

Table 14. Reproductive Toxicity Studies

Species	Study	Doses (mg/kg/day)
Rat	Fertility	0, 15, 75, 300
Rat	Teratogenicity	0, 14, 127, 361
Rabbit	Teratogenicity	0, 15, 150, 300
Rat	Pari-postnatal	0, 15, 75, 300

Fenofibrate produced no effects on fertility or their offspring when administered to male rats at up to 300 mg/kg/day.⁵⁸ In female rats, however, the compound delayed parturition, reduced litter size, increased post-implantation loss and caused poor survival and retarded growth of offspring. The NOAEL in this part of the study was 15 mg/kg/day.

Fenofibrate was not teratogenic in rats⁵⁹ up to 361 mg/kg/day and in rabbits⁶⁰ up to 300 mg/kg/day when administered orally up to a maternal toxic dose. Embryotoxic effects (abortions, fetal weight reduction, post-implantation resorptions, fetal death) were observed particularly in the rabbit, which was shown to be the more sensitive species. In rabbits, the NOAEL for maternal and fetal toxicity was 15 mg/kg/day.

Administration to pregnant female rats during late gestation through weaning resulted in increased fetal loss, decreased pup survival and retarded growth of offspring at the highest dosage of 300 mg/kg/day.⁶¹ The NOAEL in this study for fetal and pup toxicity was 75 mg/kg/day.

OVERALL SUMMARY AND EVALUATION:

In the current proposal, sponsor wants to develop fenofibric acid as a drug. Fenofibrate has been previously approved (NDA 19-304 as Tricor capsules and NDA 21-203/NDA 21-656 as Tricor tablets). Fenofibrate is an ester that is converted by esterases to its active circulating fenofibric acid, which is the active ingredient in the currently marketed TriCor tablets (NDA 21-656). Extensive non-clinical studies have been conducted with approved fenofibrate, therefore toxicity studies conducted with fenofibrate are adequate to support the fenofibric acid choline salt.

Tricor has undergone several formulation changes to improve bioavailability and to reduce food effect. The most recent formulation of fenofibrate (Tricor) by Abbott laboratories approved was 48 and 145 mg tablets and contained _____ the drug product (NDA 21-656).

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In animals, reduction of fenofibric acid to the reduced fenofibric acid metabolite predominates, in contrast in humans, the major route of metabolism is the formation of the ester glucuronide of fenofibric acid.

Sponsor has conducted 3-month toxicity studies with fenofibric acid choline salt in rats and dogs which were provided under IND 70,345 and in the present NDA application.

Safety Evaluation:

The proposed human dose in this study is 135 mg/day (with AUC values of approximately 183 µg.h/ml). The NOAEL dose of fenofibric acid choline salt in a 3-month oral toxicity study in rats was <10 mg/kg/day (with mean AUC exposures of 530 µg.h/ml in males+females). Based on AUC exposures of 183 µg.h/ml in humans, safety factor at the 130 mg/day human dose in rats is <3-fold. In dogs, the NOAEL was <25 mg/kg/day (with mean AUC exposures of 250 µg.h/ml in males+females), and safety factor at the human dose (of 130 mg/day) in dogs is approximately 1-fold.

Safety margins in humans are based on AUC exposures of 183 ug.h/ml and NOAEL's of <10 and <25 mg/kg/day (from 3-month studies) in rats and dogs respectively.

Species	NOAEL (m/k/d)	AUC µg.h/ml in males/female respectively	Safety margins in humans based on AUC exposures
			130 mg/day dose
Rat	<10	530	<3X
Dog	<25	250	~ 1X
Human dose			
130 mg/day multiple doses		183	

In rats, liver (both sexes) and pituitary (males only) toxicity was noted at <3X the human exposures, while the heart and muscle toxicity was noted at 15X and 60X the human exposures respectively. In dogs, testicular/ ovarian toxicity was noted at equivalent human therapeutic doses, liver/ stomach/ heart/thymus toxicity was noted at 5-12X the human exposures. However testicular and ovarian toxicity was reversible in dogs after the 6-week drug free recovery period.

Also note that in a five-week bridging study in rats with fenofibric acid (A770335.0 at 0, 10, 30, 75, 130 mg/kg/day, not a choline salt) vs fenofibrate (A52779, at 0, 100, 300 mg/kg/day), the TK of fenofibrate at 300 mg/kg/day in this study (AUC exposures were 15.3-19.3 mg.h/ml) was roughly equivalent to fenofibric acid 150 mg/kg/day (AUC exposures 14.2-20.2 mg.h/ml). Both Fenofibrate (100-300 mg/kg/day) and fenofibric acid (75-150 mg/kg/day) in general produced similar decreases in BWs, food consumption and changes in hematological (red blood cell parameters, e.g. decreases in hematocrit, and increases in RDW) and clinical chemistry parameters (ALT/ASTALP were increased by up to 2 fold in males). Target organs of toxicity with both fenofibrate (100-300 mg/kg/day) and fenofibric acid (75-150 mg/kg/day) were liver (centrilobular hypertrophy), skeletal muscle (myofiber degeneration), and heart (lesions with myofiber

degeneration). Only differences between these two were the gross findings in the stomach (red foci in the glandular mucosa less than 1 mm diameter) which were observed with fenofibric acid (in 1/20 and 3/20 rats at 75 & 150 mg/kg/day respectively), but not with fenofibrate.

Thus in rats (3-month study), the target organs of toxicity were liver (all doses), skeletal muscle (at a high dose), thymus (at a high dose), pituitary gland in males (all doses), kidneys in females (at a high dose). Note that the liver and pituitary gland toxicity was noted in rats at the lowest dose (which provides safety margin of <3-fold in rats to humans, based on AUC exposures). All other toxicities in rats (skeletal muscle, thymus, kidneys) are noted at 15 to 60X the human exposures.

In dogs (3-month study), the target organs of toxicity were liver (mid and high dose), ovaries/testis (all doses), thymus/stomach/skeletal muscle (mid and high doses), and heart (at a high dose). Again, toxicity in ovaries/testis was noted in dogs at equivalent of human therapeutic doses, but these were at least partially reversible after the 6-week of drug free recovery period. The thymus/stomach/skeletal muscle and heart toxicities were observed in dogs at 5-12 X the human exposures.

Note that liver toxicity can be monitored in humans with liver enzymes and pituitary toxicity (vacuolation) was of minimal severity and appears only in male rats. Thus there is a sufficient safety margin for the heart, stomach, and muscle toxicity in rats/dogs. There is also clinical experience with the approved fenofibrate (NDA21-203/NDA 19-304/NDA 21-656) in humans with no major adverse events.

Trilipix is indicated alone or in combination therapy with statins or ezetimibe. No pre-clinical toxicity studies have been conducted with fenofibric acid in co-administration with any of the statins (simvastatin, atorvastatin, rosuvastatin, pravastatin, fluvastatin) or with ezetimibe. However, sponsor has conducted pharmacokinetic interaction studies of fenofibric acid with various marketed statins in humans, and the current label indicates that there is some interaction following concomitant administration of fenofibric acid with pravastatin and fluvastatin, see below. Since there is human drug-drug interaction studies with these combination, no pre-clinical toxicity studies are required for combination therapy.

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HMG-CoA Reductase Inhibitors (Statins)

Concomitant administration of TRADE NAME 135 mg capsule and rosuvastatin 40 mg once daily for 10 days has no significant effects on the pharmacokinetics of fenofibric acid or the AUC of rosuvastatin. The mean rosuvastatin C_{max} was increased by 20% which is not considered clinically important.

Concomitant administration of fenofibrate (equivalent to TRADE NAME 135 mg) with pravastatin 40 mg once daily for 10 days has been shown to increase the mean C_{max} and AUC values for pravastatin by 36% (range from 69% decrease to 321% increase) and 28% (range from 54% decrease to 128% increase), respectively, and for 3 α -hydroxy-iso-pravastatin by 55% (range from 32% decrease to 314% increase) and 39% (range from 24% decrease to 261% increase), respectively, in 23 healthy adults.

Concomitant administration of a single dose of fenofibrate (equivalent to TRADE NAME 135 mg) and a single dose of fluvastatin 40 mg resulted in a small increase (approximately 15-16%) in exposure to (+)3R,5S-fluvastatin, the active enantiomer of fluvastatin.

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

Concomitant administration of fenofibrate (equivalent to TRADE NAME 135 mg) with atorvastatin 20 mg once daily for 10 days resulted in approximately 17% decrease (range from 67% decrease to 44% increase) in atorvastatin AUC values in 22 healthy males. The atorvastatin C_{max} values were not significantly affected by fenofibrate. The pharmacokinetics of fenofibric acid were not significantly affected by atorvastatin.

Cholesterol Absorption Inhibitor – Ezetimibe

Concomitant administration of fenofibrate (equivalent to TRADE NAME 135 mg) with ezetimibe 10 mg once daily for 10 days to 18 healthy adults resulted in increases in total ezetimibe AUC, C_{max} and C_{min} of approximately 43%, 33%, and 56%, respectively, and increases in ezetimibe glucuronide AUC, C_{max} , and C_{min} of approximately 49%, 34%, and 62%, respectively. The pharmacokinetics of fenofibric acid were not significantly affected by ezetimibe and the multiple-dose pharmacokinetics of free (unconjugated) ezetimibe were not significantly affected by fenofibrate.

Labeling Review: The pharmacology toxicology labeling in general is similar to the Abbott's labeling supplement of fenofibrate (NDA 21-856/004) approved on 8/10/06, in this supplement carcinogenicity and pregnancy sections were re-reviewed. In the current application, the submitted PLR label in pharmacology/toxicity sections (Pregnancy and Carcinogenesis, mutagenesis and impairment of fertility) are identical to the approved fenofibrate Tricor label (NDA 21-856/004). However changes to the animal pharmacology and /or toxicology are recommended, see the reviewer's recommendations below.

Following is sponsor's proposed label from 12/7/07 submission:

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1 Page(s) Withheld

 Trade Secret / Confidential (b4)

 ✓ Draft Labeling (b4)

 Draft Labeling (b5)

 Deliberative Process (b5)

NDA 22-224/000

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

Signatures (optional):

Reviewer Signature _____

Supervisor Signature _____

Concurrence Yes ___ No ___

cc: IND Arch
 HFD-510
 HFD-510/davisbruno/antonipillai/golden/johnson
 Review code: AP
 File name: nda22224 (fenofibric acid choline salt alone and with statins)

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/s/

Indra Antonipillai
8/28/2008 01:54:35 PM
PHARMACOLOGIST

From the pharm/tox point of view, approval of this
application is recommended pending labeling changes.
This application is recommended for approval pending labeling changes

Karen Davis-Bruno
8/28/2008 01:56:49 PM
PHARMACOLOGIST

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2/7/08

Signed off in DFS on 2/4/08

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

NDA 22-224: This NDA is a 505(b)(2) application.

Submission date: 12/7/2007

Sponsor: Abbott Laboratories, Abbott Park, IL.

Drug: Choline fenofibrate capsules (choline salt of fenofibric acid) in strengths of 45 and 135 mg.

Introduction: Fenofibrate is a third generation compound in the fibrate class of hypolipidemia therapies. Fenofibrate is an ester that is converted by esterases to its active circulating form of fenofibric acid. Fenofibrate is insoluble in water which limits its absorption and contributes to the significant food effect. Therefore different complex formulations have been developed to enhance its solubility and absorption to overcome these problems. Fenofibric acid has higher solubility at alkaline pH and higher permeability, it is expected to be absorbed at a greater extent, and have lesser food effect. Therefore the sponsor has developed the current drug i.e. Choline fenofibrate for monotherapy (for primary hyper-cholesterolemia/hyper-triglyceridemia) or in co-administration with statins (for mixed dyslipidemia). The reference listed drug for this application is fenofibrate (Tricor oral tablets 48 and 145 mg tablets, approved under NDA 21-656). Sponsor has submitted initial studies for this drug under IND 70,345.

ITEM: NDA 22-224	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		

<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>Carcinogenicity studies have not been conducted with choline fenofibrate, since this is a 505(b)(2) application. Sponsor refers to RLD fenofibrate (Tricor oral tablets 48 and 145 mg tablets, approved under NDA 21-656).</p> <p>Thus toxicity studies with fenofibrate have been reviewed under two NDAs. Majority of studies were conducted with fenofibrate (ABT-770799 or ABT-779) rather than with fenofibric acid (ABT-770335 or ABT-335.0) at that time. However because fenofibrate is rapidly converted to fenofibric acid (either during or immediately following absorption in animals and humans), the relevant pharmacology and toxicity studies of fenofibrate generally apply to fenofibric acid.</p> <p>Note that the sponsor has provided two 3-month toxicity studies in rats and dogs with choline fenofibrate in the current application.</p> <p>The sponsor has provided drug-drug interaction studies of fenofibrate + all statins including a study of choline fenofibrate + rosuvastain, and also with ezetimibe in clinical pharmacology studies. Other studies of fenofibrate + simvastatin are supported by literature reference and from zocor package insert.</p>
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ITEM	YES	NO	COMMENT
<p>5) Were the studies adequately designed (i.e., appropriate number of animals, adequate monitoring consistent with the proposed clinical use, state-of-the art protocols, etc.)?</p>			<p>Yes.</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 (i.e., adequate repeat studies using the marketed product and/or adequate justification for why such repetition would not be necessary)?</p>	<p>Yes</p>	<p>Each capsule contains a discrete number of enteric coated choline fenofibrate mini-tablets inside a gelatin capsule. The number of mini-tablets encapsulated determines the dose of each capsule. The mini-tablets are coated with enteric coating</p> <p>Sponsor has a DMF on choline fenofibrate mini tablets (submitted in the 4th quarter/07) and on</p> <p>These choline fenofibrate capsules have been tested in several bioequivalence studies. Sponsor states that in a bioequivalence study changing the key</p> <p>did not significantly affect the impact on AUC and Cmax values compared to RLD Tricor.</p> <p>No information on impurities or degradants is provided, the chemist (Su Tran) in the 74-day letter will ask for validation data for the impurity test method in support of their claim that they find no impurities/degradants in the drug product.</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>	

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NDA 22-224/Filing

<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 pharmacology/toxicity labeling submitted in general is similar to the approved fenofibrate label, and data express human dose multiples in mg/m² or AUC levels.</p>
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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>		
<p>10) Reasons for refusal to file: Not applicable</p>			

Reviewing Pharmacologist: Indra Antonipillai, HFD-510

Supervisory Pharmacologist: Karen Davis-Bruno

File name: 22-224 filing

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

/s/

Indra Antonipillai

2/4/2008 11:57:43 AM

PHARMACOLOGIST

From the pharm/tox point of view this application is
fileable.

This application is fileable.

Karen Davis-Bruno

2/7/2008 08:43:48 AM

PHARMACOLOGIST

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