerely,  
ABBOTT LABORATORIES



Marilou Reed  
Associate Director, Regulatory Affairs  
(847) 937-6844, fax (847) 937-8002

REVIEWS COMPLETED	
CSO ACTION:	
<input type="checkbox"/> LETTER	<input type="checkbox"/> N.A.I. <input type="checkbox"/> MEMO
CSO INITIALS	DATE

APPEARS THIS WAY  
ON ORIGINAL



**ABBOTT**

**ORIGINAL**

**Pharmaceutical Products Division**

Abbott Laboratories  
100 Abbott Park Road  
D-491, AP6B-1SW  
Abbott Park, Illinois 60064-6108

**NDA SUPP AMEND**  
*501-005/B2*



March 2, 2000

**Dr. Solomon Sobel**  
Director, Division of Metabolism & Endocrine  
Drug Products  
Food and Drug Administration, HFD-510  
ATTN: Document Control Room 14B-19  
5600 Fishers Lane  
Rockville, MD 20857

**RE: TRICOR™, (fenofibrate capsules), micronized  
NDA 19-304/S-005**

**RESPONSE TO FDA REQUEST  
FOR INFORMATION**  
Clinical/Statistical

Dear Dr. Sobel,

Reference is made to our approved New Drug Application 19-304 for Tricor™ (fenofibrate capsules), micronized and to our pending Supplement 005 which provides for an additional indication for Type II hyperlipidemia. Reference is also made to a telephone conversation between Dr. David Hoberman and myself on February 28, 2000 during which Dr. Hoberman requested additional information on the group of subjects used for the efficacy analysis.

We are herewith submitting the additional information as a follow-up to the telefax of February 29, 2000 that included the appended information.

Should you have any questions concerning this information, please do not hesitate to contact me directly.

Sincerely,  
ABBOTT LABORATORIES

**Marilou Reed**  
Associate Director, Regulatory Affairs  
(847) 937-6844, fax (847) 937-8002

REVIEWS COMPLETED	
CSO ACTION:	
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CSO INITIALS	DATE

**ABBOTT**

**ORIGINAL**

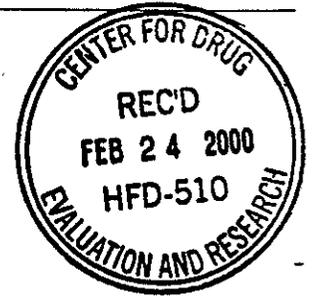
**Pharmaceutical Products Division**

Abbott Laboratories  
100 Abbott Park Road  
D-491, AP6B-1SW  
Abbott Park, Illinois. 60064-6108

February 23, 2000

**NDA SUPP AMEND**

*SEI-005-BM*



Dr. Solomon Sobel  
Director, Division of Metabolism & Endocrine  
Drug Products  
Food and Drug Administration, HFD-510  
ATTN: Document Control Room 14B-19  
5600 Fishers Lane  
Rockville, MD 20857

**RE: TRICOR™, (fenofibrate capsules), micronized  
NDA 19-304/S-005**

**RESPONSE TO FDA REQUEST  
FOR INFORMATION  
Clinical**

Dear Dr. Sobel,

Reference is made to our approved New Drug Application 19-304 for Tricor™ (fenofibrate capsules), micronized and to our pending Supplement 005 which provides for an additional indication for Type II hyperlipidemia. Reference is also made to a telephone conversation between Dr. Mary Parks and myself on February 22, 2000 during which Dr. Parks requested additional information on the group of subjects used for the efficacy analysis.

We are herewith submitting the additional information as a follow-up to the telefax of February 22, 2000 that included the appended information.

Should you have any questions concerning this information, please do not hesitate to contact me directly.

Sincerely,  
**ABBOTT LABORATORIES**

Mariou Reed  
Associate Director, Regulatory Affairs  
(847) 937-6844, fax (847) 937-8002

REVIEWS COMPLETED	
CSO ACTION:	
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CSO INITIALS	DATE



**ABBOTT**

**ORIGINAL**

**Pharmaceutical Products Division**

Abbott Laboratories  
100 Abbott Park Road  
D-491, AP6B-1SW  
Abbott Park, Illinois 60064-6108

**SUPPL NEW CORRESP**  
*SEI-005/SAC*

September 16, 1999



Dr. Solomon Sobel  
Director, Division of Metabolism & Endocrine  
Drug Products  
Food and Drug Administration, HFD-510  
ATTN: Document Control Room 14B-19  
5600 Fishers Lane  
Rockville, MD 20857

**RE: TRICOR™, (fenofibrate capsules), micronized  
NDA 19-304/S-005**

**AMENDMENT TO PENDING  
SUPPLEMENT  
Pediatric waiver**

Dear Dr. Sobel,

Reference is made to our approved New Drug Application 19-304 for Tricor™ (fenofibrate capsules), micronized, and to our pending supplement to our application to provide for the additional indication of adjunctive therapy to diet for treatment of adult patients with hypercholesterolemia (Fredrickson Type II hyperlipidemia), and to your letter dated July 14, 1999, acknowledging receipt of this supplement and requesting either a pediatric use development plan or waiver. We are herewith complying with that request.

Appended is a summary of information of the use of fenofibrate in the pediatric population along with our request for a waiver for pediatric development for Tricor. The basis of the waiver request is that the population that would benefit from this treatment is very small and that fenofibrate does not represent a meaningful therapeutic benefit over existing treatments.

Should you have any questions regarding this submission, please do not hesitate to contact me directly.

Sincerely,  
ABBOTT LABORATORIES

Marilou Reed  
Associate Director, Regulatory Affairs  
(847) 937-6844  
Fax (847) 937-8002

REVIEWS COMPLETED	
CSC ACTION:	
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INITIALS	DATE



**ABBOTT**

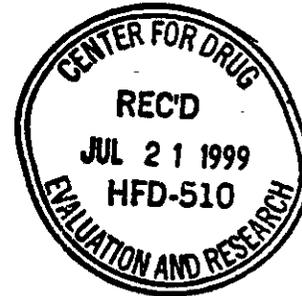
**Pharmaceutical Products Division**

Abbott Laboratories  
100 Abbott Park Road  
D-491, AP6B-1SW  
Abbott Park, Illinois 60064-6108

July 20, 1999

Dr. Solomon Sobel  
Director, Division of Metabolism & Endocrine  
Drug Products  
Food and Drug Administration, HFD-510  
ATTN: Document Control Room 14B-19  
5600 Fishers Lane  
Rockville, MD 20857

51101 NEW CORRESP  
SEI-005/SNC



**RE: TRICOR™, (fenofibrate capsules), micronized  
NDA 19-304/S-005**

**AMENDMENT TO PENDING  
SUPPLEMENT  
CD ROM discs**

Dear Dr. Sobel,

Reference is made to our approved New Drug Application 19-304 for Tricor™ (fenofibrate capsules), micronized and to our pending supplement to our application to provide for the additional indication of adjunctive therapy to diet for treatment of adult patients with hypercholesterolemia (Fredrickson Type II hyperlipidemia). In our original submission we had made the commitment to provide certain information on CD ROM as a review aid within three weeks of that submission. We are hereby fulfilling that commitment by providing one set of discs in the Archival copy and one set each in the Clinical and Statistical Technical Review copies.

Included in this submission is a User's Guide describing the background of the information on each disc and the complete table of contents for each disc. There is no commitment that the information on the discs is a representation on a page-by-page basis of the paper copy of the submission. However, we do commit that the information contained on the discs is an accurate representation of the information in the official paper copy.

Should you have any questions concerning this submission, please do not hesitate to contact me directly.

Sincerely,  
**ABBOTT LABORATORIES**

Marlou Reed  
Associate Director, Regulatory Affairs  
(847) 937-5844  
Fax (847) 937-8002

**APPEARS THIS WAY  
ON ORIGINAL**

**SIMONEAUM  
APPOINTMENT DETAILED  
24-Mar-2000 to 24-Mar-2000**

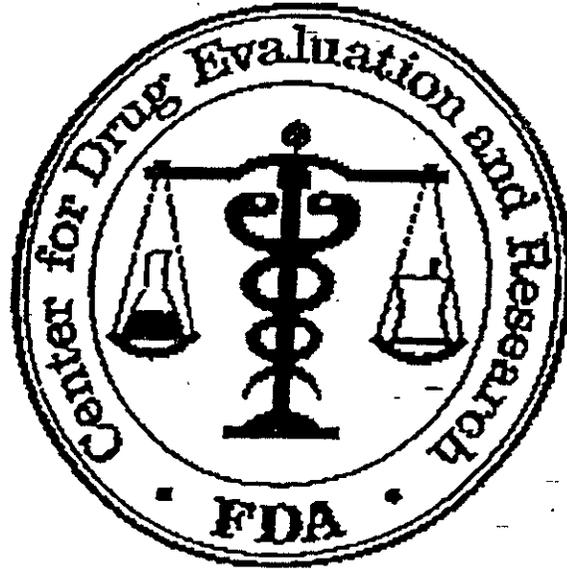
Date: Friday, 24-Mar-2000	Time: 10:30am	Length: 01:00 Hrs:Min
Subject: NDA 19-304/S-005 Tricor	Loc: #PKLN_1456	
Attendees		
<b>SIMONEAUM, AHNH, JOHNSONST, #510CAL,</b>		
Agenda		
T-con labeling meeting with Abbott to discuss biopharm comments faxed to sponsor on March 23rd --		
Abbott Attendees: Marilou Reed Jim Ferrero		
<b>APPEARS THIS WAY ON ORIGINAL</b>		

**Key to Attendee Status**

<b>Bold</b> = Confirmed	<u>Underline</u> = Rejected	All Others = Pending
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FOOD AND DRUG ADMINISTRATION  
DIVISION OF METABOLIC AND  
ENDOCRINE DRUG PRODUCTS  
5600 FISHERS LANE  
ROCKVILLE, MARYLAND 20857

DATE: *March 23, 2000*



TO:

Name: *Marilyn Reed*

Fax No.: *847-937-8002*

Phone No.: *847-937-6844*

Location: *Abbott*

Pages: *3* (including cover)

FROM:

Name: Margaret Simoneau

Fax No.: (301) 443-9282

Phone No.: (301) 827-6418

Location: FDA

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Comments:

*NDA 19-304/S-005*

*Clin Pharm + Biopharm Review Comments*

NDA 19-304 Tricor  
Abbott Laboratories  
Submission date: June 30, 1999  
Supplement 005  
Clinical Pharmacology and Biopharmaceutics Review Comments  
Labeling Comments

(Where applicable, ~~strikeout~~ text should be removed from labeling. Double underlined text should be added to labeling. \* Indicates an explanation only and is not intended to be included in the labeling).

#### **Pharmacokinetics/Metabolism**

Clinical experience has been obtained with two different formulations of fenofibrate: a "micronized" and "non-micronized" formulation, which have been demonstrated to be bioequivalent. Comparisons of blood levels following oral administration of both formulations in healthy volunteers demonstrate that a single capsule containing 67 mg of the "micronized" formulation is bioequivalent to 100 mg of the "non-micronized" formulation. Three capsules containing 67 mg TRICOR are bioequivalent to a single 200 mg TRICOR capsule.

\* These changes are acceptable. Bioequivalence between the micronized and non-micronized formulation was established in the original NDA, 19-304. Dosage-form equivalence between 67 mg and 200 mg capsules was established in supplement 003.

#### **Metabolism**

Following oral administration, fenofibrate is rapidly hydrolyzed by esterases to the active metabolite, fenofibric acid; no unchanged fenofibrate is detected in plasma.

Fenofibric acid is primarily conjugated with glucuronic acid and then excreted in urine. A small amount of fenofibric acid is reduced at the carbonyl moiety to a benzhydrol metabolite which is, in turn, conjugated with glucuronic acid and excreted in urine.

*In vivo* metabolism data indicate that neither fenofibrate or fenofibric acid undergo oxidative metabolism (e.g., cytochrome P450) to a significant extent.

\* This claim is substantiated in the following citation: Weil A, Caldwell J, Strolin-Benedetti M. The metabolism and disposition of <sup>14</sup>C-fenofibrate in human volunteers. *Drug Metab Dispos.* 1987;18(1):115-120. Metabolites of this study include fenofibric acid, the benzhydrol, and their ester glucuronides.

#### **Excretion**

After absorption, fenofibrate is mainly excreted in the urine in the form of metabolites, primarily fenofibric acid and fenofibric acid glucuronide. After administration of radiolabelled fenofibrate, approximately 60% of the dose appeared in the urine and 25% was excreted in the feces.

Fenofibric acid is eliminated with a half-life of 20 hours, allowing once daily administration in a clinical setting.

\* This clarification is acceptable.

#### **Special Populations**

##### ***Pediatrics***

TRICOR has not been investigated in adequate and well-controlled trials in pediatric patients.

\* Wording is changed to reflect the FDA's more recent language used for the pediatrics subheading.

##### ***Race***

The influence of race on the pharmacokinetics of fenofibrate has not been studied, however, fenofibrate is not metabolized by enzymes known for exhibiting inter-ethnic variability. Therefore, inter-ethnic pharmacokinetic differences are very unlikely.

\* Acceptable

6\* The grammatical correction is acceptable.

### Drug-drug Interactions

6\* Further *in vitro* drug interaction studies using S-warfarin should be completed.

**Concomitant HMG-CoA reductase inhibitors:** The combined use of TRICOR and HMG-CoA reductase inhibitors should be avoided unless the benefit of further alterations in lipid levels is likely to outweigh the increased risk of this drug combination.

In a single-dose drug interaction study in 23 healthy adults \_\_\_\_\_, the concomitant administration of TRICOR and pravastatin \_\_\_\_\_ resulted in no clinically important difference in the pharmacokinetics of fenofibric acid, pravastatin or its active metabolite 3 $\alpha$ -hydroxy iso-pravastatin when compared to either drug given alone.

\_\_\_\_\_ fibric acid derivatives and HMG-CoA reductase inhibitors has been associated, in numerous case reports, with rhabdomyolysis, markedly elevated creatine kinase (CK) levels and myoglobinuria, leading in a high proportion of cases to acute renal failure.

6\* The language used in this section is misleading and has an overtone that suggests that the combinations of Tricor™ and HMG-CoA reductase inhibitors are not associated with rhabdomyolysis – see Medwatch report # 1973813 (MFR Report #: B032673). In addition, the short-term studies, cited as the basis for these labeling additions, are not sufficient. In many of these studies, either low doses of HMG-CoA reductase inhibitor or fibrate derivative was used, or the concomitant agents were given in a manner which would decrease the bioavailability of one of the agents. Finally, results of the *in vivo* study submitted in this application shows increased parent pravastatin concentrations and statistically significant differences in  $C_{max}$  and AUC values for the pravastatin metabolite when administered with Tricor™. However, this was only a single dose study and "clinical significance" may be understated.

### Drug Interactions

**Oral Anticoagulants:** CAUTION SHOULD BE EXERCISED WHEN ANTICOAGULANTS ARE GIVEN IN CONJUNCTION WITH TRICOR. THE DOSAGE OF THE ANTICOAGULANTS SHOULD BE REDUCED TO MAINTAIN THE PROTHROMBIN TIME AT THE DESIRED LEVEL TO PREVENT BLEEDING COMPLICATIONS. FREQUENT PROTHROMBIN DETERMINATIONS ARE ADVISABLE UNTIL IT HAS BEEN DEFINITELY DETERMINED THAT THE PROTHROMBIN LEVEL HAS STABILIZED.

6\* The position does not seem to be changed.

**HMG-CoA reductase inhibitors:** The combined use of TRICOR and HMG-CoA reductase inhibitors should be avoided unless the benefit of further alterations in lipid levels is likely to outweigh the increased risk of this drug combination (see WARNINGS).

6\* Changes are acceptable.

Cleared for faxing by: \_\_\_\_\_

IS/ 3/23/00

SIMONEAUM  
APPOINTMENT DETAILED  
17-Mar-2000 to 17-Mar-2000

Date: Friday, 17-Mar-2000

Time: 09:30am

Length: 01:00 Hrs:Min

Subject: NDA 19-304/S-005

Loc: #PKLN\_1456

Attendees

**SIMONEAUM**, **ORLOFFD**, **PARKSM**, #510CAL,

Agenda

T-con with Abbott to discuss labeling (regarding clinical sections)  
Biopharm comments will be discussed at a later date

Abbott Attendees:

J. Lancaster  
J. Devlin  
R. Altman  
M. Reed  
M. Drew

Contract Research Attendees:

\_\_\_\_\_  
\_\_\_\_\_  
\_\_\_\_\_  
\_\_\_\_\_

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ON ORIGINAL

Key to Attendee Status

**Bold** = Confirmed

Underline

= Rejected

All Others = Pending

8 Page(s) Redacted

Draft

Labeling

## Meeting Minutes

Division of Metabolic and Endocrine Drug Products  
NDA 19-304/S-005

Date: Wednesday, August 4, 1999

Location: Parklawn 1456

Time: 12:00-12:45 PM

### FDA Attendees:

Dr. Orloff

Dr. Parks

H. Ahn

R. Steigerwalt

D. Hoberman

M. Simoneau

This was a **Filing Meeting** for Tricor (fenofibrate capsules), micronized, efficacy supplement S-005. The supplement is to provide for an additional indication as adjunctive therapy to diet for the reduction of LDL-C, total Cholesterol, Triglycerides and Apo B in adult patients with primary hypercholesterolemia or mixed dyslipidemia (Frederickson Types 11a and 11b) with triglycerides less than 250 mg/dL.

### Discussion:

- Clinical- no filing issues and the financial disclosure form was submitted.
- Pharmacology- Ron Steigerwalt said that there were no pharm/ tox issues.
- Chemistry- Prior to the meeting, Chien-Hua Niu said that there were no chemistry issues.
- Biopharm- There were no filing issues according to Hae-Young Ahn.
- Biostatistics- David Hoberman said there were no filing issues.
- DSI- none needed.
- S-005 will be a standard review.
- Clinical Audits- none needed; trials have been completed.
- Advisory Committee- not needed.
- Review Goal Date with labeling- May 1, 2000 (User Fee at 10 months). Reviews are to be done by April 1, 1999.

Minutes preparer: M. Simoneau

IS/

8/5/99

Concurrence Chairman: Dr. Orloff

IS/

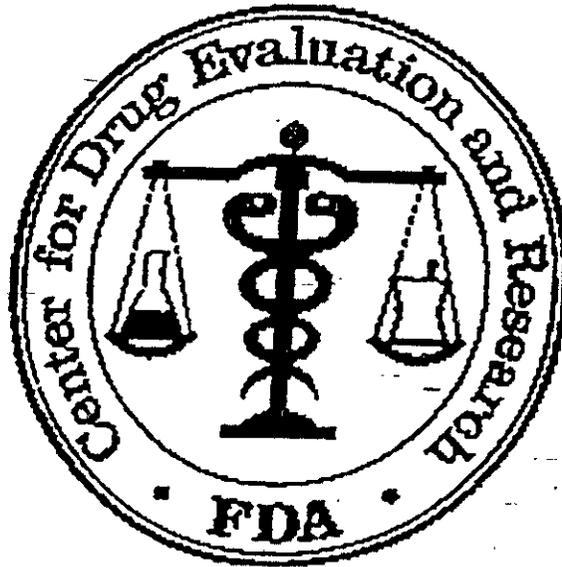
8/5/99

cc:Original NDA 19-304/S-005

DivFile

FOOD AND DRUG ADMINISTRATION  
DIVISION OF METABOLIC AND  
ENDOCRINE DRUG PRODUCTS  
5600 FISHERS LANE  
ROCKVILLE, MARYLAND 20857

DATE: *March 23, 2000*



TO:

Name: *Marion Reed*

x No.: *847-937-8002*

Phone No.: *847-937-6844*

Location: *Abbott*

Pages: *2* (including cover)

FROM:

Name: Margaret Simoneau

Fax No.: (301) 443-9282

Phone No.: (301) 827-6418

Location: FDA

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Comments:

*NOA 19-304/S-005*

*Clin Pharm + Biopharm Review Comments  
Revision*



# TELEFAX

TO: Marilou Reed

Abbott Laboratories

FAX: 1-847-937-8002

PHONE: \_\_\_\_\_

FROM: Mary Parks, MD

Food and Drug Administration  
Division of New Drug Chemistry II  
5600 Fishers Lane, HFD-820  
Rockville, Maryland 20857-1706

FAX: (301)827-0878

PHONE: (301)827-6420

DATE:

PAGES: 9 (Inclusive)

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Food and Drug Administration  
Division of New Drug Chemistry II  
5600 Fishers Lane- HFD-820  
Rockville, Maryland 20857-1706

8 Page(s) Redacted

Draft

Labeling

# Electronic Mail Message

Date: 4/19/00 10:59:11 AM  
From: Mary Parks ( PARKSM )  
To: Margaret Simoneau ( SIMONEAUM )  
To: Enid Galliers ( GALLIERS )  
Subject: tricor

Margaret,

There were no safety updates submitted for NDA 19-304/S-005 because all the trials reviewed in this application were conducted during the time period 1984 go 1994. Safety information for these trials were complete and sent with the initial efficacy submission.

Mary

ISI  
4-19-00

APPEARS THIS WAY  
ON ORIGINAL

Memorandum

Department of Health and Human Services  
Public Health Service  
Food and Drug Administration  
Center for Drug Evaluation and Research

Date:

From: David Hoberman, Ph.D., HFD-715

Subject: Label for fenofibrate Capsules (Tricor)

To: File (NDA# 19-305/S-005)

The only statistical issue in this application concerned a table which listed percent changes from baseline in four serum lab values (Total Cholesterol, LDL-C, HDL-C and Triglycerides) for three subgroups culled from four randomized controlled trials: all patients, Fredrickson 2a patients and Fredrickson 2b patients. The sponsor had simply pooled patients over the trials to construct a 'meta-analysis'. This reviewer produced a corresponding table using ANOVA with treatment and trial as factors using lsmeans as estimates. Results were very similar to those produced by the sponsor.

ISI

David Hoberman, Ph.D.

Concur: Dr. Sahlroot

ISI 3/23/00

Dr. Nevius

ISI 3/23/00

cc:

Arch NDA# 19-305

HFD-510

HFD-510/MParks, DOrloff

HFD-715/DHoberman, DOB2, Chron

APPEARS THIS WAY  
ON ORIGINAL

Mariou Reed  
D-491, AP68-1  
100 Abbott Park Road  
Abbott Park, IL 60064-3500  
(847) 937-6844  
fax - (847) 937-8002

**APPROVED**

APR 24 2000

*Dr. Orloff*

**Abbott Laboratories**

**Fax**

**BEST POSSIBLE COPY**

To: Margaret Simonese From: Mariou Reed  
Fax: (301) 443-9282 Pages: 14  
Phone: (301) 827-6418 Date: April 11, 2000  
Re: Draft Labeling CC:

Urgent     For Review     Please Comment     Please Reply     Please Recycle

Comments:

Dear Margaret,

Attached is the revised draft labeling containing all the changes that were discussed with Dr. Orloff on 4/10/00 and 4/11/00. The hard copy was Fed-Xed today so you should have it tomorrow.

Thanks,

*Mariou*  
Mariou

*Labeling accepted*

*ISI*  
*4-13-00*

13 Page(s) Redacted

DRAFT

LABELING



**ABBOTT**

DUPLICATE

**Pharmaceutical Products Division**

Abbott Laboratories  
100 Abbott Park Road  
D-491 AP6B-1SW  
Abbott Park, Illinois 60064-6108

April 11, 2000

Dr. John Jenkins  
Acting Director, Division of Metabolism & Endocrine  
Drug Products  
Food and Drug Administration, HFD-510  
ATTN: Document Control Room 14B-19  
5600 Fishers Lane  
Rockville, MD 20857



RE: **TRICOR™, (fenofibrate capsules), micronized  
NDA 19-304/S-005**

**RESPONSE TO FDA REQUEST  
FOR INFORMATION  
Draft Labeling**

Dear Dr. Jenkins,

Reference is made to our approved New Drug Application 19-304 for Tricor™ (fenofibrate capsules), micronized and to our pending Supplement 005 which provides for an additional indication for Type II hyperlipidemia and to a teleconference between Ms. Margaret Simoneau and Dr. David Orloff of your Division and myself during which Dr. Orloff requested changes to the current draft labeling. Reference is also made to a telefax sent on April 10, 2000 that included revised draft labeling which contained the requested changes. Additional reference is made to further telephone conversations today between Ms. Simoneau and myself during which an additional change was made to the Adverse Events section of labeling in agreement with Dr. Orloff.

We are herewith submitting the draft labeling identical to the text submitted by telefax on April 10, 2000 with the one additional change made to the Adverse Events section.

Should you have any questions concerning this information, please do not hesitate to contact me directly.

Sincerely,  
ABBOTT LABORATORIES

Marilou Reed  
Associate Director, Regulatory Affairs  
(847) 937-6844, fax (847) 937-8002

**APPEARS THIS WAY  
ON ORIGINAL**

DEPARTMENT OF HEALTH AND HUMAN SERVICES  
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN  
ANTIBIOTIC DRUG FOR HUMAN USE  
(Title 21, Code of Federal Regulations, 314 & 601)

Form Approved: OMB No. 0910-0338  
Expiration Date: April 30, 2000  
See OMB Statement on page 2

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT Abbott Laboratories	DATE OF SUBMISSION April 11, 2000
TELEPHONE NO (Include Area Code) (847) 937-6844	FACSIMILE (FAX) Number (Include Area Code) (847) 937-8002
APPLICANT ADDRESS (Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued) D-491/AP6B-1 100 Abbott Park Road Abbott Park, IL 60064-6108	AUTHORIZED U.S. AGENT NAME & ADDRESS (Number, Street, City, State, ZIP Code, telephone & FAX number) IF APPLICABLE

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (if previously issued)		NDA No. 19-304
ESTABLISHED NAME (e.g., Proper name, USP/USAN name) fenofibrate capsules, micronized	PROPRIETARY NAME (trade name) IF ANY Incor <sup>TM</sup>	
CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME (if any) 2-[4-(4-chlorobenzoyl)phenoxy]-2-methyl-propanoic acid, 1-methylethyl ester	CODE NAME (if any)	
DOSAGE FORM Capsule	STRENGTHS 67 mg, 134 mg, 200 mg	ROUTE OF ADMINISTRATION Oral
(PROPOSED) INDICATION(S) FOR USE Type IV, V hyperlipidemia, Type II hyperlipidemia		

APPLICATION INFORMATION

APPLICATION TYPE (check one) <input checked="" type="checkbox"/> NEW DRUG APPLICATION (21 CFR 314.50) <input type="checkbox"/> ABBREVIATED APPLICATION (ANDA, AADA, 21 CFR 314.94) <input type="checkbox"/> BIOLOGICS LICENSE APPLICATION (21 CFR part 601)
IF AN NDA, IDENTIFY THE APPROPRIATE TYPE <input checked="" type="checkbox"/> 505 (b) (1) <input type="checkbox"/> 505 (b) (2) <input type="checkbox"/> 507
IF AN ANDA OR AADA, IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION Name of Drug: _____ Holder of Approved Application: _____
TYPE OF SUBMISSION (check one) <input type="checkbox"/> ORIGINAL APPLICATION <input checked="" type="checkbox"/> AMENDMENT TO A PENDING APPLICATION <input type="checkbox"/> RESUBMISSION <input type="checkbox"/> PRESUBMISSION <input type="checkbox"/> ANNUAL REPORT <input type="checkbox"/> ESTABLISHMENT DESCRIPTION SUPPLEMENT <input type="checkbox"/> SUPAC SUPPLEMENT <input type="checkbox"/> EFFICACY SUPPLEMENT <input type="checkbox"/> LABELING SUPPLEMENT <input type="checkbox"/> CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT <input checked="" type="checkbox"/> OTHER
REASON FOR SUBMISSION Revised draft labeling
PROPOSED MARKETING STATUS (check one) <input checked="" type="checkbox"/> PRESCRIPTION PRODUCT (Rx) <input type="checkbox"/> OVER THE COUNTER PRODUCT (OTC)
NUMBER OF VOLUMES SUBMITTED: _____ THIS APPLICATION IS <input checked="" type="checkbox"/> PAPER <input type="checkbox"/> PAPER AND ELECTRONIC <input type="checkbox"/> ELECTRONIC

ESTABLISHMENT INFORMATION

Provide locations of a) manufacturing, packaging and control sites for drug substance and drug product (combination sheets may be used if necessary) y) include name, address, contact telephone number, registration number (CFR), DMF number and manufacturing steps and/or type of testing (e.g. Final dosage form conducted at the site. Please indicate whether the site is ready for inspection or not, when it will be ready. Stability testing)

Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)

This application contains the following items: (Check all that apply)

1	Index
<input checked="" type="checkbox"/>	2 Labeling (check one) <input checked="" type="checkbox"/> Draft Labeling <input type="checkbox"/> Final Printed Labeling
3	Summary (21 CFR 314.50 (c))
4	Chemistry section
	A. Chemistry, manufacturing, and controls information (e.g. 21 CFR 314.50 (d) (1), 21 CFR 601.2)
	B. Samples (21 CFR 314.50 (e) (1), 21 CFR 601.2 (e)) (Submit only upon FDA's request)
	C. Methods validation package (e.g. 21 CFR 314.50 (e) (2) (i), 21 CFR 601.2)
5	Nonclinical pharmacology and toxicology section (e.g. 21 CFR 314.50 (d) (2), 21 CFR 601.2)
6	Human pharmacokinetics and bioavailability section (e.g. 21 CFR 314.50 (d) (3), 21 CFR 601.2)
7	Clinical Microbiology (e.g. 21 CFR 314.50 (d) (4))
8	Clinical data section (e.g. 21 CFR 314.50 (d) (5), 21 CFR 601.2)
9	Safety update report (e.g. 21 CFR 314.50 (d) (5) (vi) (b), 21 CFR 601.2)
10	Statistical section (e.g. 21 CFR 314.50 (d) (6), 21 CFR 601.2)
11	Case report tabulations (e.g. 21 CFR 314.50 (f) (1), 21 CFR 601.2)
12	Case reports forms (e.g. 21 CFR 314.50 (f) (2), 21 CFR 601.2)
13	Patent information on any patent which claims the drug (21 U.S.C. 355 (b) or (c))
14	A patent certification with respect to any patent which claims the drug (21 U.S.C 355 (b) (2) or (j) (2) (A))
15	Establishment description (21 CFR Part 600, if applicable)
16	Debarment certification (FD&C Act 306 (k)(1))
17	Field copy certification (21 CFR 314.50 (k) (3))
18	User Fee Cover Sheet (Form FDA 3397)
19	OTHER (Specify)

**CERTIFICATION**

I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

1. Good manufacturing practice regulations in 21 CFR 210 and 211, 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600
3. Labeling regulations in 21 CFR 201, 606, 610, 660 and/or 609
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR 202
5. Regulations on making changes in application in 21 CFR 314.70, 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on reports in 21 CFR 314.80, 314.81, 600.80 and 600.81
7. Local, state and Federal environmental impact laws

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate. Warning: a willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT <i>Marion Reed</i>	TYPED NAME AND TITLE Marion Reed, Associate Director	DATE April 11, 2000
ADDRESS (Street, City, State, and ZIP Code) 100 Abbott Park Road, D-491, AP6B-1 Abbott Park, IL 60014-6100		Telephone Number (847) 937-6844

Public reporting burden for this collection of information is estimated to average 40 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

DHHS Reports Clearance Officer  
Paperwork Reduction Project (0910-0338)  
Hubert H. Humphrey Building, Room 531-H  
200 Independence Avenue, S.W.  
Washington, DC 20201

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

Please DO NOT RETURN this form to this address

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Draft

Labeling

Marlou Reed  
D-491, AP58-1  
100 Abbott Park Road  
Abbott Park, IL 60084-3500  
(847) 937-6844  
fax (847) 937-8002

**Abbott Laboratories**

# Fax

**To:** Margaret Simoneau                      **From:** Marlou Reed

---

**Fax:** (301) 443-9282                      **Pages:** 14

---

**Phone:** (301) 827-6418                      **Date:** April 10, 2000

---

**Re:** Telecon 4/10/00                      **CC:**

---

**Urgent**       **For Review**       **Please Comment**       **Please Reply**       **Please Recycle**

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**Comments:**

Dear Margaret.

Attached is the revised labeling we have discussed today with Dr. Orloff. For ease of review I have put brackets around the text that was changed today. They changes are on pages 3, 7 and 8 of the labeling. Please let me know when I should send the hard copy.

Thanks,

*Marlou*  
Marlou Reed

**APPEARS THIS WAY  
ON ORIGINAL**

13 Page(s) Redacted

Draft

Labeling

Marlou Reed  
D-491, AP6B-1  
100 Abbott Park Road  
Abbott Park, IL 60094-3500  
(847) 937-6844  
fax (847) 937-8002

**Abbott Laboratories**

# Fax

**To:** Margaret Simoneau

**From:** Marlou Reed

**Fax:** (301) 443-9282

**Pages:** 14

**Phone:** (301) 827-6418

**Date:** April 7, 2000

**Re:** Telecon 4/7/00

**CC:**

**Urgent**

**For Review**

**Please Comment**

**Please Reply**

**Please Recycle**

**Comments:**

Dear Margaret,

Attached is the revised labeling we have discussed today with Dr. Orloff. For ease of review I have put brackets around the text that was changed today. Please let me know if I should send the hard copy of the labeling today.

Thanks,

*Marlou Reed*  
Marlou Reed

APPEARS THIS WAY  
ON ORIGINAL

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Draft

Labeling



**ABBOTT**

**NDA SUPP AMEND**  
**SEI-005-06**

**Pharmaceutical Products Division**

Abbott Laboratories  
100 Abbott Park Road  
D-491, AP6B-1SW  
Abbott Park, Illinois 60064-6108

March 24, 2000

**DUPLICATE**



Dr. John Jenkins  
Acting Director, Division of Metabolism & Endocrine  
Drug Products  
Food and Drug Administration, HFD-510  
ATTN: Document Control Room 14B-19  
5600 Fishers Lane  
Rockville, MD 20857

**RE: TRICOR™, (fenofibrate capsules), micronized**  
**NDA 19-304/S-005**

**RESPONSE TO FDA REQUEST FOR**  
**INFORMATION**  
Draft Labeling

Dear Dr. Jenkins,

Reference is made to our approved New Drug Application 19-304 for Tricor™ (fenofibrate capsules), micronized and to our pending Supplement 005 which provides for an additional indication for Type II hyperlipidemia and to a telefax dated March 23, 2000 which provided comments on the draft labeling from the Biopharmaceutics reviewers and to a telefax received today March 24, 2000 with further minor changes. Reference is also made to two telephone conversations between Abbott representatives and representatives of your Division and the Division of Biopharmaceutics during which labeling changes were discussed.

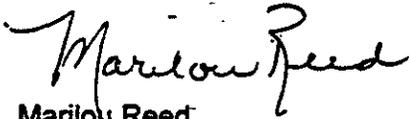
In the telephone conversation between Dr. Parks and I it was agreed that the last sentence in the third paragraph under "Dosage and Administration" could be changed to read "The maximum dose is 200 mg per day."

In the telephone conversation between Margaret Simoneau, Dr. Hae Young Ahn, and Dr. Steve Johnson and Abbott representatives Dr. Jim Ferraro and I it was discussed whether the term mild-to-moderate was accurate in describing the in vitro CYP2C9 results and whether additional studies using S-warfarin should be completed. Changes have been made in the draft labeling conforming to the requested by the Agency as received in a telefax on March 24, 2000 and it is understood no further drug interaction studies will be required:

Appended is the final draft labeling with all changes made in accordance with the latest telefax and the further agreements in the telephone conversations since the last submission dated March 17, 2000. One copy has all changes from the original draft labeling highlighted for ease of review and the other copy is a clean copy of the final text.

Should you have any questions concerning this information, please do not hesitate to contact me directly.

Sincerely,  
ABBOTT LABORATORIES

A handwritten signature in cursive script that reads "Marilou Reed". The signature is written in black ink and is positioned above the typed name.

Marilou Reed  
Associate Director, Regulatory Affairs  
(847) 937-6844, fax (847) 937-8002

APPEARS THIS WAY  
ON ORIGINAL

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Draft

Labeling



**ABBOTT**

**Pharmaceutical Products Division**

Abbott Laboratories  
100 Abbott Park Road  
P.O. Box 191 AP6B 1SW  
Abbott Park Illinois, 60064 6108

**April 3, 2000**

**Dr. John Jenkins  
Acting Director, Division of Metabolism & Endocrine  
Drug Products  
Food and Drug Administration, HFD-510  
ATTN: Document Control Room 14B-19  
5800 Fishers Lane  
Rockville, MD 20857**

**RE: TRICOR™, (fenofibrate capsules), micronized  
NDA 19-304/S-005**

**RESPONSE TO FDA REQUEST  
FOR INFORMATION  
Patent Information**

Dear Dr. Jenkins,

Reference is made to our approved New Drug Application 19-304 for Tricor™ (fenofibrate capsules), micronized, to our pending Supplement 005 which provides for an additional indication for Type II hyperlipidemia and to a request from Ms. Margaret Simoneau of your Division to provide patent information regarding this pending Supplement. We are herewith responding to that request.

All patent information regarding Supplement 005 to NDA 19-304 is cross-referred to the existing patent information contained in the currently approved application. There is no new patent information pertaining to Supplement 005.

Should you have any questions concerning this information, please do not hesitate to contact me directly.

Sincerely,  
**ABBOTT LABORATORIES**

**Marjolein Reed  
Associate Director, Regulatory Affairs  
(847) 937-8844, fax (847) 937-8002**

**APPEARS THIS WAY  
ON ORIGINAL**