

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**21-695**

**CHEMISTRY REVIEW(S)**

**NDA 21-695**

**Antara  
(fenofibrate) Capsules**

**Reliant Pharmaceuticals, LLC**

**John C. Hill, Ph.D., Chemistry Reviewer  
ONDC / DNDCII / DMEDP (HFD-510)**

## Chemistry Review Data Sheet

1. NDA 21-695
2. Review # 002
3. REVIEW DATE: September 29, 2004
4. REVIEWER: John C. Hill, Ph.D, DMEDP, HFM-510
5. PREVIOUS DOCUMENTS

<u>Previous Documents</u>	<u>Document Date</u>
Original NDA	04-DEC-2003
BC Amendment 001(Stability Update)	28-APR-2004
BC Amendment 002(Stability Update)	14-JUN-2004
BC Amendment 003(Manufacturing/Stability Update)	06-AUG-2004

6. SUBMISSION(S) BEING REVIEWED

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
BC Amendment 004 (Stability Update)	03-SEP-2004

7. NAME & ADDRESS OF APPLICANT:

Name: Reliant Pharmaceuticals, LLC  
Address: 110 Allen Road  
Liberty Corner, NJ 07938  
Representative: Paulette F. Kosmoski  
Telephone: 908-542-4403

8. DRUG PRODUCT NAME / CODE / TYPE:

- a) Proprietary Name: Antara Capsules
- b) Non-Proprietary Name (USAN): fenofibrate capsules
- c) Code Name / # N/A (ONDC only): RP 1824
- d) Chem. Type / Submission Priority (ONDC only):  
Chem. Type: 5  
Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 505 (b) (2)

Listed Drug: TRICORE (Fenofibrate) capsules Abbott

10. PHARMECOL. CATEGORY: 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

# CHEMISTRY EVALUATION

Reliant Pharmaceuticals RP1824 (Fenofibrate capsules) 43mg, 87mg, and 130mg

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11. DOSAGE FORM: Capsules

12. STRENGTH / POTENCY: 43, 87, and 130 mg

13. ROUTE OF ADMINISTRATION: Oral

14. Rx / OTC DISPENSED: Rx

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM)

\_\_\_\_\_ SPOTS PRODUCT-FORM COMPLETED

Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

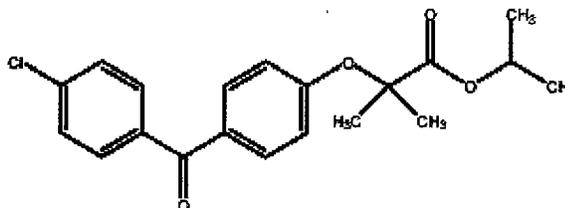
BAN: Fenofibrate

CAS No: 49562-28-9

Molecular Formula:  $C_{20}H_{21}O_4Cl$

Molecular Weight: 360.8

IUPAC Name: 2-[4-(4-chlorobenzoyl) phenoxy]-2-methyl-propanoic acid, 1-methylethyl ester



17. RELATED / SUPPORTING DOCUMENTS:

**A. DMFs:**

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE <sup>1</sup>	Review Date	STATUS <sup>2</sup>	COMMENTS
[	II			4	27-MAY-03	Adequate	LOA 04-SEP-2003
	III			4	19-FEB-03	Adequate	LOA 23-JUN-2003
	III			4	13-JUN-03	Adequate	LOA 02-SEP-2003
	III			4	13-JUN-03	Adequate	LOA 02-SEP-2003
	III			4	15-SEP-00	Adequate	LOA 16-AUG-2001
	III			4	6-AUG-02	Adequate	LOA 31-AUG-2001
	III			4	29-JUL-04	Adequate	05-SEP-2001
	III			4	6-OCT-03	Adequate	LOA 12-FEB-2003
	III			4	7-DEC-00	Adequate	LOA 21-FEB-2003
	III			4	8-AUG-02	Adequate	LOA 27-AUG-2003

<sup>1</sup> Action codes for DMF Table:  
1 – DMF Reviewed.

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Other codes indicate why the DMF was not reviewed, as follows:

- 2 – Type 1 DMF
- 3 – Reviewed previously and no revision since last review
- 4 – Sufficient information in application
- 5 – Authority to reference not granted
- 6 – DMF not available
- 7 – Other (explain under "Comments")

<sup>2</sup> Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

**B. Other Documents:**

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	66,249	Fenofibrate for the TX of hyperlipoproteinemia

18. STATUS:

**ONDC:**

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics			
EES	Acceptable	30-SEP-2004	Shawnte L. Adams
Pharm/Tox			
Biopharm	Pending		
LNC			
Methods Validation	Not needed		
OPDRA		28-SEP-2004	
EA	Acceptable	15-JUN-2004	John C. Hill, Ph.D.
Microbiology			

# Chemistry Review for NDA 21-695

## The Executive Summary

### I. Recommendations

#### A. Recommendation and Conclusion on Approvability

This application can be approved from a CMC perspective. A 24 month shelf life for the drug product is granted, as requested, based on provided and supporting stability data.

#### B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

- The sponsor agrees to conduct the primary stability study to completion, following the stability protocol; notifying the Agency of the results in a timely manner.
- The sponsor agrees to place one batch per year, for each package size, on stability.

### II. Summary of Chemistry Assessments

#### A. Description of the Drug Product(s) and Drug Substance(s)

See Chemistry review number 1. Submissions reviewed herein include stability updates, EER and labeling revisions.

#### B. Description of How the Drug Product is Intended to be Used

See Chemistry review number 1.

#### C. Basis for Approvability or Not-Approval Recommendation

All pending CMC issues have been satisfactorily addressed.

**Chemistry Assessment**

**A. Stability Update:**

The sponsor has supplemented the original drug product stability data presented in the NDA filing with an — stability data update for registration batch number 1. This stability update was submitted to the NDA on September 3, 2004.

LOT	STRENGTH	STORAGE CONDITION
D02342	43 mg	25°C/60% RH
D02344	87 mg	25°C/60% RH
D02343	130 mg	25°C/60% RH

All packaging configurations of all strengths have meet the stability protocol test specifications. The provided — stability data are within the defined specifications of the stability program. With this update, the sponsor has provided sufficient stability data for the drug product to approve a label dating period of 24 months — based on accelerated and supporting stability data).

**Evaluation:** After evaluation of the — stability data, I recommend approval of a 24 month shelf life for the drug product. This is in concurrence with the sponsors request in the NDA for a 24 month dating period for the drug product.

**B. Establishment Evaluation:**

The Office of Compliance has finished their evaluation of the manufacturing establishments used in the production of the fenofibrate capsules. An overall recommendation of “APPROVABLE” was issued by OC on 30-SEP-2004. See attached OC evaluation report for details (Attachment 1).

**Evaluation:** Satisfactory.

**C. Labeling Revisions:**

The sponsor has revised the package labeling included in the original NDA filing in response to Agency requests to:

1. Change the trade name for the drug product to “Antara”.
2. Clarify the components and colorants used in the manufacture of the gelatin capsules. (This modification is consistent with the wording approved in the innovators package insert.),
3. Choose a new color scheme for the drug product labels that clearly differentiates between the three dosage strengths,
4. Increase the prominence of the proprietary and established names on all container labels,
5. Relocate the net quantity statement on the label so that it appears away from the product strength and has less prominence.

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6. Remove the term ~ from the labeling.

**Evaluation:** These labeling issues were satisfactorily addressed in two separate e-mails from Robert Mandetta of Reliant on 30-SEP-2004. Official submissions to the NDA documenting these revisions will follow (see attachments 2 and 3 at the end of this review).

APPEARS THIS WAY  
ON ORIGINAL

CHEMISTRY EVALUATION

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ATTACHMENT 1:

Establishment Evaluation:

U:\SOP\Bk4SD\17.27c66f 30-SEP-2004 Page 1 of 4

FDA CDER EES

ESTABLISHMENT EVALUATION REQUEST

DETAIL REPORT

Application:	NDA 21695/000	Action Goal:	
Stamp:	04-DEC-2003	District Goal:	05-AUG-2004
Regulatory Due:	04-OCT-2004	Brand Name:	FENOFIBRATE CAPSU
LES, 43,		Estab. Name:	87, 130MG
Applicant:	RELIANT PHARMS INC	Generic Name:	FENOFIBRATE MICRO
	110 ALLEN RD		
NIZED			CAPSULES
	LIBERTY CORNER, NJ 07938	Dosage Form:	(CAPSULE)
Priority:	3S	Strength:	43 MG, 87 MG, 130
Org Code:	510		
MG			

Application Comment:

Contacts:	V. JIMENEZ	(HFD-510)	301-827-9090	, Project
Manager				
	J. HILL	(HFD-810)	301-827-6408	, Review C
hemist				
	S. NOORE	(HFD-510)	301-827-6401	, Team Lea
der				

Overall Recommendation: ACCEPTABLE on 30-SEP-2004 by S. ADAMS (HFD-322) 301-827-9051

Establishment: CFN

FEI

No:

AADA:

Responsibilities:

Profile: CTL

QAT Status: NONE

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Estab. Comment:  
2004 by

(on 17-AUG-

W. ADAMS (HFD-510) 301-827-9088)

Milestone Name	Date	Type	Insp. Date	Decision & Reason	C
reator					

SUBMITTED TO OC ADANSM	17-AUG-2004				
---------------------------	-------------	--	--	--	--

OC RECOMMENDATION MBROGIOJ	18-AUG-2004			ACCEPTABLE	DA
BASED ON PROFILE					

Establishment: CFN

FEI

DMF No:

AADA:

Responsibilities:

Profile:

CTL

OAI Status: NONE

Estab. Comment:  
TABILITY

(on 07-JAN-2004 by W. ADAMS (HFD-510) 301-827-9088

Milestone Name	Date	Type	Insp. Date	Decision & Reason	C
reator					



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BASED ON PROFILE

SUBMITTED TO OC  
ADAMSM 15-JAN-2004

OC RECOMMENDATION  
ERGUSONS 16-JAN-2004

ACCEPTABLE F

BASED ON PROFILE

Establishment: CFN 9612001 FEI 3002807933  
 ETHYPHARM (FORMERLY PROGRAPHARM)  
 Z. I. SAINT ARNOULT  
 CHATEAUNEUF-EN-THYMERAIS, , FR

DMF No: AADA:  
 Responsibilities: FINISHED DOSAGE OTHER TESTER

Profile: CTL OAI Status: NONE

Sub. Comment: QUALITY CONTROL TESTING OF RAW MATERIALS (on 12-JAN-2004 by W.  
 AS  
 (HFD-910; 301-827-9088).

Milestone Name	Date	Type	Insp. Date	Decision & Reason	C
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SUBMITTED TO OC ADAMSS	12-JAN-2004				C
SUBMITTED TO DO ERGUSONS	12-JAN-2004	GMP			F
SUBMITTED TO OC ADAMSM	15-JAN-2004				
SUBMITTED TO DO ERGUSONS	16-JAN-2004	GMP			F

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30-SEP-2004  
3 of 4

FDA CDER EES

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ESTABLISHMENT EVALUATION REQUEST  
DETAIL REPORT

ASSIGNED INSPECTION T 03-FEB-2004 GMP  
ADAMSS

INSPECTION PERFORMED 12-MAR-2004 12-MAR-2004  
ADAMSS

INSPECTION SCHEDULED 29-JUN-2004 12-MAR-2004  
ADAMSS

DO RECOMMENDATION 29-JUN-2004 ACCEPTABLE  
ADAMSS

INSPECTION

OC RECOMMENDATION 29-JUN-2004 ACCEPTABLE  
ADAMSS

DISTRICT RECOMMENDATION

-----  
Establishment: CFN FEI  
ETHYPHARM INDUSTRIES  
CHEMIN DE LA POUDRIERE, BP 117  
GRAND QUEVILLY, , FR 76121

DMF No: AADA:

Responsibilities: DRUG SUBSTANCE OTHER TESTER  
FINISHED DOSAGE MANUFACTURER  
FINISHED DOSAGE RELEASE TESTER

Profile: CHG OAI Status: NONE

Estab. Comment: FACILITY PERFORMS DRUG PRODUCT MANUFACTURER, PRODUCT RELEASE T  
ESTING,  
AND PARTICLE SIZE TESTING ON DRUG SUBSTANCE. (on 09-JAN-2004 b  
ADAMS (HFD-322) 301-827-9051)

Milestone Name Date Type Insp. Date Decision & Reason C  
reator

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SUBMITTED TO OC ADAMSS	12-JAN-2004		
SUBMITTED TO DO ERGUSONS	12-JAN-2004	GMP	F
SUBMITTED TO OC ADAMSS	15-JAN-2004		
SUBMITTED TO DO ERGUSONS	16-JAN-2004	GMP	F
ASSIGNED INSPECTION T ADAMSS	03-FEB-2004	GMP	
INSPECTION SCHEDULED RIVERA	15-SEP-2004		16-SEP-2004
INSPECTION PERFORMED ADAMSS	16-SEP-2004		16-SEP-2004
DO RECOMMENDATION ADAMSS	30-SEP-2004		ACCEPTABLE
			INSPECTION
BASED ON INVESTIGATOR'S RECOMMENDATION. NO 483 ISSUED. AWAITING EIR.			
OC RECOMMENDATION ADAMSS	30-SEP-2004		ACCEPTABLE
			DISTRICT RECOMMENDATION

-----

Establishment:      CFN      \_\_\_\_\_      FEI      \_\_\_\_\_

DMF No:      \_\_\_\_\_      AADA:      \_\_\_\_\_

Responsibilities:      \_\_\_\_\_

Profile:      CTL      OAI Status:      NONE

CHEMISTRY EVALUATION

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FDA CDER EES

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ESTABLISHMENT EVALUATION REQUEST

DETAIL REPORT

Estab. Comment:  
by S.

(on 09-JAN-2004

ADAMS (HFD-322) 301-827-9051}

Milestone Name	Date	Type	Insp. Date	Decision & Reason	C
----------------	------	------	------------	-------------------	---

SUBMITTED TO OC ADAMSS	12-JAN-2004				
SUBMITTED TO DO ERGUSONS	12-JAN-2004	GMP			F
SUBMITTED TO OC ADAMSM	15-JAN-2004				
SUBMITTED TO DO ERGUSONS	16-JAN-2004	GMP			F
ASSIGNED INSPECTION T ADAMSS	03-FEB-2004	GMP			
RECOMMENDATION ADAMSS	30-SEP-2004			ACCEPTABLE	

BASED ON FILE REVIEW

DUE TO UPCOMING PDUFA DATE DECISION WAS MADE, HOWEVER POST APPROVAL INSPECTION WILL STILL

BE PERFORMED.

OC RECOMMENDATION  
ADAMSS

ACCEPTABLE

DISTRICT RECOMMENDATION

Establishment: CFN

FEI

No:

ANDA:

Responsibilities:

Profile: CSN

OAI Status: NONE

# CHEMISTRY EVALUATION

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Estab. Comment:  
10) 301-

(on 07-JAN-2004 by W. ADAMS (HFD-5

827-9088)

Investigator Name or	Date	Type	Resp. Date	Decision & Reason	C
-----					
SUBMITTED TO OC ADAMSS	12-JAN-2004				
SUBMITTED TO DO ERGUSONS	12-JAN-2004	GMP			F
SUBMITTED TO OC ADAMSM	15-JAN-2004				
SUBMITTED TO DO ERGUSONS	16-JAN-2004	GMP			F
DO RECOMMENDATION ADAMSS	03-FEB-2004			ACCEPTABLE	
				BASED ON FILE REVIEW	
OC RECOMMENDATION MBROGIOJ	03-FEB-2004			ACCEPTABLE	DA
				DISTRICT RECOMMENDATION	
-----					

ATTACHMENT 2:  
Confidential E-mail:

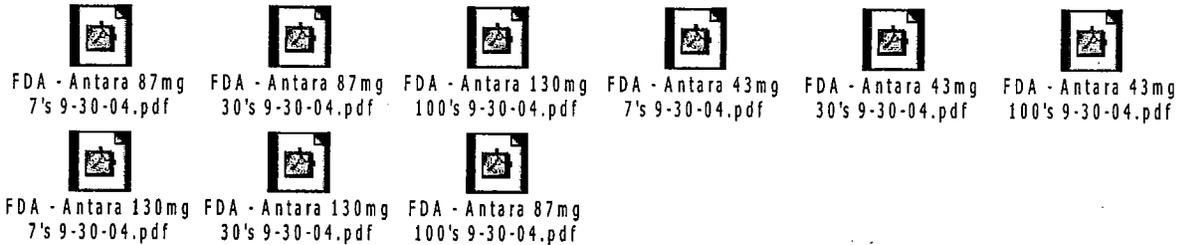
Here are the new labels with  removed. Pat

-----Original Message-----

From: Mandetta, Robert [mailto:rmandetta@reliantrx.com]  
Sent: Thursday, September 30, 2004 4:46 PM  
To: madarap@cder.fda.gov  
Subject: FW: Antara Labels NDA 21-695 - "micronized" removed

Pat,  
Attached are the revised labels. Still working on the PI.  
Bob

<<FDA - Antara 87mg 100's 9-30-04.pdf>> <<FDA - Antara 130mg 30's 9-30-04.pdf>> <<FDA - Antara 130mg 7's 9-30-04.pdf>> <<FDA - Antara 43mg 100's 9-30-04.pdf>> <<FDA - Antara 43mg 30's 9-30-04.pdf>> <<FDA - Antara 43mg 7's 9-30-04.pdf>> <<FDA - Antara 130mg 100's 9-30-04.pdf>> <<FDA - Antara 87mg 30's 9-30-04.pdf>> <<FDA - Antara 87mg 7's 9-30-04.pdf>>



ATTACHMENT 2:  
Confidential E-mail:

Hi John and Steve;

Here are the revised carton labels for Antara. The originals are in EDR. I have added the 2 ODS concerns that should be addressed in the new ones. I'm not sure you are supposed to look at these ????? Pat

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.

-----Original Message-----

**From:** Mandetta, Robert [mailto:rmandetta@reliantrx.com]

**Sent:** Thursday, September 30, 2004 9:54 AM

**To:** madarap@cder.fda.gov

**Subject:** FW: Antara (fenofibrate) Labels NDA 21-695

Pat,

As requested the Antara labels are attached. We have incorporated the changes you had requested. We are moving forward with an e-submission of the PI and these labels, both of which should arrive at central documents tomorrow. Thanks again for all your help, please let me know if you need anything else.

Bob

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

/s/

-----  
John C. Hill  
10/1/04 01:35:55 PM  
CHEMIST

Stephen Moore  
10/1/04 01:44:15 PM  
CHEMIST

### 3.4.4 Environmental Impact

The requested action for approval of this application meets the requirements for categorical exclusion from preparation of an environmental assessment as stated in 21 CFR 25.31(b) and to the applicant's knowledge, no extraordinary circumstances exist (21 CFR 25.15(d)). The request for exclusion is based on the calculation that was performed to show that the estimated concentration of the drug substance, fenofibrate, EP, at the point of entry into the aquatic environment would be below 1 part per billion (ppb).

Over five years, maximum projected US product usage of all three dosage strengths of fenofibrate capsules will be the highest in 2007, based on an approval in late 2004. The quantity of fenofibrate, EP required to yield this cumulative product volume is estimated to be

Assuming that all drug product is used with even distribution throughout the US per day, and that no metabolism or depletion mechanisms occurred, the EIC for fenofibrate, EP in 2007 for the aquatic environment is calculated (according to the July 1998 FDA "Guidance for Industry: Environmental Assessment of Human Drug and Biologic Applications") using the equation as follows:

$$\text{EIC - Aquatic (ppb)} = (A) (B) (C) (D)$$

Where: A = \_\_\_\_\_ year fenofibrate

B =  $1.214 \times 10^{11}$  /liters per day entering POTWs\*

C = 1 year/365 days

D =  $10^9$   $\mu\text{g}/\text{kg}$  (conversion factor)

\*  $1.214 \times 10^{11}$  liters per day entering publicly owned treatment works (POTWs); Source: *1996 Needs Survey, Report to Congress*

$$\begin{aligned} \text{EIC - Aquatic (ppb)} &= \frac{1}{1.214 \times 10^{11}} \times \frac{1}{365} \times 10^9 \\ &= \text{--- ppb} \end{aligned}$$

Since the potential introduction concentration is far less than 1 ppb, this product qualifies for the Tier 0 approach and categorical exclusion from preparation of an environmental assessment.

# **NDA 21-695**

**Fenofibrate capsules  
(micronized)**

**Reliant Pharmaceuticals**

**John C. Hill, Ph.D., Chemistry Reviewer  
ONDC / DNDCII / DMEDP / HFD-510**

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1. NDA 21-695
2. Review # 001
3. REVIEW DATE: June 14, 2004
4. REVIEWER: John C. Hill, Ph.D, DMEDP, HFD-510
5. PREVIOUS DOCUMENTS

Previous DocumentsDocument Date

NA

## 6. SUBMISSION(S) BEING REVIEWED

Submission(s) ReviewedDocument Date

Original NDA	01-DEC-2003
BC Amendment 001(Stability Update)	26-APR-2004
BC Amendment 002(Stability Update)	14-JUN-2004
BL Amendment 001 (tradename)	06-JUL-2004
BC Amendment 003(Manufacturing/Stability Update)	06-AUG-2004
BL Amendment 002 (marked-up package insert)	16-AUG-2004

## 7. NAME &amp; ADDRESS OF APPLICANT:

Name: Reliant Pharmaceuticals, LLC  
Address: 110 Allen Road  
Liberty Corner, NJ 07938  
Representative: Paulette F. Kosmoski  
Telephone: 908-542-4403

## 8. DRUG PRODUCT NAME / CODE / TYPE:

- a) Proprietary Name:
- b) Non-Proprietary Name (USAN):
- c) Code Name / # N/A (ONDC only): RP 1824
- d) Chem. Type / Submission Priority (ONDC only):  
Chem. Type: 5  
Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 505 (b) (2)  
Listed Drug: TRICORE (Fenofibrate) Abbott

# CHEMISTRY EVALUATION

Reliant Pharmaceuticals RP1824 (Fenofibrate capsules) 43mg, 87mg, and 130mg  
8/26/2004

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10. PHARMECOL. CATEGORY: 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

11. DOSAGE FORM: Capsules

12. STRENGTH / POTENCY: 43, 87, and 130 mg

13. ROUTE OF ADMINISTRATION: Oral

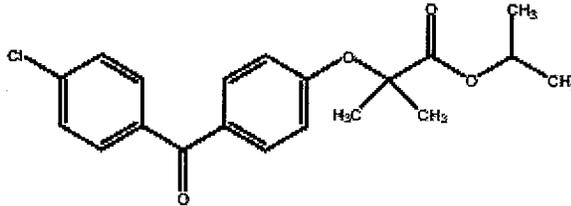
14. Rx / OTC DISPENSED: Rx

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM)  
\_\_\_\_\_ SPOTS PRODUCT-FORM COMPLETED

Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MILÉCULAR FORMULA, MOLECULAR WEIGHT:

BAN: Fenofibrate  
CAS No: 49562-28-9  
Molecular Formula:  $C_{20}H_{21}O_4Cl$   
Molecular Weight: 360.8  
IUPAC Name: 2-[4-(4-chlorobenzoyl) phenoxy]-2-8-methyl-propanoic acid, 1-methylethyl ester



17. RELATED / SUPPORTING DOCUMENTS:

**A. DMFs:**

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE <sup>1</sup>	Review Date	STATUS <sup>2</sup>	COMMENTS
7	II	/		4	27-MAY-03	Adequate	LOA 04-SEP-2003
	III			4	19-FEB-03	Adequate	LOA 23-JUN-2003
	III			4	13-JUN-03	Adequate	LOA 02-SEP-2003
	III			4	13-JUN-03	Adequate	LOA 02-SEP-2003
	III			4	15-SEP-00	Adequate	LOA 16-AUG-2001
	III			4	6-AUG-02	Adequate	LOA 31-AUG-2001
	III			4	29-JUL-04	Adequate	05-SEP-2001
	III			4	6-OCT-03	Adequate	LOA 12-FEB-2003
	III			4	7-DEC-00	Adequate	LOA 21-FEB-2003
5	III					4	8-AUG-02

**CHEMISTRY EVALUATION**

Reliant Pharmaceuticals RP1824 (Fenofibrate capsules) 43mg, 87mg, and 130mg

NDA 21-695

8/26/2004

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<sup>1</sup> Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 – Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

<sup>2</sup> Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

**B. Other Documents:**

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	66,249	Fenofibrate — . for the TX of hyperlipoproteinemia

18. STATUS:

**ONDC:**

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics			
EES	Pending		
Pharm/Tox			
Biopharm	Pending		
LNC			
Methods Validation	Not needed		
OPDRA			
EA	Acceptable (this review)		
Microbiology			

# The Chemistry Review for NDA 21-695

## The Executive Summary

### I. Recommendations

#### A. Recommendation and Conclusion on Approvability

The application is APPROVABLE pending satisfactory cGMP inspection of facility used to manufacture the drug product.

#### B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

- The sponsor agrees to conduct the primary stability study to completion, following the stability protocol; notifying the Agency of the results in a timely manner.
- The sponsor agrees to place on batch per year, for each package size, on stability.

### II. Summary of Chemistry Assessments

#### A. Description of the Drug Product(s) and Drug Substance(s)

##### 1. Drug Product

Immediate release fenofibrate capsules will be marketed in three strengths, 43 mg, 87 mg, and 130mg. Three different sizes of capsule shells (Sizes 2, 3 and 4) are filled with different fill weights of fenofibrate — produce the three drug product strengths. The fenofibrate

— These The fenofibrate capsules are packaged in — child-resistant closures — . The drug product is packaged in three count configurations: —

— 30 count in the 45 cc bottle, and a 100 count in the 90 cc bottle. Each configuration (45 cc and 90 cc bottle) also contains a desiccant canister. The filled bottles are capped with — child-resistant closures —

Formulation development studies were carried out on the relationship between particle size distribution of the active — These studies show the advantages of using micronized active ingredient —

Currently, stability data for the drug product is available for up to — at controlled room temperature and up to — under stress conditions (40 °C/75 % RH). All available test results are within specifications; no significant changes in product quality attributes have been observed. Based on the available stability data, and statistically calculated/ extrapolated shelf-life estimates, an initial shelf-life of — is recommended for the — bottle packaging configurations, instead of the 24 month shelf life requested by the sponsor.

##### 2. Drug Substance

The Drug Substance is fenofibrate (micronized) 2-[4-(4-chlorobenzoyl) phenoxy]-2- 8-methylpropanoic acid, 1-methylethyl ester). The micronized fenofibrate is obtained from — under DMF — This DMF has been previously reviewed and found to be adequate. Fenofibrate API is covered under a monograph in the European Pharmacopeia (EP) and is tested against these specifications, with three additional tests for —

\_\_\_\_\_ and particle size distribution. There is no USP monograph for fenofibrate.

The term "micronized" refers to the particle size distribution of the API in the drug product. For the purpose of this NDA, \_\_\_\_\_ fenofibrate drug substance that meets particle size acceptance criterion of "Not less than \_\_\_\_\_". This specific particle size distribution was requested by Ethypharm \_\_\_\_\_ micronization process is proprietary and described in detail in their DMF \_\_\_\_\_.

## B. Description of How the Drug Product is Intended to be Used

Fenofibrate produces reductions in total cholesterol, LDL cholesterol, apolipoprotein B, total triglycerides and triglyceride rich lipoprotein (VLDL) in treated patients. In addition, treatment with fenofibrate results in increases in high density lipoprotein (HDL) and apoproteins apo AI and apo AII. Fenofibrate is metabolized *in vivo* into the active form of fenofibric acid. The effects of fenofibric acid seen in clinical practice have been explained *in vivo* in transgenic mice and *in vitro* in human hepatocyte cultures by the activation of peroxisome proliferator activated receptor  $\alpha$  (PPAR  $\alpha$ ).

Fenofibrate capsules are an oral, immediate release, encapsulated drug product containing micronized fenofibrate as the active pharmaceutical ingredient (API).

\_\_\_\_\_ The sponsor claims that there is no food effect on the bioavailability of the drug. Fenofibrate 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. Additionally, fenofibrate is indicated as adjunctive therapy to diet for treatment of adult patients with hypertriglyceridemia (Fredrickson Types IV and V hyperlipidemia). Improving glycemic control in diabetic patients showing fasting chylomicronemia will usually reduce fasting triglycerides and eliminate chylomicronemia thereby obviating the need for pharmacologic intervention.

Drug therapy with fenofibrate is not indicated for patients with Type I hyperlipoproteinemia, who have elevations of chylomicrons and plasma triglycerides, but who have normal levels of very low density lipoprotein (VLDL).

For the treatment of adult patients with primary hypercholesterolemia or mixed hyperlipidemia, the initial dose is 130 mg per day.

For adult patients with hypertriglyceridemia, the initial dose is 43 to 130 mg per day. Dosage should be individualized according to patient response, and should be adjusted if necessary following repeat lipid determinations at 4 to 8 week intervals. The maximum dose is 130 mg per day.

For patients with \_\_\_\_\_ treatment should start at a dose of 43 mg/day and increased only after evaluation of the effects on renal function and lipid levels at this dose.

In the elderly, the initial dose should likewise be limited to 43 mg/day.

## C. Basis for Approvability or Not-Approval Recommendation

This application is approvable from a CMC viewpoint. This recommendation is based upon evaluation of the CMC information provided by the applicant. The data contained in this NDA application are substantial and detailed. The sponsor has adequately described the manufacturing process and

## CHEMISTRY EVALUATION

NDA 21-695

Reliant Pharmaceuticals RP1824 (Fenofibrate capsules) 43mg, 87mg, and 130mg  
8/26/2004

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associated process controls of the drug product. Release testing and stability protocols are adequate. Drug product quality, including consistency and stability has been adequately demonstrated.

A final recommendation by the Office of Compliance is pending.

### III. Administrative

#### A. Reviewer's Signature

See electronic signature page.

#### B. Endorsement Block

Chemist Name/Date: John C. Hill, Ph.D. / 14-JUN-2004  
Chemistry Team Leader Name/Date: Stephen K Moore, Ph.D.  
Project Manager Name/Date: Pat J. Madara

44 Page(s) Withheld

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

§ 552(b)(5) Deliberative Process

§ 552(b)(4) Draft Labeling

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

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John C. Hill  
8/26/04 06:08:00 PM  
CHEMIST

Stephen Moore  
8/26/04 06:13:12 PM  
CHEMIST

APPEARS THIS WAY  
ON ORIGINAL

ESTABLISHMENT EVALUATION REQUEST

DETAIL REPORT

Application:	NDA 21695/000	Action Goal:	
Stamp:	04-DEC-2003	District Goal:	05-AUG-2004
Regulatory Due:	04-OCT-2004	Brand Name:	FENOFIBRATE CAPSU
ES, 43,			
Applicant:	RELIANT PHARMS INC	Estab. Name:	87, 130MG
	110 ALLEN RD	Generic Name:	FENOFIBRATE MICRO
IZED			
	LIBERTY CORNER, NJ 07938		CAPSULES
Priority:	3S	Dosage Form:	(CAPSULE)
Org Code:	510	Strength:	43 MG, 87 MG, 130
MG			

Application Comment:

Contacts:	V. JIMENEZ	(HFD-510)	301-827-9090	, Project
anager				
	J. HILL	(HFD-810)	301-827-6408	, Review C
emist				
	S. MOORE	(HFD-510)	301-827-6401	, Team Lea
er				

Overall Recommendation: ACCEPTABLE on 30-SEP-2004 by S. ADAMS (HFD-322) 301-27-9051

Establishment: CFN            FEI           

Responsibilities:            AADA:

Profile: CTL OAI Status: NONE

Estab. Comment:  
004 by

(on 17-AUG-

W. ADAMS (HFD-510) 301-827-9088)

Milestone Name	Date	Type	Insp. Date	Decision & Reason	C
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SUBMITTED TO OC ADAMSM	17-AUG-2004				
OC RECOMMENDATION BROGIOJ	18-AUG-2004			ACCEPTABLE  BASED ON PROFILE	DA

Establishment: CFN FEI



DM No: AADA:

Responsibilities:

Profile: CTL OAI Status: NONE

Estab. Comment:  
ABILITY

(on 07-JAN-2004 by W. ADAMS (HFD-510) 301-827-9088

Milestone Name	Date	Type	Insp. Date	Decision & Reason	C
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ESTABLISHMENT EVALUATION REQUEST

DETAIL REPORT

SUBMITTED TO OC 12-JAN-2004  
ADAMSS

OC RECOMMENDATION 12-JAN-2004  
RUGUSONS

ACCEPTABLE F

BASED ON PROFILE

SUBMITTED TO OC 15-JAN-2004  
ADAMSM

OC RECOMMENDATION 16-JAN-2004  
RUGUSONS

ACCEPTABLE F

BASED ON PROFILE

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Establishment: CFN FEI

DMF No: AADA:

Responsibilities:

Profile: CHG OAI Status: NONE

Estab. Comment: (on 07-JAN-2004 by W. ADAMS (HFD-510)  
01-827-

9088)

Milestone Name	Date	Type	Insp. Date	Decision & Reason	C
Operator					

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SUBMITTED TO OC 12-JAN-2004  
ADAMSS

OC RECOMMENDATION 12-JAN-2004  
RUGUSONS

ACCEPTABLE F

BASED ON PROFILE

SUBMITTED TO OC 15-JAN-2004  
ADAMSM

OC RECOMMENDATION 16-JAN-2004  
MORGUSONS

ACCEPTABLE

F

BASED ON PROFILE

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Establishment: CFN 9612001 FEI 3002807933  
ETHYPHARM (FORMERLY PROGRAPHARM)  
Z.I. SAINT ARNOULT  
CHATEAUNEUF-EN-THYMERAIS, , FR

DMF No: AADA:  
Responsibilities: FINISHED DOSAGE OTHER TESTER

Profile: CTL OAI Status: NONE

Comment: QUALITY CONTROL TESTING OF RAW MATERIALS (on 12-JAN-2004 by W.  
(HFD-510) 301-827-9088)

Milestone Name	Date	Type	Insp. Date	Decision & Reason	C
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SUBMITTED TO OC ADAMSS	12-JAN-2004				
SUBMITTED TO DO MORGUSONS	12-JAN-2004	GMP			F
SUBMITTED TO OC ADAMSM	15-JAN-2004				
SUBMITTED TO DO MORGUSONS	16-JAN-2004	GMP			F

ESTABLISHMENT EVALUATION REQUEST

DETAIL REPORT

ASSIGNED INSPECTION T 03-FEB-2004 GMP  
ADAMSS

INSPECTION PERFORMED 12-MAR-2004 12-MAR-2004  
ADAMSS

INSPECTION SCHEDULED 29-JUN-2004 12-MAR-2004  
ADAMSS

DO RECOMMENDATION 29-JUN-2004 ACCEPTABLE  
ADAMSS

INSPECTION

OC RECOMMENDATION 29-JUN-2004 ACCEPTABLE  
ADAMSS

DISTRICT RECOMMENDATION

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Establishment: CFN FEI  
ETHYPHARM INDUSTRIES  
CHEMIN DE LA POUDRIERE, BP 117  
GRAND QUEVILLY, , FR 76121

DMF No: AADA:

Responsibilities: DRUG SUBSTANCE OTHER TESTER  
FINISHED DOSAGE MANUFACTURER  
FINISHED DOSAGE RELEASE TESTER

Profile: CHG OAI Status: NONE

Estab. Comment: FACILITY PERFORMS DRUG PRODUCT MANUFACTURER, PRODUCT RELEASE T  
STING,  
AND PARTICLE SIZE TESTING ON DRUG SUBSTANCE. (on 09-JAN-2004 b  
ADAMS (HFD-322) 301-827-9051)

Milestone Name Date Type Insp. Date Decision & Reason C  
eator

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SUBMITTED TO OC 12-JAN-2004  
ADAMSS

SUBMITTED TO DO 12-JAN-2004 GMP  
ERGUSONS

F

SUBMITTED TO OC 15-JAN-2004  
BEAMSM

SUBMITTED TO DO 16-JAN-2004 GMP  
ERGUSONS

F

ASSIGNED INSPECTION T 03-FEB-2004 GMP  
ADAMSS

INSPECTION SCHEDULED 15-SEP-2004 16-SEP-2004  
IRIVERA

INSPECTION PERFORMED 16-SEP-2004 16-SEP-2004  
ADAMSS

DO RECOMMENDATION 30-SEP-2004 ACCEPTABLE  
ADAMSS

INSPECTION

BASED ON INVESTIGATOR'S RECOMMENDATION. NO 483 ISSUED. AWAITING EIR.

OC RECOMMENDATION 30-SEP-2004 ACCEPTABLE  
ADAMSS

DISTRICT RECOMMENDATION

Establishment:

CFN

FEI

DMF No:

AADA:

Responsibilities:

Profile:

CTL

OAI Status: NONE

ESTABLISHMENT EVALUATION REQUEST

DETAIL REPORT

Estab. Comment:  
by S.

(on 09-JAN-2004

ADAMS (HFD-322) 301-827-9051)

Milestone Name	Date	Type	Insp. Date	Decision & Reason	C
Submitted to OC ADAMSS	12-JAN-2004				
Submitted to DO MORGUSONS	12-JAN-2004	GMP			F
Submitted to OC ADAMSM	15-JAN-2004				
Submitted to DO MORGUSONS	16-JAN-2004	GMP			F
Assigned Inspection T ADAMSS	03-FEB-2004	GMP			
Recommendation MSS	30-SEP-2004			ACCEPTABLE	

BASED ON FILE REVIEW

DUE TO UPCOMING PDUFA DATE DECISION WAS MADE; HOWEVER POST APPROVAL INSPECTION WILL STILL

BE PERFORMED.

OC Recommendation 30-SEP-2004 ACCEPTABLE

DISTRICT RECOMMENDATION

Establishment: CFN

FEI

to:

AADA:

Responsibilities:

Profile: CSN

OAI Status: NONE

Estab. Comment:  
10) 301-

(on 07-JAN-2004 by W. ADAMS (HFD-5

827-9088)

Estab. Name	Date	Type	Insp. Date	Decision & Reason	C
SUBMITTED TO OC ADAMSS	12-JAN-2004				
SUBMITTED TO DO ERGUSONS	12-JAN-2004	GMP			F
SUBMITTED TO OC ADAMSM	15-JAN-2004				
SUBMITTED TO DO ERGUSONS	16-JAN-2004	GMP			F
DO RECOMMENDATION ADAMSS	03-FEB-2004			ACCEPTABLE	
				BASED ON FILE REVIEW	
OC RECOMMENDATION MBROGIOJ	03-FEB-2004			ACCEPTABLE	DA
				DISTRICT RECOMMENDATION	