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*APPLICATION NUMBER:*

**21-695**

**PHARMACOLOGY REVIEW(S)**

NDA 21-695

Review completed: 4/6/04  
Signed off in DFS on 6/2/04

**PHARMACOLOGY/TOXICOLOGY COVER SHEET**

**NDA number:** NDA 21-695

**Review Number:** 1

**Sequence number/date/type of submission:** December 1, 2003 (original application).  
It is a 505(b)(2) application. Submission 5/14/04 (response to pharm/tox request was provided on the final particle size of the drug product)

**Information to sponsor:** Yes ( ) No (X)

**Sponsor:** Reliant pharmaceuticals LLC., Liberty corner, NJ

**Manufacturer for drug substance:** The manufacturer of the drug substance (RP fenofibrate) is \_\_\_\_\_ The drug product will be manufactured by Ethypharm Industries in France.

**Reviewer name:** Indra Antonipillai, Ph.D. Pharmacology Reviewer.

**Division:** Division of Metabolic and Endocrine Drug products, **HFD #:** 510

**Review completion date:** 4/6/2004

**Drug:**

**Trade name:** Fenofibrate \_\_\_\_\_ 43, 87 & 130 mg capsules.

Generic name (list alphabetically): Fenofibrate

Code name: Fenofibrate, RP-1824

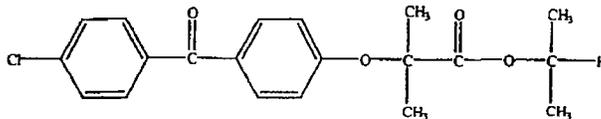
**Chemical name:** Chemical name: 2-(4-(4-chlorobenzoyl)phenoxy)-2-methylpropanoic acid-1-methylethyl ester.

CAS registry number: 49562-28-9

Mole file number: N/A

Molecular formula/molecular weight:  $C_{20}H_{21}O_4Cl/360.83$

**Structure:**



NDA 21-695

**Relevant INDs/NDAs/DMFs:** IND 66,249 (for RP-fenofibrate), NDA 19-304 (Tricor, fenofibrate). DMF numbers —  
— DMF —

**Drug class:** Fenofibrate, a phenoxyisobutyric acid isopropranol ester.

**Indication:** Treatment of primary hypercholesterolemia or mixed dyslipidemias (Fredrickson Types IIa and IIb), and hypertriglyceridemia (Fredrickson Types IV and V hyperlipidemia).

**Clinical formulation:** The drug is available in 43, 87 and 130 mg strength capsules. These contain the active drug and inactive ingredients (see Table on page 6)

Route of administration: Oral

**Proposed use:** The drug is indicated — , as an adjunctive therapy to diet for the reduction of elevated LDL-cholesterol, total cholesterol, TG, and Apo B and increase HDL-C in adult patients with primary hypercholesterolemia or mixed dyslipidemia (Fredrickson Types IIa, and IIb) at recommended doses of up to 130 mg/day in adults. It is also indicated in adult hyper-triglyceridemia patients (Fredrickson Types IV, and V hyperlipidemia)

**Disclaimer:** Tabular and graphical information is from sponsor's submission unless stated otherwise

Studies reviewed in this submission: None

**APPEARS THIS WAY  
ON ORIGINAL**

*Executive Summary*

**1. Recommendations**

**A. Recommendation on approvability**

Pharmacology recommends approval of this drug for proposed indications

**B. Recommendation for Nonclinical Studies:**

The preclinical studies are adequate to support the recommended doses up to 130 mg/day. No further pre-clinical studies are required

**C. Recommendation on Labeling:** see the labeling section on page 9

**II. Summary of Nonclinical Findings:**

**A. Brief Review of Nonclinical studies**

Fenofibrate is an approved drug for oral use in Canada, Europe and US (as Tricor, NDA 19-304/21-203). This application is a 505 b(2) which relies on our previous determination of safety for Tricor. RP-Fenofibrate is a formulation of fenofibrate with the particle size ( $D_{50}$ ) in the range of

**B. Pharmacologic activity**

Like other fenofibrates, it is a fibric acid derivative, it increases lipolysis and elimination of triglyceride rich particles from plasma by activating lipoprotein lipase.

**C. Nonclinical safety issues relevant to clinical use**

There are no new nonclinical safety issues relevant to the clinical use with the current drug product.

**III. Administrative**

A. Reviewer signature: -----

B. Supervisor signature      Concurrence:-----

Non-concurrence: -----  
(see memo attached)

cc:                    IND Arch  
                          HFD-510  
                          HFD-510/davisbruno/antonipillai/parks/jimenez  
                          Review code: AP  
                          File name: nda21695 (fenofibrate RP 1824)

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## **I. PHARMACOLOGY**

Fenofibrate is a fibric acid derivative, and is used as a lipid lowering agent. The underlying mechanisms of its action are not fully established. The major effect of the drug is to enhance triglyceride rich lipoprotein catabolism by increasing lipoprotein lipase activity. It inhibits fatty acid synthesis and stimulates mitochondrial oxidation of fatty acids in rat liver. In addition the drug decreases cholesterol biosynthesis which may in turn enhance LDL clearance by increased LDL receptor activity. The drug may also mobilize cholesterol deposited in peripheral tissues, decrease hyper-aggregability and platelet derived growth factor, and increase esterification of cholesterol in plasma, all of the above actions could contribute to inhibition of atherogenesis.

Its effects on lipid metabolism are described below (from NDA 21-695):

As shown in Table below (see Table 5.2.1.2-1), fenofibrate has been shown in animals to have a wide range of effects on both synthetic and catabolic pathways of triglyceride and cholesterol metabolism. Fibrates have been shown to modify the expression of a variety of genes involved in lipoprotein and fatty acid metabolism. Fenofibrate specifically activates the peroxisome proliferator-activated receptor  $\alpha$  (PPAR $\alpha$ ). PPAR $\alpha$ , as well as its congener PPAR $\gamma$ , are members of the steroid hormone nuclear receptor super family and could potentially interact with several proteins, including RXR $\alpha$ , NF-KB and HSP72. PPAR $\alpha$  differs from PPAR $\gamma$  by its pattern of tissue expression as well as the nature of its endogenous ligands. Hepatic and vascular expression of PPAR $\alpha$  has the potential to favorably alter several aspects of atherogenesis. In the liver, activated PPAR $\alpha$  modifies genes linking lipoprotein and fatty acid (including apo CIII, lipoprotein lipase and apo A1), cholesterol, and glucose metabolism. This effect of fibrates on PPAR $\alpha$  receptors has been confirmed with the use of gene knock-out mice lacking functional PPAR $\alpha$ . Fenofibrate has been shown to have an anti-inflammatory effect and promote apoptosis. The role of PPAR $\gamma$  in atherogenesis is still uncertain as both pro- and anti-atherogenic functions have been suggested.

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Table 5.2.1.2-1: Postulated effects of fenofibrate on cholesterol/TG metabolism.

**5.2.1.2-1 Postulated Effects of Fenofibrate on Cholesterol and Triglyceride Metabolism**

Effect	Reference
<b>Cholesterol Metabolism</b>	
<b>Synthetic Pathways</b>	
↓ cholesterol synthesis (↓ acetate uptake into hepatic cholesterol)	5, 7
(↓ ACAT activity)	8
↓ hepatic cholesterol levels (↑ secretion into bile)	5, 7, 9
<b>Catabolic Pathways</b>	
↑ aortic cholesterol ester hydrolysis (↑ aortic cholesterol ester hydrolase activity)	10
↑ hepatic cholesterol uptake	5
<b>Triglyceride Metabolism</b>	
<b>Synthetic Pathways</b>	
↓ fatty acid synthesis (↓ acetate uptake into hepatic fatty acids)	5
↑ mitochondrial fatty acid oxidation (↑ hepatic CoA, carnitine acetyl and palmitoyl transferase activity)	11, 12, 13, 14, 15
↓ triglyceride synthesis (↓ hepatic oleate and glycerol uptake)	8

Abbreviations: ACAT = acyl-CoA cholesterol acyl transferase

**Sponsor's cited references in Table 5.2.1.2-1**

5. Kritchevsky D, Tepper SA, Story JA. Influence of procetofen on lipid metabolism in normocholesteremic rats. *Pharmacological Research Communications* 1979;11:635-641.
6. Olivier P, Plancke MO, Marzin D, Clavey V, Sauzies J, et al. Effects of fenofibrate, gemfibrozil and nicotinic acid on plasma lipoprotein levels in normal and hyperlipidemic mice. A proposed model for drug screening. *Atherosclerosis* 1988;70:107-114.
7. Plancke MO, Olivier Ph, Clavey V, Martin D, Fruchart JC. Aspects of cholesterol metabolism in normal and hypercholesterolemic Syrian hamsters. Influence of fenofibrate. *Methods and Findings in Experimental and Clinical Pharmacology* 1988;109:575-579.
8. Kloer HU. Structure and biochemical effects of fenofibrate. *American Journal of Medicine* 1987;83 (Suppl. 5B):3-8.
9. Wulfert E. A new approach to atherosclerosis: procetofen in cholesterol and lipoprotein metabolism. In Carlson et al. (Eds) *International Conference on Atherosclerosis*, pp. 123-128, Raven Press, New York, 1978.
10. Kritchevsky D, Singer D, Klurfeld DM. Influence of hypocholesterolemic drugs on aortic cholesterol esterase in rabbits. *Pharmacological Research Communications* 1984;6:525-531.
11. Halvorsen O. Effects of hypolipidemic drugs on hepatic CoA. *Biochemical Pharmacology* 1983;32:1126-1128.
12. Henninger C, Clouet P, Danh HC, Pascal M, Bezaud J. Effects of fenofibrate treatment on fatty acid oxidation in liver mitochondria of obese Zucker rats. *Biochemical Pharmacology* 1987;36:3231-3236.
13. Pourbaix S, Heller F, Harvengt C. Effect of fenofibrate and LF 2151 on hepatic peroxisomes in hamsters. *Biochemical Pharmacology* 1984;33:3661-3666.

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14. Van Veldhoven P, Declercq PE, Debeer LJ, Mannaerts GP. Effects of benfluorex and fenofibrate treatment on mitochondrial and peroxisomal marker enzymes in rat liver. *Biochemical Pharmacology* 1984;33:1153-1155.

15. Wulfert E. How does fenofibrate exert its cholesterol-lowering effect? Le fenofibrate: par quel mecanisme produit-il son effect hypocholesterolemiant? *Nouvelle Presse Medicale* 1980;9: 3733-3736.

Fenofibrate is currently a marketed drug in US, as Tricor. Up to 200 mg/day are approved doses. Both micronized and non-micronized formulations are approved. The micronized 67 mg ( ) is equivalent to 100 mg of the conventional form. It is marketed in Canada as Lipidil Micro and Lipid Supra

The current sponsor (Reliant Pharmaceuticals) has come up with the new formulation of the ( ) drug, which they claim has bioavailability greater than that of the micronized form, i.e., bioavailability (BA) of 130 mg of RP-fenofibrate capsule was equivalent to 200 mg of Tricor capsules, and could be administered with or without meals. The manufacturer of the drug substance is ( ), but the manufacturer of the drug product is Ethypharm Industries in France.

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ON ORIGINAL**

The Clinical formulation contains the active drug and following inactive ingredients:

Table. Composition of RP-fenofibrate:

Table 4.3.2-1 Composition for Fenofibrate Capsules, 43 mg, 87 mg and 130 mg (R4)

Component	Reference	Function	Unit Dose (mg/capsule)		
			43 mg	87 mg	130 mg
Fenofibrate (micronized)	EP	Active Ingredient	43.00	87.00	130.00
Sugar Spheres	NF or EP				
Hypromellose	USP or EP				
Sodium Lauryl Sulfate	NF or EP				
Dimethicone	In-house monograph				
Simethicone	USP				
Hypromellose	USP or EP				
Talc	USP or EP				
	USP				
Total					
Hard Gelatin Capsules <sup>c</sup>	In-house monograph	Dosage Form			
Total					

b. \_\_\_\_\_  
<sup>c</sup> 43 mg: \_\_\_\_\_ light green cap and \_\_\_\_\_ white body (size 4), 87 mg: \_\_\_\_\_ dark green cap and opaque light green body (size 3), 130 mg: \_\_\_\_\_ dark green cap and \_\_\_\_\_ white body (size 2)  
<sup>d</sup> \_\_\_\_\_

Physical chemical properties: RP-fenofibrate is a white \_\_\_\_\_, with melting point of 79-82°C. It is practically insoluble in water, \_\_\_\_\_

RP- fenofibrate capsules are immediate release capsules and particle size of this drug product (RP fenofibrate) supposedly ranges from \_\_\_\_\_ and is \_\_\_\_\_

Diagram of the \_\_\_\_\_ fenofibrate is shown below

This new oral formulation contains dimethicone at doses up to \_\_\_\_\_/capsule. Also new formulation contains \_\_\_\_\_ titanium dioxide and \_\_\_\_\_. The excipients in the above formulation are USP or EP and all the excipients used here, including dimethicone and simethicone, have already been used in other approved NDAs (in the FDA inactive ingredient guide, 1996).

## X. DETAILED CONCLUSIONS AND RECOMMENDATIONS

RP-Fenofibrate is a new \_\_\_\_\_ formulation of fenofibrate, vs Tricor which is micronized. It is available in capsules in three strengths, each containing 43, 87 or 130 mg of the drug.

Fenofibrate is approved (NDA 19-304, Tricor) for oral use in US, Canada, and Europe for the treatment of hypertriglyceridemia, primary hypercholesterolemia or mixed dyslipidemia. Tricor is available in capsules in three strengths, each containing each containing 67, 134, or 200 mg of micronized fenofibrate. As per labeling, recommended doses of Tricor are up to 200 mg/day.

**Safety Evaluation:** Supportive information for RP-fenofibrate excipients was provided in DMF \_\_\_\_\_ (for the current drug), DMF \_\_\_\_\_. The other excipients have been either used at the recommended or higher doses in other approved products (in the FDA inactive ingredient guide, 1996).

The sponsor is proposing up to 130 mg/day dose of the current drug for primary hypercholesterolemia or for hypertriglyceridemia. Currently the recommended dose of Tricor is up to 200 mg/day in the label.

During IND 66,249 submission, sponsor demonstrated that BA of 130 mg of RP-fenofibrate was equivalent to 200 mg of Tricor capsules. Thus human PK multiple-dose studies (7-days) suggest comparable C<sub>max</sub> and AUC exposures with the current drug vs Tricor. Systemic exposure to three strengths of drug (43 mg, 87 mg, 130 mg) was linear. Additionally, 2 or 3 capsules of 43 mg of RP fenofibrate given concurrently were dose equivalent to single capsule of 87 and 130 mg respectively. The bioavailability of fenofibric acid was unaffected when RP-fenofibrate was given either in a fasted state or with low fat meal,

**APPEARS THIS WAY  
ON ORIGINAL**

**Labeling Review:** The preclinical sections of the label for RP-fenofibrate are similar to the approved Tricor label. However, the following changes in labeling are recommended:

**Sponsor's label:**

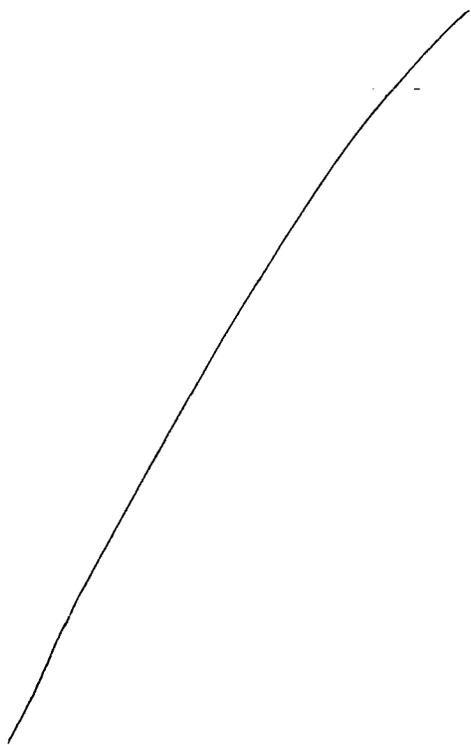
**1. Carcinogenesis, Mutagenesis, Impairment of Fertility:** In a 24-month study in rats (10, 45, and 200 mg/kg; 0.3, 1, and 6 times the maximum recommended human dose on the basis of mg/meter<sup>2</sup> of surface area), the incidence of liver carcinomas was significantly increased at 6 times the maximum recommended human dose in males and females. A statistically significant increase in pancreatic carcinomas occurred in males at 1 and 6 times the maximum recommended human dose; there were also increases in pancreatic adenomas and benign testicular interstitial cell tumors at 6 times the maximum recommended human dose in males. In a second 24-month study in a different strain of rats (doses of 10 and 60 mg/kg; 0.3 and 2 times the maximum recommended human dose based on mg/meter<sup>2</sup> surface area), there were significant increase in the incidence of pancreatic acinar adenomas in both sexes and increases in interstitial cell tumors of the testes at 2 times the maximum recommended human dose

A comparative carcinogenicity study was done in rats comparing three drugs; fenofibrate (10 and 70 mg/kg; 0.3 and 1.6 times the maximum recommended human dose), clofibrate (400 mg/kg/day; 1.6 times the human dose), and gemfibrozil (250 mg/kg; 1.7 times the human dose, multiples based on mg/meter<sup>2</sup> surface area). Pancreatic acinar adenomas were increased in males and females on fenofibrate; hepatocellular carcinomas and pancreatic acinar adenomas were increased in males and hepatic neoplastic nodules in females treated with clofibrate; hepatic neoplastic nodules were increased in males and females treated with gemfibrozil while testicular interstitial cell tumors were increased in males on all three drugs

In a 21-month study in mice at doses of 10, 45 and 200 mg/kg (approximately 0.2, 0.7, and 3 times the maximum recommended human dose on basis of mg/meter<sup>2</sup> surface area) there were statistically significant increases in liver carcinoma at 3 times the maximum recommended human dose in both males and females. In a second 18-month study at the same doses, there was a significant increase in liver carcinoma in male mice and liver adenoma in female mice at 3 times the maximum recommended human dose.

**Reviewer's recommended changes:**

**Carcinogenesis and Mutagenesis**



**Sponsor's label:**

**2. Pregnancy Category C:** Fenofibrate has been shown to be embryocidal and teratogenic in rats given in doses 7 to 10 times the maximum recommended human dose and embryocidal in rabbits when given at 9 times the maximum recommended human dose (on the basis of mg/meter<sup>2</sup> surface area). There are no adequate and well-controlled studies in pregnant women. Fenofibrate should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Administration of 9 times the maximum recommended human dose of fenofibrate to female rats before and throughout gestation caused 100 % of dams to delay delivery and resulted in a 60% increase in post-implantation loss, a decrease in litter size, a decrease in birth weight, a 40% survival of pups at birth, a 4% survival of pups at neonates, and a 0% survival of pups to weaning, and an increase in spina bifida.

Administration of 10 times the maximum recommended human dose to female rats on days 6-15 of gestation caused an increase in gross, visceral and skeletal findings in fetuses (domed head/hunched shoulders/rounded body/abnormal chest, kyphosis, stunted fetuses, elongated sternal ribs, malformed sternbrae, extra foramen in palatine, misshapen vertebrae, supernumerary ribs)

Administration of 7 times the maximum recommended human dose to female rats from day 15 to gestation through weaning caused delay in delivery, a 40% decrease in live births, a 75% decrease in neonatal survival, and decreases in pup weight, at as well as on days 4 and 21 post-partum

Administration of 9 and 18 times the maximum recommended human dose to female rabbits caused abortions in 10% of dams at 9 times and 25% of dams at 18 times the maximum recommended human dose and death of 7% of fetuses at 18 times the maximum recommended human dose

**Reviewer's recommended changes:**

**Pregnancy : Teratogenic Effects, Pregnancy Category C:**

Fenofibrate has been shown to be embryocidal and teratogenic in rats when given in doses 7 to 10 times the maximum recommended human dose (*MRHD*) and embryocidal in rabbits when given at 9 times the *MRHD* (on the basis of mg/meter<sup>2</sup> surface area). There are no adequate and well-controlled studies in pregnant women. Fenofibrate should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Administration of \_\_\_\_\_ 9 times the *MRHD* of fenofibrate to female rats before and throughout gestation caused 100% of dams to delay delivery and resulted in a 60% increase in post-implantation loss, a decrease in litter size, a decrease in birth weight, a 40% survival of pups at birth, a 4% survival of pups as neonates, and a 0% survival of pups to weaning, and an increase in spina bifida.

Administration of \_\_\_\_\_ 10 times the *MRHD* of fenofibrate to female rats on days 6-15 of gestation caused an increase in gross, visceral and skeletal findings in fetuses (domed head/hunched shoulders/rounded body/abnormal

chest, kyphosis, stunted fetuses, elongated sternal ribs, malformed sternbrae, extra foramen in palatine, misshapen vertebrae, supernumerary ribs).

Administration of \_\_\_\_\_ 7 times the *MRHD* to female rats from day 15 of gestation through weaning caused a delay in delivery, a 40% decrease in live births, a 75% decrease in neonatal survival, and decreases in pup weight at birth, as well as on days 4 and 21 post-partum

Administration of fenofibrate at 9 to 18 times the *MRHD* to female rabbits caused abortions in 10% to 25% of dams, and death in 7% of fetuses at 18 times the *MRHD*.

**External Recommendation:** From the preclinical standpoint, approval of this application is recommended, pending labeling changes.

A. Reviewer signature: Indra Antonipillai

B. Supervisor signature      Concurrence:-----

Non-concurrence: -----  
(see memo attached)

cc:            IND Arch  
                HFD-510  
                HFD-510/davisbruno/antonipillai/parks/jimenez  
                Review code: AP  
                File name: nda21695 (RP fenofibrate)

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/s/  
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Indra Antonipillai

6/2/04 12:31:12 PM

PHARMACOLOGIST

This application is approvable pending labeling changes

Approval of this application is recommended pending labeling changes

Karen Davis-Bruno

6/3/04 09:15:00 AM

PHARMACOLOGIST

concur with recommendations

Review completed 1/20/04  
Signed off in DFS on 1/21/04

**45 Day Meeting Checklist  
NONCLINICAL PHARMACOLOGY/TOXICOLOGY**

**NDA 21-695:** This NDA is a 505(b)(2) application.

**Submission date:** 12/1/03

**Sponsor:** Reliant pharmaceuticals LLC., Liberty corner, NJ

**Drug:** RP 1824 (Fenofibrate micronized)

**Introduction:** RP-1824 is a new improved \_\_\_\_\_ formulation of fenofibrate vs Tricor which is a micronized formulation. Tricor has been approved since 1998 (NDA 19-304). The \_\_\_\_\_ of the drug supposedly makes this fenofibrate more bioavailable, & \_\_\_\_\_

The current drug product (RP fenofibrate) is in the form of \_\_\_\_\_ Three different sizes of capsule shells are filled with different fill weights of fenofibrate to produce 43, 87 & 130 mg of drug product. \_\_\_\_\_

\_\_\_\_\_ All the excipients used here, including dimethcone and simethicone, have already been used in other approved NDAs (in the FDA inactive ingredient guide, 1996). This RP fenofibrate \_\_\_\_\_ vs Tricor which is micronized

ITEM: NDA 21-695	YES	NO	COMMENT
1) Does this section of the NDA appear to be organized (according to 21 CFR 314 and current guidelines for format and content) in a manner that would allow a substantive review to be completed?	Yes		
2) Is this section of the NDA indexed and paginated in a manner to enable a timely and substantive review?	Yes		

<p>3) Is this section of the NDA sufficiently legible so that a substantive review can be done? Has the data been presented in an appropriate manner (consider tables, graphs, complete study reports, inclusion of individual animal data, appropriate data analysis, etc.)?</p>	<p>Yes</p>	<p>No new pharm/tox data have been provided. Sponsor refers to two previously marketed fenofibrates NDA 21-203 (tablets) and NDA 19-304 (capsules).</p>
<p>4) Are all necessary and appropriate studies for this agent, including special studies/data requested by the Division during pre-submission communications/discussions, completed and submitted in this NDA? Please itemize the critical studies included and indicate any significant studies that were omitted from the NDA (genotox, reprotox, adequate duration of chronic tox, carcinogenicity)</p>	<p>Yes</p>	<p>Have electronic files of the carcinogenicity studies been submitted for statistical review?</p> <p>No, because non-clinical studies have already been conducted with the approved fenofibrate (Tricor under NDA 19-304), and are not considered necessary for this RP-fenofibrate.</p>

ITEM	YES	NO	COMMENT
<p>5) Were the studies adequately designed (ie., appropriate number of animals, adequate monitoring consistent with the proposed clinical use, state-of-the art protocols, etc.)?</p>			<p>Not applicable. Since non-clinical studies have already been conducted with the approved fenofibrate Tricor under NDA 19-304</p>

<p>6) If the formulation to be marketed is not identical to the formulation used in the toxicology studies (including the impurity profiles), has the sponsor clearly defined the differences and submitted reviewable supportive data (ie., adequate repeat studies using the marketed product and/or adequate justification for why such repetition would not be necessary)?</p>	<p>Yes</p>	<p>The current drug product is _____</p> <p>As indicated earlier, the current drug is _____, vs Tricor (the approved fenofibrate) which is micronized. All the excipients are USP/EP, and have already been used in other approved NDAs (in the FDA inactive ingredient guide, 1996). The excipient dimethicone is _____ and has also been used before (DMF _____)</p>
<p>7) Does the route of administration used in animal studies appear to be the same as the intended human exposure route? If not, has the sponsor submitted supportive data and/or an adequate scientific rationale to justify the alternative route?</p>	<p>Yes</p>	<p>The route of administration is oral in tox studies in NDA (19-304), which is the intended route in humans</p>
<p>8) Has the proposed draft labeling been submitted? Are the appropriate sections for the product included and generally in accordance with 21 CFR 201.577? Is information available to express human dose multiples in either mg/m2 or comparative serum/plasma AUC levels?</p>	<p>Yes</p>	<p>Yes, the draft labeling submitted in general is similar to the approved Tricor fenofibrate label, and data express human dose multiples in mg/m2.</p>

ITEM	YES	NO	COMMENT
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/s/

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Indra Antonipillai  
1/21/04 03:05:49 PM  
PHARMACOLOGIST

No comments need to be communicated to the sponsor  
at this time. This application is filable.  
From the pharm/tox point of view this application is filable

Karen Davis-Bruno  
1/21/04 03:07:43 PM  
PHARMACOLOGIST  
concur with filing recommendation