CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-224

PHARMACOLOGY REVIEW

10/1/08

Pharmacology/Toxicology Memo
NDA 22-224/Trilipix (fenofibric acid choline salt)/ Abbott Laboratories
Karen Davis-Bruno PhD; Supervisory Pharmacologist; DMEP
9/30/08

Fenofibric acid is the active ingredient in marketed fenofibrate (Tricor NDAs 19-304/21-203/21-656). Fenofibrate is converted to its active form following enzymatic conversion in the intestine and single pass metabolism through the hepatic circulation. Similarly, the choline salt of fenofibric acid undergoes chemical disassociation in the gastrointestinal tract to form fenofibric acid. Abbott Laboratories is the sponsor of this NDA as well as those for Tricor. Based on their prior extensive experience with Tricor (fenofibrate), Abbott has conducted 5-week toxicity studies in rat with fenofibric acid and fenofibrate as well as 3-month toxicity studies with fenofibric acid in rats and dogs to support this NDA 22-224 for fenofibric acid. These studies have been reviewed in the Pharmacology/Toxicology Review of NDA 22-224 for Trilipix dated 8/28/08 which recommended approval without requiring further preclinical studies. Following this review, the medical team expressed concern about hepatotoxicity from the animal studies based on a clinical signal for elevated transaminases (>3X ULN) with trilipix.

Plasma exposure to fenofibric acid in both 13-week rat and dog toxicity studies are equal or higher than those described after chronic dosing with fenofibrate in rat (78-week) or dog (52 week) studies. The demonstration of active ingredient exposure at levels equivalent to the listed product have provided a sufficient bridge for many 505(b)2 NDA applications, allowing reliance on the Agency's previous decision of safety.

Table 14. No-Observed-Adverse-Effect-Levels (NOAEL) and Exposures from Repeated Dose Toxicity Studies in Rat and Dog with Fenofibrate and Fenofibric Acid

	Dosing with Fenofibrate		Fenofibric Acid	
Species	NOAEL (mg/kg/day)	Dose for PK (mg/kg)	C_{max} (µg/mL)	AUC (µg • h/mL)
Rat (78-week) (diet)	13	20[a]	33.2	384
		80[a]	161	2647
		320[a]	394	7388
Rat (5-week) (diet)	< 100	100	134 – 226	2850 – 4823
		300	677 - 842	15275 - 19333
Dog (52-week) (capsules)	25	25	12.7 – 16.8	88 – 136
		100	40.6 – 41.3	360 – 427
		400	77.6 – 97.4	1167 – 1470
	Dosing with Fenofibric Acid		Fenofibric Acid	
Species	NOAEL (mg/kg/day)	Dose for PK (mg/kg)	C_{max} (µg/mL)	AUC (µg • h/mL)
Rat (2-week) (gavage)	< 100	100	599	9386
		300	675	14312
		500	757	16678
Rat (2-week) (choline/calcium salt)	< 30	30	132	2213
		100	492	9346
		300	666	13811
Rat (5-week) (diet)	10	10	21 – 28	370 – 625
		30	84 – 164	1514 – 3506
		75	409 – 472	8788 – 10791
		150	611 – 787	14213 – 20237
Rat (13-week) (choline salt)	< 10	10	40.9 – 45.9	527 – 530
		30	183 – 188	2586 – 3209
		100	609 - 679	12021 - 12194
Dog (13-week) (choline salt)	< 25	25	53.1 – 64.1	222 – 272
		50	115 – 144	833 – 1098
		100	225 - 245	1887 – 2565
Human		1.9 (135 mg fenofibric acid/70 kg)	12.1	183

a. PK data available only after single dosing from a different study

The pharmacology/toxicology review of NDA 22-224 indicates that in the 3-month rat toxicity study target organs of toxicity were: liver (all doses), skeletal muscle (at HD), thymus (HD), pituitary gland vacuolation in males (all doses) and kidney in females (HD). The liver and pituitary gland findings were noted in rats at <3X human exposure based on the 135 mg fenofibric acid clinical dose (AUC=183 μg h/ml). All the remaining target organ toxicities in rat (skeletal muscle, thymus, kidneys) are observed at higher exposure multiples of 15-60 times maximum therapeutic exposure.

Multifocal coagulative necrosis appears in male rats given ≥10 mg/kg/day fenofibric acid (not dose related) and a single incidence in females at 30 mg/kg/day. Liver hypertrophy is observed at ≥10 mg/kg/day and is consistent with peroxisome proliferation and the observed increase in absolute liver weight (42-179%). Peroxisome proliferation indicated by electron microscopy occurred as early as 2 weeks post-dose with 200 mg/kg/day fenofibrate (Toxicology 41:169-191, 1986). Body weight decreased at 100 mg/kg/day in both sexes by 14%. ALT/AST elevations of ~2X occur at doses ≥30 mg/kg/day and are not significantly different from control at 10 mg/kg/day. The NOAEL for the study was <10 mg/kg/day.

3-Month Rat	Fenofibric Acid Dose							
Histopathology	0 mg/kg/day		10 mg/kg/day		30 mg/kg/day		100 mg/kg/day	
Findings	M	F	M	F	M	F	M	F
Liver Coagulative Necrosis multifocal minimal-mild	0	0	3/10	1/10	4/10	0	2/10	0
Liver Hypertrophy (moderate-marked)	0	0	0	6/10	10/10	10/10	10/10	9/10
Pituitary vacuolation minimal	0	0	6/10	0	9/10	0	10/10	0
Skeletal muscle degeneration minimal-moderate	0	0	0	0	0	0	10/10	10/10
Renal medulla multifocal mineralization	0	3/10	0	NE	0	NE	0	6/10
Thymus hemorrhage	4/10	0	NE	NE	NE	NE	6/10	3/10
Exposure Multiple			3		14-18		66-67	

NE= not examined

3-Month Rat	Fenofibric Acid Dose							
Liver Enzymes	0 mg/kg/day		10 mg/kg/day		30 mg/kg/day		100 mg/kg/day	
	M	F	M	F	M	F	M	F
ALT (U/L)	32	37	45	29	69	39	56	38
AST(U/L)	125	108	109	85	146	91	176	146

The sponsor provided 5-week bridging studies in rats with fenofibric acid (not choline salt) and fenofibrate to NDA 22-224. These studies were independent studies conducted using different doses. Exposure to fenofibric acid given at 150 mg/kg/day results in an AUC=14213-20237 μg h/ml which is equivalent to rats treated with fenofibrate at 300 mg/kg/day (AUC=15275-19333 μg h/ml) based on a comparison of exposure to the active moiety (fenofibric acid). A similar comparison with the hepatic histopathology from these studies suggests a slightly higher incidence of single cell necrosis (males, females) and the appearance of multifocal coagulative necrosis in 2/10 males at 150 mg/kg/day fenofibric acid compared to 8/10 males having single cell necrosis with 300 mg/kg/day fenofibrate after 5 weeks despite comparable exposures of fenofibric acid in plasma (see sponsor Table 1 below). A comparison of the 5 week fenofibrate/fenofibric acid rat toxicity studies is not provided in the pharmacology/toxicology review of NDA 22-224.

Table 1. Animal Toxicology Data From Five- and Thirteen-Week Studies

Study (mg/kg/day)	AUC (μg•h/mL) Range	ALT (U/L) Mean, M/F	AST (U/L) Mean, M/F	Liver weight (M / F; in g)	Histopathology
5-week fenofibrate rat (R&D/03/824)					
Control	NA	28 / 31	91 / 96	12.9 / 6.9	CN, f: 1M/1F
100	2850-4823	34 / 23	93 / 76	26.6 / 12.1	CN, mf: 4M/1F SCN: 3M
300	15274-19333	57 / 38	300 / 192	27.9 / 13.0	SCN: 8M
5-week fenofibric acid rat (R&D/03/823)					
Control	NA	24 / 21	83 / 73	12.2 / 7.1	-
10	370-625	27 / 35	75 / 83	18.7 / 9.2	CN, mf: 1M
30	1514-3506	34 / 21	88 / 67	24.1 / 11.4	CN, mf: 1M
75	8788-10791	42 / 26	124 / 104	26.1 / 13.2	CN, mf: 3M SCN: 4M
150	14213-20237	67 / 38	238 / 192	27.0 / 13.6	CN, mf: 2M SCN: 10M/2F
13-week fenofibric acid rat (R&D/05/344)					
Control	NA	32 / 37	125 / 108	14.8 / 7.8	-
10	527-530	45 / 29	109 / 85	23.5 / 11.4	CN: 3M/1F
30	2586-3209	69 / 39	146 / 91	31.6 / 14.4	CN: 4M
100	12021-12194	56 / 38	176 / 146	35.0 / 16.7	CN: 2M
13-week fenofibric acid dog (R&D/05/459)					
Control	NA	38 / 30	30 / 27	347 / 288	-
25	222-273	197* / 59	60 / 40	340 / 315	HD, f: 1M
50	833-1098	82 / 59	43 / 44	269 / 293	SCN: 1M
100	1887-2565	73 / 33	49 / 36	395 / 254	SCN: 1F
Human					
135 mg	183				

f = focal; mf = multifocal; CN = Coagulative necrosis; SCN = Single cell necrosis; HD = Hepatocellular degeneration

* includes one animal with ALT value of 944 U/L

The sponsor concludes that the toxicology findings with fenofibric acid are consistent with those observed from chronic dosing with fenofibrate. The findings are qualitatively similar as would be expected since the active component is the same (e.g. fenofibric acid). Differences in the actual incidence and description of the liver findings differ across these independent studies. None of the studies have been performed comparing fenofibric acid and fenofibrate in the same study in animals. A 78-week Wistar rat dietary toxicity study was performed by Abbott with dosing equivalents of 13, 60, 200 mg/kg/day fenofibrate. Rat histopathology incidences are not provided or available from prior reviews. The NOAEL for liver changes was considered 13 mg/kg/day (~2X human exposure to fenofibric acid), which is consistent with findings with fenofibrate in longer duration studies (see NDA 19-304).

In the 3-month dog toxicity study the target organ toxicities were: liver, thymus, stomach, skeletal muscle (MD/HD); ovaries/testes (all doses) and heart (HD). The ovarian/testicular findings occurred at human therapeutic exposures, but were partially reversible following a 6 week recovery period. The other findings occurred at higher exposures; 5-14 times maximum therapeutic exposure. The NOAEL for this study was <25 mg/kg/day. The liver findings consist of single cell necrosis and and/or minimal to mild mixed inflammatory cell infiltrates. Minimal single cell necrosis of hepatocytes was identified in 1/10 males at 50 mg/kg/day and in 1/10 females at 100 mg/kg/day. The histopathology table in the pharmacology/toxicology study combines the incidence of single cell necrosis with those of mixed inflammatory cell infiltration. Approximately 2-fold increases in ALT and AST were observed at ≥50 mg/kg/day (5-10 fold maximum therapeutic exposure). Liver weights were unchanged in dog, consistent with reduced peroxisome proliferation compared to the rat.

3-Month Dog	Fenofibric Acid Dose							
Histopathology	0 mg/kg/day		25 mg/kg/day		50 mg/kg/day		100 mg/kg/day	
Findings	M	F	M	F	M	F	M	F
Liver single cell necrosis& mixed inflamm. cell infiltrates minimal	0	0	0	0	2/4	1/4	3/4	1/4
Heart infiltration of mononuclear cells Tricuspid value hematoma							2/4	 1/4
Skeletal muscle Infiltration of monomuclear cells					¼		1/4	
Stomach multi-focal mucosa atrophy Lymphoid atrophy		 2/4				 3/4	1/4	 3/4
Thymus lymphoid atrophy	¼	2/4	2/4		¾	¾	1/4	3/4
Testes tubular vacuolation & hypo spermatogenesis			2/4		¾		3/4	
Immature ovary				¼		2/4		2/4
Exposure Multiple			1-2		5-6		10-14	

6 WK. RECOVERY 3-Month Dog	Fenofibric Acid Dose following 6 WK. RECOVERY							
Histopathology	0 mg/kg/day		25 mg/kg/day		50 mg/kg/day		100 mg/kg/day	
Findings	M	F	M	F	M	F	M	F
Diffuse hepatocellular vacuolation				½		2/2		1/2
Heart infiltration of monomuclear cells, focal hypertrophy or hyperplasia			½	½	½	½	1/1	½

Skeletal muscle infiltration of mononuclear cells				1/2			1/1	½
Tongue infiltration of inflamm/mononuclear cells			½		1/2			1/2

A 13-week dog toxicity study was not performed with fenofibrate in this or prior NDAs. Chronic dosing with fenofibrate in a 52-week dog toxicity study reveals increases in ALT and signs of hepatic peroxisome proliferation at 1167-1470 µg h/ml comparable to the exposures in dog with fenofibric acid at 50 and 100 mg/kg/day. This suggests that the development of liver findings is not time-related, rather it appears to be related to exposure. Liver histopathology findings related to fenofibrate treatment in the 52-week dog study consists of minimal monocytes infiltration in 2/3 males (1/3 controls) and 1/3 males with minimal brown pigmentation of Kupffer cells given 400 mg/kg/day (6-8 X human AUC to fenofibric acid). Minimal to slight brown pigmentation of Kupffer cells is also seen in 3/3 females given 400 mg/kg/day.

Table 5-1 Histopathology in male dogs treated orally with fenofibrate for 52 weeks

Sex	Organ / Finding	Dose (mg/kg)	Control				25				100				400			
		Grade*	–	±	+	++	–	±	+	++	–	±	+	++	–	±	+	++
	Heart		3				2	1			3				3			
	Spleen																	
	Brown pigment deposition		1	2			2		1		2		1			2	1	
	Thyroid																	
	Involution		1		2		1		2			2	1		1	1	1	
	Cyst		2		1			3			2		1		2	1		
	Femoral bone marrow																	
	Brown pigment deposition		3	2			1	1	1		1	2			2	1		
	Lymph node (Submandibular)																	
	Brown pigment deposition		2		1		2		1		3				2	1		
	Lung																	
	Pleural cell in alveolus		3				3				2	1			3			
	Organized clump, fatal		3				2	1			3				3			
	Osteoid in alveolus		3				2	1			3				3			
	Esophagus																	
	Mononuclear cell infiltration in submucosa		3				2	1			2	1			3			
	Liver																	
	Epithelial infiltration		2		1		3				2	1			3			
	Mononuclear cell infiltration		2	1			3				3				1	2		
	Brown pigment in Kupffer cell		3				3				3				2	1		
Male	Kidney																	
	Mineralization in renal papilla		1	2			1	2			1	2				3		
	Interstitial mononuclear cell and eosinophil infiltration in cortex		2		1		2			1	2	1			3			
	Testis																	
	Immature seminiferous tubule		3				3				3				2			1
	Epididymis																	
	Interstitial mononuclear cell infiltration		2			1	3				3				3			
	Prostate																	
	Interstitial mononuclear cell infiltration		2		1		3				2		1		3			
	Pituitary																	
	Cyst		3				3				3				2		1	
	Thyroid																	
	C-cell hyperplasia			2	1			3				2	1			3		
	Lymphocytic thyroiditis		3				3				3				1			2
	Mineralization of colloid		1	1		1	3				3				3			
	Parathyroid																	
	Cyst		1	1	1		1		2		3				3			
	Submandibular gland																	
	Interstitial mononuclear cell infiltration		3				3				2	1			2	1		

* Gradings of the finding were recorded as follows: – : None, ± : Very Slight, + : Slight, ++ : Moderate

Table 5-3 Histopathology in female dogs treated orally with fenofibrate for 52 weeks

Sex	Organ / Findings	Dose (mg/kg)	Control				25				100				400			
		Grade*	–	±	+	++	–	±	+	++	–	±	+	++	–	±	+	++
Female	Heart																	
	Granuloma		3				3				2		1		3			
	Mineralization in papillary muscle		3				3				3				2	1		
	Spleen																	
	Brown pigment deposition			2	1			3				3			1	2		
	Thymus																	
	Involution			2	1		1	1	1		2		1			2		1
	Cyst		1	2			3				2	1			2			1
	Femoral bone marrow																	
	Brown pigment deposition		1	2				3				3				2	1	
	Sternal bone marrow																	
	Brown pigment deposition		3				3				2	1				3		
	Lymph node (Submandibular)																	
	Brown pigment deposition		3				2	1			1		2		3			
	Esophagus																	
	Mononuclear cell infiltration in submucosa		3				3				2	1			3			
	Adrenal																	
	Vacuolation in zona reticularis cell		3				3				3				2		1	
	Liver																	
	Microgranuloma		3				2	1			3				3			
	Mononuclear cell infiltration		1	2			2	1			2	1			1	2		
	Brown pigment in Kupffer cell		3				3				3					2	1	
	Kidney																	
	Mineralization in renal papilla		1	2			1	2				3			1	2		
	Interstitial mononuclear cell and eosinophil infiltration in cortex		3				2	1			2		1		3			
	Ovary																	
	Follicular cyst		2		1		3				3				3			
	Pituitary																	
	Cyst		2			1	3				2		1		2	1		
	Thyroid																	
	C-cell hyperplasia			1	2		1		2			2	1			1	2	
	Lymphocytic thyroiditis		3				3				2		1		3			
	Cyst		3				3				2		1		2		1	
	Mineralization of colloid		2	1			3				2		1		3			
	Parathyroid																	
	Cyst		3				2		1		1	2			2	1		
	Lacrimal gland																	
	Interstitial mononuclear cell infiltration		3				2	1			3				3			
	Submandibular gland																	
	Interstitial mononuclear cell infiltration		3				3				2	1			3			

* Gradings of the finding were recorded as follows: – : None, ± : Very Slight, + : Slight, ++ : Moderate

NDA 19-304 identifies target organ toxicity in liver, pancreas, kidney and to a lesser extent testicular interstitial tissue and provides additional insight into the hepatotoxicity findings with longer duration fenofibrate dosing. Hepatomegaly is present in animals given > 30 mg/kg/day. Liver enzyme elevations were observed consistent with other fibrates. The NOEL of 10 mg/kg/day for liver toxicity and hepatic carcinoma is noted. This dose was approximately 1.5-times the approved human clinical Tricor dose and is consistent with the NOAEL observed in the rat. The hepatic findings following repeat dosing in several species are summarized in the table below.

Duration of testing/species	Fenofibrate Dose (mg/kg/day)	Hepatic Findings
3 Month Rat (Wistar)	50	↑ liver weight ↑ liver enzymes No significant histopathology
	250	
	500	
	1000	
80 Week Mice (Swiss)	10	↑ liver weight
	45	↑ liver weight
	200	↑ liver weight Hepatomegaly, cholethiasis Hepatocellular carcinomas
22 Month Mice (Swiss)	50	↑ liver weight Cholelithiasis Degenerative changes in hepatocytes No tumors
24 Month Dog	25	Cholelithiasis No hepatomegaly
52 Week Monkey (Rhesus)	12	No treatment related peroxisome proliferation No gross lesions
	50	
	200	
2 Year Rat (Wistar)	10	NOAEL
	45	Bile stasis
	200	Liver cell carcinoma & adenoma
104 Week Mice (CD1)	10	↑ transaminases M>F
	60	↑ transaminases M>F ↑ liver weight M>F
	200	↑ transaminases M>F ↑ liver weight M>F Nodular structure/dysplasia Hepatocyte hypertrophy Kupffer cell pigmentation ↑ liver tumors

Plasma exposure to fenofibric acid in both rat and dog toxicity studies are equal or higher than those described after chronic dosing with fenofibrate in rat (78-week) or dog (52 week) studies. The demonstration of active ingredient exposure at levels equivalent to the listed product have allowed a sufficient bridge for many 505(b)2 NDA applications, allowing for reliance on the Agency's previous decision of safety. Furthermore, hepatic findings in animals given fenofibrate are equivalent with hepatic findings observed with fenofibric acid. Fenofibrate is a currently marketed product, despite the liver findings observed in various animals at relatively low exposure multiples of the therapeutic dose. There is a reasonable correlation between increases in liver enzymes and the histopathological correlates in animals. Many of the rat hepatic findings are attributed to the increased peroxisome proliferative response mediated by the established PPARα activity of fibrates. While peroxisome proliferation is seen in several species including dog, primates and humans, it does not occur to the same extent as in rodents. Clinical monitoring of liver enzymes has been a standard safety measurement for marketed fibrates for many years. The nonclinical studies provided in NDA 22-224 as well as Abbott's response from 9/26/08 to DMEP's request for information on fenofibric acid have provided an adequate bridge to the prior approved Abbott Tricor NDAs 19-304/21-203/21-656. The nonclinical hepatotoxicity findings are qualitatively similar across studies with fenofibric acid and fenofibrate.

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/s/

Karen Davis-Bruno
10/1/2008 01:00:09 PM
PHARMACOLOGIST
P/T Supervisor's Memo re: hepatotoxicity

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NDA 22-224/000

Signed off in DFS on 8/28/08

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY REVIEW AND EVALUATION

NDA NUMBER:	22-224
SERIAL NUMBER:	000
DATE RECEIVED BY CENTER:	12/7/2007
PRODUCT:	Trilipix or Choline fenofibrate capsules (choline salt of fenofibric acid).
INTENDED CLINICAL POPULATION:	Hypercholesterolemia, hypertriglyceridemic patients
SPONSOR:	Abbott Laboratories, Abbott Park, Illinois.
DOCUMENTS REVIEWED:	e-CTD submission.
REVIEW DIVISION:	Division of Metabolism and Endocrinology Products.
PHARM/TOX REVIEWER:	Indra Antonipillai
PHARM/TOX SUPERVISOR:	Karen Davis Bruno
DIVISION DIRECTOR:	Mary Parks
PROJECT MANAGER:	Kati Johnson

Date of review submission to Division File System (DFS): 8/28/08

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Executive Summary

1. Recommendations

A. Recommendation on approvability

Pharmacology recommends approval of fenofibric acid for the proposed indication.

B. Recommendation for Nonclinical Studies:

The previous studies conducted with fenofibrate Tricor under NDA 19-304/21-203 and NDA 21-656 (approved on 11/5/2004) are adequate to support the current drug product. In addition, Abbott has conducted a 5-week bridging palatability study in rats with fenofibrate and fenofibric acid as well as 3-month toxicity studies with fenofibric acid choline salt in rats and dogs under IND 70,345, which are also provided in the current NDA 22-224. No further pre-clinical studies are required

C. Recommendation on Labeling: see the labeling section on page 32-33.

II. Summary of Nonclinical Findings:

A. Brief Review of Nonclinical studies

Fenofibric acid is the active ingredient in the currently marketed fenofibrate Tricor (Abbott), therefore toxicity studies conducted with fenofibrate are adequate to support the fenofibric acid choline salt. However, the current sponsor (Abbott laboratories) has conducted 5-week bridging studies in rats, and 3-month toxicity studies with fenofibric acid choline salt in rats and dogs. **In a five-week bridging study in rats** with fenofibric acid (0, 10, 30, 75, 130 mg/kg/day, not a choline salt) vs fenofibrate (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 in a 5-week study (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 seen with fenofibric acid (in 1/20 and 3/20 rats at 75 & 150 mg/kg/day respectively), but not with fenofibrate. Another comparative 14-day toxicity study of fenofibric acid (LF 01-0153) and fenofibrate (LF 01-0178) conducted in female SD rats (at 0, 100, 300, 500 mg/kg/day in 0.5% methylcellulose by oral gavage) in general suggested higher toxicity with fenofibric acid than with fenofibrate. Note that in the above 14-day study, toxicity was observed in the glandular stomach with both fenofibrate and fenofibric acid from the dose of 300 mg/kg/day in rats, but this was not seen in the 2-week study with fenofibric acid choline salt in a previous study at doses up to 300 mg/kg/day, which would suggest that choline salt of fenofibric acid is better tolerated for GI toxicity.

In a 3-month oral toxicity study of fenofibric acid choline salt in rats (0, 10, 30, 100 mg/kg/day), the mean AUC values of fenofibric acid in combined sexes on day 86 were higher (530, 2898, 12108 ug.h/ml at 10, 30, 100 mg/kg/day respectively) than on day 0 (337, 1533, 5240 ug.h/ml respectively). A high dose (HD) produced alopecia and/or thin hair in forelegs/forepaws, and red stained muzzle (10/20 vs 0/20 in controls). High dose decreased BW (by up to 14% in both sexes), and BW gains (by up to 86%). A 30-100 mg/kg/day dose produced changes in hematological (decreases in hematocrit, and increases in reticulocytes and platelets), and clinical chemistry parameters (ALT and AST increased by 2 fold at mid and high doses, ALP and serum albumin levels were increased at all doses). Fenofibric acid produced increases in organ weights, such as heart (21-46%), kidneys (up to 17%), and liver (by 42-179%) at all doses. Target organs of toxicity were liver (centrilobular hypertrophy of mild to moderate severity in 0/20, 6/20, 20/20, 19/20 at 0, 10, 30, 100 mg/kg/day respectively), skeletal muscle (at a HD in soleus muscle 20/20 vs 0/20 in controls, and in gastrocnemius muscle 20/20 vs vs 0/20 in controls, with minimal to moderate severity), pituitary gland in males (4/10, 6/10, 9/10, 10/10 respectively), kidneys in females (mineralization at a HD 6/10 vs 3/10 in controls) and thymus in both sexes (hemorrhage at a HD 4/20 vs 9/20). No drug free recovery period was assessed in this rat study. The AUC exposures following multiple dosing of 135 mg of fenofibric acid in humans are 183 µg.h/ml. Since liver findings were noted at all doses and heart and skeletal findings were noted at MD/HD (with higher incidences), the NOAEL or tolerated dose of the drug in a 3-month oral toxicity study in rats is <10 mg/kg/day, which provides safety margin of <3-fold in rats to humans (fenofibric acid AUC values in rats at 10 mg/kg/day =530/183 µg.h/ml= <3X). Thus, liver toxicity was noted at <3X the human exposures, while the heart and muscle toxicity was noted in rats at approximately 15X and 60X the human exposures respectively.

In a 3-month oral toxicity study of fenofibric acid choline salt in dogs (0, 25, 50, 100 mg/kg/day), followed by a 6-week drug free recovery period, the mean AUC values in combined sexes on day 84 were higher at MD/HD (247, 965, 2226 ug.h/ml at 25, 50, 100 mg/kg/day respectively) than on day 0 (males 298, 657, 1665 ug.h/ml respectively). A HD produced increased incidences of GI findings (emesis, abnormal stools) which correlated with decreases in BWs. One high dose (HD) male was euthanized due to decreases in BWS (by 30%) and GI findings. A mid and high dose decreased body weights (BWs) by up to 10-26% in both sexes. During the drug free recovery period, the BWs were still lower in HD males (by 20%). A 50-100 mg/kg/day dose produced changes in hematological (decreases in hematocrit, RBC, and hemoglobin and increases in APTT), and clinical chemistry parameters (ALT and AST were increased). Weights of ovaries (2.2, 1.0, 0.95, 0.81 g at 0, 25, 50, 100 mg/kg/day respectively, decreased by 55-63%), and testis (14.1, 13.5, 13.3, 13.1 g respectively, by up to 7%) were decreased at all doses. Relative heart weights were significantly increased during treatment (by up to 26%) but not during recovery period. Target organs of toxicity were liver (cell necrosis and/or mixed inflammatory cell infiltrates in 0/8, 0/8, 3/8, 4/8 dogs respectively), ovaries (immature in 0/4, ¼, 2/4, 2/4 dogs respectively), testis (tubular vacuolation and hypo-spermatogenesis in 0/4, 2/4, ¾, ¾ respectively), thymus (lymphoid atrophy (3/8, 2/8, 6/8, 4/8 respectively) and stomach (atrophy 2/8, 0/8, 3/8, 4/8 respectively). Additionally a HD produced toxicity in the heart (mononuclear cell

infiltration and focal tricuspid valve in 3/8 vs 0/8 in controls) and skeletal muscle (in males mononuclear cell infiltration in ¼ dogs at MD/HD vs 0/4 in controls). Stomach toxicity was also noted at MD/HD (mucosal or lymphoid atrophy in 2/8, 0/8, 3/8, 4/8 dogs respectively). During recovery, no toxicity was noted in the stomach, testis and ovaries in dogs, but was still present in the heart (infiltration of mononuclear cells or hypertrophy, or hyperplasia in males: 0/2, ½, ½, ½ respectively; females: 0/2, ½, ½, ½ respectively) and liver (in females diffuse vacuolation in 0/2, 1/2, 2/2, ½ respectively). The sponsor states that the mucosal atrophy, epithelial cell generation and chronic inflammation (consistent with healed ulcer or erosion) in ¼ males, and focally extensive pyloric ulcer in 1/4 females at a HD are related to the drug, and so are the findings in the liver and thymus. The NOAEL or tolerated dose of fenofibric acid in a 3-month oral toxicity study in dogs is not identified as all doses produced findings in testis and ovaries. The safety margins at the lowest dose of 25 mg/kg/day was non-existent in dogs to humans (mean fenofibric acid AUC values in M+F dogs at 25 mg/kg/day =247/183 ug.h/ml= ~1X), based on AUC exposures. Note that the liver, stomach, heart and thymus toxicity was noted in dogs at 5-12X the human exposures. The histopathology findings in testis and ovaries in the dog were observed at equivalent of the human therapeutic doses (based on exposures), but these were reversible after 6-weeks of the drug free recovery period. Thus, there is a sufficient safety margin for the heart, stomach, and muscle toxicity in rats and dogs.

Note that during the 6-week drug free recovery period, the toxicity in the heart (infiltration of mononuclear cells or hypertrophy, or hyperplasia (in both males + females in 0/4, 2/4, 2/4, 2/3 at 0, 25, 50, 100 mg/kg/day respectively) and in the liver (in females diffuse vacuolation in 0/2, 1/2, 2/2, ½ respectively) was still present, and was observed at equivalent of human therapeutic doses (based on exposures), but the number of animals in the recovery group is small, so it is not clear if these are a cause for concern.

Thus in a 3-month rat study, the target organs of toxicity were liver (all doses), skeletal muscle (at a HD), thymus (at a HD), pituitary gland in males (all doses), and kidneys is females (at a HD). Note that the liver and pituitary gland toxicity was noted in rats at <3-times the human doses, based on exposures. However, all other toxicities in rats (skeletal muscle, thymus, kidneys) are noted at 15 to 60X the human exposures.

In a 3-month dog study, the target organs of toxicity were liver (MD/HD), ovaries/testis (all doses), thymus/stomach/skeletal muscle (MD/HD), and heart (at a HD). 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 in males only and not in females. There is also a clinical experience with the approved fenofibrate in humans with no major AEs (NDA21-203/NDA 19-304/NDA 21-656).

B. Pharmacologic activity

Fenofibric acid like other fenofibrates, 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 of fenofibric acid choline salt.

2.6 PHARMACOLOGY/TOXICOLOGY REVIEW

NDA number: NDA 22-224
Review Number: 1

Sequence number/date/type of submission: December 7, 2007 (original application) it is a 505(b)(2) application submitted in an electronic format (e-CTD). The prior fenofibrate application (NDA 21-656) by Abbott was approved on 11/5/04.

Information to sponsor: Yes ( ) No (X)
Sponsor: Abbott Laboratories, Pharmaceuticals Products Div., Abbott Park, Illinois.

Manufacturer for drug substance: The drug product will be manufactured by Abbott Laboratories Barcelonata, Spain, and at Fournier Laboratories Ireland Limited, Ireland.

Reviewer name: Indra Antonipillai, Ph.D. Pharmacology Reviewer.
Division: Division of Metabolism and Endocrinology Products (DMEP).
Review completion date: 8/11/2008

Drug:

Trade name: TriLipix, it is available in 48 and 135 mg modified release capsule strengths.

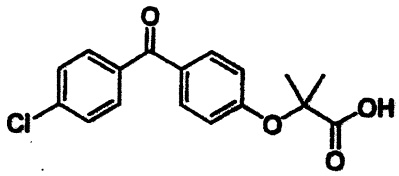
Generic name (list alphabetically): The choline salt of fenofibric acid.
Code name: A770335.115 (fenofibric acid choline salt), it is also called ABT-335.

Chemical name: 2-(4-(4-clorobenzoyl)phenoxy)-2-methyl-propanoic acid,(2-hydroxyethyl)trimethylammonium salt.

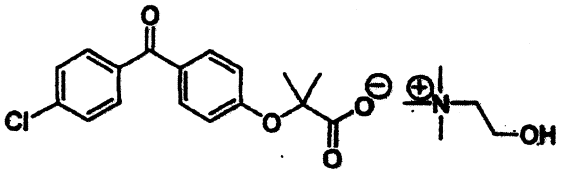
CAS registry number: For fenofibric acid is not provided (but for fenofibrate is 49562-28-9)
Molecular formula/molecular weight of fenofibric acid choline salt:
$C_{22}H_{28}ClNO_5$ /421.91

Structures of fenofibric acid and its choline salt are shown below

The chemical structure of A-770335.0 (fenofibric acid) is shown below.



The chemical structure of A-770335.115 (fenofibric acid choline salt) is shown below.



Relevant INDs/NDAs/DMFs: NDA 21-656 (Tricor, fenofibrate tablets from Abbott, approved 11/5/04), NDAs 19-304/21-203 (Tricor, fenofibrate capsules and tablets, also from Abbott), IND 70,345 (fenofibric acid choline salt), DMF ——— b(4)
DMF numbers 20895, 20896 (choline fenofibrate drug substance and drug product).

Drug class: Fenofibric acid, a phenoxyisobutyric acid isopropranolol ester.

Clinical formulation:

Choline fenofibrate capsules consist of a discrete number of coated mini-tablets in hard Gelatin capsules. There are two different drug product dosage strengths,135 mg or 45 mg (free acid equivalent). The dosage forms differ only in the number of mini-tablets in the capsule and the capsule color, size, and markings. The 135 mg capsule contains ——— mini-tablets in a ——— whereas the 45 mg capsule contains ——— mini-tablets in a ——— Each mini-tablet consists of ———

——— The tablets are coated with an enteric coating polymer ———

Thus, the manufacturing process for choline fenofibrate capsules consists of ——— manufacturing steps: ——— b(4)

Table. Composition of choline fenofibrate 135 mg strength capsule containing the active drug and following inactive ingredients is shown below:

Table 1. Composition of Choline Fenofibrate 135 mg Capsule

Component	Quality Standard	Function	Amount/unit
Mini-tablet Cores			
Choline Fenofibrate Mini-Tablets	DMF [a]	Drug Product	[redacted] mini-tablets
Encapsulation			
Capsule, Gelatin [redacted]	[redacted]	[redacted]	1 capsule [b]
Body:			
[redacted] ellow Iron Oxide	NF		
Titanium Dioxide	USP		
Gelatin	USP		
Cap:			
FD&C Blue #2	CFR21		
Titanium Dioxide	USP		
Gelatin	USP		
[redacted]	USP		
[redacted]	USP		

a Composition of choline fenofibrate mini-tablet intermediate is provided in DMF "Choline Fenofibrate Mini-Tablet Intermediate ", submitted by Abbott 4th Quarter 2007. See Letter of Authorization in Module 1.

b [redacted] See Letter of Authorization in Module 1.

b(4)

b(4)

Fenofibric acid has good solubility at intestinal pH (approximately 7mg/ml in pH 6.8) and low solubility in gastric pH (<1 ug/ml in pH 1.0).

Route of administration: Oral

Proposed use: The drug is indicated to be used alone (as monotherapy), 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 hypercholestrolemia or mixed dyslipidemia (Fredrickson Types IIa, and IIb), the recommended dose is 135 mg once daily. It is also indicated in adult hyper-triglyceridemia patients (Fredrickson Types IV, and V hyperlipidemia), with recommended dose of 45-135 mg once daily. Additionally, it is indicated for combination therapy with HMG CoA reductase inhibitors (statins) in adult patients with mixed dyslipidemia.

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

Data reliance: This is a 505(b)(2) application.

Studies reviewed in this submission: Three month toxicity studies with fenofibric acid in rats and dogs and the PLR label.

2.6.1. INTRODUCTION AND DRUG HISTORY

Fenofibric acid, the active metabolite of fenofibrate, is the active ingredient in the currently marketed Tricor tablets (NDA 21-656) in USA. The current sponsor (Abbott Pharmaceuticals) has now developed oral formulation of choline fenofibric acid for the treatment of dyslipidema. Fenofibrate (Tricor) is approved at doses up to 200 mg/day, both micronized and non-micronized formulations are approved, but the micronized drug has increased absorption. The Tricor capsules (67 & 200 mg strengths, NDA 19-304) and Tricor tablets (54 & 160 mg strengths, NDA 21-203) have substantial food effects, thus making its absorption still variable/incomplete and dependent on food. The micronized 67 mg [redacted] is equivalent to 100 mg of the conventional form. As per labeling, recommended doses of Tricor capsules are up to 200 mg/day, and of tablets are up to 160 mg/day. Fenofibrate produces beneficial effects on serum total cholesterol, LDL, and HDL via peroxisome proliferator-activated receptor alpha (PPAR α) activation. Through this mechanism fenofibrate increases lipolysis and eliminates TG rich particles from plasma by activating lipoprotein lipase and reduces production of apo C-III (an inhibitor of lipoprotein lipase activity). Fenofibrate is an ester that is converted by esterases to its active circulating form of fenofibric acid, which is the active ingredient in currently marketed TriCor tablets. 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.

tb(4)

Trilipix (ABT-335 or A77033.115) is a member of the fibric acid class of lipid-altering agents that acts via activation of peroxisome proliferator activated receptor alpha (PPAR α). 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, and therefore the sponsor is now developing fenofibric acid choline salt as a drug for the treatment of dyslipidema as a monotherapy and in combination with statin for patients with mixed dyslipidemia. Pharmacology/toxicity of fenofibric acid is expected to be similar to fenofibrate in rats and dogs. The only differences may be at the gastrointestinal level due to direct exposure to GI tract and due to the rate of absorption of the acid.

2.6.2 PHARMACOLOGY

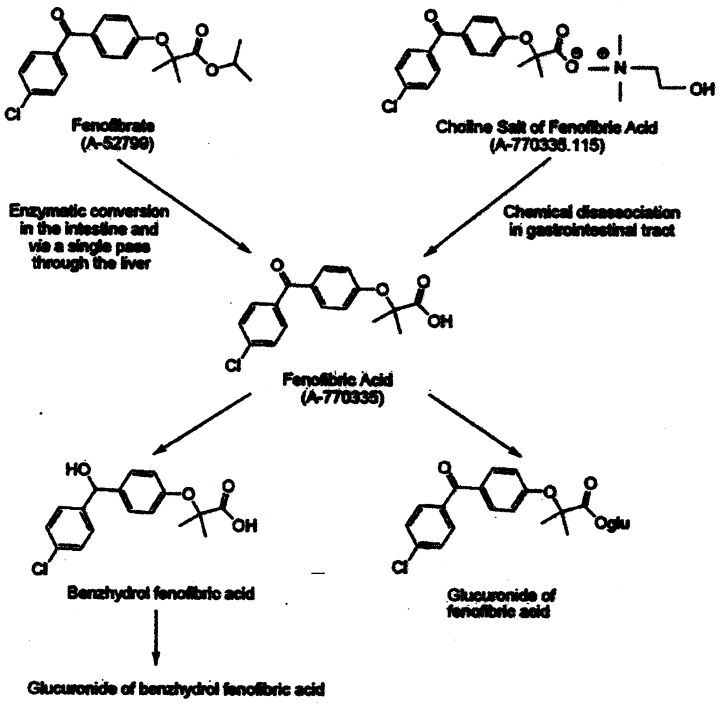
The underlying mechanisms of actions of fenofibrate are not fully established. The major effect of the drug is to enhance triglyceride rich lipoprotein catabolism by increasing lipoprotein lipase activity. It inhibits fatty acid synthesis and stimulates mitochondrial oxidation of fatty acids in rat liver. In addition the drug decreases cholesterol biosynthesis which may in turn enhance LDL clearance by increased LDL receptor activity. In addition fenofibrate improves insulin sensitivity and maintains lipid-glucose homeostatasis.

In vitro in human hepatocyte cultures and in vivo in transgenic mice, fenofibrate activates proxisome proliferator receptor α (PPAR α). It is believed that by this mechanism the drug increases lipolysis and elimination of TG rich particles from plasma by activating lipoprotein lipase and reducing production of apoprotein C-III (an inhibitor of lipoprotein lipase activity).

In vitro studies in human hepatocyte cultures have shown that effects of fenofibrate and fenofibric acid seen in the clinic could be explained *via* the activation of the specific transcription factor PPARα. PPARα controls the transcription of many genes involved in the regulation of fatty acids and cholesterol. These include genes that stimulate oxidation of fatty acids, increase lipase activity and are involved in the catabolism of triglycerides and cholesterol. Fenofibrate also mediates its effects through non-lipid mechanisms including a reduction of inflammation and alteration of lipid metabolism in the aortic vasculature. As a result of these varied effects, fenofibric acid significantly decreases dyslipidemia and the associated risk of cardiovascular disease as well as assisting in the normalization of dyslipidemia.

In vitro data have shown that the conversion of fenofibrate to fenofibric acid is driven by microsomal enzymes. In the presence of human liver microsomes, the conversion was rapid and complete, suggesting that fenofibrate is likely converted to fenofibric acid in the intestine and via a single pass through the liver after oral administration. ABT-335 is chemically disassociated to form the free acid in the gastrointestinal tract. Therefore, the metabolic pathway of fenofibric acid determined in humans following ^{14}C-fenofibrate administration is applicable to ABT-335. The proposed metabolic pathway is illustrated in Figure 1.

Figure 1. **Proposed Metabolic Pathway for Fenofibrate and Fenofibric Acid in Humans**



In physiologically normal rats fasted for 16 or 24 hours, administration of 5-300 mg/kg fenofibrate significantly lowered total lipids in a dose-dependent manner at all doses ≥ 20 mg/kg.[12] The effect plateaued at doses of 100 mg/kg or higher. Similarly, depression of blood cholesterol in these rats was significant at doses ≥ 20 mg/kg with maximal effect obtained at 300 mg/kg. The decrease in cholesterol induced by treatment with fenofibrate was similar to that observed with clofibrate at comparable doses although clofibrate did not demonstrate similar lipid lowering at these doses.[12]

Fenofibrate lowered plasma lipids in a high-fat, fructose-enriched dyslipidemia/diabetic hamster model over seven days of treatment (361 mg/kg/day).[10] Plasma triglycerides and cholesterol decreased by 30% and 76%, respectively. The activity of lipoprotein lipase in liver, adipose tissue and small intestine was up-regulated. Fenofibrate treatment improved insulin secretion by 81%, which was likely responsible for a fall in plasma glucose (33%). Fenofibrate treatment also reduced body weight and enhanced the fecal excretion of total lipids, cholic acid and deoxycholic acid. Thus, fenofibrate induced broad-spectrum lipid lowering along with inhibition of hepatic lipid biosynthesis, while maintaining lipid-glucose homeostasis.

It appears that animals such as rats, dogs make more reduced fenofibric acid metabolite (RFD) or (-) isomer than humans, i.e. the enantiomeric ratio of (-/+) in animals is 95:5 vs that in humans is 52:48. It is not known if that produces more gastrointestinal (GI) toxicity in animals

2.6.6
Toxicology:

Since fenofibrate is a previously approved drug (NDA 19-304 as Tricor capsules, and NDA 21-203/NDA 21-656 as Tricor tablets), toxicity studies with fenofibrate have been reviewed under these NDAs. Majority of studies in these applications 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 both in animals and humans), the relevant pharmacology and toxicity studies of fenofibrate also apply to fenofibric acid.

The toxicities with Tricor is briefly summarized (reviewed under IND 70,345 in DARRTS).

The drug produces proxisome proliferation at doses above 30 mg/kg in rats. In acute toxicity, single doses of fenofibrate up to 5000 mg/kg did not cause mortalities in mice, rats, hamsters. In dogs, doses up to 4000 mg/kg/day did not cause mortalities in dogs (see Table below). Several repeat dose toxicity studies have been conducted. In repeat dose studies (see Table below), 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 carcinogenicity 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 (160 mg/day).

Fenofibrate is labeled as Pregnancy Category C (see the Tricor label and the labeling supplement with changes to carcinogenicity and pregnancy sections in NDA 21-656/S-004 in DFS, approved on 8/10/06)

Following toxicity studies have been conducted with fenofibrate and fenofibric acid (reviewed under IND 70,345 in DARRTS).

2.6.6.2 Single dose Oral or Acute Toxicity studies:

Table 5. Single Dose Toxicity Studies with Fenofibrate and Fenofibric Acid

Species	Route of Administration	Fenofibrate (mg/kg)	LD_{50} (mg/kg)
Mouse	PO	0, 5000	> 5000
Rat	PO or IP	0, 5000	> 5000
Hamster	PO or IP	0, 5000	> 5000
Dog	PO	1000, 2000, 4000	> 4000
Rat	PO	100, 300, 1000	> 1000
		Fenofibric acid (mg/kg)	
Rat	PO	100, 300, 1000	> 1000

The acute toxicity of fenofibrate has been studied in mice, rats, hamsters and dogs[37] by oral and intraperitoneal administration. The compound has a low level of acute toxicity; no mortality or morbidity was observed at the doses used in these studies (Table 6). In an exploratory single dose study, administration of a 1000 mg/kg dose of fenofibric acid, more than 300 times the highest proposed clinical dose, produced a significant ulcerogenic response in the rat stomach. No effects were observed at doses up to 300 mg/kg for fenofibric acid or 1000 mg/kg for fenofibrate in the rat.[38]

2.6.6.3 Repeat Dose Toxicity Studies:

The following studies have been conducted with fenofibrate.

Table 1. Studies Conducted with Fenofibrate (A-52779.0; ABT-799)

b(4)

Species	Duration of Treatment and Route of Administration	Doses (mg/kg/day)	IND — Location of full report: Vol/page
Mouse[1]	Single dose, PO	0 and 5000	1.4/365
Rat[1]	Single dose, PO or IP	0 and 5000	1.4/370, 376
Hamster[1]	Single dose, PO or IP	0 and 5000	1.4/382, 388
Dog[1]	Single dose, PO	1000, 2000 and 4000	1.4/400
Rat (Wistar)[2]	78 weeks, PO	0, 13, 60 and 200	NA1
Dog (Beagle)[3]	52 weeks, PO	0, 25, 100 and 400	NA1
Monkey (Rhesus)[4]	52 weeks, PO	0, 12, 50 and 200	1.5/307 1.17/1725
Mouse (CF1)[5]	80 weeks, PO	0, 10, 45 and 200	1.11/269
Mouse (CD1)[6]	93 weeks, PO	0, 10, 60 and 200	1.19/10.0018 (NDA)
Rat (Wistar)[7]	104 weeks, PO	0, 10, 45 and 200	1.12/1
Rat (Sprague-Dawley)[8]	117 weeks, PO	0, 10 and 60	1.13/1
Rat[9]	Fertility, PO	0, 15, 75 and 300	1.8/1
Rat[10]	Teratogenicity, PO	0, 14, 127 and 361	1.6/175
Rabbit[11]	Teratogenicity, PO	0, 15, 150 and 300	1.7/1
Rat[12]	Peri/postnatal, PO	0, 15, 75 and 300	1.11/1
Ames/Salmonella[13]	Gene mutation (*in vitro*)	3.7 to 366.9 µg/plate	1.11/261
Ames/Salmonella and Saccharomyces[14]	Gene mutation (*in vitro*)	0.1 to 500 µg/plate	1.11/181
Rat bone marrow†[15]	Chromosome damage (*in vivo*)	0, 30, 200, 1000 and 5000	NA2
Guinea pig[16]	Maximization test	ut to 0.5 g/animal	NA2
Rat (Wistar)[17]	Single dose, PO	0, 100, 300 and 1000	NA2
Rat (Sprague-Dawley)[18]	2 weeks, PO	0, 100, 300 and 500	NA2
Rat (Sprague-Dawley)[19]	5 weeks, PO (diet)	0, 100 and 300	NA2

NA: not applicable

NA1: published report

NA2: submitted within this application

Following studies have been conducted with fenofibric acid (from the current NDA submission, toxicity summary section 2.6.6.1)

Table 2. Studies Conducted with ABT-335 [A-770335.0 (fenofibric acid), A-770335.115 (choline fenofibrate), A-770335.45 (calcium fenofibrate)]

Species	Duration of Treatment and Route of Administration	Doses (mg/kg/day)	IND 19056 Location of full report: Vol/page
Rat (Wistar)[2]	Single dose, PO	0, 100, 300, 1000	NA2
Rat (Sprague-Dawley)[3]	2 weeks, PO (gavage)	0, 100, 300, 500	NA2
Rat (Sprague-Dawley)[20]	2 weeks, PO (gavage)	0, 30, 100, 300	NA2
Rat (Sprague-Dawley)[21]	2 weeks, PO (gavage)	0, 30, 100, 300	NA2
Rat (Sprague-Dawley)[22]	5 weeks, PO (diet)	0, 10, 30, 75, 150	NA2
Rat (Sprague-Dawley)[23]	13 weeks, PO (gavage)	0, 10, 30, 100	NA2
Dog (Beagle)[24]	Single dose, PO (capsule)	150, 300, 600	NA2
	2 weeks, PO (capsule)	0, 30, 100, 300	
Dog (Beagle)[25]	2 weeks, PO (capsule)	0, 75, 150, 225	NA2
Dog (Beagle)[26]	13 weeks, PO (capsule)	0, 10, 30, 100	NA2
Mouse lymphoma cells[28]	Gene mutation (*in vitro*)	0.05 to 0.4 mg/mL	NA2
CHO cells[29]	Sister chromatid exchange	1.98 to 198 µg/mL	NA2
	Chromosome aberration (*in vitro*)	150 to 1200 µg/mL	
UDS/rat hepatocytes[30]	DNA repair (*in vitro*)	Up to 50.7 µg/mL	NA2

NA2 – submitted with this application

The following studies conducted with fenofibrate and fenofibric acid show the NOAEL doses in various toxicity studies (from the current NDA submission, section 2.4, page 58). Sponsor states that the fenofibric acid plasma exposures following multiple 135 mg oral daily doses of fenofibric acid in humans are 183 ug.h/ml.

Data summarized below also show that fenofibric acid exposures in both 13-week studies are equal or even higher than those described after chronic dosing with fenofibrate in rat (78-week) and dog (52-week) studies.

Table 14. No-Observed-Adverse-Effect-Levels (NOAEL) and Exposures from Repeated Dose Toxicity Studies in Rat and Dog with Fenofibrate and Fenofibric Acid

	Dosing with Fenofibrate		Fenofibric Acid	
Species	NOAEL (mg/kg/day)	Dose for PK (mg/kg)	C_{max} (µg/mL)	AUC (µg • h/mL)
Rat (78-week)	13	20[a]	33.2	384
(diet)		80[a]	161	2647
		320[a]	394	7388
Rat (5-week)	< 100	100	134 – 226	2850 – 4823
(diet)		300	677 - 842	15275 - 19333
Dog (52-week)	25	25	12.7 – 16.8	88 –136
(capsules)		100	40.6 – 41.3	360 – 427
		400	77.6 – 97.4	1167 – 1470
	Dosing with Fenofibric Acid		Fenofibric Acid	
Species	NOAEL (mg/kg/day)	Dose for PK (mg/kg)	C_{max} (µg/mL)	AUC (µg • h/mL)
Rat (2-week)	< 100	100	599	9386
(gavage)		300	675	14312
		500	757	16678
Rat (2-week)	< 30	30	132	2213
(choline/calcium salt)		100	492	9346
		300	666	13811
Rat (5-week)	10	10	21 – 28	370 – 625
(diet)		30	84 – 164	1514 – 3506
		75	409 – 472	8788 – 10791
		150	611 – 787	14213 – 20237
Rat (13-week)	< 10	10	40.9 –45.9	527 – 530
(choline salt)		30	183 – 188	2586 – 3209
		100	609 - 679	12021 - 12194
Dog (13-week)	< 25	25	53.1 – 64.1	222 – 272
(choline salt)		50	115 – 144	833 – 1098
		100	225 - 245	1887 – 2565
Human		1.9 (135 mg fenofibric acid/70 kg)	12.1	183

a. PK data available only after single dosing from a different study

Following is a brief summary of toxicity studies with fenofibric acid (for full review see IND 70,345 in DARRTS).

A comparative 14-day tox study of fenofibric acid (LF 01-0153) and fenofibrate (LF 01-0178) was conducted in female SD rats. Each drug was administered at 0, 100, 300, 500 mg/kg/day in 0.5% methylcellulose by oral gavage. Additional 9 rats/group were used for TK analysis. At ≥ 300 mg/kg/day fenofibric acid produced clinical signs (piloerection, this was also noted at 100 mg/kg/day in 1 female), as well as dose dependent decrease in weight gain (by up to 10%) and decreased FC (30-35%) in rats. Fenofibric acid affected hematological parameters (decreased mean corpuscular volume, decrease in reticulocyte count, decrease in prothrombin time). Both drugs increased clinical chemistry parameters (increases in ALT and AST, TG levels at ≥ 300 mg/kg/day, but total bilirubin increased at a HD with fenofibric acid). Target organs of toxicity with both drugs were liver (hepatocellular hypertrophy which correlated with gross liver enlargement), and glandular stomach, where petechiae and /or ulcers were observed at all doses of fenofibric acid or fenofibrate. In the glandular stomach, erosions, submucosal edema, focal mucosal congestion were noted from the dose of 300 mg/kg/day, but severity was increased with fenofibric acid and not so much with fenofibrate. Thymic atrophy was only noted at a HD with fenofibric acid which correlated with the dose dependent decrease in thymic weights in rats. Sponsor's NOAEL dose was 100 mg/kg/day for both drugs and plasma exposures of fenofibric acid were 9.4 and 5.4 mg.h/ml with this dose of fenofibric acid and fenofibrate respectively. Thus with fenofibric acid, almost 2-fold higher exposures are observed. Histopathology Tables were very poorly presented and were hard to read. This study in general suggests higher toxicity with fenofibric acid than with fenofibrate. It is interesting to note that toxicity was observed from the dose of 300 mg/kg/day in the glandular stomach in this 2-week study with both fenofibrate and fenofibric acid, and not in the 2-week study with fenofibric acid choline salt at doses up to 300 mg/kg/day, which would suggest that choline salt of fenofibric acid is better tolerated as for the GI toxicity is concerned.

In a single dose non-GLP study, the ulcerogenic potential of fenofibrate and fenofibric acid was evaluated in a groups of rats (6/sex/group). Effects of micronized fenofibrate and fenofibric acid on gastric ulcerogenic potential and PK were examined. Vehicle group were given 3% gum Arabic and acetylsalicylic acid (ASA) was given to 6 rats/sex/group as a positive control. The pharmacokinetic effects are shown below. Only fenofibric acid produced a significant ulcerogenic effect at a HD of 1000 mg/kg/day. The total lesions (including hyperplasia of petechiae, pinhead ulcers) seen with fenofibric acid were higher (6/12, 7/12, 10/12*, at 100, 300, 1000 mg/kg/day, *$p<0.05$) vs the control (5/12). Fenofibrate also induced these lesions (5/12, 6/12, 7/12 at 100, 300, 1000 mg/kg/day), but were not significant. The assay was valid as the positive control ASA showed these lesions in 12/12 rats. It is not clear why 5/12 controls had these lesions.

Toxicokinetic parameters for fenofibric fcid following dosing with either fenofibrate (LF 01-0178) or fenofibric fcid (LF 01-0153) are summarized in the following table.

	Fenofibrate					
Daily Dose (mg acid/kg)	100		300		1000	
Number of Animals	M: 6	F: 6	M: 6	F: 6	M: 6	F: 6
C_{max} (µg/mL)	85.7	243.0	194.9	390.5	309.6	416.6
T_{max} (h)	4	12	8	8	4	8
AUC_{0-24} (µg•h/mL)	1904	6357	5364	11860	10644	13258

	Fenofibric Acid					
Daily Dose (mg acid/kg)	100		300		1000	
Number of Animals	M: 6	F: 6	M: 6	F: 6	M: 6	F: 6
C_{max} (µg/mL)	393.5	454.3	578.9	687.7	903.1	1074.8
T_{max} (h)	2	8	0.5	8	2	8
AUC_{0-24} (µg•h/mL)	5482	11609	12904	25626	29223	42646

Under the experimental conditions of this study, a statistically significant ulcerogenic effect, characterized by a significant increase in the incidence and severity of gastric damage, was only detected with fenofibric acid at the highest dose (1000 mg/kg). The damage was located in the corpus of the stomach and included petechiae, pinhead ulcers and/or ulcer furrows. This dose level correlated with fenofibric acid plasma exposures of 29,223 and 42646 µg•h/mL in male and female rats, respectively. No significant ulcerogenic activity was noted in rats administered fenofibric acid at 100 or 300 mg/kg or in rats administered fenofibrate at 100, 300, or 1000 mg/kg. Under similar experimental conditions, rats administered ASA (method-control) at 100 mg/kg developed gastric damage, confirming the validity of the method used.

Similarly, five-week bridging studies with conducted in rats with fenofibric acid (0, 10, 30, 75, 130 mg/kg/day) vs fenofibrate (0, 100, 300 mg/kg/day). These studies were conducted at different times using different doses. The study with fenofibric acid was GLP, while with fenofibrate was non-GLP study. Doses used were different. Also fenofibric acid used was not a choline salt (see IND 70,345 review in DARRTS). However, 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 in a 5-week study (AUC exposures were 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 seen with fenofibric acid (in 1/20 and 3/20 rats at 75 & 150 mg/kg/day respectively), but not with fenofibrate.

Following is a brief summary of 3-month toxicity studies with fenofibric acid (for complete review see IND 70,345 in DARRTS).

Rats

In a 3-month oral toxicity study of fenofibric acid choline salt in rats, (n= 10/sex/dose, rats 7 weeks of age), doses of 0, 10, 30, 100 mg/kg/day were used. The drug accumulated over time and AUC values on day 86 were higher (males 527, 3209, 12021 ug.h/ml at 10, 30, 100 mg/kg/day respectively; females 530, 2586, 12194 ug.h/ml respectively) than on day 0 (males 223, 975, 5241 ug.h/ml at 10, 30, 100 mg/kg/day respectively; females 451, 2092, na ug.h/ml respectively, na=not available). A HD produced alopecia and/or thin hair in forelegs/forepaws, red stained muzzle (10/20 vs 0/20 in controls) and dark colored tail (in males). High dose decreased body weights (BWs by up to 14% in both sexes), BW gains (by up to 86%), and food consumption in females during the third week (by 11%). A 30-100 mg/kg/day dose produced changes in hematological (decreases in hematocrit, and increases in reticulocytes and platelets), and clinical chemistry parameters (ALT and AST were increased by 2 fold, ALP and serum albumin levels were increased at all doses). Weights of several organs, such as heart (21-46%), kidneys, and liver (by 42-179%) were increased at all doses, and were associated with histopathology changes in these organs. Target organs of toxicity were liver (centrilobular hypertrophy of mild to moderate severity in 0/20, 6/20, 20/20, 19/20 at 0, 10, 30, 100 mg/kg/day respectively), skeletal muscle (at a HD in soleus muscle 20/20 vs 0/20 in controls, and in gastrocnemius muscle 20/20 vs vs 0/20 in controls, with minimal to moderate severity), pituitary gland in males (4/10, 6/10, 9/10, 10/10 respectively), kidneys in females (mineralization at a HD 6/10 vs 3/10 in controls) and thymus in both sexes (hemorrhage at a HD 4/20 vs 9/20 in controls). No drug free recovery period was assessed in this rat study. Sponsor states that in humans the AUC exposures at multiple dose of 135 mg oral daily dosing of fenofibric acid are183 µg.h/ml (see page 16, Table 14 of this review). The proposed dose of fenofibric acid is intended to provide the same plasma exposures as that achieved with a reference 200 mg capsule.

Since liver findings were noted at all doses and heart and skeletal findings were noted at MD/HD (with higher incidences), the NOAEL or tolerated dose of the drug in a 3-month oral toxicity study in rats is <10 mg/kg/day, which provides safety margin of <3-fold in rats to humans (mean fenofibric acid AUC values in male + female rats at 10 mg/kg/day =530/183 µg.h/ml= <3X). Note that liver toxicity was noted at <3X the human exposures, while the heart and muscle toxicity was noted at 15X and >60X the human exposures respectively.

Tabulated summary of histopathology data in a 3-month toxicity study in rats with fenofibric acid choline salt (A770335.115) are shown below:

	Males (0, 10, 30, 100 mg/kg/day)	Females (0, 10, 30, 100 mg/kg/day)
Heart degeneration (minimal to mild)	5/10, 3/10, 6/10, 9/10	3/10, 2/10, 5/10, 5/10
Liver, coagulative necrosis	0/10, 3/10, 4/10, 2/10	0/10, 1/10, 0/10, 0/10
Liver, hypertrophy (moderate to marked)	0/10, 0/10, 10/10, 10/10	0/10, 6/10, 10/10, 9/10
Pituitary vacuolation, in pars distalis, minimal	4/10, 6/10, 9/10, 10/10	----------
Soleus muscle degeneration of myofiber, multifocal mild to moderate	0/10, 0/10, 0/10, 10/10	0/10, 0/10, 0/10, 10/10
Gastrochemius muscle degeneration of myofiber, minimal to mild	0/10, 0/10, 0/10, 10/10	0/10, 0/10, 0/10, 10/10
Kidney multifocal medulla mineralization	----------	3/10, ne, ne, 6/10
Thymus hemorrhage	4/10, ne, ne, 6/10	0/10, ne, ne, 3/10

Sponsor explains below that there are sufficient safety margins in the toxicity findings with fenofibric acid in the above13-week study in rats:

> Plasma exposure of fenofibric acid (Table 14) in rats at minimally toxic dosages (peroxisome activation) following 13 weeks of daily administration of fenofibric acid are approximately three-four-fold greater than the intended exposures following fenofibric acid administration in humans. At exposure multiples of about 15-20-fold, cardiac myofiber damage was seen and at higher dosages, with exposures of ≥ 50-fold those expected in humans, anemia, skeletal muscle degeneration and decreased body weight gain were observed. An identical spectrum of toxicity at comparable multiples above human exposure was seen after dosing with fenofibrate (five-week study).

Sponsor states that in rats, no ulcerogenic effects were found following oral (gavage) administration of the choline salt of fenofibric acid. In these studies, the exposure levels of fenofibric acid (approximately 12000 µg•h/mL) were ≥ 60-fold higher than the clinical exposure at the 135 mg dose (183 µg•h/mL).

Dogs

In a 3-month oral toxicity study of fenofibric acid choline salt in dogs (n=4/sex/dose), doses of 25, 50, 100 mg/kg/day were used followed by the 6-week of the drug free recovery period. The drug accumulated over time at MD/HD and AUC values on day 84 in combined sexes were higher (males 222, 832, 1886 ug.h/ml at 25, 50, 100 mg/kg/day respectively; females 271, 1098, 2564 ug.h/ml respectively) than on day 0 (males 225, 662, 1553 ug.h/ml; females 372, 652, 1777 ug.h/ml respectively). A HD produced increased incidences of GI findings (emesis, abnormal stools) which correlated with decreases in BWs. One HD male was euthanized due to decreases in BWS (by 30%) and due to GI findings. MD/HD decreased BWs (by up to 10-26% in both sexes). During the drug free recovery period, the BWS were still lower in HD males (by 20%). A 50-100 mg/kg/day dose produced changes in hematological (decreases in hematocrit, RBC, and hemoglobin and increases in APTT), and clinical chemistry parameters (ALT and AST were increased). Weights of several organs, such as ovaries (2.2, 1.0, 0.95, 0.81 g at 0, 25, 50, 100 mg/kg/day respectively, by 55-63%), and testis (14.1, 13.5, 13.3, 13.1 g respectively, by up to 7%) were decreased at all doses, and were associated with histopathology changes in these organs. Relative heart weights were significantly increased during treatment (by up to 26%) but not during recovery period. Target organs of toxicity were liver (cell necrosis and/or mixed inflammatory cell infiltrates in 0/8, 0/8, 3/8, 4/8 dogs respectively), ovaries (immature in 0/4, ¼, 2/4, 2/4 dogs respectively), testis (tubular vacuolation and hypo-spermatogenesis in 0/4, 2/4, ¾, ¾ respectively), thymus (lymphoid atrophy (3/8, 2/8, 6/8, 4/8 respectively) and stomach (atrophy 2/8, 0/8, 3/8, 4/8 respectively). Additionally, HD produced toxicity in the heart (mononuclear cell infiltration and focal tricuspid valve in 3/8 vs 0/8 in controls) and skeletal muscle (in males mononuclear cell infiltration in ¼ dogs at MD/HD vs 0/4 in controls). Stomach toxicity was also noted at MD/HD (mucosal or lymphoid atrophy in 2/8, 0/8, 3/8, 4/8 dogs respectively). During recovery, the toxicity was not seen in the testis and ovaries, but was still present in the heart (infiltration of mononuclear cells or hypertrophy, or hyperplasia in males: 0/2, ½, ½, ½ respectively; females: 0/2, ½, ½, ½ respectively) and liver (in females diffuse vacuolation in 0/2, 1/2, 2/2, ½ respectively).

Also in the heart in electrocardiographic evaluation, QT intervals were significantly increased at a HD in females on days 76-77 (185, 180, 196, 205 seconds at 0, 25, 50, 100 mg/kg/day respectively) but not during the drug free recovery period. QRS were significantly decreased in females at a HD both during the treatment (on days 76-77 were 1.42, 1.10, 0.93, 0.83 mv respectively) and recovery period (day 126 were 2.2, 2.1, 1.85, 1.40 mv respectively. QTcf (213, 220, 217, 235 msec respectively) and QTcv (213, 219, 217, 233 msec respectively) were also significantly altered at a HD during treatment (by approximately 20 msec) but not during recovery periods. These changes were observed in females. The data were considered significant at the p value of =0.05 for each variable. Sponsor states that no drug related effects were observed on electrocardiography (for complete review see IND 70,345 in DARRTS).

The NOAEL or tolerated dose of the drug in a 3-month oral toxicity study in dogs was <25 mg/kg/day as all doses produced findings in testis and ovaries. There was no safety margins at the lowest dose of 25 mg/kg/day in humans (mean fenofibric acid AUC values in male+ female dogs at 25 mg/kg/day were 247/183 ug.h/ml= 1X) as these toxicities occurred at equivalent of human therapeutic doses, based on AUC exposures. Thus, liver, heart, stomach and thymus toxicity was noted in dogs at 5X-12X the human exposures. Testicular and ovarian findings were reversible after 6-weeks of drug free recovery period

Tabulated summary of histopathology data in a 3-month toxicity study in dogs with fenofibric acid choline salt (A770335.115) during treatment are shown below (n=4/sex/dose):

	Males (0, 25, 50, 100 mg/kg/day)	Females (0, 25, 50, 100 mg/kg/day)
Heart, infiltration of mononuclear cells in males, and hematoma, focal in tricuspid valve in females	0/4, 0/4, 0/4, 2/4	0/4, 0/4, 0/4, ¼
Stomach, atrophy in the mucosa, multifocal in males, lymphoid atrophy in females	0/4, 0/4, 0/4, 1/4	2/4, 0/4, ¾, 3/4
Liver, single cell necrosis and/or mixed inflammatory cell infiltrates (minimal to mild)	0/4, 0/4, 2/4, 3/4	0/4, 0/4, ¼, ¼
Testis, tubular vacuolation and hypo-spermatogenesis	0/4, 2/4, ¾, 3/4	----------
Skeletal muscle, infiltration of mononuclear cells	0/4, 0/4, ¼, ¼	----------
Thymus lymphoid atrophy	¼, 2/4, ¾, 1/4	2/4, 0/4, ¾, 3/4
Ovary, immature	----------	0/4, ¼, 2/4, 2/4

Tabulated summary of histopathology data during recovery are shown below (n=2/sex/dose): *Note that* One male animal in the recovery group at a HD of 100 mg/kg/day was euthanized on day 39.

	Males (0, 25, 50, 100 mg/kg/day)	Females (0, 25, 50, 100 mg/kg/day)
Heart, infiltration of mononuclear cells, focal hypertrophy or focal hyperplasia	0/2, 1/2,1/2, 1/1	0/2, 1/2,1/2, ½
Liver, diffuse hepatocellular vacuolation	----------	0/2, 1/2 , 2/2, 1/2
Skeletal muscle, infiltration of mononuclear cells	0/2, 0/2, 0/2, 1/1	0/2, ½, 0/2, ½
Tongue, infiltration of mixed inflammatory muscle or mononuclear cells	0/2, ½, ½, 0/1	0/2, 0/2, 0/2, 1/2

Sponsor states that testicular findings in dogs i.e. presence of vacuoles and hypo-spermatogenesis (in 0/4, 2/4, ¾, ¾ respectively) has been previously reported with several HMG CoA reductase inhibitors with no changes or negligible changes in these or semen parameters in men.

Thus, weight loss was significant in both rats and dogs, similar changes in hematological and clinical chemistry parameters were noted with choline salt in both 3-month rat and dog studies. Target organs of toxicity in both species were liver (hypertrophy/necrosis in rats, necrosis/mixed inflammatory cell infiltrates in dogs), skeletal muscle (degeneration in rats, mononuclear cell infiltration in dogs) and heart (increases in heart weighs, with degeneration in rats and mononuclear cell infiltration in dogs at MD/HDs) . No safety pharmacology studies with fenofibric acid choline salt have been conducted to further evaluate the heart findings. Plasma exposures were higher in rats (500, 2000, 10000 ug.h/ml at 10, 30, 100 mg/kg/day) than in dogs (247, 966, 2226 ug.h/ml at 25, 50, 100 mg/kg/day respectively). In a 3-month rat study 1/10 male rat was found dead on day 83 at a HD of 100 mg/kg/day, no cause of death was identified, but rats in this dose group lost significant weight (by 14%). Similarly, in a 3-month dog study, 1/6 male dog (including 2/sex/dose from the recovery group) was euthanized at 100 mg/kg/day due to GI signs (emesis, abnormal stools) and weight loss of 30%. In the stomach mucosal or lymphoid atrophy was increased at a MD/HD in dogs (2/8, 0/8, 3/8, 4/8 dogs at 0, 10, 30, 100 mg/kg/day respectively). In rats no GI findings were noted in this study but in a 5-week study with fenofibric acid (not the choline salt), 75-150 mg/kg/day produced red foci in the glandular mucosa (1/10 and 4/10 rats at 75 and 150 mg/kg/day respectively). Additionally, testis (decreases in weights, tubular vacuolation and hypo-spermatogenesis in 0/4, 2/4, ¾, ¾ respectively) and ovaries (decreases in weights and immature in 0/4, ¼, 2/4, 2/4 dogs respectively) were target organ of toxicity in dogs. Sponsor states that the testicular findings in dogs have been previously reported with several HMG CoA

reductase inhibitors with no changes in these parameters in men. Note that during the drug free recovery period, the toxicity in stomach, testis and ovaries was not seen, but the toxicity in the heart (infiltration of mononuclear cells or hypertrophy, or hyperplasia (in both males + females in 0/4, 2/4, 2/4, 2/3 at 0, 25, 50, 100 mg/kg/day respectively) and in liver (in females diffuse vacuolation in 0/2, 1/2, 2/2, ½ respectively) was still present, and was observed at equivalent of human therapeutic doses, based on exposures, thus there appears to be no safety margin in dogs to humans. However, the number of animals in recovery group is small and there is prior experience with fenofibrate in humans. Also dogs at MD/HD (including recovery animals) received dietary supplementation which controls did not.

Sponsor explains that none of these findings are a concern as stated below:

In dogs gastric lesions were found at 75 mg/kg/day (2-week study) and 100 mg/kg/day (13-week study) corresponding to fenofibric acid plasma exposure (approximately 2500 to 4500 µg•h/mL) of approximately 17 to 31-fold the highest proposed dose in humans. Tubular vacuolation of the testes was a consistent finding in the 2-week and the 13-week studies where young dogs (about 7 to 9 months at necropsy) were administered fenofibric acid or fenofibric acid choline salt. By 13 weeks of dosing the vacuolation was associated with a partial depletion of germ cells from the seminiferous tubules from the low dose onwards (25 mg/kg/day, about 2-fold the human exposure). Hypospermatogenesis, which can be seen as part of the background pathology present in approximately 30% of normal beagle dogs[72], was not noted, however, after long-term treatment (up to 52 weeks) with the pro-drug fenofibrate.[40] Effects on dog testes have been described for a number of lipid-lowering compounds, including clofibrate[73] and various statins.[74,75] The described lesions after fenofibric acid treatment are very similar to those observed after statin treatment and were shown to be reversible. Although these changes provide a low safety margin in animals for both, fenofibric acid and statins, clinical studies in humans with several statins have demonstrated negligible or no changes in hormones or semen parameters in human.[76,77,78] In addition, a review of all individual adverse event reports for testicular and epididymal events contained in our spontaneous and clinical safety reporting database revealed no trend consistent with the pathological finding in the preclinical dog study.[79] Moderately decreased ovary weights that correlated microscopically with immaturity were observed in all treated female dogs. The testicular and ovarian findings were not present in dogs following a six-week recovery period. In conclusion, the testicular and ovarian findings are not expected to have clinical significance and no further preclinical studies with fenofibric acid are needed to further investigate these findings.[80]

Sponsor has not provided any comparisons of fenofibric acid with fenofibrate for dog studies. However, target organs of toxicity with fenofibrate in multiple dose toxicity studies in dogs may be kidney, liver, and gallbladder. No testicular or ovarian toxicity has been mentioned with fenofibrate in dogs. In the Triocr label under the heading "Carcinogenesis, Mutagenesis, Impairment of Fertility, there is no mention of fertility studies, however it is stated that fenofibrate produces benign testicular interstitial cell tumors at 6 times the Maximum recommended human dose (MRHD) in males in one strain of rats, and these tumors are observed at 2 times the MRHD (200 mg/day) in a second study in another strain of rats.

6.6.6.4 GENETIC TOXICOLOGY

Following Gene-toxicity studies have been conducted with fenofibrate or fenofibric acid

Table 15. Genotoxicity Studies

Test	Test/Species	Compound	Results
Gene mutation (*in vitro*)	Ames/Salmonella test	Fenofibrate	Negative
Gene mutation (*in vitro*)	Ames/Salmonella and Saccharomyces	Fenofibrate/Fenofibric acid	Negative
Chromosome damage (*in vitro*)	SCE/CHO cells	Fenofibric acid	Negative
Chromosome damage (*in vitro*)	Mouse lymphoma cells	Fenofibric acid	Negative
Chromosome damage (*in vivo*)	Bone marrow chromosomes/rat	Fenofibric acid	Negative
DNA repair (*in vitro*)	UDS/primary culture of rat hepatocytes	Fenofibric acid	Negative

No evidence of mutagenic or clastogenic activity was observed in any of the genotoxicity studies conducted using either fenofibrate or fenofibric acid.[62,63,64,65,66,67]

Following studies have been conducted with fenofibrate and fenofibric acid (from current NDA submission of NDA, section 2.4.4.5, pages 46-47)

Table 12. Summary of Genetic Toxicology Studies on Fenofibrate and Fenofibric Acid

Type Study	Method	Dose Range (mg/mL, µg/mL, or mg/kg/day)	Findings	Laboratory	Report No.	IND 19856 Vol/page
Gene mutation in Bacteria – Ames Test	3 Strains (TA 98, 100 and 1535), ± rat liver Aroclor induced S9 metabolic activation	Fenofibrate at 3.7 – 367 µg/plate	Negative	[redacted]	R&D/06/614	1.11/261
Gene mutation in Salmonella typh.	5 Strains (TA 98, 100, 1535, 1537 and 1538)	Fenofibrate and Fenofibric acid at 0.1 – 500 µg/plate	Negative	[redacted]	R&D/06/615	1.11/181
Saccharomyces cerev	D4 (± rat liver Aroclor induced S9 metabolic activation, human liver S9 mix)					
Mouse Lymphoma Forward Mutation Assay	4 h treatment of suspended cells (± rat liver S9 metabolic activation), followed by plating and culture for 2 days	Gemfibrozil 0.005 – 0.3 (-S9) 0.005 – 0.3 (+S9) Clofibric Acid 0.01 – 1.0 (-S9) 0.005 – 0.25 (+S9) Fenofibric Acid 0.05 – 0.4 (-S9) 0.05 – 0.4 (+S9)	Negative	[redacted]	R&D/06/618	NA
Sister Chromatid Exchange	2 h treatment and cultured for ~23 h	Gemfibrozil 2.02– 202 (-S9) 20.1 – 670 (+S9) Clofibric Acid 19.6 – 654 (-S9) 66.7 – 2000 (+S9) Fenofibric Acid 1.98 – 198 (-S9) 20.1 – 669 (+S9)	Negative	[redacted]	R&D/06/617	NA

NA = Not applicable

Table 12. Summary of Genetic Toxicology Studies on Fenofibrate and Fenofibric Acid (Cont.)

Type Study	Method	Dose Range (mg/mL, µg/mL, or mg/kg/day)	Findings	Laboratory	Report No.	IND 19856 Vol/page
Chromosomal Aberration (Human lymphocytes)	Cells treated for ~17 h (-S9) or ~8 h (+S9)	Gemfibrozil 103 – 574 (-S9) 100 – 501 (+S9) Clofibric Acid 507 – 2020 (-S9) 501 – 2000 (+S9) Fenofibric Acid 150 – 980 (-S9) 250 – 1000 (+S9)	Negative			
Unscheduled DNA Synthesis	Cells treated for ~18 h in the presence of ^{3}H-thymidine	Gemfibrozil 0.25 – 10.0 Clofibric Acid 1.01 – 50.5 Fenofibric Acid 1.01 – 50.7	Negative	[redacted]	R&D/06/620	NA
Rat Bone Marrow Chromosome damage	*In vivo* chromosome damage in rats Single dose with evaluations at 6, 24, or 48 h post-dose	Fenofibrate 0, 200, 1000, 5000	Negative	[redacted]	R&D/06/616	NA

NA = Not applicable

b(4)

b(4)

b(4)

Carcinogenicity (from the current NDA submission)

2.6.7.1 Toxicology–Overview (Cont.)

Test Article: Choline Fenofibra

Type of Study	Species and Strain	Method of Administration	Duration of Dosing	Doses (mg/kg)*	GLP Compliance	Testing Facility	Study Number	Location Vol.	Location Sect
Carcinogenicity	Mouse (CD1)	PO (diet)	80-weeks[a]	0, 10, 45, 200	No	[redacted]	R&D/06/626		
	Mouse (CD1)	PO (diet)	93-weeks[a]	0, 10, 60, 200	Yes	[redacted]	R&D/06/622		
	Rat (Wistar)	PO (diet)	104-weeks[a]	0, 10, 45, 200	No	[redacted]	R&D/06/623		
	Rat (Sprague-Dawley)	PO (diet)	117-weeks[a]	0, 10, 60	Yes	[redacted]	R&D/06/608		

b(4)

* Unless otherwise specified. For Repeat-Dose Toxicity, the highest No Observed Adverse Effect Level (NOAEL) is underlined.
a. Fenofibrate; b. Fenofibric acid (free acid)

2.6.6.6 Reproductive and developmental toxicology

Following repro-toxicity studies have been conducted with fenofibrate