

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**21-350**

**PHARMACOLOGY REVIEW**

Signed off in DFS on 4/7/05

**PHARMACOLOGY/TOXICOLOGY COVER SHEET**

**NDA number:** NDA 21-350, a 505(B)2 application

**Review Number:** 3

**Sequence number/date/type of submission:** January 28/2005, sponsor has provided a complete response to our approvable letter of 1/18/2005. Original application was submitted on 6/22/2001. It was a 505(b)(2) application.

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

**Sponsor:** Initially the sponsor was RTP Pharma Inc. *Ile des Soeurs, Quebec, Canada*. Now it is SkyePharma, San Deigo, CA

**Manufacturer for drug substance:** Laboratorio Chimico Internazionale S.P.A. (Labochim), Milan, Italy.

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

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

**Review completion date:** 4/5/2005

**Drug:**

**Trade name:** Triglide, [REDACTED] or IDD-P™ Fenofibrate (Insoluble Drug Delivery-Microparticle Fenofibrate) tablets. Fifty and 160 mg strength tablets will be marketed.

**Generic name** (list alphabetically): Fenofibrate

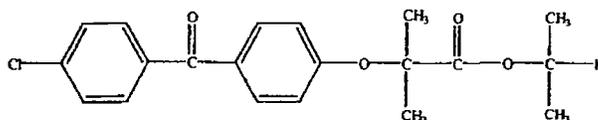
**Code Name:** [REDACTED]

**Chemical Name:** Procetofen 2-(4-(4-chlorobenzoyl)phenoxy)-2-methyl-propanoic acid-1-methylethyl ester.

**CAS Registry Number:** of fenofibrate is 49562-28-9.

**Molecular Formula/ Molecular Weight:** C<sub>20</sub>H<sub>21</sub>O<sub>4</sub>Cl/360.83

**Structure:**



**Relevant INDs/NDAs/DMFs:** IND 60,743 (IDD-P), NDA 19-304, tricor (approved in 1993), DMF [REDACTED] (fenofibrate), DMF [REDACTED] (egg lecithin),

NDA 21-350/03

Drug Class: Fenofibrate, a phenoxyisobutyric acid isopropranol ester. It is a synthetic fenofibric acid prodrug used for the treatment of dyslipidemia.

Indication: Treatment of hypercholesterolemia and mixed dyslipidemia (Type IIa/IIb, Type III, IV and V hyperlipidemia)

**Clinical formulation:** The drug is available in 50 and 160 mg tablet strengths. These contain the active drug and inactive ingredients

Route of administration: oral.

Proposed use: The drug is indicated for hypercholesterolemia. (as an adjunctive therapy to diet) and for the treatment hypertriglyceridemia (Fredrickson Types IV and V hyperlipidemia).

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

**Studies reviewed in this submission:** A complete response from the sponsor to our approvable letter dated 1/18/2005 is reviewed. Additionally, in the same submission, CMC/biopharm issues are also provided.

Studies not reviewed in this submission: None

***Following pertains to the issues under the NDA approvable letter of 1/18/05***

In an approvable letter of 1/18/2005, the CMC had indicated to the sponsor that the drug product specification appearance was not acceptable and sponsor was asked to justify the discoloration, i.e. to provide the cause of yellow color and to indicate why it was not a safety concern. Sponsor in a current submission (1/28/05) states that the egg lecithin (Lipoid E80), which is an excipient in the drug may undergo chemical degradation primarily by hydrolysis of ester linkages and oxidation of unsaturated fatty acid moieties, which result in darkening of the material and do not impact the functionality of the drug product. They further state that these decompositions are normal outcome for lecithin used in oral products.

The yellow in the drug product is from the oxidation of unsaturated fatty acid which involves preferential attack of molecular oxygen at an allylic carbon center yielding hydroperoxide as a final product. Similarly hydrolysis of the ester linkages of the fatty acid moieties results in the preferential cleavage of the acyl chain at the glycerol C<sub>2</sub> position. It is this phenomenon that is responsible for yellow discoloration which is particularly noticed under high stress and accelerated storage conditions. This yellow discoloration does not occur when recommended storage conditions (such as temperature and required humidity) are maintained. The available literature suggests that these by-products in ingested lecithin do not pose a safety concern.

The IDD-P fenofibrate contains \_\_\_\_\_ of egg lecithin, \_\_\_\_\_ sponsor states that it is a natural substance. The proposed daily dose of this excipient (i.e. egg lecithin) in the drug is \_\_\_\_\_ which corresponds to approximately \_\_\_\_\_ of the amount in one \_\_\_\_\_ egg (no reference is provided, but calculations are provided based on \_\_\_\_\_ lecithin per egg). Lecithin is generally regarded as safe (GRAS), it has been used in a number of NDAs (in the FDA inactive ingredient guide, 1996) up to doses of 20 mg.

The primary component of egg lecithin is phosphatidylcholine (PC), which itself is a mixture of fatty acid diesters of glycerophosphorylcholine. Similar mixture is found in highly \_\_\_\_\_. Thus fatty acid constituents of egg and soya PC are shown in a Table below, and are comprised of a similar mixture of saturated and unsaturated PCs. The major unsaturated fatty acid in egg PC is oleic acid, while in soya PC it is linoleic acid. The total unsaturated fatty acid content in egg PC is 51-61%, this in soya PC is 77%.

Table 1. Fatty Acid Content of Egg Phosphatidylcholine and Soya Phosphatidylcholine

Fatty Acid	Carbon Atoms:Double Bonds	Egg PC <sup>a</sup> Approximate %	Soya PC <sup>b</sup> Approximate %
_____			
Unsaturated/Saturated ratio <sup>c</sup>	NA	1.6 to 1:1	3.3:1

<sup>a</sup> Linoil EPC (Linoil Germany)

<sup>c</sup> These are calculated by 51:49 = 1:1, 61:39 = 1.6:1 and 77:23 = 3.3:1

The sponsor has correlated the color changes in the triglide tablets with the lecithin degradation. These are based on code 0 (at release), and code 1, 2 or 2/3. As shown in the Table below, sponsor states that lecithin degradation is significantly positively correlated to the degree of the tablet discoloration denoted by the formation of \_\_\_\_\_ in the tablet.

Batch	Appearance	Phosphatidylcholine (PC) mg/g	Phosphatidylethaloamine (PE) mg/g
J906	_____	_____	_____
J921	_____	_____	_____
J936	_____	_____	_____
<i>Mean: 0.8</i>			
H904	_____	_____	_____
H904	_____	_____	_____
H904	_____	_____	_____
Correlation coefficient (r): 0.9827			

Sponsor has conducted one pilot single dose PK study in dogs under IND 60,743 with a preliminary formulation of IDD-P, and has compared it to the European-approved fenofibrate (Lipanthyl 67M). The above formulation (which contained 11% of phospholipon 100H, a hydrogenated soy lecithin) showed that the AUC and Cmax values with the new drug (IDD-P) were 20-40% higher vs the micronized formulation, but no significant differences were observed between two formulations. In the current marketed formulation, egg lecithin (with a phosphatidylcholine specification of [redacted] and phosphatidylethanolamine specification of [redacted]) is used vs soy lecithin that was used in the dog PK study (i.e. phospholipon 100H, which contained purified soy lecithin with a phosphatidylcholine specification of [redacted]). This study was reviewed in the original submission signed off in DFS on 10/17/01.

However, above PK study does not qualify the yellow discoloration in the drug product, because it was done with purified soya lecithin which did not contain the [redacted] responsible for discoloration in the product), and it was a single dose study.

In the current submission, sponsor has provided several toxicity studies with soya phosphatidylcholine (PC) including acute tox studies (in mice, rats, dogs and rabbits after oral administration (which showed no toxicity at doses up to 20 mg/kg in rats/mice and at 5-10 mg/kg in rabbits/dogs), sub-chronic and chronic tox studies (with high NOAELs in rats and dogs) as well as mutagenicity and repro-tox studies. However, all of these studies were conducted with soya PC and do not qualify the current discoloration in the IDD-P fenofibrate which is supposedly due to [redacted]

Table. Acute tox studies with soya phosphatidylcholine (PC) in various animal species

**Table 2. Acute Toxicity Testing of Soya Phosphatidylcholine in Multiple Species (Phospholipon® 80/Phospholipon® 90)**

Species	Route of Administration	Maximal Non-Toxic* Dose (g/kg)
Mouse	p.o.	20.0
	i.v.	4.0
	i.p.	10.0
	s.c.	10.0
Rat	p.o.	20.0
	i.v.	2.0
	i.p.	4.0
	s.c.	4.0
Rabbit	p.o.	5.0
	i.v.	0.5
	i.p.	1.0
	s.c.	1.0
Dog	p.o.	10.0

\*Measured as lethality.

Table. Subchronic and chronic tox studies with soya phosphatidylcholine (PC) in rat and dogs

**Table 3. Subchronic and Chronic Toxicity Testing of Soya Phosphatidylcholine in Rats and Dogs (Phospholipon® 80/Phospholipon® 90)**

Species	Route of Administration	Exposure Period (weeks)	NOEL* (mg/kg/day)
Rat	p.o.	4	> 800
	p.o.	6	> 1350
	p.o.	12	> 2800
	p.o.	24	> 2800
	p.o.	48	> 2800
	i.v.	4	316-1000
	i.v.	12	100-1000
Dog	p.o.	6	> 1900
	p.o.	52	> 750
	i.v.	4	> 100

\* No Observed Effect Level

Table. Repro-tox, and mutagenicity studies with soya phosphatidylcholine

**Table 4. Reproductive Toxicity and Teratogenicity Testing with Soya Phosphatidylcholine (Phospholipon® 80/Phospholipon® 90)**

Species	Route	Parameters Examined	Treatment Period (gestation days)	LOEL* (mg/kg/day)
Rat	p.o.	Maternal survival and teratogenicity	6-15	> 750
	i.v.	Maternal survival and teratogenicity	6-15	> 1000
Rabbit**	p.o.	Maternal survival and teratogenicity	1-6	> 1000
			5-18	> 500
Rat	p.o.	Peri- and post-natal toxicity	16-end of 3rd week postpartum	> 2800
	i.v.	Peri- and post-natal toxicity	16-end of 3rd week postpartum	> 1000
	p.o.	Fertility	16-end of 3rd week postpartum	> 2800

\* Lowest Observed Effect Level

\*\* Results of two independent studies

**4.5 MUTAGENICITY**

Highly purified soya phosphatidylcholine was demonstrated not to be mutagenic in vitro in five *Salmonella* strains (Ames test), three yeast strains, and human embryonic epithelial cells; negative results were also demonstrated using the mouse host-mediated and urinary assays in vivo<sup>1,8</sup>.

**4.6 CARCINOGENICITY**

While no specific carcinogenicity studies have been performed with soya PC, the FDA's GRAS failed to find any evidence of carcinogenicity and to the contrary reported a study in which soya PC inhibited experimental tumor induction in mice<sup>2</sup>.

**4.7 DERMAL SAFETY IN HUMANS**

Topically-applied soya phosphatidylcholine (1%) has been used for over 30 years as a component of Essaven<sup>®</sup> Gel for the treatment of peripheral venous insufficiency. No cases of intolerance have been reported<sup>4</sup>.

Egg lecithin is an excipient in the drug product (Triglide), and its amount is [redacted] in 160 mg tablet, which corresponds to approximately [redacted] of the amount in one egg. Lecithin is generally regarded as safe (GRAS), it has been used in a number of NDAs. Sponsor has further shown that lecithin degradation is positively correlated with the formation of [redacted] which corresponds to the degree of the tablet discoloration.

Oxidation of egg lecithin or its fatty acid components is not a safety concern. It is a well established mechanism of lipid degradation and occurs spontaneously under environmental conditions. As indicated above, egg lecithin is an inactive excipient in Triglide, therefore its degradation would not be expected to alter the pharmacologic activity of triglide, nor is the degraded [redacted] No

information on [redacted] was available in the topline search. [redacted] is a normal component of membrane phospholipids present in CSF, bile, and plasma membranes at levels much higher than present here. According to CMC, dissolution is unaffected following lipid degradation, and therefore should not affect the drug activity. Assuming CMC specification [redacted], then a 160 mg tablet could contain [redacted]

Therefore from the pharm/tox point of view, this yellow discoloration does not pose any safety concerns.

**Internal Recommendation:** Egg lecithin is an inactive excipient in triglide, and its degradation is not expected to alter the pharmacologic activity of triglide, or its degradant lysophosphatidylcholine (which is responsible for discoloration in tablets). The dissolution of the drug is not affected following degradation of phosphatidylcholine, and therefore should not affect the drug activity. Oxidation of egg lecithin or its fatty acid components is not a safety concern. From the preclinical standpoint, this is not a safety concern and approval of this application is recommended.

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: nda21350-03 (Triglide, [redacted] or IDDP-fenofibrate)

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/s/  
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Indra Antonipillai  
4/7/05 07:42:47 AM  
PHARMACOLOGIST

There are no pharm/tox safety concerns following review of  
the submission 1/28/05, and approval of this application  
is recommended.

There are no pharm/tox safety concerns in a submission  
of 1/28/05, which is a complete response to  
our approvable letter of 1/18/05

Karen Davis-Bruno  
4/8/05 11:37:39 AM  
PHARMACOLOGIST

CMC concern about discoloration is not a safety concern

Signed off in DFS on 6/28/04

**PHARMACOLOGY/TOXICOLOGY COVER SHEET**

**NDA number:** NDA 21-350, a 505(B)2 application

**Review Number:** 2

**Sequence number/date/type of submission:** March 31/2004, a complete response to our approvable letter. April 21/2004 was a response to FDA request on particle size of the drug. Original application was submitted on 6/22/2001. It was a 505(b)(2) application.

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

**Sponsor:** Initially the sponsor was RTP Pharma Inc. *Ile des Soeurs, Quebec, Canada.* Now it is SkyePharma, San Deigo, CA

**Manufacturer for drug substance:** Laboratorio Chimico Internazionale S.P.A. (Labochim), Milan, Italy.

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

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

**Review completion date:** 6/25/2004

**Drug:**

**Trade name:** XXXXXXXXXX IDD-P™ Fenofibrate (Insoluble Drug Delivery-Microparticle Fenofibrate) tablets. Fifty and 160 mg strength tablets will be marketed.

**Generic name** (list alphabetically): Fenofibrate

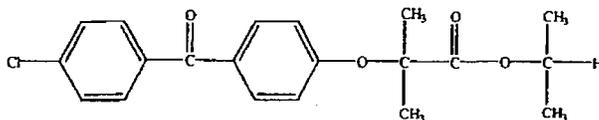
**Code Name:** XXXXXXXXXX

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

**CAS Registry Number:** of fenofibrate is 49562-28-9.

**Molecular Formula/ Molecular Weight:** C<sub>20</sub>H<sub>21</sub>O<sub>4</sub>Cl/360.83

**Structure:**



Relevant INDs/NDAs/DMFs: IND 60,743 (IDD-P), NDA 19-304, tricolor (approved in 1993), DMF [REDACTED] (fenofibrate), DMF [REDACTED] (egg lecithin),

Drug Class: Fenofibrate, a phenoxyisobutyric acid isopropranol ester. It is a synthetic fenofibric acid prodrug used for the treatment of dyslipidemia.

Indication: Treatment of hypercholesterolemia and mixed dyslipidemia (Type IIa/IIb, Type III, IV and V hyperlipidemia)

Clinical formulation: The drug is available in 50 and 160 mg tablet strengths. These contain the active drug and inactive ingredients

Route of administration: oral.

Proposed use: The drug is indicated for hypercholesterolemia. (as an adjunctive therapy to diet) and for the treatment hypertriglyceridemia (Fredrickson Types IV and V hyperlipidemia).

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

**Studies reviewed in this submission:** A complete response from the sponsor of 3/31/2004 to our approvable letter is reviewed. Additionally, 4/21/2004 response to FDA request on particle size of the drug, CMC/biopharm issues (after an internal meeting on 4/15/04) is also reviewed here.

Studies not reviewed in this submission: None

***Pharm/tox had recommended labeling changes under the 'Carcinogenesis and mutagenesis' and 'Teratogenic effects'.*** These changes have been made by the sponsor.

Sponsor has also changed the formulation in a complete response submission dated 3/31/04, however all excipients used in the new formulation have been used at recommended or higher doses in other approved drug products

The particle size of this fenofibrate [REDACTED] was considered as it has been shown that the particle size in the range of [REDACTED] size may have a different toxicity profile compared to the initial formulation with the standard particle size. Sponsor in a submission on 4/21/04 states that the smallest particle size in the drug. [REDACTED] following a disintegration test. Thus, both this drug and the approved micronized fenofibrate Tricolor have similar particle size [REDACTED] which is in the range of [REDACTED]. Therefore from the pharm/tox point of view this formulation does not pose any cause for concern in

NDA 21-350/02

terms of particle size being less than [REDACTED] and having different distribution or clearance profiles

**External Recommendation:** Labeling changes have been made by the sponsor in this response submission as recommended previously. From the preclinical standpoint, approval of this application is recommended.

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: nda21350-02 [REDACTED] IDDP-fenofibrate)

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/s/  
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Indra Antonipillai

6/28/04 04:04:48 PM

PHARMACOLOGIST

Sponsor has made the labeling changes. From the pharm/tox point of view this application is recommended for approval.

The labeling changes have been made by the sponsor in a complete response submission. This application is recommended for approval

Karen Davis-Bruno

6/28/04 04:18:17 PM

PHARMACOLOGIST

concur with recommendations

Review completed: October 15, 2001

## REVIEW AND EVALUATION OF PHARMACOLOGY/TOXICOLOGY DATA

**KEY WORDS:** Fibric acid derivative, antilipemic, lipid lowering, dyslipidemia hypercholesterolemia

Reviewer Name: Indra Antonipillai, Ph.D. Pharmacology Reviewer.

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

Review Completion Date: October 15, 2001.

Review number: 1

**IND/NDA NUMBER:** NDA 21-350, a 505(B)2 application

Serial number/date/type of submission: June 22, 2001, original application,

Information to Sponsor: Yes ( ) No (X)

Sponsor or agent: RTP Pharma Inc. *Ile des Soeurs, Quebec, Canada.* Local regulatory contact is Cato Research Ltd. Durham, NC

Manufacturer (if different) for drug substance: Laboratorio Chimico Internazionale S.P.A. (Labochim), Milan, Italy.

**Drug:**

Code Name: IDD-P™ Fenofibrate (Insoluble Drug Delivery-Microparticle Fenofibrate) tablets. Fifty and 160 mg strength tablets will be marketed.

Generic Name: N/A

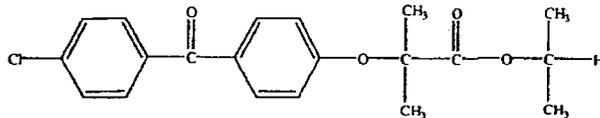
Trade Name: N/A

Chemical Name: Procetofen 2-(4-(4-chlorobenzoyl)phenoxy)-2-methylpropanoic acid-1-methylethyl ester.

CAS Registry Number: of fenofibrate is 49562-28-9.

Molecular Formula/ Molecular Weight: C<sub>20</sub>H<sub>21</sub>O<sub>4</sub>Cl/360.83

Structure:



NDA 21-350

Sponsor: RTP Pharma Inc. *Ile des Soeurs*, Quebec, Canada. Regulatory contact in US is Cato Research Ltd. Durham, NC.

Date Submitted: June 22, 2001

Date Received: June 25, 2001

Drug Class: Fenofibrate, a phenoxyisobutyric acid isopropranol ester. It is a synthetic fenofibric acid prodrug used for the treatment of dyslipidemia.

Category: Fibric acid derivative, antilipemic, lipid altering agent/regulator.

Indication: Treatment of hypercholesterolemia and mixed dyslipidemia (Type IIa/IIb, Type III, IV and V hyperlipidemia)

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Indra Antonipillai, Ph.D.

cc: IND Arch  
HFD-510  
HFD-510/davisbruno/antonipillai/koch  
Review code:Ap  
File name: nda21350 (IDDP fenofibrate)

Relevant INDs/NDAs/DMFs: IND 60,743 (IDD-P), NDA 19-304, tricor (approved in 1993), DMF [redacted] (fenofibrate), DMF [redacted] (egg lecithin),

Clinical formulation (and components): 160 mg tablets or capsules of the active drug contain the following:

Ingredients	Quantity/tablet or capsule	Purpose
<b>Core blend</b>		
Fenofibrate, EP	160 mg	Active ingredient
Egg lecithin		
[redacted]		
Monobasic sodium phosphate, USP		
[redacted]		
[redacted]		
Magnesium stearate, NF		
Collidal silicon dioxide, NF		

NF- National Formulary.

Sponsor indicates that lecithin is a naturally occurring phospholipid, present in many food products. Lecithin is listed as GRAS in CFR (184.1400). Egg lecithin [redacted] DMF [redacted] is in FDA inactive ingredient guide, and has been used as a component in several US approved parenteral, and in two oral (as lipoid E-80) products. Sponsor states that the proposed daily dose of egg lecithin in IDD-P corresponds to approximately [redacted] of the amount in one egg [redacted]

Other excipients such as [redacted] magnesium stearate are listed as GRAS (CFR [redacted])

184.1835, 1845 and 1440 respectively). Colloidal silicon dioxide, \_\_\_\_\_ listed as food additives (CFR 573.940, CFR 172.874/868, CFR 175.300, CFR 73.1575 respectively).

Route of administration: oral.

Proposed clinical use: The drug is indicated for hypercholesterolemia. (as an adjunctive therapy to diet) and for the treatment hypertriglyceridemia (Fredrickson Types IV and V hyperlipidemia). The sponsor had submitted an IND 60,743 on this drug.

**INTRODUCTION AND DRUG HISTORY:**

Fenofibrate is currently a marketed drug in US as Tricor. It is structurally related to other fibric acid derivatives such as clofibrate, ciprofibrate, gemfibrozil and bezafibrate. These agents by activating PPAR $\alpha$  (peroxisome proliferator receptor) reduce the production of apoprotein C-III, (an inhibitor of lipoprotein lipase, LPL), activate LPL, which increases lipolysis and eliminates TG-rich particles from plasma. Tricor was first approved in France in 1975. It is marketed in Europe as Lipanthyl and Lipantil, in Canada as Lipidil Micro and Lipid Supra. It is also marketed in several other countries. The first fenofibrate, Tricor was initially approved for the treatment of hypertriglyceridemia (Fredrickson Types IV and V), subsequently it was approved for the treatment of primary hypercholesterolemia or mixed dyslipidemia (Type IIa/IIb, Type III hyperlipidemia). Because the drug is virtually insoluble in water, it is poorly absorbed orally. Its absorption is increased when it is taken with food, and is dependent on the fat content of the food. Micronization of the drug \_\_\_\_\_ increases the absorption. Thus, second generation of fenofibrate formulation (e.g. Lipidil Micro, Lipanthyl, Tricor) improves PK, and allows lower dosage administration, but absorption is still incomplete and dependent on food. Labeling for the approved drug specifies that it should be taken with meals to optimize bioavailability (BA), as relatively high variability in oral absorption is due to the food effect. The current sponsor \_\_\_\_\_ has a new oral formulation of fenofibrate microparticle drug, the IDD-P<sup>TM</sup>.

Their new formulation makes \_\_\_\_\_ sized particles stabilized in the presence of egg lecithin, which enhances the digestive absorption of the drug, and supposedly eliminates the effect of food on the drug. This new \_\_\_\_\_ formulation would increase the bioavailability ( BA), would allow a lower dose of the new drug to be used, compared to the micronized fenofibrate (e.g. Tricor).

Because most of the available animal studies for the ingredients in IDD-P have been conducted with the approved fenofibrate, Tricor (under NDA 19-304), no additional non-clinical studies are conducted with IDD-P. Supportive information for IDD-P excipients is provided by use in the approved products and in FDA

GRAS listing (in item 7). Only one pilot PK study in dogs was conducted under IND 60,743 with a preliminary formulation of IDD-P, which compares it to the European-approved fenofibrate (Lipanthyl 67M). They have conducted a similar PK study with the above two formulations in humans (foreign study), which they claim shows that the IDD-P has improved BA and reduced effect of food.

Studies reviewed within this submission: As indicated earlier, additional animal studies are not considered necessary here. One PK study in dogs is provided.

	Studies	Page #
A	Single dose oral PK study in dogs (Study # FEN 100-PC01S)	5
B	Overall summary and evaluation	6

### PHARMACOKINETIC STUDY

#### **A comparative single dose PK study in dogs with Microparticulate (MP) fenofibrate (IDD-P) vs European-approved micronized Lipanthyl 67M formulation of fenofibrate.**

**Methods:** The objective was to compare the PK of the new MP formulation of fenofibrate (IDD-P, the preliminary formulation, appendix 1, Table 1) vs the approved European Lipanthyl 67M in dogs. In the same study the sponsor had also examined the [redacted] formulation of fenofibrate, but data on that formulation were not provided. Sponsor states that the animal phase of the study was non-GLP, but analytical part was GLP. It was a double crossover study in fed dogs, 67 mg (capsule) of the single oral fenofibrate- [redacted] (group 1) or lipanthyl 67M (group 2) was given to dogs (2/sex/group). Ten days later group 1 dogs received lipanthyl 67M, group 2 received fenofibrate- [redacted]. Following a 19-day wash out period, two groups received MP-fenofibrate (lot # 121697.01.73) and lipanthyl 67M the first time, and 10 days later lipanthyl 67M and MP-fenofibrate the second time.

**Results:** Total bilirubin was increased with both fenofibrate formulations (from 0.36 to 0.56-0.61 mg/dl) during the second crossover study. The AUC (0-48 hrs) values were higher by 20% (34.1 vs 28.7 ug.h/ml) and Cmax were higher by 40% (3.1 vs 2.2 ug/ml, by 40%) for MP formulation vs lipanthyl 67M formulation. Tmax was shorter by 50% for MP vs lipanthyl (2.2 vs 4.8 hrs) formulation. However the above findings were not significantly different between IDD-P and lipanthyl (p=0.06) by ANOVA, see appendix 1 (Tables 1 & 2).

## OVERALL SUMMARY AND EVALUATION

IDD-P™ Fenofibrate (Insoluble Drug Delivery-Microparticle) is a new formulation of fenofibrate, which contains the [REDACTED] size particles (vs Tricor which contains the micron size particles). This change in new formulation supposedly enhances the digestive absorption of the drug, eliminates the effect of food, increases the BA, and would allow a lower dose of the new drug to be used, compared to the micronized fenofibrate (e.g. Tricor). IDD-P™ will be available in tablets in two strengths, each containing 50, or 160 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 67, 134, or 200 mg of micronized fenofibrate. As per labeling, recommended doses of Tricor are up to 200 mg/day.

**Safety Evaluation:** Since extensive non-clinical studies have been conducted with the approved fenofibrate Tricor (under NDA 19-304), no additional non-clinical studies have been considered necessary, and have not been provided with IDD-P. One non-clinical PK study of the new drug IDD-P, using the preliminary formulation (which contains 11% of phospholipon 100H, a hydrogenated soy lecithin) has been conducted in dogs, where the PK of the drug were compared to the European micronized formulation. This study showed that the AUC and Cmax values with the new drug (IDD-P) were 20-40% higher vs the micronized formulation, but no significant differences were observed between two formulations. In the current marketed formulation, egg lecithin (with a phosphatidylcholine specification of [REDACTED], and phosphatidylethanolamine specification of [REDACTED]) is used vs soy lecithin was used in the dog PK study (i.e. phospholipon 100H, which contained purified soy lecithin with a phosphatidylcholine specification of [REDACTED]).

Supportive information for IDD-P excipients was provided in Generally Regarded as Safe (GRAS) products, as food additives, as well as by use in the other approved products. The only substance of concern is egg lecithin, [REDACTED] in the current product. However, sponsor states that it is a natural substance, and in the current formulation, the proposed daily dose of egg lecithin of [REDACTED] corresponds to approximately [REDACTED] of the amount in one egg (no reference is provided, but calculations are provided based on [REDACTED]). Lecithin is generally regarded as safe, it has been used in a number of NDAs (in the FDA inactive ingredient guide, 1996) up to doses of 20 mg. The other excipients have been used at the recommended or higher doses in other approved products (in the FDA inactive ingredient guide, 1996).

The following summary provides the toxicity of fenofibrate (Tricor) from the NDA review.

**Toxicity of Tricor:** The drug produces proxisome proliferation at doses above 30 mg/kg in rats. In acute toxicity, single doses up to 5000 mg/kg did not cause mortalities in mice, rats, hamsters and dogs over a 7-day period. In repeat dose toxicity studies, liver and kidneys were the target organs of toxicity. Liver toxicity was dose related in rats, but not observed in dogs or monkeys. In dogs (7-24 month tox studies), 25-100 mg/kg/day induced weight loss associated with cholelithiasis and some nephritis. In monkeys, doses up to 50 mg/kg/day did not produce any toxicity. As per label, the drug fenofibrate (Tricor) does not have a mutagenic potential, but in 24 month rat CAC study the drug produces liver and pancreas carcinomas, pancreatic adenomas, and benign testicular interstitial tumors (in male rats). In mice it produces liver carcinomas. These effects are noted at 0.3-6 times the maximum recommended human dose.

Fenofibrate (Tricor) produces embryocidal and teratogenic effects in rats and embryocidal effects in rabbits at 7-10 times the maximum recommended human dose, and is labeled as category 'C'.

The sponsor is proposing 160 mg/day, which is lower than the recommended 200 mg/day for Tricor in the label.

Also sponsor claims that there is extensive clinical experience with the drug with the current formulation. The sponsor has provided the comparative BA after single dose of IDD-P fenofibrate (160 mg tablet) vs micronized fenofibrate (200 mg capsule) in humans, as well as the effect of food on BA of IDD-P fenofibrate. In the above single dose human PK study, IDD-P had equivalent bioavailability to the micronized fenofibrate. The PK with IDD-P including C<sub>max</sub> (11.2 vs 10.4 mg/L with micronized fenofibrate), T<sub>max</sub> (3.2 vs 4.8 hrs), T<sub>1/2</sub> (15.7 vs 17.8 hr), AUC<sub>0-4</sub> (137.6 vs 149.3 mg.h/ml) and BA (94 vs 100%) have been provided.

**Labeling Review:** In general, the preclinical sections of the label for IDD-P are similar to the approved Tricor label, however some modifications have been made. The following changes in labeling are recommended:

**Sponsor's Suggested label:**



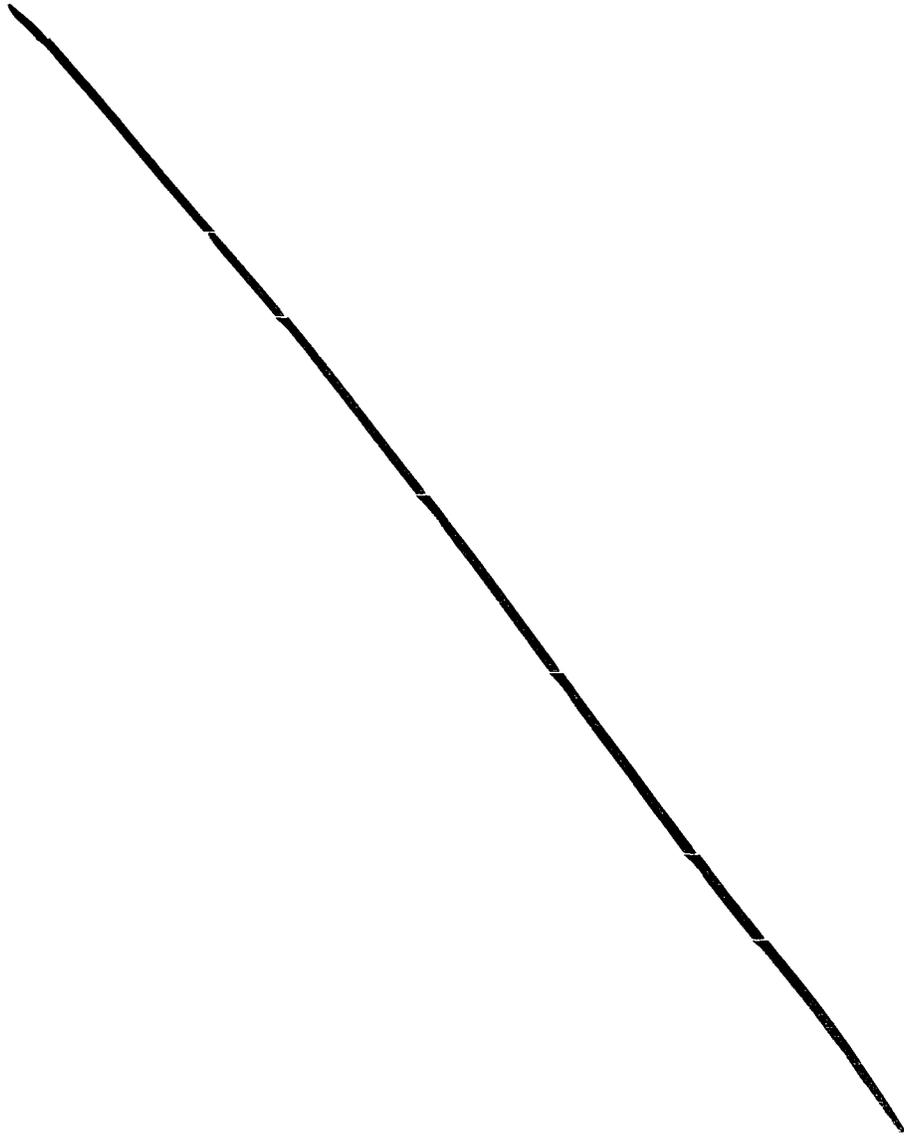
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✓ Draft Labeling

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**4. Following sections in the sponsor's label are acceptable**

**Nursing mothers:** Fenofibrate should not be used in nursing mothers. Because of the potential for tumorigenicity seen in animal studies, a decision should be made whether to discontinue nursing or to discontinue the drug.

**Pediatric Use:** Safety and efficacy in pediatric patients have not been established.

NDA 21-350

**Internal comments:** Since fenofibrate (marketed as Tricor) is an approved drug, its safety profile has been well characterized. The current drug (IDD-P fenofibrate) will be used at lower doses (160 mg/day) than the approved drug Tricor (200 mg/day), the approval (AP) of this application is recommended.

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

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Indra Antonipillai, Ph.D.  
Pharmacologist, HFD-510

cc: NDA Arch  
HFD510  
HFD510/antonipillai/davisbruno/parks/koch  
Review code: ██████  
Filename: nda21350

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       Draft Labeling

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/s/  
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Indra Antonipillai  
10/17/01 02:04:30 PM  
PHARMACOLOGIST

Approval of this application is recommended, pending labeling changes.  
Please communicate the labeling changes to the sponsor.  
Labeling changes need to be communicated to the sponsor

Karen Davis-Bruno  
10/19/01 09:08:37 AM  
PHARMACOLOGIST

10/4/01

NDA 21-350

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

**NDA 21-350:** This NDA is a 505(b)(2) application.

**Submission date:** 6/22/01

**Sponsor:** RTP Pharma Inc.

**Drug:** IDD-P™ Fenofibrate (Insoluble Drug Delivery-Microparticle)

**Introduction:** IDD-P is a new formulation of the approved drug fenofibrate Tricor (NDA 19-304). The new drug IDD-P formulation contains the ~~micronized~~ size particles (vs Tricor which contains the micron size particles).

ITEM: NDA 21-350	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		
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.)?	Yes		Only one single dose PK study in dogs has been provided to compare the PK of the current drug vs the micronized fenofibrate formulation

NDA 21-350

<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 carcinogenicity or other preclinical studies were conducted with the current drug, except one PK study in dogs. This is because non-clinical studies have already been conducted with the approved fenofibrate Tricor under NDA 19-304. Therefore no additional non-clinical studies have been provided with IDD-P and are considered necessary.</p>
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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>Sponsor has used new formulation in the current product, therefore they have provided supportive information for IDD-P excipients. The products used were Generally Regarded as Safe (GRAS) products, or these excipients have already been used in other NDAs (in the FDA inactive ingredient guide, 1996)</p>

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<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 in the single PK study conducted in dogs was similar i.e. oral, 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/m<sup>2</sup> 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/m<sup>2</sup>.</p>

ITEM	YES	NO	COMMENT
<p>9) From a pharmacology/toxicology perspective, is this NDA fileable? If not, please state in item # 10 below why it is not.</p>	<p>Yes</p>		

NDA 21-350

10) Reasons for refusal to file: Not applicable

**Reviewing Pharmacologist:** Indra Antonipillai, HFD-510

**Supervisory Pharmacologist:** Karen Davis-Bruno

File name: 21350-45dfiling

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/s/

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Indra Antonipillai  
10/4/01 03:28:23 PM  
PHARMACOLOGIST  
From the pharm/Tox aspect this NDA is filable  
This NDA application is filable

Karen Davis-Bruno  
10/4/01 04:31:45 PM  
PHARMACOLOGIST