CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-656

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

EXCLUSIVITY SUMMARY FOR NDA # ____21-656___ SUPPL #_____

Trade Name ___TriCor Tablets____ Generic Name __fenofibrate __

Applicant Name ___Abbott Labs___ HFD # _____510_____

Approval Date If Known ___~ 11.05.2004_

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following question about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?
YES /_x_/ NO /___/

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3,SE4, SE5, SE6, SE7, SE8

_____

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES /___/ NO /__x__/

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

_____

_____

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

_____

_____

d) Did the applicant request exclusivity?

YES /___/ NO /_x_/

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

_____

e) Has pediatric exclusivity been granted for this Active Moiety?

YES /___/ NO /__x/

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Writen Request?

_____

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES /___/ NO /_x_/

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product. N/A

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /___/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# _____ _____

NDA# _____ _____

NDA# _____ _____

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES /___/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# _____ _____

NDA# _____ _____

NDA# _____ _____

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.) IF "YES" GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete

remainder of summary for that investigation.

YES /___/ NO /__x/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES /___/ NO /___/

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

_____

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /___/ NO /___/

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /___/ NO /___/

If yes, explain:

_____

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /___/ NO /___/

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES /___/ NO /___/

Investigation #2 YES /___/ NO /___/

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

_____ _____

_____ _____

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES /___/ NO /___/

Investigation #2 YES /___/ NO /___/

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

_____ _____

_____ _____

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

_____ _____

_____ _____

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1 !

IND # _____ YES /___/ ! NO /___/ Explain: _____

Investigation #2

IND # _____ YES /___/ ! NO /___/ Explain: _____

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1

YES /___/ Explain _____ ! NO /___/ Explain _____

_____ ! _____

_____ ! _____

Investigation #2

YES /___/ Explain _____ ! NO /___/ Explain _____

_____ ! _____

_____ ! _____

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /___/ NO /___/

If yes, explain: _____

_____

Signature Enid Galliers Date November 5, 2004
Title: CPMS, DMEDP (HFD-510)

Signature of Deputy Division Director: Mary H. Parks, MD
Date:

Form OGD-011347 Revised 05/10/2004

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/s/

Mary Parks
11/5/04 04:47:45 PM

PEDIATRIC PAGE

(Complete for all filed original applications and efficacy supplements)

NDA/BLA # : 21-656 **Supplement Type (e.g. SE5):** _____ **Supplement Number:**

Stamp Date: 30-OCT-2003 **Action Date:** 05-NOV-2004

HFD-510 **Trade and generic names/dosage form:** TriCor (fenofibrate) Tablets, 48 mg, 145 mg

Applicant: Abbott Labs **Therapeutic Class:** lipid altering agent

Indication(s) previously approved: Tricor (fenofibrate) Tablets, 48 mg and 145 mg, as adjunctive therapy to diet for treatment of adult patients with hypertriglyceridemia (Fredrickson Types IV and V hyperlipidemia) and to reduce elevated LDL-C, Total-C, Triglycerides and Apo B, and to increase HDL-C in adult patients with primary hypercholesterolemia or mixed dyslipidemia (Fredrickson Types IIa and IIb).

Each approved indication must have pediatric studies: Completed, Deferred, and/or Waived.

Number of indications for this application(s): 0 new indications - This is a new formulation with lower nominal strengths and dosing can be done without regard to meals (i.e., no food effect.)

Indication #1: _____

Is there a full waiver for this indication (check one)?

- ☐ **Yes: Please proceed to Section A.**
- ☐ **No: Please check all that apply: ____Partial Waiver ____Deferred ____Completed**
  NOTE: More than one may apply
  Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☒ **Other: This class of drugs is not effective for the one indication (heterozygous familial hypercholesterolemia) which would be treated in the pediatric population.**

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived:

Min_____	kg_____	mo._____	yr._____	Tanner Stage_____
Max_____	kg_____	mo._____	yr._____	Tanner Stage_____

Reason(s) for partial waiver:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**

- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Adult studies ready for approval**
- ☐ **Formulation needed**
- ☐ **Other:**_____

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred:

Min _____ **kg**_____ **mo.**_____ **yr.**_____ **Tanner Stage**_____
Max_____ **kg**_____ **mo.**_____ **yr.**_____ **Tanner Stage**_____

Reason(s) for deferral:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Adult studies ready for approval**
- ☐ **Formulation needed**

Other:_____

Date studies are due (mm/dd/yy): _____

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies:

Min _____ **kg**_____ **mo.**_____ **yr.**_____ **Tanner Stage**_____
Max_____ **kg**_____ **mo.**_____ **yr.**_____ **Tanner Stage**_____

Comments:

If there are additional indications, please proceed to Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

{See appended electronic signature page}

_____
Regulatory Project Manager

cc: **NDA 21-656**
HFD-960/ Grace Carmouze

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE DIVISION OF PEDIATRIC DRUG DEVELOPMENT, HFD-960, 301-594-7337.
(revised 12-22-03)

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/s/

Enid Galliers
11/5/04 05:15:44 PM

Division of Metabolic & Endocrine Drug Products

PROJECT MANAGER LABELING REVIEW #2

Application Number: NDA 21-656

Name of Drug: Tricor® (fenofibrate tablets), 48 mg and 154 mg

Sponsor: Abbott Laboratories

Materials Reviewed:

Submission Date(s): Draft Labeling September 9, 2004; received September 10, 2004:
Package Insert (PI)
Container labels: 48 mg/90-count bottle
48 mg/7-count Physician blister
145 mg/90-count bottle
145 mg/7-count Physician blister
Carton labels: 48 mg/4 Physician samples; 7-count each
145 mg/4 Physician samples; 7-count each

Background and Summary

On August 30, 2004, an Approvable letter was issued to Abbott Laboratories for the Tricor New Drug Application (NDA). A complete response was submitted to the Agency on September 9, 2004, reflecting the Agency proposed changes.

Review

Package Insert

The Agency proposed labeling issued in the August 30, 2004, action letter was compared to the currently proposed labeling dated September 9, 2004. Except for minor editorial changes, the Agency proposed changes from the August 30, 2004, action letter have been accepted by the firm.

Note: The firm states in their September 9, 2004, submission that under the Carcinogenesis, Mutagenesis, Impairment of Fertility section, a typographical error was identified in the proposed labeling as well as in the approved product Tricor (NDA 21-203) and was changed from:

[redacted]

to

"A 117-week carcinogenicity study was conducted in rats comparing three drugs: fenofibrate 10 and 60 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."

This change is acceptable per the Pharmacology/Toxicology Reviewer, Indra Antonipillai, Ph.D. on September 21, 2004.

The August 30, 2004, action letter has requested the firm to revise the list of excipients to indicate the actual ingredients in the film-coatings instead of the trade names for the coating materials. The firm has agreed and has made the following revisions:

Under the **DESCRIPTION** section, **Inactive Ingredients** subsection; from:

[redacted]

to

"48 mg tablets: polyvinyl alcohol, titanium dioxide, talc, soybean lecithin, xanthan gum, D & C Yellow #10 aluminium lake, FD&C Yellow #6/sunset yellow FCF aluminum lake, FD&C Blue #2/indigo carmine aluminum lake.

145 mg tablets: polyvinyl alcohol, titanium dioxide, talc, soybean lecithin, xanthan gum."

This change is acceptable per the August 30, 2004, action letter and the chemists review dated September 12, 2004.

STORAGE STATEMENT:
The August 30, 2004, action letter requested revision of the controlled room temperature statement to conform to the USP definition. The firm has completed this change.

Carton and Container Labels

STORAGE STATEMENT:
The August 30, 2004, action letter requested revision of the controlled room temperature statement to conform to the USP definition. The firm has completed this change.

Note: In the September 9, 2004, response to the August 30, 2004, action letter, the firm states that mock-ups of labeling for cartons (for bottles) are not provided because the bottles are shipped in corrugate boxes without any cartons. However, mock-up labeling for the physician sample, 7-count blister carton for 48 mg and 145 mg tablets was provided.

Conclusion

An approval letter should be drafted and final printed labeling requested.

Valerie Jimenez
Regulatory Project Manager, HFD-510

Drafted: V.J./Sept. 21, 2004
Revised/Initialed: E.G/ Sept. 27 and Oct. 28, 2004
Finalized: November X, 2004
Filename: C:/Tricor-N21656/Tricor-N21656/NDA.LR2.doc

CSO LABELING REVIEW

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/s/

Valerie Jimenez
11/3/04 01:19:19 PM
CSO

9/28/04

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

NDA 21-656

Abbott Laboratories
Attention: Ernesto J. Rivera, Pharm D.
Regulatory Affairs Manager
200 Abbott Park Road
D-491/AP30-1E
Abbott Park, IL 60064-6157

Dear Mr. Rivera:

We acknowledge receipt on September 10, 2004, of your September 9, 2004, resubmission to your new drug application for Tricor (fenofibrate) Tablets, 48 mg and 145 mg.

We consider this a complete, class 1 response to our August 30, 2004, action letter. Therefore, the user fee goal date is November 10, 2004.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We note that you have not fulfilled the requirement. We are waiving the requirement for pediatric studies for this application.

If you have any question, call me at (301) 827-9090.

Sincerely,

{See appended electronic signature page}

Valerie Jimenez
Regulatory Project Manager
Division of Metabolic and Endocrine Drug Products, HFD-510
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

Valerie Jimenez
9/28/04 10:07:07 AM

8/30/04

Division of Metabolic & Endocrine Drug Products

PROJECT MANAGER LABELING REVIEW

Application Number: NDA 21-656

Name of Drug: Tricor® (fenofibrate tablets), 48 mg and 154 mg

Sponsor: Abbott Laboratories

Materials Reviewed:

Submission Date(s): Draft Labeling: Package Insert (PI), container labels, carton labels, and 7-count blister package, October 29, 2003; received October 30, 2003. Amended labeling submitted June 1, 2004; received June 2, 2004.

Background and Summary

Lipidil (fenofibrate) Capsule, NDA 19-304, was approved on December 31, 1993, in 100 mg strength; however, it was never marketed in the United States. Abbott Laboratories acquired the application and the name was then changed to Tricor (fenofibrate) Capsules, and a micronized formulation which was approved for 67 mg strength in SCF-001 on February 9, 1998 in a supplement to NDA 19-304, 134 mg and 200 mg strengths were approved in SCF-003 on June 30, 1999. On November 10, 1999, the firm submitted an application for a new formulation of Tricor (fenofibrate) Tablets, 54 mg and 160 mg strengths, which was approved on September 4, 2001. On October 30, 2003, the firm submitted an application for Tricor which is indicated as adjunctive therapy to diet to reduce elevated LDL-C, Total-Cholesterol, Triglycerides and Apo B, and to increase HDL-C in adult patients with primary hypercholesterolemia or mixed dyslipidemia (Frederickson Types IIa and IIb). It is also indicated as adjunctive therapy to diet for treatment of adult patients with hypertriglyceridemia (Fredrickson Types IV and V hyperlipidemia). On May 14, 2004, the firm submitted a proposal for their trade name, changing Tricor (NDA 21-656) to Tricor and discontinuing their currently approved Tricor (NDA 21-203) product. The June 1, 2004, submission contains revised labeling (package insert (PI), stock bottles, and physician samples) that reflect the proposed Tricor trade name.

Review

Package Insert

The proposed labeling, submitted June 1, 2004, was compared to the referenced listed drug, Tricor (NDA 21-203, approved September 4, 2001). The following revisions have been made.

1. Throughout the package insert, has been removed from the trade name TRICOR.

This is an acceptable change per review by the Division of Medication Errors and Technical Support (DMETS) dated March 29, 2004, per DMEDP, and per Labeling and Nomenclature Committee.

2. All strengths have been changed from (**NDA 21-203**) 54 mg and 160 mg to (**NDA 21-656**) 48 mg and 154 mg.

This is an acceptable change.

In the review dated August 4, 2004, the biopharmaceutics reviewer recommended the Concomitant HMG-CoA Reductase Inhibitors subsection should be replaced with the text below.

The biopharmaceutics review dated August 4, 2004, requires revision of the **CLINICAL PHARMACOLOGY** section, **Pharmacokinetics/Metabolism, Drug-Drug Interactions,** and **Concomitant HMG-CoA Reductase Inhibitors** subsections in which the current subsection should be replaced with the text below.

Pharmacokinetics/Metabolism

Plasma concentrations of fenofibric acid after administration of three 48 mg or one 145 mg tablets are equivalent under fed conditions to one 200 mg capsule.

Drug-drug interactions

In vitro studies using human liver microsomes indicate that fenofibrate and fenofibric acid are not inhibitors of cytochrome (CYP) P450 isoforms CYP3A4, CYP2D6, CYP2E1, or CYP1A2. They are weak inhibitors of CYP2C19 and CYP2A6, and mild-to-moderate inhibitors of CYP2C9 at therapeutic concentrations.

Potentiation of coumarin-type anticoagulants has been observed with prolongation of the prothrombin time/INR.

Bile acid sequestrants have been shown to bind other drugs given concurrently. Therefore, fenofibrate should be taken at least 1 hour before or 4-6 hours after a bile acid binding resin to avoid impeding its absorption. (See WARNINGS and PRECAUTIONS).

Concomitant administration of fenofibrate (equivalent to 145 mg TRICOR) with pravastatin (40 mg) once daily for 10 days has been shown to increase the mean C_{max} and AUC values for pravastatin by 36% (range from 69% decrease to 321% increase) and 28% (range from 54% decrease to 128% increase), respectively, and for 3α-hydroxy-iso-pravastatin by 55% (range from 32% decrease to 314% increase) and 39% (range from 24% decrease to 261% increase), respectively, in 23 healthy adults.

A single dose of pravastatin had no clinically important effect on the pharmacokinetics of fenofibric acid.

Concomitant administration of fenofibrate (equivalent to 145 mg TRICOR) with atorvastatin (20 mg) once daily for 10 days resulted in an approximately 17% decrease (range from 67% decrease to 44% increase) in atorvastatin AUC values in 22 healthy males. The atorvastatin C_{max}values were not significantly affected by fenofibrate. The pharmacokinetics of fenofibric acid were not significantly affected by atorvastatin.

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.

Concomitant administration of fenofibrate (equivalent to 145 mg TRICOR) and pravastatin (40 mg) once daily for 10 days increased the mean C_{max} and AUC values for pravastatin by 36% (range from 69% decrease to 321% increase) and 28% (range from 54% decrease to 128% increase), respectively, and for 3α-hydroxy-iso-pravastatin by 55% (range from 32% decrease to 314% increase) and 39% (range from 24% decrease to 261% increase), respectively. (See also CLINICAL PHARMACOLOGY, Drug-drug interactions). The combined use of fibric acid derivatives and HMG-CoA reductase inhibitors has been associated, in the absence of a marked pharmacokinetic interaction, 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.

The use of fibrates alone, including TRICOR, may occasionally be associated with myositis, myopathy, or rhabdomyolysis. Patients receiving TRICOR and complaining of muscle pain, tenderness, or weakness should have prompt medical

evaluation for myopathy, including serum creatine kinase level determination. If myopathy/myositis is suspected or diagnosed, TRICOR therapy should be stopped.

The pharmacology/toxicology review dated July 13, 2004, requires revision of the **PRECAUTIONS** section, **Carcinogenesis, Mutagenesis, Impairment of Fertility** (replace only the first paragraphs) and **Pregnancy Category C** subsections in which the current subsection should be replaced with the text below.

Carcinogenesis, Mutagenesis, Impairment of Fertility:
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.

Pregnancy Category C:
Safety in pregnant women 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.

6. Changes in the **HOW SUPPLIED** section:
From (NDA 21-203)-
54 mg yellow tablets, imprinted with (Abbott symbol) and Abbo-Code identification letters "TA", available in bottles of 90 (**NDC** 0074-4009-90).

154 mg white tablets, imprinted with (Abbott symbol) and Abbo-Code identification letters "TC", available in bottles of 90 (**NDC** 0074-4013-90).

To (NDA 21-656)-
48 mg yellow tablets, imprinted with (Abbott symbol) and Abbo-Code identification letters "FI", available in bottles of 90 (**NDC** 0074-6122-90).

145 mg white tablets, imprinted with (Abbott symbol) and Abbo-Code identification letters "FO", available in bottles of 90 (**NDC** 0074-6123-90).

This an acceptable editorial change.

Container Labels

The currently approved draft bottle labels dated December 10, 2002, were compared to the submitted draft labels (June 1, 2004). The following changes were made:

1. To the 48 mg and 154 mg/90-count container label:
-Identifier changed from (NDA 21-203) 02-8331-R1 to (NDA 21-656) DN0994-V1.
-48 mg strength: Barcode and NDC number changed from (NDA 21-203) 300744009902 to (NDA 21-656) 300746122906.
-154 mg strength: Barcode and NDC number changed from (NDA 21-203) 300744013909 to (NDA 21-656) 300746123903.
-The distributor name was changed from (NDA 21-203):

"Manufactured for Abbott Laboratories,
North Chicago, IL 60064, U.S.A.
by Laboratoires Fournier, S.A.
21300 Chenôve, France
Made in France"

to (NDA 21-656):

"Manufactured for Abbott Laboratories,
North Chicago, IL 60064, U.S.A.
by Fournier Laboratories
Ireland Limited
Anngrove, Carrigtwohill
Co. Cork, Ireland
Product of Spain"

These changes are acceptable per the Chemists review dated August 12, 2004.

2. Changes to the 7-count blister package:

   - Included in the ODS consult response dated March 29, 2004, recommendations for the strength of the product to appear on each blister have been addressed in the June 1, 2004, submission. The labeling submitted subsequent to the March 29, 2004, review has the strengths on each blister.

Carton Labels

The carton labels for the 48 mg and 154 mg strengths were not submitted. The following changes were noted.

- The ODS consult response dated March 29, 2004, recommends changing the color of the Tricor 145 mg container label to a color aside from blue to further differentiate the 160 mg carton from the 145 mg carton. However, the firm plans to discontinue the 160 mg tablet of Tricor, therefore this will eliminate the potential for adverse events or incorrect dosing.

STORAGE STATEMENT:
The chemistry review requests revision of the controlled room temperature statement to conform to the USP definition.

Conclusion

An approvable letter should be drafted and labeling changes requested.

Valerie Jimenez
Regulatory Project Manager, HFD-510

Drafted: V.J./August 17, 2004
Revised/Initialed: E.G/ August 27 and 30, 2004
Finalized: August 30, 2004
Filename: C:/Tricor-N21656/Tricor-N21656/NDA.LR.doc

CSO LABELING REVIEW

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/s/

Valerie Jimenez
8/30/04 12:21:53 PM
CSO

Memorandum

Date: August 16th, 2004

From: David B. Lewis, Ph.D.

Subject: Nomenclature and labeling for TRICOR® (fenofibrate tablets, 48 mg and 145 mg)

To: NDA 21-656 Division File

This memorandum addresses an August 12, 2004, meeting held between members of the Labeling and Nomenclature Committee (LNC), Division of Medical Errors (DMETS), and Division of Metabolic and Endocrine Drug Products (DMEDP, HFD-510), regarding nomenclature and labeling issues for NDA 20-656. LNC input was requested *via* consult from the NDA 20-560 CSO, Valerie Jimenez.

The following FDA personnel attended the meeting:

Guiragos Poochikian, Chemist and Acting Chair of LNC
David B. Lewis, Chemist, LNC member, and current FDA representative on the USAN Council
W. Mike Adams, CMC Reviewer for NDA 21-656, co-located with HFD-510
Stephen Moore, CMC Team Leader for NDA 21-656
Valerie Jimenez, Regulatory Project Manager (RPM), HFD-510, for NDA 21-656
Yana Mille, Director Compendial Operations Staff, OPS
Denise Toyer, Deputy Director DMETS, ODS
Felecia Duffy, Reviewer, DMETS, ODS
CC: Carol Holquist, Director DMETS, ODS (attended earlier meeting on same subject)

Background: The nomenclature for NDA 21-656 TRICOR® (fenofibrate tablets, 48 mg and 145 mg) was addressed, regarding suitability for the drug product. NDA 21-656 provides for a reformulated drug product containing a drug substance (fenofibrate), which was processed by a different technique, to different physicochemical parameters (e.g., particle size), and proposed for market in different strengths; 48 and 145 mg, as opposed to 54 and 160 mg for the previously approved TRICOR® (fenofibrate) tablets. The Division required nomenclature that would differentiate between the presently approved TRICOR® product and the proposed NDA 21-656 product, which will replace the previous product after approval.

Conclusions from the meeting:

- The reformulated TRICOR® drug product, covered by NDA 21-656, is adequately differentiated from the presently approved TRICOR® drug product, covered by NDA 21-203, *by the difference in tablet strengths* (145 and 48 mg for NDA 21-656 *vs.* 160 and 54 mg for NDA 21-203).
- The use of the modifiers " [redacted] " is not recommended (concur with the DMETS consult review conclusion).
- [redacted]
- No further changes to the nomenclature are suggested.
- Drug product container and carton label should be flagged for a period of time (*e.g.*, 6 months) to alert the practitioner to the new product strength.
- The Description section of the Package Insert may contain factual information on particle size. The accuracy and appropriateness of the proposed text should ~~to~~ be reviewed by the HFD-510 (and co-locate) staff.
- A "Dear Doctor" and "Dear Pharmacist" letters should be drafted by the NDA applicant. These letters are to convey the following information:
    - The 48 mg and 145 mg Tricor® tablets replace the previously marketed 54 mg and 160 mg Tricor® tablets, which are being phased out following approval of NDA 21-656.
    - The linkage (comparison) between the 48 and 145 mg strengths and the 54 and 160 mg strengths should be appropriately addressed. The acceptability of the proposed text will ~~to~~ be reviewed by the HFD-510 (and co-locate) staff.
    - Any clinical or therapeutic differences (*e.g.*, food effect, adverse reactions) between the old and new tablet formulations should be described.

The Division should be alerted to very carefully examine the "Dear Doctor/Dear Pharmacist" letters, in order to prevent a situation allowing Abbott free reign to craft a letter that will allow them to discourage practitioners from using generic equivalents to the Tricor 54 mg and 160 mg tablets when they become available. For this reason, special attention should be given to the directions pertaining to switching patients from the 54 and 160 mg tablets to the new (reformulated) 48 and 145 mg tablets.

This opinion should be forwarded to DMEDP, and included in the NDA 21-656 Division File.

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/s/

David Lewis
8/27/04 03:26:38 PM
CHEMIST
Revised on the basis of suggestions/recommendations from G. Poochikian, E. Duffy, Y. Mille, and V. Jimenez. Consult review; not binding.

7/24/03

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-203

Abbott Laboratories
Attention: Marilou Reed
Associate Director, Regulatory Affairs
D-491/AP30-1E
200 Abbott Park Road
Abbott Park, IL 60064-6157

Dear Ms. Reed:

We received your June 18, 2003, correspondence on June 19, 2003, requesting a pre-NDA meeting to discuss submission of an NDA for a new formulation of fenofibrate (pre-assigned NDA 21-656). We considered your request and concluded the meeting is unnecessary. However, in order to assist you in your drug development program, we are providing the following information in response to questions included in your meeting request.

Abbott Questions are shown in regular font and FDA answers follow in bold text.

1. We propose to use the CTD format for the content and format of the documents, but the NDA will be organized in the e-NDA structure as defined in the Guidance for Industry, "Providing Regulatory Submissions in Electronic Format – NDAs" and "Submitting Marketing Applications According to the ICH-CTD Format – General Considerations".
    a. Items not included in the NDA will be listed as "Not Applicable".
    b. Abbott intends on including, by cross-reference, all previously submitted documentation throughout the NDA.

   Does the Agency agree with this plan?

   FDA Response:
   This is acceptable. If you have questions regarding technical aspects of electronic submissions, address them to the following email address: esubs@cder.fda.gov.

2. Will the Division consider waiving fully, or in part, the requirement for the paper review copy?

   FDA Response:
   The Agency waives the requirement for submission of complete paper review copies. However, it would be very helpful to receive a paper copy of Module 1 – jacketed in the appropriate color – for each review discipline.

3. Our plan is to provide copies of publications upon request and to not include them in the application. Is this acceptable?

   FDA Response:
   This is acceptable.

4. Abbott proposes to submit Case Report Tabulations following the Guidance for Industry noted in question 1 for only the two primary studies included in the submission (the definitive Biostudy M02-558 and the Food Effect Study). However, Abbott plans not to include patient profiles in the submission. Is this acceptable?

   FDA Response:
   This is acceptable.

If you disagree with our decision regarding your meeting request, you may discuss the matter with Enid Galliers, Chief, Project Management Staff, at (301) 827-6429. If the issue cannot be resolved at the division level, you may formally request reconsideration according to our guidance for industry titled *Formal Dispute Resolution: Appeals Above the Division Level* (February 2000). The guidance can be found at http://www.fda.gov/cder/guidance/2740fnl.htm.

Sincerely,

David G Orloff, M.D.
Director
Division of Metabolic and Endocrine Drug Products, HFD-510
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

Mary Parks
7/24/03 04:31:17 PM
for Dr. Orloff

5/13/04

MEMORANDUM OF TELECON

DATE: April 15, 2004

APPLICATION NUMBER: NDA 21-656, TriCor (fenofibrate) Tablets

BETWEEN:

Name: James Stolzenbach, Ph. D., Global Project Team Head
Guenter Bliach, Ph. D., Toxicology
Linda Gustavson, Ph. D., clinical Pharmacokinetics
Kathy McFarland, Ph.D., Regulatory Affairs
Todd E. Chermak, M.S., CMC Regulatory Affairs
Jeanne M. Fox, Regulatory Affairs
Gerard Heneghan, Ph. D., Project Leader, Pharmaceutical Analytical Research and Development
Yeshwant Sanzgiri, Ph. D., Pharmaceutical Analytical Research and Development
Ernesto J. Rivera, Pharm. D., Regulatory Affairs

Phone: (877) 950-3234
Representing: Abbott Laboratories

AND

Name: Karen Davis Bruno, Ph. D., Pharmacology/Toxicology Team Leader
Stephen Moore, Ph. D., Chemistry Team Leader
Indra Antonipillai, Ph. D., Pharmacology/Toxicology Reviewer
Mike Adams, Ph. D., Chemistry Reviewer
Valerie Jimenez, Regulatory Project Manager

Division of Metabolic and Endocrine Drug Products, HFD-510

SUBJECT: Fenofibrate final particle size

BACKGROUND: On October 29, 2003 Abbott Laboratories submitted a New Drug Application (NDA) for TriCor EZ (fenofibrate) Tablets. Upon review of the application, the Division found it necessary to have telephone conference with the sponsor to clarify what the final particle size is for their fenofibrate product.

- The Agency expressed their concern regarding a potential safety issue. New information from the literature on nanoparticle technology

- Abbott responded that the particle size is covered under the DMF and they therefore did not have direct access.
- The Agency reviewed all of the DMF files however; this issue was not addressed in the application.
- Abbott stated that they would have to contact the DMF holder to see if the information was available and address the issue and submit the information.

_____

Valerie Jimenez
Regulatory Project Manager

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/s/

Valerie Jimenez
5/13/04 11:04:34 AM
CSO

1/12/04

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

FILING COMMUNICATION

NDA 21-656

Abbott Laboratories, Inc.
Attention: Ernesto J. Rivers
Regulatory Affairs Manager
200 Abbott Park Road
D-491/AP30-1E
Abbott Park, IL 60064-6157

Dear Mr. Rivera:

Please refer to your October 29, 2003, new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Tricor® (fenofibrate) Tablets, 48 mg and 145 mg.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, this application has been filed under section 505(b) of the Act on December 29, 2003, in accordance with 21 CFR 314.101(a).

At this time, we have not identified any potential filing review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review.

If you have any questions, call Valerie Jimenez, Regulatory Project Manager, at (301) 827-9090.

Sincerely,

{See appended electronic signature page}

Enid Galliers
Chief, Project Management Staff
Division of Metabolic and Endocrine Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

Valerie Jimenez
1/12/04 02:51:19 PM
Signing for Enid Galliers, Chief, Project Management Staff

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

NDA 21-656

Abbott Laboratories
Attention: Ernesto J. Rivera
Regulatory Affairs Manager
200 Abbott Park Road
D-491/AP30-1E
Abbott Park, IL 60064-6157

Dear Mr. Rivera:

We have received your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: Tricor®— (fenofibrate) Tablets

Review Priority Classification: Standard (S)

Date of Application: October 29, 2003

Date of Receipt: October 30, 2003

Our Reference Number: NDA 21-656

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on December 29, 2003, in accordance with 21 CFR 314.101(a). If the application is filed, the user fee goal date will be August 30, 2004.

Please cite the NDA number listed above at the top of the first page of any communications concerning this application. Address all communications concerning this NDA as follows:

U.S. Postal Service/ Courier/Overnight Mail:
Center for Drug Evaluation and Research
Division of Metabolic and Endocrine Drug Products, HFD-510
Attention: Fishers Document Room, 8B-45
5600 Fishers Lane
Rockville, Maryland 20857

If you have any questions, call me at (301) 827-9090.

Sincerely,

{See appended electronic signature page}

Valerie Jimenez
Regulatory Project Manager
Division of Metabolic and Endocrine Drug Products, HFD-510
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

Valerie Jimenez
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2/3/03

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-203

Abbott Laboratories
Attention: Marilou Reed
Associate Director, Regulatory Affairs
D-491/AP30-1E
200 Abbott Park Road
Abbott Park, IL 60064-6157

Dear Ms. Reed:

We received your November 14, 2002, correspondence on November 15, 2002, requesting a meeting to discuss requirements for filing a new drug application (NDA) for a new formulation of Tricor (fenofibrate) Tablets. We considered your request and concluded the meeting is unnecessary. However, in order to assist you in your drug development program, we are providing the following information in response to questions included in your meeting request.

CHEMISTRY

QUESTION:

1. We propose manufacturing pilot lots at contract facilities for pivotal clinical studies and primary stability studies. We will execute full-scale batches at the commercial site and provide manufacturing and lot release data from these lots. We will bridge the manufacturing sites based on dissolution testing. (See Manufacturing Plan in the CMC section). Is the Agency in agreement with the proposed plan to produce the pilot drug product lots and the commercial lots to support stability studies, biobatches and commercial distribution?

DIVISION RESPONSE:

We accept your proposal to bridge the change of manufacturing sites based on dissolution testing. However, you should also provide data from in-process controls, including but not limited to the particle size distribution of the API after it is milled by ——— ———. (pilot scale) or by FLI (full scale commercial scale). Also, Certificates of Analysis of pilot lots and full scale commercial lots of the drug product should be provided.

QUESTION:

2a. We propose submitting the NDA with 3 months of stability (including accelerated studies) from the pilot lots. During review we will amend with 12-month real time data from pilot lots and 6-month data (including 3-month accelerated) from full scale lots (See Stability Plan in the CMC Section). Is the Agency in agreement with the proposed submission of stability data?

2b. What is the latest point in the review cycle the Agency would accept a stability amendment?

DIVISION RESPONSE:

2a. The application should be complete including at least 12 months real-time stability data when submitted. For filing purposes, however, we accept your proposal to submit 3-month stability data initially for 3 pilot lots of different strengths, and to submit an amendment with 12-month real-time data from pilot lots and 6 months data from full scale lots.

2b. Your proposal to update the stability data is reasonable, and the amendment, up until 3 months before the User Fee Goal Date, has a good probability of being reviewed during that review cycle.

BIOPHARMACEUTICS

We plan to conduct two pivotal bioavailability studies. The first study will examine the effect of food on the bioavailability of fenofibric acid from a 145 mg tablet formulation of fenofibrate. The study will be conducted according to a single-dose, open-label, two-period, randomized crossover design enrolling 46 subjects. The 145 mg tablet will be administered following the standard high-fat breakfast and under fasting conditions. The study synopsis appears in the Biopharmaceutics section.

The second study will determine the bioavailability of fenofibric acid from two test fenofibrate tablet dosage strengths (one 145 mg and three 48 mg tablets) relative to that of a reference 200 mg micronized fenofibrate capsule. All the fenofibrate dosage forms will be administered under nonfasting (low-fat meal) conditions. This single-dose, open-label study will be conducted according to a three-period, randomized complete crossover design. Seventy-two (72) subjects will be enrolled, 12 for each of the six sequences of regimens. The study synopsis appears in the Biopharmaceutics section.

QUESTION:

3. Does the Agency agree with the design of the bioequivalence and effect of food effect studies?

DIVISION RESPONSE:

The Division agrees with the design of the studies. However, a low-fat fed arm is suggested for the food-effect study since bioequivalence studies are conducted under low-fat conditions.

QUESTION:

4. [redacted]

DIVISION RESPONSE:

The Division considers this proposal to be acceptable.

GENERAL

QUESTION:

5. To differentiate this product in the marketplace, we are planning to either get a new Tradename or add a suffix to the existing Tricor tradename.
   a. Are both options acceptable?
   b. If a suffix is acceptable, are there any guidances available on the use of suffixes and their selection?

DIVISION RESPONSE:

5.a. The Division recommends that two choices of tradenames be submitted for the proposed new NDA. One of the choices should utilize the applicant's preferred suffix to the existing Tricor tradename and the other choice should be a new, novel tradename that does not use a suffix.

5.b. The only general guidance the Division can provide on the use of suffixes is to remind the applicant that the suffix should distinguish the product from other look-alike or sound-alike drug product tradenames.

QUESTION:

6. Is the Agency in agreement with the plan to cross-reference NDA 19-304 and NDA 21-203 to support the toxicology and clinical safety and efficacy of the new NDA?

DIVISION RESPONSE:

The Division agrees with this proposal.

If you disagree with our decision, you may discuss the matter with William C. Koch, R.Ph.. Regulatory Project Manager, at (301) 827-6412. If the issue cannot be resolved at the division level, you may formally request reconsideration according to our guidance for industry titled *Formal Dispute Resolution: Appeals Above the Division Level* (February 2000). The guidance can be found at http://www.fda.gov/cder/guidance/2740fnl.htm.

Sincerely,

{See appended electronic signature page}

David G. Orloff, M.D.
Director
Division of Metabolic
and Endocrine Drug Products, HFD-510
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

Mary Parks
2/3/03 03:18:02 PM
for Dr. Orloff