

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**21-695**

**ADMINISTRATIVE**  
**DOCUMENTS/CORRESPONDENCE**

EXCLUSIVITY SUMMARY FOR NDA # 21-695 SUPPL # \_\_\_\_\_

Trade Name Antara Generic Name fenofibrate, micronized

Applicant Name Reliant Pharmaceuticals HFD # 510

Approval Date If Known \_\_\_

**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 /XX/ NO /\_\_\_/

If yes, what type? Specify **505(b)(2)**

\_\_\_\_\_

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 /XX/

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.

**Studies were submitted as bioequivalence studies. All studies compared test drug to Tricor Capsules (NDA 19-304).**

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 /XX/

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 /XX/

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written 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 /XX/

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.

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 /XXX/ NO /\_\_\_/



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 /xx/

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:

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(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:

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(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:

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(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:

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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.



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 \_\_\_\_\_  
 !  
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 \_\_\_\_\_ !  
 \_\_\_\_\_ !



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/s/

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Patricia Madara  
12/6/04 11:51:28 AM

David Orloff  
12/7/04 01:02:16 PM

# PEDIATRIC PAGE

(Complete for all filed original applications and efficacy supplements)

ANDA/BLA #: 21-695 Supplement Type (e.g. SE5): \_\_\_\_\_ Supplement Number: \_\_\_\_\_

Stamp Date: December 4, 2003 Action Date: October 4, 2004

HFD 510 Trade and generic names/dosage form: (fenofibrate capsules), micronized

Applicant: Reliant Pharmaceuticals Therapeutic Class: 3021620

Indication(s) previously approved:

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

Number of indications for this application(s): 2

Indication #1: (adjunctive therapy to diet) for treatment of hypercholesterolemia in adults

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

**XX 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: standard of care indicates therapy with another class of agents is more effective than fenofibrate

*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}

\_\_\_\_\_  
Pat Madara  
Regulatory Project Manager, DMEDP

cc: NDA 21-695  
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)

**Attachment A**

(This attachment is to be completed for those applications with multiple indications only.)

**Indication #2:** \_\_\_\_\_ (adjunctive therapy to diet) for treatment of hypertriglyceridemia in adults

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: \_\_\_\_\_

*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 copy the fields above and complete pediatric information as directed. If there are no other indications, this Pediatric Page is complete and should be entered into DFS.*

This page was completed by:

*{See appended electronic signature page}*

\_\_\_\_\_  
Pat Madara  
Regulatory Project Manager, DMEDP

cc: NDA ##-###  
HFD-960/ Grace Carmouze

**FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE DIVISION OF PEDIATRIC DRUG DEVELOPMENT, HFD-960, 301-594-7337.**

(revised 10-14-03)

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/s/

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Patricia Madara  
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## NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

### Application Information

NDA 21-695	Efficacy Supplement Type SE-	Supplement Number
Drug: Antara (fenofibrate) Capsules, 43, 87, and 130 mg		Applicant: Reliant Pharmaceuticals
RPM: Pat Madara		HFD- 510      Phone # 301-827-6416
<p>Application Type: ( ) 505(b)(1) (X) 505(b)(2)          (This can be determined by consulting page 1 of the NDA Regulatory Filing Review for this application or Appendix A to this Action Package Checklist.)</p> <p>If this is a 505(b)(2) application, please review and confirm the information previously provided in Appendix B to the NDA Regulatory Filing Review. Please update any information (including patent certification information) that is no longer correct.</p> <p>(X) Confirmed and/or corrected</p>		<p>Listed drug(s) referred to in 505(b)(2) application (NDA #(s), Drug name(s)):</p> <p><b>Tricor Capsules, NDA 19-304</b></p>
❖ Application Classifications:		
• Review priority		(X) Standard ( ) Priority
• Chem class (NDAs only)		5
• Other (e.g., orphan, OTC)		n/a
User Fee Goal Dates		October 4, 2004
❖ Special programs (indicate all that apply)		
		(X) None Subpart H ( ) 21 CFR 314.510 (accelerated approval) ( ) 21 CFR 314.520 (restricted distribution) ( ) Fast Track ( ) Rolling Review ( ) CMA Pilot 1 ( ) CMA Pilot 2
❖ User Fee Information		
• User Fee		(X) Paid UF ID number 4627
• User Fee waiver		( ) Small business ( ) Public health ( ) Barrier-to-Innovation ( ) Other (specify)
• User Fee exception		( ) Orphan designation ( ) No-fee 505(b)(2) (see NDA Regulatory Filing Review for instructions) ( ) Other (specify)
Application Integrity Policy (AIP)		
• Applicant is on the AIP		( ) Yes (X) No



(Note: This can be determined by confirming whether the Division has received a written notice from the applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)).

*If "No," the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.*

- (4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)? ( ) Yes (X) No

*If "Yes," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next box below (Exclusivity).*

*If "No," continue with question (5).*

- (5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification? ( ) Yes (X) No

(Note: This can be determined by confirming whether the Division has received a written notice from the applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period).

*If "No," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next box below (Exclusivity).*

*If "Yes," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007) and attach a summary of the response.*

❖ Exclusivity (approvals only)	
<ul style="list-style-type: none"> <li>Exclusivity summary</li> <li>Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? (Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</li> </ul>	No
<ul style="list-style-type: none"> <li>Is there existing orphan drug exclusivity protection for the "same drug" for the proposed indication(s)? Refer to 21 CFR 316.3(b)(13) for the definition of "same drug" for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.</li> </ul>	( ) Yes, Application # _____ (X) No
❖ Administrative Reviews (Project Manager, ADRA) (indicate date of each review)	August 13, 2004

General Information	
<b>Actions</b>	
• Proposed action	(X) AP ( ) TA ( ) AE ( ) NA
• Previous actions (specify type and date for each action taken)	
• Status of advertising (approvals only)	(X) Materials requested in AP letter ( ) Reviewed for Subpart H
❖ <b>Public communications</b>	
• Press Office notified of action (approval only)	( ) Yes (X) Not applicable
• Indicate what types (if any) of information dissemination are anticipated	(X) None ( ) Press Release ( ) Talk Paper ( ) Dear Health Care Professional Letter
❖ <b>Labeling (package insert, patient package insert (if applicable), MedGuide (if applicable))</b>	
• Division's proposed labeling (only if generated after latest applicant submission of labeling)	
• Most recent applicant-proposed labeling	October 6 and 29, 2004
• Original applicant-proposed labeling	
• Labeling reviews (including DDMAC, DMETS, DSRCS) and minutes of labeling meetings (indicate dates of reviews and meetings)	September 28, 2004
• Other relevant labeling (e.g., most recent 3 in class, class labeling)	
❖ <b>Labels (immediate container &amp; carton labels)</b>	
• Division proposed (only if generated after latest applicant submission)	
• Applicant proposed	October 29, 2004
• Reviews	
❖ <b>Post-marketing commitments</b>	none
• Agency request for post-marketing commitments	
• Documentation of discussions and/or agreements relating to post-marketing commitments	
❖ <b>Outgoing correspondence (i.e., letters, E-mails, faxes)</b>	
❖ <b>Memoranda and Telecons</b>	
❖ <b>Minutes of Meetings</b>	
• EOP2 meeting (indicate date)	
• Pre-NDA meeting (indicate date)	June 17, 2003
• Pre-Approval Safety Conference (indicate date; approvals only)	
• Other	
❖ <b>Advisory Committee Meeting</b>	n/a
• Date of Meeting	
• 48-hour alert	
❖ <b>Federal Register Notices, DESI documents, NAS/NRC reports (if applicable)</b>	

## Summary Application Review

Summary Reviews (e.g., Office Director, Division Director, Medical Team Leader)  
(indicate date for each review)

Medical team leader memo

## Clinical Information

❖ Clinical review(s) (indicate date for each review)	NN
❖ Microbiology (efficacy) review(s) (indicate date for each review)	NN
❖ Safety Update review(s) (indicate date or location if incorporated in another review)	NN
❖ Risk Management Plan review(s) (indicate date/location if incorporated in another rev)	NN
❖ Pediatric Page(separate page for each indication addressing status of all age groups)	
❖ Demographic Worksheet (NME approvals only)	NN
❖ Statistical review(s) (indicate date for each review)	NN
❖ Biopharmaceutical review(s) (indicate date for each review)	September 8, 2004
❖ Controlled Substance Staff review(s) and recommendation for scheduling (indicate date for each review)	NN
❖ Clinical Inspection Review Summary (DSI)	
• Clinical studies	NN
• Bioequivalence studies	

## CMC Information

❖ CMC review(s) (indicate date for each review)	August 26, 2004
❖ Environmental Assessment	
• Categorical Exclusion (indicate review date)	August 26, 2004
• Review & FONSI (indicate date of review)	
• Review & Environmental Impact Statement (indicate date of each review)	
❖ Microbiology (validation of sterilization & product sterility) review(s) (indicate date for each review)	NN
❖ Facilities inspection (provide EER report)	Date completed: (X) Acceptable ( ) Withhold recommendation
❖ Methods validation	(X) Completed ( ) Requested ( ) Not yet requested

## Nonclinical Pharm/Tox Information

❖ Pharm/tox review(s), including referenced IND reviews (indicate date for each review)	June 3, 2004
❖ Nonclinical inspection review summary	NN
❖ Statistical review(s) of carcinogenicity studies (indicate date for each review)	NN
❖ CAC/ECAC report	NN

### Appendix A to NDA/Efficacy Supplement Action Package Checklist

An application is likely to be a 505(b)(2) application if:

- (1) it relies on literature to meet any of the approval requirements (unless the applicant has a written right of reference to the underlying data)
- (2) it relies on the Agency's previous approval of another sponsor's drug product (which may be evidenced by reference to publicly available FDA reviews, or labeling of another drug sponsor's drug product) to meet any of the approval requirements (unless the application includes a written right of reference to data in the other sponsor's NDA)
- (3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)
- (4) it seeks approval for a change from a product described in an OTC monograph and relies on the monograph to establish the safety or effectiveness of one or more aspects of the drug product for which approval is sought (see 21 CFR 330.11).

Products that may be likely to be described in a 505(b)(2) application include combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations), OTC monograph deviations, new dosage forms, new indications, and new salts.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, please consult with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007).

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Patricia Madara  
12/6/04 11:44:29 AM

**Division of Metabolic and Endocrine Drug Products**  
**REGULATORY PROJECT MANAGER REVIEW**

**Application Number: NDA 21-695**

**Name of Drug: Antara (fenofibrate) Capsules, micronized**

**Applicant: Reliant Pharmaceuticals, Inc**

**Material Reviewed:**

**Submission Date:   October 6, 2004; October 29, 2004**  
**Draft Labeling, Package Insert (PI) and Immediate**  
**Container Labels**

**Background and Summary**

This is a new NDA submitted as a 505b(2) application. Five bioequivalence studies were reviewed and the test drug was found to be equivalent to Tricor Capsules (NDA 19-304). Antara is indicated as adjunctive therapy to diet 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). Antara is also indicated as adjunctive therapy to diet for treatment of adult patients with hypertriglyceridemia (Fredrickson Types IV and V hyperlipidemia).

The Medical Officer requested that draft labeling comparing Antara to the last approved Tricor Capsule label be submitted.

The final agreed upon draft label was officially submitted on October 6, 2004 and a very minor amendment to the container labels was submitted on October 29, 2004. These submissions are reviewed here.

**Review**

**Package Insert**

The submitted draft package insert, identified as **340F100** was compared to the final approved package insert for Tricor Capsules (NDA 19-304), identified as **03-5037-R4-Rev. April, 2000**.

In the **TITLE**: “micronized” has been eliminated as a descriptor.

In the **DESCRIPTION** section:

**The Tricor label states:**

“TRICOR (fenofibrate capsules), micronized, is a lipid regulating agent available as capsules for oral administration. Each capsule contains 67 mg, 134 mg or 200 mg of micronized fenofibrate. The chemical name for fenofibrate is 2-[4-(4-chlorobenzoyl) phenoxy]-2-methyl-propanoic acid,



The empirical formula is  $C_{20}H_{21}O_4Cl$  and the molecular weight is 360.83; fenofibrate is insoluble in water. The melting point is 79-82°C. Fenofibrate is a white solid which is stable under ordinary conditions.

**Inactive Ingredients:** Each capsule also contains crospovidone, iron oxide, lactose, magnesium stearate, pregelatinized starch, sodium lauryl sulfate, and titanium dioxide.”

**The Antara label has been changed to:**

“Antara (fenofibrate) Capsules, is a lipid regulating agent available as capsules for oral administration. Each capsule contains 43 mg, 87 mg, or 130 mg of micronized fenofibrate. The chemical name for fenofibrate is 2-[4-(4-chlorobenzoyl) phenoxy]-2-methylpropanoic acid, 1-methylethyl ester with the following structural formula:



The empirical formula is  $C_{20}H_{21}O_4Cl$  and the molecular weight is 360.83; fenofibrate is insoluble in water. The melting point is 79-82°C. Fenofibrate is a white solid which is stable under ordinary conditions.

**Inactive Ingredients:** Each gelatin capsule contains sugar spheres, hypromellose, sodium lauryl sulfate, dimethicone, simethicone, and talc. The gelatin capsules also contain sulfur dioxide, titanium dioxide, yellow iron oxide, Indigo carmine FD&C Blue #2, D&C Yellow #10 and black ink.”

**Comment:** These changes reflect the new name, new dosage sizes, different inactive ingredients, and deletion of “micronized” as a descriptor. The name change has been approved. The list of inactive ingredients has been reviewed by chemists, Dr. John Hill and team leader, Dr. Stephen Moore. They agree with these changes. The chemists requested deletion of the word “micronized” as a descriptor.

**CLINICAL PHARMACOLOGY** introductory section: Unchanged (i.e. identical to Tricor Capsules).

**Pharmacokinetics/Metabolism** subsection:

**The Tricor label states:**

“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.”

**The Antara label has been changed to read:**

“Plasma concentrations of fenofibric acid after multiple dose administration of Antara 130 mg capsules are equivalent, under low-fat fed conditions, to 200 mg Fenofibrate capsules.”

**Comment:** This change reflects the findings from the bioequivalence studies conducted by the sponsor of Antara. This wording was suggested by the reviewing biopharmacologist (Dr. Jaya Vaidyanathan) the the team leader, Dr. Hae Young Ahn. The Medical Officer concurs with this change.

Absorption subsection:

**The Tricor label states:**

“The absolute bioavailability of fenofibrate cannot be determined as the compound is virtually insoluble in aqueous media suitable for injection. However, fenofibrate is well absorbed from the gastrointestinal tract. Following oral administration in healthy volunteers, approximately 60% of a single dose of radiolabelled fenofibrate appeared in urine, primarily as fenofibric acid and its glucuronate conjugate, and 25% was excreted in the feces. Peak plasma levels of fenofibric acid from TRADENAME occur within 6 to 8 hours after administration.

The absorption of fenofibrate is increased when administered with food. With micronized fenofibrate, the absorption is increased by approximately 35% under fed as compared to fasting conditions.”

**The Antara label has been changed to read:**

“The absolute bioavailability of fenofibrate cannot be determined as the compound is virtually insoluble in aqueous media suitable for injection. However, fenofibrate is well absorbed from the gastrointestinal tract. Following oral administration in healthy volunteers, approximately 60% of a single dose of radiolabelled fenofibrate appeared in urine, primarily as fenofibric acid and its glucuronate conjugate, and 25% was excreted in the feces. Peak plasma levels of fenofibric acid from Antara occur within 4 to 8 hours after administration.

There was less than dose-proportional increase in the systemic exposure of fenofibric acid from three strengths (43 mg, 87 mg, and 130 mg) of Antara under fasting conditions.

Doses of two- or three-capsules of 43 mg Antara given concurrently were dose-equivalent to single-capsule doses of 87 mg and 130 mg, respectively.

The extent of absorption of fenofibric acid was unaffected when Antara was taken either in fasted state or with a low-fat meal. However, the C<sub>max</sub> of Antara increased in presence of a low fat meal. T<sub>max</sub> was unaffected in the presence of a low-fat meal. In the presence of a high-fat meal, there was a 26% increase in AUC and 108% increase in C<sub>max</sub> of fenofibric acid from Antara relative to fasting state.”

**Comment:** These changes reflect the findings from the bioequivalence studies conducted by the sponsor of Antara. This wording was suggested by the reviewing biopharmacologist (Dr. Jaya Vaidyanathan) and the the team leader, Dr. Hae Young Ahn. The Medical Officer concurs with this change.

**Distribution subsection:**

**The Tricor label states:**

“In healthy volunteers, steady-state plasma levels of fenofibric acid were shown to be achieved within 5 days of dosing with single oral doses equivalent to 67 mg TRICOR and did not demonstrate accumulation across time following multiple dose administration. Serum protein binding was approximately 99% in normal and hyperlipidemic subjects.”

**The Antara label has been changed to read:**

“In healthy volunteers, steady-state plasma levels of fenofibric acid were shown to be achieved within a week of dosing and did not demonstrate accumulation across time following multiple dose administration. Serum protein binding was approximately 99% in normal and hyperlipidemic subjects.”

**Comment: This change reflects the findings from the bioequivalence studies conducted by the sponsor of Antara. This wording was approved by the reviewing biopharmacologist (Dr. Jaya Vaidyanathan) the the team leader, Dr. Hae Young Ahn. The Medical Officer concurs with this change.**

The **Metabolism** subsection is unchanged.

In the **Excretion** subsection:

The final sentence has been changed from: “Fenofibrate acid is eliminated with a half-life of 20 hours, allowing once daily administration in a clinical setting” in the Tricor label to “Fenofibrate acid from Antara is eliminated with a half-life of 23 hours, allowing once daily administration in a clinical setting.

**Comment: This change reflects the findings from the bioequivalence studies conducted by the sponsor of Antara. This wording was approved by the reviewing biopharmacologist (Dr. Jaya Vaidyanathan) the the team leader, Dr. Hae Young Ahn. The Medical Officer concurs with this change.**

In the **Special Populations** subsection: The only change was the name, from Tricor to Antara.

**Comment: This is an acceptable change and reflects the different name of this product.**

In the **Clinical Trials** subsection: The only changes involved changing the dose size studied (Tricor used 200 mg - this was changed to 130 mg – the size used in the Antara studies.) In addition, the name Tricor was changed to Antara or, in some instances, replaced with the generic word, fenofibrate.

Tables 1 and 2 remain unchanged except for replacing “Tricor” with “Fenofibrate”

**INDICATIONS AND USAGE section:**

**The Treatment of Hypercholesterolemia subsection:**

**The Tricor label states:**

“TRICOR (fenofibrate capsules), micronized, is indicated as adjunctive therapy to diet for the reduction of LDL-C, Total-C, Triglycerides and Apo B in adult patients with primary hypercholesterolemia or mixed dyslipidemia (Fredrickson Types IIa and IIb). Lipid-altering agents should be used in addition to a diet restricted in saturated fat and cholesterol when response to diet and non-pharmacological interventions alone has been inadequate (see National Cholesterol Education Program [NCEP] Treatment Guidelines, below).”

**The Antara label has been changed to read:**

“Antara is indicated as adjunctive therapy to diet 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). Lipid-altering agents should be used in addition to a diet restricted in saturated fat and cholesterol when response to diet and non-pharmacological interventions alone has been inadequate (see National Cholesterol Education Program [NCEP] Treatment Guidelines, below).

**Comment:** These changes were approved by the biopharmacologists and medical officer.

The **Treatment of Hypertriglyceridemia** subsection is unchanged EXCEPT for changing the name from “Tricor” to “Antara”.

The **Fredrickson Classification of Hyperlipoproteinemias** table is unchanged.

The **NCEP Treatment Guidelines** table has been changed:

**The Tricor label states:**

NCEP Treatment Guidelines			
Definite Atherosclerotic Disease <sup>a</sup>	Two or More Other Risk Factors <sup>b</sup>	LDL-Cholesterol mg/dL (mmol/L)	Initiation Level
No	No	≥90(≥.9)	<160(<4.1)
No	Yes	≥60(≥.1)	<130(<3.4)
Yes	Yes or No	≥30 <sup>c</sup> (≥.4)	<100(<2.6)

<sup>(a)</sup> Coronary heart disease or peripheral vascular disease (including symptomatic carotid artery disease).

<sup>(b)</sup> Other risk factors for coronary heart disease (CHD) include: age (male: ≥5 years; females: ≥5 years of premature menopause without estrogen replacement therapy); family history of premature CHD; current cigarette smoking; hypertension; confirmed HDL-C <35 mg/dL (<0.91 mmol/L); and diabetes mellitus. Subtract 1 risk factor if HDL-C is ≥60 mg/dL (>1.6 mmol/L).

<sup>(c)</sup> In CHD patients with LDL-C levels 100 to 129 mg/dL, the physician should exercise clinical judgment in deciding whether to initiate drug treatment.

**The new label states:**

**Rx only** (added, not in Tricor label)

October 2004



Manufactured for:  
Reliant Pharmaceuticals, Inc.  
Liberty Corner, NJ 07938, USA  
By:  
Ethypharm Industries  
Le Grand Quevilly, France

**The following section has been added:**

**Address Medical Inquiries to:**  
Reliant Pharmaceuticals, Inc.  
**Medical Affairs**  
110 Allen Road  
Liberty Corner, NJ 07938, USA

©2004 Reliant Pharmaceuticals, Inc.  
PRINTED IN USA

340F100

**Draft Container Labels:**

Revised as recommended by chemists and Office of Drug Safety. "Micronized" has been removed from the label. Chemists find acceptable. Each label includes a distinct barcode and identifier. The label for each strength capsule includes a different color band.

A minor labeling amendment dated October 29, 2004 revises the following statement on all container labels:

**From:** "See USP Controlled Room Temp."

**To:** "See USP Controlled Room Temperature."

**Comment:** This is an acceptable editorial change which improves clarity.

### **Conclusions**

All the changes to this labeling have been reviewed by the DMEDP medical officer, biopharmacologists, chemists, and pharmacologists and found acceptable. This labeling can be approved.

---

Pat Madara  
Regulatory Project Manager  
Division of Metabolic and Endocrine  
Drug Products

### **CSO LABELING REVIEW**

Note: This labeling review has been reviewed by CPMS, Enid Galliers, and found acceptable.

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/s/

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Patricia Madara  
12/6/04 11:23:53 AM  
CSO



NDA 21-695

**DISCIPLINE REVIEW LETTER**

Reliant Pharmaceuticals Inc.  
Attention: Paulette F. Kosmoski  
Senior Director, Regulatory Affairs  
110 Allen Road  
Liberty Corner, NJ 07938

Dear Ms. Kosmoski:

Please refer to your December 1, 2003 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Fenofibrate Capsules.

We also refer to your submission dated July 6, 2004.

The review by the Office of Drug Safety, Division of Medical Errors and Technical Support is complete, and we have the following recommendations:

1. Increase the prominence of the proprietary and established names on all container labels.
2. On all container labels, relocate the net quantity statement so that it appears away from the product strength and has less prominence.

We are providing these comments to you before we complete our review of the entire application to give you preliminary notice of issues that we have identified. In conformance with the prescription drug user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and subject to change as we finalize our review of your application. In addition, we may identify other information that must be provided before we can approve this application. If you respond to these issues during this review cycle, depending on the timing of your response, and in conformance with the user fee reauthorization agreements, we may not be able to consider your response before we take an action on your application during this review cycle.

If you have any questions call Pat Madara, Regulatory Project Manager, at (301) 827-6416.

Sincerely,

*{See appended electronic signature page}*

Kati Johnson  
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/

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Kati Johnson

9/29/04 09:54:28 AM

MEMO TO THE FILE

APPLICATION: NDA 21-695 Antara (fenofibrate) Capsules  
DATE: 29 November 2004-11-29  
SUBJECT: Patent certifications required for this 505(b)(2) NDA

NDA 21-695, a 505(b)(2) application, provides for 43 mg, 87 mg, and 130 mg capsules of fenofibrate. There is no approved product with the same strengths of fenofibrate. However, the applicant, Reliant Pharmaceuticals, relies on the Agency's approval of the "pharmaceutical alternative," TriCor (fenofibrate) Capsules, micronized, 67 mg, 134 mg, and 200 mg (NDA 19-304), which it cites as the listed drug.

Abbott Laboratories owns NDA 19-304, and Laboratoires Fournier owns the patent which NDA 19-304 claims. In addition, Abbott owns two NDAs for fenofibrate tablets for the same indications but with different strengths. They are TriCor Tablets, 54 mg and 160 mg (NDA 21-203), and TriCor Tablets, 48 mg and 145 mg (NDA 21-656).

Approval of the Reliant NDA has been delayed due to preparation of a response to a Citizen Petition (C.P.) submitted on August 31, 2004, by Arnold & Porter on behalf of Abbott Laboratories and Laboratoires Fournier, in which the petitioners requested that the application not be approved without having patent certifications made by Reliant Pharmaceuticals against NDA 21-203 TriCor Tablets, 54 mg and 160 mg. On September 24, 2004, Reliant Pharmaceuticals submitted comments on the pending C.P., and on November 1, 2004, Arnold & Porter submitted an amendment to its C.P.

In the original application, Reliant Pharmaceuticals submitted a paragraph IV certification against the one patent claimed by NDA 19-304. Neither Abbott nor Fournier filed a patent infringement suit against Reliant for this patent.

The Reliant NDA provides for the same capsule dosage form as in NDA 19-304, but with different strengths. Reliant conducted its bioequivalence study against 200 mg micronized TriCor Capsules.

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/s/

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Enid Galliers  
11/29/04 08:05:03 PM  
CSO



NDA 21-695

**DISCIPLINE REVIEW LETTER**

Reliant Pharmaceuticals, Inc.  
Attention: Paulette F. Kosmoski  
Senior Director, Regulatory Affairs  
110 Allen Road  
Liberty Corner, NJ 07938

Dear Ms. Kosmoski:

Please refer to your December 1, 2003 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Fenofibrate Capsules.

We also refer to your submission dated July 7, 2004.

Our review of the Clinical Pharmacology/Biopharmaceutics section of your submission is complete and we recommend the following dissolution method and specification:

Medium:	0.5% sodium laurel sulfate (SLS)
Apparatus:	USP Apparatus 2
Speed:	75 rpm
Tolerance Specifications:	NLT —(Q) @ 30 minutes

Your proposed concentration of 0.72% SLS is acceptable on an interim basis, until the method using 0.5% SLS is validated. However, instead of your proposed specification of Q = — at 30 minutes using 0.72% SLS, we recommend Q = — at 30 minutes.

We are providing these comments to you before we complete our review of the entire application to give you preliminary notice of issues that we have identified. In conformance with the prescription drug user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and subject to change as we finalize our review of your application. In addition, we may identify other information that must be provided before we can approve this application. If you respond to these issues during this review cycle, depending on the timing of your response, and in conformance with the user fee reauthorization agreements, we may not be able to consider your response before we take an action on your application during this review cycle.

If you have any questions, call Pat Madara, Regulatory Project Manager, at (301) 827-6416.

Sincerely,

*{See appended electronic signature page}*

Kati Johnson  
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/

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Patricia Madara

9/23/04 10:36:31 AM

Pat Madara, Regulatory Project Manager signing for Kati Johnson,  
CPMS

**CONSULTATION RESPONSE**  
**DIVISION OF MEDICATION ERRORS AND TECHNICAL SUPPORT**  
**OFFICE OF DRUG SAFETY**  
**(DMETS; HFD-420)**

**DATE RECEIVED:** July 1, 2004

**DESIRED COMPLETION**

**ODS CONSULT #:** 04-0184

**DATE:** Sept. 1, 2004

**PDUFA DATE:** Oct. 4, 2004

**TO:** David Orloff, M.D.  
Director, Division of Metabolic and Endocrine Drug Products  
HFD-510

**THROUGH:** Pat Madara  
Project Manager, Division of Metabolic and Endocrine Drug Products  
HFD-510

**PRODUCT NAME:**

**Antara** (Primary Name)  
— (Secondary Name)  
(Fenofibrate Capsules)  
43 mg, 87 mg, and 130 mg

**SPONSOR:** Reliant Pharmaceuticals

**NDA #:** 21-695

**SAFETY EVALUATOR:** Tia M. Harper-Velazquez, Pharm.D.

**RECOMMENDATIONS:**

1. DMETS has no objections to the use of the proprietary names Antara and [redacted]. This is considered final decision. Please note: DMETS does not routinely evaluate secondary names if the first name has been found acceptable. Due to the anticipated approval of this product, and the Division's concerns, we included both. However, if the approval of this application is delayed beyond 90 days from the signature date of this document, the names must be re-evaluated. A re-review of the names will rule out any objections based upon approval of other proprietary or established names from the signature date of this document.
2. DMETS recommends implementation of the labeling revisions as outlined in Section III of this review in order to minimize potential errors with the use of this product.
3. DDMAC finds the proprietary names Antara and [redacted] acceptable from a promotional perspective.

Carol Holquist, R.Ph.  
Director  
Division of Medication Errors and Technical Support  
Office of Drug Safety  
Phone: (301) 827-3242 Fax: (301) 443-9664

**Division of Medication Errors and Technical Support  
Office of Drug Safety  
HFD-420; Parklawn Rm. 6-34  
Center for Drug Evaluation and Research**

**PROPRIETARY NAME REVIEW**

**DATE OF REVIEW:** July 30, 2004

**NDA NUMBER:** 21-695

**NAME OF DRUG:** Antara (Primary Name)  
— (Secondary Name)  
(Fenofibrate Capsules)  
43 mg, 87 mg, and 130 mg

**NDA SPONSOR:** Reliant Pharmaceuticals

**\*\*\*Note:** This review contains proprietary and confidential information that should not be released to the public.\*\*\*

**I. INTRODUCTION**

This consult was written in response to a request from the Division of Metabolic and Endocrine Drug Products, for an assessment of the proprietary names “Antara” and “—” regarding potential name confusion with other proprietary or established drug names. The container labels and package insert labeling for Antara and “—” were reviewed for possible interventions that will minimize medication errors.

**PRODUCT INFORMATION**

Antara/ — are the proposed names for fenofibrate, a micronized, lipid regulating agent available as a capsule for oral administration. The usual adult dose ranges from 43 mg to 130 mg once daily. Antara/ — will be available in strengths of 43 mg, 87 mg, and 130 mg, packaged in bottles of thirty count.

**II. RISK ASSESSMENT**

The medication error staff of DMETS conducted a search of several standard published drug product reference texts<sup>i,ii</sup> as well as several FDA databases<sup>iii</sup> for existing drug names which sound-alike or look-alike to “Antara/ —” to a degree where potential confusion between drug names could occur under the usual clinical practice settings. A search of the electronic online version of the U.S. Patent and Trademark Office’s Text and Image Database<sup>iv</sup> and the data provided by Thomson &

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<sup>i</sup> MICROMEDEX Integrated Index, 2004, MICROMEDEX, Inc., 6200 South Syracuse Way, Suite 300, Englewood, Colorado 80111-4740, which includes all products/databases within ChemKnowledge, DrugKnowledge, and RegsKnowledge Systems.

<sup>ii</sup> Facts and Comparisons, online version, Facts and Comparisons, St. Louis, MO.

<sup>iii</sup> AMF Decision Support System [DSS], the Division of Medication Errors and Technical Support proprietary name consultation requests, New Drug Approvals 1998-2004, and the electronic online version of the FDA Orange Book.

<sup>iv</sup> WWW location <http://www.uspto.gov>.

Thomson's SAEGIS™ Online Service<sup>v</sup> were also conducted. An expert panel discussion was conducted to review all findings from the searches. In addition, DMETS conducted three prescription analysis studies consisting of two written prescription studies (inpatient and outpatient) and one verbal prescription study, involving health care practitioners within FDA. This exercise was conducted to simulate the prescription ordering process in order to evaluate potential errors in handwriting and verbal communication of the name.

#### A. EXPERT PANEL DISCUSSION

An Expert Panel discussion was held by DMETS to gather professional opinions on the safety of the proprietary names, Antara and — Potential concerns regarding drug marketing and promotion related to the proposed name was also discussed. This group is composed of DMETS Medication Errors Prevention Staff and representation from the Division of Drug Marketing, Advertising, and Communications (DDMAC). The group relies on their clinical and other professional experiences and a number of standard references when making a decision on the acceptability of a proprietary name.

1. DDMAC did not have any concerns from a promotional perspective regarding the proposed names Antara or —
2. The Expert Panel identified six proprietary names that have potential for confusion with Antara. The Expert Panel identified ten names that have potential for confusion with —. These products are listed in Table 1 and Table 2 along with the dosage forms available and usual dosage (pages 4 and 5).

**APPEARS THIS WAY  
ON ORIGINAL**

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<sup>v</sup> Data provided by Thomson & Thomson's SAEGIS(tm) Online Service, available at [www.thomson-thomson.com](http://www.thomson-thomson.com).

Table 1: Potential Sound-Alike/Look-Alike Names Identified by DMETS Expert Panel for Antara

Product Name	Dosage form(s), Established Name	Usual adult Dose*	Other**
Antara (Rx)	Penofibrate Capsules 43 mg, 87 mg, 130 mg	<u>Primary hypercholesterolemia</u> 130 mg per day. <u>Mixed Hyperlipidemia</u> 130 mg per day. <u>Hypertriglyceridemia</u> 43 mg to 130 mg per day.	
Aldara (Rx)	Imiquimod Cream 5%	<u>External Genital Warts</u> Apply thin layer to warts and rub in before bedtime 3 times per week; wash off with soap and water 6 to 10 hours later; use for a maximum of 16 weeks. <u>Actinic Keratoses</u> Apply to affected area on face or scalp and rub in before bedtime 2 times per week; wash off with soap and water 8 hours later. <u>Superficial Basal Cell Carcinoma</u> Use five times per week for 6 weeks.	**L/A, S/A
			**L/A, S/A
Arava (Rx)	Leflunomide Tablets 10 mg, 20 mg, and 100 mg	<u>Loading dose:</u> 100 mg daily for 3 days. <u>Maintenance Dose:</u> 20 mg daily.	**L/A
Atarax (Rx)	Hydroxyzine Tablets: 10 mg, 25 mg, 50 mg, and 100 mg Syrup: 10 mg/5 mL	<u>Anxiety:</u> 50 mg to 100 mg 4 times daily. <u>Allergic pruritus:</u> 25 mg 3 to 4 times daily.	**L/A, S/A
Covera-HS (Rx)	Verapamil Extended Release Tablets 180 mg and 240 mg	180 mg daily at bedtime initially; may titrate upwards in steps to 20 mg, then 360 mg, then 480 mg, if necessary.	**L/A
Certiva (Rx)	Diphtheria, Tetanus and Pertussis Vaccine	A 0.5 mL intramuscular injection is recommended for administration at 2, 4, and 6 months of age, at intervals of six to eight weeks, with a fourth dose given at 15 to 20 months of age.	**L/A
<p>*Frequently used, not all-inclusive.                      **L/A (look-alike), S/A (sound-alike)                      ***NOTE: This review contains proprietary and confidential information that should not be released to the public.***</p>			

Table 2: Potential Sound-Alike/Look-Alike Names Identified by DMETS Expert Panel for

Product Name	Dosage form(s), Established name	Usual adult Dose*	Other**
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## B. PHONETIC ORTHOGRAPHIC COMPUTER ANALYSIS (POCA)

As part of the name similarity assessment, proposed names are evaluated via a phonetic/orthographic algorithm. The proposed proprietary names were converted into their phonemic representation before they run through the phonetic algorithm. The phonetic search modules return a numeric score to the search engine based on the phonetic similarity to the input text. Likewise, an orthographic algorithm exists which operates in a similar fashion. All names considered to have significant phonetic or orthographic similarities to Antara and — were discussed by the Expert Panel (EPD).

## C. PRESCRIPTION ANALYSIS STUDIES

### 1. Methodology:

Six separate studies were conducted within the Centers of the FDA for the proposed proprietary names to determine the degree of confusion of Antara and — with other U.S. drug names due to similarity in visual appearance with handwritten prescriptions or verbal pronunciation of the drug name. These studies employed a total of 129 health care professionals (pharmacists, physicians, and nurses) for each name. This exercise was conducted in an attempt to simulate the prescription ordering process. An inpatient order and outpatient prescriptions were written, each consisting of a combination of marketed and unapproved drug products and a prescription for Antara and — (see page 6). These prescriptions were optically scanned and one prescription was delivered to a random sample of the participating health professionals via e-

mail. In addition, the outpatient orders were recorded on voice mail. The voice mail messages were then sent to a random sample of the participating health professionals for their interpretations and review. After receiving either the written or verbal prescription orders, the participants sent their interpretations of the orders via e-mail to the medication error staff.

**Antara**

HANDWRITTEN PRESCRIPTION	VERBAL PRESCRIPTION
<p><u>Outpatient RX:</u></p> <p>Antara 43mg            1 po qd            #30</p>	<p>Antara 43 mg, take one by mouth daily, dispense #30.</p>
<p><u>Inpatient RX:</u></p> <p><del>Antara 43mg, Sig: 1 po qd #30</del></p>	

HANDWRITTEN PRESCRIPTION	VERBAL PRESCRIPTION
<p><u>Outpatient RX:</u></p> <p><i>(Handwritten scribbles)</i></p>	<p><i>(Faint handwritten text: "th")</i></p>

2. Results for Antara:

None of the interpretations of the proposed name overlap, sound similar, or look similar to any currently marketed U.S. product. See Appendix for the complete listing of interpretations from the verbal and written studies.

### 3. Results for —

#### D. SAFETY EVALUATOR RISK ASSESSMENT

##### 1. Antara

In reviewing the proprietary name “Antara”, the primary concerns raised were related to five look-alike and/or sound-alike names currently marketed in the United States, and one proposed proprietary name currently under review at the Agency. The products considered to have potential for name confusion with Antara were: Aldara, —, Arava, Atarax, and Certiva. Upon further review of the names gathered from EPD and POCA, the name Certiva was not further reviewed due to numerous differentiating product characteristics such as dosage form, route of administration, dosing regimen, and patient population.

We conducted prescription studies to simulate the prescription ordering process. Our study did not confirm confusion between Antara and Aldara, —, Arava, Atarax, or Certiva. However, a negative finding does not discount the potential for name confusion given the limited predictive value of these studies, primarily due to the sample size. The majority of the incorrect interpretations of the written and verbal studies were misspelled/phonetic variations of the proposed name, Antara.

- a. Aldara was identified to look and sound similar to the proposed name, Antara. Aldara contains imiquimod. It is indicated for the treatment of actinic keratosis on the face and scalp, for the treatment of external genital warts, and for the treatment of basal cell carcinoma. For the treatment of actinic keratosis, Aldara is applied to the affected area and rubbed in before bedtime two times per week, then washed off with soap and water eight hours later. For the treatment of genital warts, a thin layer of Aldara is applied to the affected area before bedtime three times per week, then washed off with soap and water six to ten hours later. For the treatment of superficial basal cell carcinoma, Aldara is applied five times a week for six weeks. The look-alike and sound-alike similarities between the names can be attributed to the identical letter combination at the end of each name (“ara”). Additionally, both names begin with the letter “A”, and consist of six letters and three syllables. Aldara and Antara each contain similar looking letters that create an upstroke in the third position (“d” vs. “t”). Although both products are administered at bedtime, the products differ in dosage form (cream vs. capsules), route of administration (oral vs. topical), strength (5% vs. 43 mg, 87 mg, and 130 mg), and dosing interval (two, three or five times per week vs. daily). Although the names share some phonetic and orthographic similarities, product differences such as route of administration, dosage form, and dosing regimen minimizes the potential that Aldara and Antara will be confused for one another.

Aldara

Antara

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\*\* Note: This review contains proprietary and confidential information that should not be released to the public.\*\*

*Arava Antara*

/

- c. Arava was identified to look similar to the proposed name, Antara. Arava is the proprietary name for leflunomide tablets. It is indicated for the treatment of acute rheumatoid arthritis, by reducing the signs and symptoms, inhibiting structural damage, and improving physical function. It may be used in conjunction with aspirin, non-steroidal anti-inflammatory drugs, and low-dose corticosteroids. Arava is available as an oral tablet, in strengths of 10 mg, 20 mg, and 100 mg. Both names begin with the letter "A". The second letter ("r" vs. "n"), as well as ending of each name ("ara" vs. "ava), can also look similar depending on how they are scripted. The names differ in number of letters (5 vs. 6), and the presence of the upstroke letter "t" in Antara, which aids in the distinguishing the names from each other visually. Arava and Antara share an overlapping route of administration (oral), and dosing regimen (once daily). However, they differ in strength (10 mg, 20 mg, and 100 mg vs. 43 mg, 87 mg, and 130 mg). Although Arava and Antara share some overlapping product characteristics, DMETS believes that the lack of convincing look-alike similarity, in addition to the difference in strength decrease the risk of confusion between Arava and Antara.

Arava

Antara

*Arava*

*Antara*

- d. Atarax was identified to look similar and sound similar to Antara. Atarax contains hydroxyzine, and is indicated for the treatment of anxiety, as well as the treatment of allergic pruritus. It is available as a tablet in strengths of 10 mg, 25 mg, 50 mg, and 100 mg; and as a syrup in a strength of 10 mg/5 mL. The recommended dose ranges from 25 mg to 100 mg three to four times daily, depending on the condition being treated. Both names consist of three syllables, seven letters, and begin with the letter "A". Although located in different positions, the letter "t" and letter combination "ara" appear in each name, which adds to the look-alike as well as the sound-alike similarities between the names. However, the presence of the letter "x" in Atarax, helps to distinguish the names from each other phonetically. If the letter "x" is not prominent, or is not crossed when the name is written, it could appear that the name Atarax ends with the letter "a", which increases its look-alike similarity to the proposed name. The differences in strength (10 mg, 25 mg, 50 mg, and 100 mg vs. 43 mg, 87 mg, and 130 mg) as well the difference in dosing regimen (three to four times daily vs. once daily), would help to distinguish the products. Although the products look-similar to each, DMETS believes that the difference in strength, dosing regimen, as well as the minimal sound-alike similarities between the names will minimize the potential for confusion and

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\*\* Note: This review contains proprietary and confidential information that should not be released to the public.\*\*

errors between Atarax and Antara.

Atarax

Antara

*Atarax Antara*

- e. Covera-HS was identified to look-similar to the proposed name, Antara, when the modifier “HS” is omitted (see below). Covera-HS is the proprietary name for verapamil extended release tablets. It is indicated for the treatment of angina and hypertension. The recommended dose of Covera-HS is 180 mg to 240 mg administered once daily at bedtime. The names share look-alike similarity in that the beginning letter combination (“Cov” vs. “An”) and ending letter combination (“era” vs. “ara”) can look similar when scripted. However, the upstroke of the letter “t” in Antara helps to distinguish the names from each other visibly, as does the presence of the modifier “HS”. Covera and Antara share an overlapping route of administration (oral), and dosing regimen (once daily). However, the modifier “HS” also serves as the dosing regimen, which may help distinguish the two products. The products differ in indication (hypertension and angina vs. lipid lowering), and strength (180 mg and 240 mg vs. 43 mg, 87 mg, and 130 mg). It should be noted, however, that the strengths 180 mg (Covera) and 130 mg (Antara) can look similar when scripted. DMETS believes that the names are orthographically different enough from each other that the potential for confusion is minimal. The presence of the modifier “HS” in Covera-HS, which will also help to further distinguish the names from each other when written.

Covera

Antara

*Covera Antara*

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\*\* Note: This review contains proprietary and confidential information that should not be released to the public.\*\*\*

A

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  ✓   § 552(b)(4) Trade Secret / Confidential

       § 552(b)(5) Deliberative Process

       § 552(b)(4) Draft Labeling

### III. LABELING, PACKAGING, AND SAFETY RELATED ISSUES

In review of the container labels, carton and insert labeling of Aldara and DMETS has attempted to focus on safety issues relating to possible medication errors. DMETS has identified the following areas of possible improvement, which might minimize potential user error.

CONTAINER LABEL (Professional Sample, 30 count, and 100 count)

- A. Please increase the prominence of the proprietary and established names.
- B. Currently the various strengths of the product are highlighted in the . In addition, a of the same color appears on the left side of the label. This presentation makes the bottles look similar when compared side by side. Thus, in order to decrease the occurrence of selection errors, the multiple strengths should be differentiated using contrasting color, boxing, or some other means. Additionally, it would be helpful if the stripe corresponded with each strength.
- C. Please relocate the net quantity statement so that it appears away from the product strength and has less prominence.

**APPEARS THIS WAY  
ON ORIGINAL**

#### IV. RECOMMENDATIONS

- A. DMETS has no objections to the use of the proprietary names Antara or — This is considered final decision. Please note: DMETS does not routinely evaluate secondary names if the first name has been found acceptable. Due to the anticipated approval of this product, and the Division's concerns, we included both. However, if the approval of this application is delayed beyond 90 days from the signature date of this document, the names must be re-evaluated. A re-review of the names will rule out any objections based upon approval of other proprietary or established names from the signature date of this document.
- B. DMETS recommends implementation of the labeling revisions as outlined in Section III of this review in order to minimize potential errors with the use of this product.
- C. DDMAC finds the proprietary names Antara and — acceptable from a promotional perspective.

DMETS would appreciate feedback of the final outcome of this consult (e.g., copy of revised labels/labeling). We are willing to meet with the Division for further discussion as well. If you have any questions concerning this review, please contact Sammie Beam at 301-827-3242.

---

Tia M. Harper-Velazquez, Pharm.D.  
Safety Evaluator  
Division of Medication Errors and Technical Support  
Office of Drug Safety

Concur:

---

Denise Toyer, Pharm.D.  
Deputy Director  
Division of Medication Errors and Technical Support  
Office of Drug Safety

Appendix A. DMETS prescription study results for Antara

<u>Voicemail</u>	<u>Outpatient</u>	<u>Inpatient</u>
Entara	Antara	Antara
Entera	Antara	Antara
Enterra	Antara	Antara
Enterra	Antata	Antara
Enterra	Antora	Antara
Intera		Antara
Invera		Antara

B

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       § 552(b)(4) Trade Secret / Confidential

       § 552(b)(5) Deliberative Process

       § 552(b)(4) Draft Labeling

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/s/  
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Tia Harper-Velazquez  
9/28/04 10:14:16 AM  
DRUG SAFETY OFFICE REVIEWER

Denise Toyer  
9/28/04 04:04:58 PM  
DRUG SAFETY OFFICE REVIEWER  
Signing for Carol Holquist, Director, Division of Medication Errors  
and Technical Support

C

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       § 552(b)(4) Trade Secret / Confidential

✓ § 552(b)(5) Deliberative Process

       § 552(b)(4) Draft Labeling



*If you need assistance in determining if the applicant is claiming a new indication for a use, please contact the user fee staff.*

- Is there any 5-year or 3-year exclusivity on this active moiety in an approved (b)(1) or (b)(2) application? NO

If yes, explain:

- Does another drug have orphan drug exclusivity for the same indication? NO

- If yes, is the drug considered to be the same drug according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]? YES      NO

If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007).

- Is the application affected by the Application Integrity Policy (AIP)? NO  
If yes, explain.

- If yes, has OC/DMPQ been notified of the submission? YES      NO

- Does the submission contain an accurate comprehensive index? YES

- Was form 356h included with an authorized signature? YES  
**If foreign applicant, both the applicant and the U.S. agent must sign.**

- Submission complete as required under 21 CFR 314.50? YES

If no, explain:

- If an electronic NDA, does it follow the Guidance? YES  
**If an electronic NDA, all certifications must be in paper and require a signature.**  
Which parts of the application were submitted in electronic format?  
All except for certifications

Additional comments:

- If in Common Technical Document format, does it follow the guidance? N/A

- Is it an electronic CTD? N/A

**If an electronic CTD, all certifications must be in paper and require a signature.**  
Which parts of the application were submitted in electronic format?

Additional comments:

- Patent information submitted on form FDA 3542a? YES
- Exclusivity requested? NO  
*NOTE: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.*

- Correctly worded Debarment Certification included with authorized signature? YES  
**If foreign applicant, both the applicant and the U.S. Agent must sign the certification.**

*NOTE: Debarment Certification should use wording in FD&C Act section 306(k)(1) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as "To the best of my knowledge . . . ."*

- Financial Disclosure forms included with authorized signature? YES  
**(Forms 3454 and 3455 must be used and must be signed by the APPLICANT.)**
- Field Copy Certification (that it is a true copy of the CMC technical section)? YES

**Refer to 21 CFR 314.101(d) for Filing Requirements**

- PDUFA and Action Goal dates correct in COMIS? YES  
If not, have the document room staff correct them immediately. These are the dates EES uses for calculating inspection dates.
- Drug name/Applicant name correct in COMIS? If not, have the Document Room make the corrections.
- List referenced IND numbers: 66,247
- End-of-Phase 2 Meeting(s)? NO  
If yes, distribute minutes before filing meeting.
- Pre-NDA Meeting(s)? Date(s) June 17, 2003  
If yes, distribute minutes before filing meeting.

**Project Management**

- All labeling (PI, PPI, MedGuide, carton and immediate container labels) consulted to DDMAC? YES
- Trade name (plus PI and all labels and labeling) consulted to ODS/DMETS? YES
- MedGuide and/or PPI (plus PI) consulted to ODS/DSRCS? N/A
- If a drug with abuse potential, was an Abuse Liability Assessment, including a proposal for scheduling, submitted? N/A

**If Rx-to-OTC Switch application:**

- OTC label comprehension studies, all OTC labeling, and current approved PI consulted to ODS/DSRCS? N/A
- Has DOTCDP been notified of the OTC switch application?

**Clinical**

- If a controlled substance, has a consult been sent to the Controlled Substance Staff? N/A

**Chemistry**

- Did applicant request categorical exclusion for environmental assessment? YES  
If no, did applicant submit a complete environmental assessment?  
If EA submitted, consulted to Florian Zielinski (HFD-357)? YES NO
- Establishment Evaluation Request (EER) submitted to DMPQ? YES
- If a parenteral product, consulted to Microbiology Team (HFD-805)?

ATTACHMENT

**MEMO OF FILING MEETING**

DATE:

**BACKGROUND:**

This is a 505b(2) application which references NDA 19-304 (Tricor Capsules, micronized)

ATTENDEES:

ASSIGNED REVIEWERS:

**Discipline**

**Reviewer**

Medical:

Mary Parks, M.D.

Pharmacology:

Karen Davis Bruno, Ph.D., team leader

Pharmacology:

Indra Antonipillai, Ph.D.

Chemistry:

Steve Moore, Ph.D., team leader

Chemistry:

Mike Adams, Ph.D.

Biopharmaceutical:

Hae Young Ahn, Ph.D., team leader

Biopharmaceutical:

Wei Qiu, Ph.D.

DSI:

Regulatory Project Management:

Valerie Jimenez

Other Consults:

Per reviewers, are all parts in English or English translation?

YES

If no, explain:

CLINICAL

FILE XX

REFUSE TO FILE \_\_\_\_\_

- Clinical site inspection needed: NO
- Advisory Committee Meeting needed? NO
- If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? N/A

CLINICAL MICROBIOLOGY

NA XX FILE \_\_\_\_\_

REFUSE TO FILE \_\_\_\_\_

STATISTICS

NA XX FILE \_\_\_\_\_

REFUSE TO FILE \_\_\_\_\_

BIOPHARMACEUTICS

FILE XX

REFUSE TO FILE \_\_\_\_\_

- Biopharm. inspection needed: YES

PHARMACOLOGY

NA \_\_\_\_\_ FILE XX

REFUSE TO FILE \_\_\_\_\_

- GLP inspection needed:

NO

CHEMISTRY

FILE XX

REFUSE TO FILE \_\_\_\_\_

- Establishment(s) ready for inspection?
- Microbiology

YES  
NO

**ELECTRONIC SUBMISSION:**

Any comments:

**REGULATORY CONCLUSIONS/DEFICIENCIES:**

\_\_\_\_\_ The application is unsuitable for filing. Explain why:

XX The application, on its face, appears to be well organized and indexed. The application appears to be suitable for filing.

XX No filing issues have been identified.

\_\_\_\_\_ Filing issues to be communicated by Day 74. List (optional):

**ACTION ITEMS:**

1. If RTF, notify everybody who already received a consult request of the RTF action. Cancel the EER.
2. If filed and the application is under the AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
3. Document filing issues/no filing issues conveyed to applicant by Day 74.

\_\_\_\_\_  
Regulatory Project Manager, HFD-

## Appendix A to NDA Regulatory Filing Review

An application is likely to be a 505(b)(2) application if:

- (1) it relies on literature to meet any of the approval requirements (unless the applicant has a written right of reference to the underlying data)
- (2) it relies on the Agency's previous approval of another sponsor's drug product (which may be evidenced by reference to publicly available FDA reviews, or labeling of another drug sponsor's drug product) to meet any of the approval requirements (unless the application includes a written right of reference to data in the other sponsor's NDA)
- (3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)
- (4) it seeks approval for a change from a product described in an OTC monograph and relies on the monograph to establish the safety or effectiveness of one or more aspects of the drug product for which approval is sought (see 21 CFR 330.11).

Products that may be likely to be described in a 505(b)(2) application include combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations), OTC monograph deviations, new dosage forms, new indications, and new salts.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, please consult with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007).

**Appendix B to NDA Regulatory Filing Review  
Questions for 505(b)(2) Applications**

1. Does the application reference a listed drug (approved drug)? YES

*If "No," skip to question 3.*

2. Name of listed drug(s) referenced by the applicant (if any) and NDA/ANDA #(s):

Tricor Capsules, NDA 19-304

3. The purpose of this and the questions below (questions 3 to 5) is to determine if there is an approved drug product that is equivalent or very similar to the product proposed for approval and that should be referenced as a listed drug in the pending application.

- (a) Is there a pharmaceutical equivalent(s) to the product proposed in the 505(b)(2) application that is already approved?

NO

*(Pharmaceutical equivalents are drug products in identical dosage forms that: (1) contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; (2) do not necessarily contain the same inactive ingredients; and (3) meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates. (21 CFR 320.1(c))*

*If "No," skip to question 4. Otherwise, answer part (b).*

- (b) Is the approved pharmaceutical equivalent(s) cited as the listed drug(s)? YES NO  
(The approved pharmaceutical equivalent(s) should be cited as the listed drug(s).)

*If "Yes," skip to question 6. Otherwise, answer part (c).*

- (c) Have you conferred with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (ORP) (HFD-007)?

YES NO

*If "No," please contact the Director, Division of Regulatory Policy II, ORP. Proceed to question 6.*

4. (a) Is there a pharmaceutical alternative(s) already approved? YES

*(Pharmaceutical alternatives are drug products that contain the identical therapeutic moiety, or its precursor, but not necessarily in the same amount or dosage form or as the same salt or ester. Each such drug product individually meets either the identical or its own respective compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times and/or dissolution rates. (21 CFR 320.1(d)) Different dosage forms and strengths within a product line by a single manufacturer are thus pharmaceutical alternatives, as are extended-release products when compared with immediate- or standard-release formulations of the same active ingredient.)*

If "No," skip to question 5. Otherwise, answer part (b).

- (b) Is the approved pharmaceutical alternative(s) cited as the listed drug(s)? YES  
(The approved pharmaceutical alternative(s) should be cited as the listed drug(s).)

*NOTE: If there is more than one pharmaceutical alternative approved, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (ORP) (HFD-007) to determine if the appropriate pharmaceutical alternatives are referenced.*

If "Yes," skip to question 6. Otherwise, answer part (c).

- (c) Have you conferred with the Director, Division of Regulatory Policy II, YES  
ORP? *Per tcon with Elaine Tseng on 5/12/0; the correct pharmaceutical alternative has been cited*

If "No," please contact the Director, Division of Regulatory Policy II, ORP. Proceed to question 6.

5. (a) Is there an approved drug product that does not meet the definition of "pharmaceutical equivalent" or "pharmaceutical alternative," as provided in questions 3(a) and 4(a), above, but that is otherwise very similar to the proposed product?

YES NO

If "No," skip to question 6.

If "Yes," please describe how the approved drug product is similar to the proposed one and answer part (b) of this question. Please also contact the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007), to further discuss.

- (b) Is the approved drug product cited as the listed drug? YES NO

6. Describe the change from the listed drug(s) provided for in this (b)(2) application (for example, "This application provides for a new indication, otitis media" or "This application provides for a change in dosage form, from capsules to solution").

*This application provides for changes in the dosage strengths and a change in formulation such that there is increased bioavailability — compared to Tricor Capsules (NDA 19-304).*

7. Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? (Normally, FDA will refuse-to-file such NDAs (see 21 CFR 314.101(d)(9)). NO
8. Is the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action less than that of the reference listed drug (RLD)? (See 314.54(b)(1)). If yes, the application should be refused for filing under 21 CFR 314.101(d)(9)). NO

9. Is the rate at which the product's active ingredient(s) is absorbed or otherwise made available to the site of action unintentionally less than that of the RLD (see 21 CFR 314.54(b)(2))? If yes, the application should be refused for filing under 21 CFR 314.101(d)(9). NO

10. Are there certifications for each of the patents listed for the listed drug(s)? YES

11. Which of the following patent certifications does the application contain? (Check all that apply and identify the patents to which each type of certification was made, as appropriate.)

21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA. (Paragraph I certification)

21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired. (Paragraph II certification)

21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire. (Paragraph III certification)

21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted. (Paragraph IV certification)

*IF FILED, and if the applicant made a "Paragraph IV" certification [21 CFR 314.50(i)(1)(i)(A)(4)], the applicant must **subsequently** submit a signed certification stating that the NDA holder and patent owner(s) were notified the NDA was filed [21 CFR 314.52(b)]. The applicant must also submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)].*

21 CFR 314.50(i)(1)(ii): No relevant patents.

21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent as described in the corresponding use code in the Orange Book. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications. (Section viii statement)

21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above).

\_\_\_\_ Written statement from patent owner that it consents to an immediate effective date upon approval of the application.

12. Did the applicant:

- Identify which parts of the application rely on information (e.g. literature, prior approval of another sponsor's application) that the applicant does not own or to which the applicant does not have a right of reference?

*Pharm/Tox and Clinical Safety and Efficacy* YES

- Submit a statement as to whether the listed drug(s) identified has received a period of marketing exclusivity? *Per Orange Book, there is no unexpired exclusivity for the listed drug.*

NO

- Submit a bioavailability/bioequivalence (BA/BE) study comparing the proposed product to the listed drug?

YES

- Certify that it is seeking approval only for a new indication and not for the indications approved for the listed drug if the listed drug has patent protection for the approved indications and the applicant is requesting only the new indication (21 CFR 314.54(a)(1)(iv).?

N/A

13. If the (b)(2) applicant is requesting 3-year exclusivity, did the applicant submit the following information required by 21 CFR 314.50(j)(4): N/A

- Certification that at least one of the investigations included meets the definition of "new clinical investigation" as set forth at 314.108(a).

YES NO

- A list of all published studies or publicly available reports that are relevant to the conditions for which the applicant is seeking approval.

YES NO

- EITHER

The number of the applicant's IND under which the studies essential to approval were conducted.

IND # \_\_\_\_\_ NO

OR

A certification that the NDA sponsor provided substantial support for the clinical investigation(s) essential to approval if it was not the sponsor of the IND under which those clinical studies were conducted?

YES NO

14. Has the Associate Director for Regulatory Affairs, OND, been notified of the existence of the (b)(2) application?

YES

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/s/

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Patricia Madara  
8/13/04 10:01:37 AM  
CSO



NDA 21-695

**INFORMATION REQUEST LETTER**

Reliant Pharmaceuticals, LLC  
Attention: Paulette F. Kosmoski  
Senior Director, Regulatory Affairs  
110 Allen Road  
Liberty Corner, NJ 07938

Dear Ms. Kosmoski:

Please refer to your December 4, 2003 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Fenofibrate Capsules.

We are reviewing the Clinical Pharmacology and Biopharmaceutical section of your submission and have the following request for information. We request a prompt written response in order to continue our evaluation of your NDA.

- Provide dissolution data for your drug product using 0.25% sodium laurel sulfate (SLS).

If you have any questions, call Pat Madara, Regulatory Project Manager, at (301) 827-6416.

Sincerely,

*{See appended electronic signature page.}*

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

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/s/

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David Orloff  
6/10/04 04:14:58 PM



NDA 21-695

**INFORMATION REQUEST LETTER**

Reliant Pharmaceuticals, Inc.  
Attention: Keith S. Rotenberg, Ph.D.  
Senior Vice President, Research & Development  
110 Allen Road  
Liberty Corner, NJ 07938

Dear Dr. Rotenberg:

Please refer to your December 1, 2003 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for RP 1824 (fenofibrate micronized) 43 mg, 87 mg, and 130 mg Capsules.

We are reviewing the Pharmacology/Toxicology section of your submission. Please provide the final particle size of the active pharmaceutical released from the drug product during dissolution. Recently it has come to our attention that particles  $\sim$  . $\mu$ m can have altered tissue distribution and toxicity profiles. We request a prompt written response in order to continue our evaluation of your NDA.

If you have any questions, call Pat Madara, Regulatory Project Manager, at (301) 827-6416.

Sincerely,

*{See appended electronic signature page}*

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

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/s/

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David Orloff

4/30/04 12:06:25 PM

2/13/04



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service  
Food and Drug Administration  
Rockville, MD 20857

**FILING COMMUNICATION**

NDA 21-695

Reliant Pharmaceuticals  
Attention: Keith S. Rotenberg, Ph. D.  
Senior Vice President, Research and Development  
110 Allen Road  
Liberty Corner, NJ 07938

Dear Dr. Rotenberg:

Please refer to your December 1, 2004, new drug application (NDA) submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Fenofibrate (micronized) Tablets, 43 mg, 87 mg, and 130 mg.

We also refer to your submission dated January 26, 2004.

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 February 2, 2004, 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/

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Valerie Jimenez  
2/13/04 09:28:33 AM  
Signing for Enid Galliers, Chief, Project Management Staff



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Rockville, MD 20857

12/15/03

NDA 21-695

Reliant Pharmaceuticals  
Attn: Keith S. Rotenberg, Ph.D.  
Senior Vice President, Research and Development  
100 Allen Road  
Liberty Corner, NJ 07938

Dear Dr. Rotenberg:

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: RP 1824 (fenofibrate micronized) Capsules, 43 mg, 87 mg, 130 mg

Review Priority Classification: Standard (S)

Date of Application: December 1, 2003

Date of Receipt: December 4, 2003

Our Reference Number: NDA 21-695

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 February 2, 2004 in accordance with 21 CFR 314.101(a). If we file the application, the user fee goal date will be October 4, 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:  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Division of Metabolic & Endocrine Drug Products, HFD-510  
Attention: Fishers Document Room, 8B45  
5600 Fishers Lane  
Rockville, Maryland 20857

NDA 21-695

Page 2

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 & Endocrine Drug Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

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this page is the manifestation of the electronic signature.**  
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/s/

-----  
Enid Galliers  
12/15/03 05:30:46 PM  
Signing for Valerie Jimenez

USER FEE PAYMENT & PDUFA/FDAMA VALIDATION SHEET

to be completed for ALL original NDAs, efficacy supplements and initial rolling review submissions

NDA # 21-695 SUPP TYPE & # N-000 Division 510 UFID # 4627

Applicant Name: Reliant Pharmaceuticals Drug Name: Fenebrbrate(micronized) Capsules

For assistance in filling out this form see the Document Processing Manual for complete instructions and examples.

- 1. Was a Cover Sheet submitted? [X] Yes [ ] No
2. Firm in Arrears? [ ] Yes [X] No
3. Bundling Policy Applied Appropriately? Refer to Draft "Guidance for Industry: Submitting Separate Marketing Applications and Clinical Data for Purposes of Assessing User Fees" http://www.fda.gov/cder/guidance [X] Yes [ ] No (explain in comments)

4. Administrative Split? (list all NDA#s and Divisions)
Table with columns: NDA #/Doc Type, Div., Fee? (Y/N)

5. Type 6? [ ] Yes [X] No
Type 6 to which other application?
NDA # \_\_\_\_\_ Supp Type & # \_\_\_\_\_

6. Clinical Data Required for Approval? (Check one)
[ ] Yes\*
[ ] Yes, by reference to another application
NDA # \_\_\_\_\_ Supp Type & # \_\_\_\_\_
[X] No

\* Yes if NDA contains study or literature reports of what are explicitly or implicitly represented by the application to be adequate and well-controlled trials.

- 7. 505(b)(2) application? (NDA original applications only) Refer to Draft "Guidance for Industry Applications Covered by Section 505(b)(2)" http://www.fda.gov/cder/guidance [X] Yes [ ] No [ ] To be determined
8. Subpart H (Accelerated Approval/Restricted Distribution)? [ ] Yes [X] No [ ] To be determined
9. Exclusion from fees? (Circle the appropriate exclusion. For questions, contact User Fee staff)
List of exclusions:
2- No fee - administrative split
4- No fee - 505b2
7- Supplement fee - administrative split
9- No fee Subpart H supplement- confirmatory study
11- No fee Orphan Exception
13- No fee State/Federal exemption from fees
10. Waiver Granted? [ ] Yes (letter enclosed) [X] No
Select Waiver Type below: Letter Date: \_\_\_\_\_
[ ] Small Business [ ] Barrier-to-Innovation
[ ] Public Health [ ] Other (explain)
11. If required, was the appropriate fee paid? [X] Yes [ ] No
12. Application Review Priority [ ] Priority [X] Standard [ ] To be determined
13. Fast Track/Rolling Review Presubmission? [ ] Yes [X] No

Comments
[Signature] 12/11/03
PM Signature/Date
for Valerie Jimenez

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5/18/03



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Rockville, MD 20857

IND 66,249

Reliant Pharmaceuticals, LLC  
Attention: Robert J. Mandetta  
Director, Regulatory Affairs  
110 Allen Road  
Liberty Corner, NE 07938

Dear Mr. Mandetta:

Please refer to the meeting between representatives of your firm and FDA on June 17, 2003. The purpose of the meeting was to discuss a new drug application for a 505(b)(2) submission of fenofibrate capsules as adjunctive therapy to diet for treatment of patients with elevated serum Triglyceride levels.

The official minutes of that meeting are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

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  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

Enclosure

**MEMORANDUM OF MEETING MINUTES**

**MEETING DATE:** June 17, 2003

**TIME:** 11:00 a.m. – 12:00 noon

**LOCATION:** Parklawn Conference Center, Room L

**SPONSOR:** Reliant Pharmaceuticals, LLC

**TYPE OF MEETING:** Pre-NDA

**DRUG:** RP 1824 Capsules (fenofibrate)

**APPLICATION:** IND 60,941

**MEETING CHAIR:** Mary Parks, M.D., Deputy Director, Division of Metabolic and Endocrine Drug Products (DMEDP)

**MEETING RECORDER:** Valerie Jimenez, Regulatory Project Manager

**FDA ATTENDEES, TITLES, AND OFFICE/DIVISION**

<u>Name of FDA Attendee</u>	<u>Title</u>	<u>Division Name &amp; HFD#</u>
1. Mary Parks, M.D.	Deputy Director and Medical Team Leader	DMEDP, HFD-510
2. Karen Mahoney, M.D.	Medical Reviewer	DMEDP, HFD-510
3. Stephen Moore, Ph.D.	Chemistry Team Leader	DNDC II, DMEDP, HFD-510
4. Hae-Young Ahn, Ph.D.	Biopharmaceutics Team Leader	DPEII, OCPB, HFD-870
5. Sharon Kelly, Ph.D.	Chemistry Reviewer	DMEDP, HFD-510
6. Wei Qiu, Ph.D.	Biopharmaceutics Reviewer	DPEII, OCPB, HFD-870
7. Kati Johnson	Regulatory Project Management	DMEDP, HFD-510
8. Valerie Jimenez	Regulatory Project Manager	DMEDP, HFD-510

**EXTERNAL ATTENDEES AND TITLES:**

<u>External Attendee</u>	<u>Title</u>	<u>Sponsor/Firm Name</u>
1. George Bobotas, Ph.D.	Vice President, Scientific Affairs	Reliant Pharmaceuticals
2. Paulette Kosmoski	Senior Director, Regulatory Affairs	Reliant Pharmaceuticals
3. Robert Mandetta	Director, Regulatory Affairs	Reliant Pharmaceuticals
4. Keith Rotenberg, Ph.D.	Senior Vice President, Research And Development	Reliant Pharmaceuticals

**BACKGROUND:**

On April 25, 2003, the sponsor requested a Pre-NDA guidance meeting to discuss questions regarding RP 1824 Capsules, a formulation of fenofibrate as adjunctive therapy to diet for treatment of patients with elevated serum triglyceride levels.

**MEETING OBJECTIVES:**

1. Obtain input from the Agency regarding the sponsor's proposed clinical plan to support the Phase II/III dose-ranging trial following IND submission.
2. Obtain input from the Agency on the proposal of recommendations for Phase II/III study and monitoring plan.

**DISCUSSION:****Input on additional questions:**

1. Reliant has conducted five bioavailability/pharmacokinetic studies to demonstrate that RP 1824 (130 mg) is as bioavailable as Tricor® 200 mg capsules and that RP 1824 is dose proportional from 43 mg to 130 mg. Is this adequate for the purpose of a 505(b)(2)?

**FDA Response:**

- *The proposed studies will likely be adequate to support a 505(b)(2) filing.*

2. Reliant proposes in its labeling for RP 1824 that \_\_\_\_\_  
\_\_\_\_\_ Do you agree with that labeling statement?

**FDA Response:**

- *Specific labeling comments cannot occur until after the Agency has reviewed the full data submitted with the NDA. The Agency's position at this time is that*

3. **Reliant has conducted a bioavailability/pharmacokinetic study to demonstrate the dose equivalence of RP 1824 43 mg capsules to RP 1824 87 mg and 130 mg capsules. Is this adequate for the purposes of a 505(b)(2)?**

**FDA response:**

- *Yes.*

4. **Reliant plans to file an eNDA. Does the Division desire hard copies of specific review sections? If so, which ones?**

**FDA Response:**

- *The majority of the NDA can be submitted entirely electronically. If the electronic NDA submission is easily navigable, paper submission will likely not be requested for most sections. The Chemistry reviewer would like to have two paper copies of the Analytical Methods section for use by the FDA laboratories. The Agency recognizes the logistical difficulty of generating paper copies of specific sections after initial electronic NDA submission. However, if the reviewer(s) cannot satisfactorily access all parts of the NDA electronically, paper copies of specific sections may then be requested.*

5. **Reliant will be submitting data from five bioavailability/PK type studies in its RP 1824 505(b)(2) submission. Due to this, Reliant is requesting a waiver from the requirements for an ISS, ISE, and literature summary. Reliant will provide an overall summary of the bioavailability studies conducted. Is this acceptable to the Division?**

**FDA response:**

- *Yes.*

6. **How many levels of hyperlink/bookmarks does the FDA want?**

**FDA response:**

- *Technical questions regarding electronic submission requirements can be directed to [esub@cder.fda.gov](mailto:esub@cder.fda.gov). Primary point of contact is Ken Edmunds; Gary Gensinger can also answer questions. The Division requests that Reliant ensure ease of navigability for reviewers, and that Reliant provide technical support for reviewers' e-sub-related*

*questions. The Division asks that the sponsor provide working hyperlinks from all tables, figures, and lists; these links would connect to and from the appropriate text.*

**7. The drug product manufacturer's**

**FDA response:**

- 

**8. As the submission will follow the eNDA format, is there any additional CTD-Q information the FDA would propose Reliant to consider for incorporation into the NDA?**

**FDA response:**

- *No.*

**9**

**FDA response:**

**10.**

**FDA response:**

-

11. Reliant would like to propose the acceptance criteria for "any other single impurity" be changed to            rather than           , as indicated in the IND submission. This acceptance criterion is in accordance with

           The maximum daily dose for fenofibrate is 130 mg/day. The most recent stability data from the first set of registration batches indicate that a degradation product is present at           . Is this acceptable to the FDA?

**FDA response:**

- *This is deferred as a review issue.*

12. With the pharmacopoeial harmonization process underway for interchangeability of various chapters and monographs, we wish to propose conformance to the requirements of the current European Pharmacopoeia for release testing of formulation excipients and drug substance as the manufacturer is a foreign firm. Is this approach acceptable to the FDA?

**FDA response:**

- *Yes, since there is no USP monograph for fenofibrate.*

13. For background information, the choice of the dissolution methodology was based on the IS patent 6,277,405 (Stamm, et al.) filed May 18, 2000. The rationale employed was to produce a drug product dissolution profile outside of the constraints of the primary claim to avoid patent infringement. Due to internal time point selection of 5 minutes in addition to the regulatory control at 30 minutes to ensure that the patent is not breached. The results from both time points will be used to decide internal disposition of the product to Reliant and release for US commercial distribution. It should be noted that only the 30 minutes time point is filed as the regulatory release and stability acceptance criteria for drug product dissolution. Is this approach acceptable the FDA?

**FDA response:**

- *This is deferred as a review issue. The firm will need to compare results*

14. The three strengths of fenofibrate capsules are manufactured with the                       different fill weight and capsule sizes. Including an executed batch record for each strength would be unnecessarily redundant. Therefore, Reliant proposes that only one executed batch record for a single strength is submitted in the NDA for ease of review and as it would be representative of the multiple strengths of the drug product. Is this approach acceptable to the FDA?

**FDA response:**

- *Yes.*

15. We believe that the likelihood of the reduced stability program would lead to the successful prediction of the expiration-dating period with this study design. Is the design of the revised primary NDA stability program acceptable to the Division?

FDA response:

- Yes.

16. At the time of NDA submission, a primary stability database of \_\_\_\_\_ of real time and accelerated, site specific data under ICH conditions will be available for one batch of each strength of drug product. In addition, \_\_\_\_\_, of stability data will be available on two batches of each strength. This represents a total of \_\_\_\_\_ batches of drug product packaged in 3 \_\_\_\_\_ bottle trade presentations. The plan is to submit further accumulated data updates from the ongoing primary and supportive stability studies periodically during the NDA assessment period. Is this approach to post submission of stability updating acceptable to the FDA?

FDA response:

- \_\_\_\_\_ stability data is expected at filing.

**Additional Recommendations:**

1. Bioequivalence appears marginal in the summary of the single-dose low-fat meal study (FF4c), with the lower limit of the 90% confidence intervals for both AUC measures at 75.9%. The single-dose study is the preferred method to establish bioequivalence. If the steady-state low-fat meal study (FF3) is to lend support to bioequivalence,  $C_{min}$  becomes an important measure, as it is reflective of the chronic level one expects with clinical use of the drug.  $C_{min}$  is considered reflective of likely clinical efficacy. The summary data presented for FF3 appear to show that the steady state  $C_{min}$  for RP1824 130 mg is also marginal when compared to Tricor® 200 mg (82%). These data do not appear to robustly support pharmacokinetic bioequivalence. Reliant could consider a clinical efficacy study, on a low-fat diet, of RP1824 vs placebo with blood lipid level(s) as endpoint(s). A positive result in a clinical efficacy study could provide more support for approval.

2. The study summaries indicate that data for some study subjects who completed studies FF3, FF2, and FF4 were not included in the PK analysis. For study FF4b, it appears that two non-completers were included in the PK analysis. An explanation will need to be included in the NDA submission.

Minutes Prepared by /s/ 07/23/03

Valerie Jimenez  
Project Manager, HFD-510

Chair Concurrence: /s/ 07/29/03

Mary Parks, M.D.  
Deputy Division Director, HFD-510

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**This is a representation of an electronic record that was signed electronically and  
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/s/

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Valerie Jimenez  
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