2.4 NONCLINICAL OVERVIEW- ADDENDUM

CONCERNED CCDS SECTIONS: 4.6 – Fertility, Pregnancy and Lactation
5.3 – Preclinical Safety Data

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1 NONCLINICAL OVERVIEW –ADDENDUM

1.1 Introduction

This document supports the Company Core Data Sheet (CCDS) update of fenofibrate.

The current CCDS is based on preclinical data available at initial submission of the preclinical dossier in 2004. After this point, a few repeat-dose toxicity studies were conducted with fenofibrate and its active metabolite fenofibric acid in rats and dogs in order to support the clinical development of fenofibric acid choline salt.

The current update includes information obtained during these studies into the CCDS. In addition, the update ensures CCDS compliance with the recommendations of the current CPMP 'Guideline on the Summary of Product Characteristics' (September 2009) by including a section on fertility into 4.6

1.2 Pharmacology

Not applicable

1.3 Pharmacokinetics

Not applicable

1.4 Toxicology

CCDS section 4.6 - Fertility, pregnancy and lactation

Current text:

A subsection "Fertility" currently does not exist.

Proposed text:

Fertility

Reversible effects on fertility have been observed in animals (see section 5.3). There are no clinical data on fertility from the use of Trademark.

Justification for the change:

Please refer to justification for changes in section 5.3

CCDS section 5.3 - Preclinical Safety Data

Current text:

Chronic toxicity studies have yielded no relevant information about specific toxicity of fenofibrate.

Studies on mutagenicity of fenofibrate have been negative.

In rats and mice, liver tumours have been found at high dosages, which are attributable to peroxisome proliferation. These changes are specific to small rodents and have not been observed in other animal species. This is of no relevance to therapeutic use in man.

Studies in mice, rats and rabbits did not reveal any teratogenic effect. Embryotoxic effects were observed at doses in the range of maternal toxicity. Prolongation of the gestation period and difficulties during delivery were observed at high doses.

No sign of any effect has been detected.

Proposed text:

Acute toxicity studies have yielded no relevant information about specific toxicity of fenofibrate.

In a three-month oral nonclinical study in the rat species with fenofibric acid, the active metabolite of fenofibrate, toxicity for the skeletal muscles (particularly those rich in type I - slow oxidative - myofibres) and cardiac degeneration, anemia and decreased body weight were seen at exposure levels $\geq$ 50-fold the human exposure for the skeletal toxicity and > 15-fold for the cardiomyotoxicity. Reversible ulcers and erosions in the gastro-intestinal tract occurred in dogs treated during 3 months at exposures approximately 7-fold the clinical AUC.

Studies on mutagenicity of fenofibrate have been negative.

In rats and mice, liver tumours have been found at high dosages, which are attributable to peroxisome proliferation. These changes are specific to small rodents and have not been observed in other animal species. This is of no relevance to therapeutic use in man.

Studies in mice, rats and rabbits did not reveal any teratogenic effect. Embryotoxic effects were observed at doses in the range of maternal toxicity. Prolongation of the gestation period and difficulties during delivery were observed at high doses.

No effects on fertility were detected in non-clinical reproductive toxicity studies conducted with fenofibrate. However reversible hypospermia and testicular vacuolation and immaturity of the ovaries were observed in a repeat-dose toxicity study with fenofibric acid in young dogs.

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Rat data

In a three months oral toxicity study ([redacted]) fenofibric acid choline salt was administered as an oral dose (gavage) to male and female Sprague-Dawley rats at dosages of 0, 10, 30 and 100 mg/kg/day for 13 weeks (GLP-compliant study). There were two deaths prior to scheduled necropsy; one control was euthanized due to dosing trauma and one male administered 100 mg/kg/day was found dead on Study Day 83, due to unknown cause. Clinical signs observed during second half of the dosing period at 100 mg/kg/day were red-stained muzzle, dark-colored tails (males) and urine-stained abdomen. The group mean body weights were slightly decreased throughout the study without an effect on food consumption. A mild dose-dependent decrease in hematocrit, hemoglobin and red blood cell values was observed in both males and females at all dosages. Slightly increased liver enzyme activities consisted of ALT (all dosages: end of study (males)), AST (100 mg/kg/day: mid-study (males) and end-study), and alkaline phosphatase (all dosages males: mid-study (except low dose) and end-study). Absolute and relative livers weights were increased in all dose groups and were noted grossly as enlarged livers. Histologic changes in the liver included dose-dependent centrilobular hepatocellular hypertrophy and hepatic coagulative necrosis, with increased incidence in males compared to females. Microscopic findings in skeletal muscle (i.e., myofiber degeneration) occurred in the gastrocnemius and soleus muscles dosed at 100 mg/kg/day with a slightly increased severity in males compared to females. Lesions of the soleus muscle (rich in type I fibers) were of increased severity relative to those in the gastrocnemius muscle (predominantly type II fibers). Histologic lesions in the heart, characterized by focal loss and degeneration of myofibers and infiltration of mononuclear inflammatory cells, were found in males at 30 and 100 mg/kg/day and were associated with increased absolute and/or relative heart weights in rats in these groups. The No Observed Adverse Effect Level (NOAEL) for rodent-specific liver peroxisome proliferation was < 10 mg/kg/day corresponding to an AUC of about 530 µg•hr/mL. The NOAEL for heart changes was 10 mg/kg/day and the NOAEL for skeletal muscle changes was 30 mg/kg/day for both males and females with a corresponding plasma exposure (AUC) of 2600 to 3200 µg•hr/mL.

Dog data

In a three month oral toxicity study [redacted] choline fenofibrate was administered orally via capsules, daily to male and female Beagle dogs (seven to eight months old at the start of dosing) at dosages of 0, 25, 50 and 100 mg/kg/day for 89-92 consecutive days (GLP-compliant study). The reversibility of findings was evaluated following a six-week recovery period. Control animals received empty gelatin capsules.

One male dog in the 100 mg/kg/day dosage group was euthanized on Day 39 due to severe weight loss (~30%). Treatment-related clinical observations in this dog were limited to sporadic emesis, which was less severe than in other dogs in this dosage group. Treatment-related clinical pathology changes at the time of necropsy were consistent with those noted at Day 29, were generally mild and included: decreased hematocrit, hemoglobin and absolute reticulocytes;

increased activated thromboplastin time; decreased cholesterol, triglycerides, serum protein and albumin; and proteinuria (slight; trace amounts of blood present). There were no gross findings at necropsy and microscopic findings included lymphoid atrophy in the thymus (attributed to the severe weight loss) and minimal hypospermatogenesis in the testes, which were qualitatively similar to findings in males at the end of the three- month treatment period.

Treatment-related clinical findings during the study were limited to those associated with the gastrointestinal tract and included emesis and abnormal stools (loose and/or mucoid). These effects were generally mild and inconsistently observed in individual dogs. Mean body weights in dogs given 50 and 100 mg/kg/day were significantly decreased relative to control dogs on Day 88 (17 and 21% lower in males and 10 and 26% lower in females given 50 and 100 mg/kg/day, respectively). There was no consistent effect of choline fenofibrate on mean group food consumption; however, individual dogs experienced anorexia and required dietary supplementation. During the recovery period, there were no treatment-related clinical signs and dogs gained body weight in a dose dependent fashion. There were no choline fenofibrate effects noted on ophthalmoscopic or electrocardiographic evaluations.

In the 50 and 100 mg/kg/day dosage groups, choline fenofibrate produced generally mild changes in several clinical pathology parameters including: decreased erythrocytic mass (red blood cell count, hematocrit, and hemoglobin), transiently decreased reticulocyte counts (present on Day 29, but not on Day 84) and an increased activated partial thromboplastin time; increased ALT and AST levels (only present at the 100 mg/kg/day). Total cholesterol and triglyceride values were also decreased in the 100 mg/kg/day dogs, which was attributed to the pharmacological effects of fenofibric acid. None of the changes in clinical pathology parameters was evident at the end of the recovery period.

Treatment-related pathology findings included the following: moderately decreased mean ovary weights in all treated groups that correlated microscopically with immaturity; mildly decreased testis weights in all treated groups that correlated microscopically with hypospermatogenesis and was associated with vacuolation; gross stomach findings of depressed fundic surface and pinpoint discolorations of the pylorus in one male and female, respectively, from the 100 mg/kg/day group that correlated microscopically with ulcers or healed ulcers or erosions; and minimal single cell necrosis, accompanied by minimal to mild mixed inflammatory cell infiltrates in the liver of males and females in the 50 and 100 mg/kg/day dosage groups. No evidence of these changes was noted in dogs at the end of the recovery period.

The overall NOAEL in dogs following three-months administration of choline fenofibrate in this study was < 25 mg/kg/day due to test item-related findings in the testes and ovaries at all dosages. The NOAEL for stomach findings was 50 mg/kg with a corresponding plasma exposure (AUC) of 830 to 1100 µg•hr/mL.

Table 1. Plasma Exposure to Fenofibric Acid in Rat and Dog Repeat-Dose Toxicity Studies Conducted with Fenofibric Acid Choline Salt, and Comparison with Human Data

Species and Duration	Dosing with Fenofibric Acid		
	Dose for PK (mg/kg)	C_{max} (µg/mL)	AUC (µg.h/mL)
Rat ([redacted])	10	40.9 –45.9	527 – 530
(13-week; gavage)	30	183 – 188	2586 – 3209
	100	609 – 679	12021 - 12194
Dog ([redacted])	25	53.1 – 64.1	222 – 272
(13-week; capsules)	50	115 – 144	833 – 1098
	100	225 – 245	1887 – 2565
Human (repeat dose)	(135 mg/70 kg ≈1.9)	12.1	183

1.5 Benefit and risk conclusion

The modification of the current labeled text is proposed to provide more clarity and give more relevant non-clinical information. It does not alter the benefit/ risk balance of fenofibrate.