2.5 Clinical Overview

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This section is not applicable to this submission.

2.5.2 Overview of Biopharmaceutics

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This section is not applicable to this submission.

2.5.4 Overview of Efficacy

This section is not applicable to this submission.

2.5.5 Overview of Safety

2.5.5.1 Contraindications

2.5.5.1.1 Hepatic Insufficiency

On the basis of data presented in PSUR FENO 13 - May 2006 - Nov 2007 and in order to be consistent with the contraindication section worldwide (TriCor® United States Prescribing Information), it was recommended to replace "severe liver dysfunction" with "hepatic insufficiency" in the following statement in the company core safety information (CCSI)/Summary of Product Characteristics (SmPC):

> *Hepatic insufficiency (including biliary cirrhosis and unexplained persistent liver function abnormality e.g. persistent elevations in serum transaminases).*

Biliary cirrhosis, which is already mentioned in the contraindications, is proposed to be regrouped under the more global term, hepatic insufficiency.

2.5.5.1.2 Pregnancy and Lactation

To comply with the Guideline on Summary of Product Characteristics – Revision 2, September 2009, we propose to delete the reference to Section 4.6, *Pregnancy and lactation,* from Section 4.3 *Contraindications*.

As of 31 July 2010, 24 pregnancy cases were captured in the Abbott product safety database (see PSUR FENO 16 - 01 Aug 2009 - 31 Jul 2011). Analysis of these cases did not identify a signal. Therefore, it is not known whether fenofibrate may have harmful effects if taken during pregnancy.

The Guideline on Summary of Product Characteristics – Revision 2, September 2009 clearly states that patient populations not studied should not be mentioned in the contraindication section unless patients have been excluded due to a contraindication on grounds of safety. If pregnancy is contraindicated, more information should be provided in the pregnancy section.

The pregnancy section of the fenofibrate label currently states:

> Pregnancy: There are no adequate data from the use of fenofibrate in pregnant women. Animal studies have not demonstrated any teratogenic effects. Embryotoxic effects have been shown at doses in the range of maternal toxicity (see section Preclinical safety data of SmPC). The potential risk for humans is unknown. Therefore, fenofibrate should only be used during pregnancy after a careful benefit/risk assessment.

Therefore, it is proposed to remove pregnancy as contraindication in order to be consistent within the label.

2.5.5.2 Special Warnings and Precautions for Use (Section 4.4)

To be in line with the most recent text approved during the fenofibrate MRP (Supralip® 160 mg), we have updated the liver function warning accordingly. The new wording does not modify the general warning, but provides additional details.

In this section, we recommend monitoring of transaminases every 3 months during the first 12 months of treatment. As already previously reported, but also confirmed in the 2 recent and large clinical studies FIELD[1] and ACCORD,[2] the increases in transaminases were observed throughout the studies but predominantly at the beginning of treatment. This supports our proposal to monitor transaminases during the entire treatment duration. The periodicity should then be less strict than during the first year of treatment. "Periodically," as proposed to be added in the SmPC, has to be determined at the physician's discretion, but we could recommend monitoring transaminases once a year after the first year of treatment.

To be in agreement with the Guideline on Summary of Product Characteristics – Revision 2, September 2009, the statement "When symptoms (e.g. jaundice, pruritus) indicative of hepatitis occur, laboratory tests are to be conducted for verification and fenofibrate discontinued, if applicable" initially mentioned in Section 4.8 *Liver* has been moved to the warnings section. In addition, this wording was modified slightly to give clearer recommendation to the prescriber.

The new section should read as follows:

> *As with other lipid lowering agents, increases have been reported in transaminase levels in some patients. In the majority of cases these elevations were transient, minor and asypmtomatic.* It is recommended that transaminase *levels are* monitored every 3 months during the first 12 months of treatment *and thereafter periodically. Attention should be paid to patients who develop increase in transaminase levels and therapy should be discontinued if AST (SGOT) and ALT (SGPT) levels increase to more than 3 times the upper limit of the normal range. When symptoms indicative of hepatitis occur (e.g. jaundice, pruritus), and diagnosis is confirmed by laboratory testing, fenofibrate therapy should be discontinued.*

2.5.5.3 Interactions

2.5.5.3.1 Interactions with Glitazones

In PSUR FENO 15 - Nov 2008 - July 2009, a signal evaluation reported a paradoxical decrease of high-density lipoprotein cholesterol (HDL-C) could occur due to an interaction between fenofibrate and glitazones (Report Number S11_FENO_ HDLdecrease _11Nov2008).

In July 2009, an update of the signal evaluation on decreased HDL-C (S11_FENO_HDLDECREASE_14JUL2009) confirmed this signal and it was recommended that this possible interaction should be added to the CCSI with the following wording:

> *Glitazones*
>
> *Some cases of reversible paradoxical reduction of HDL-cholesterol have been reported during concomitant administration of fenofibrate and glitazones. Therefore it is recommended to monitor HDL-cholesterol if one of these components is added to the other and stopping of either therapy if HDL-cholesterol is too low.*

2.5.5.3.2 Cytochrome P450 Enzymes

The involvement of cytochrome P450 (CYP) during the metabolism of fenofibrate is very unlikely. It is however, possible that a drug, even not metabolized by CYP, may nevertheless inhibit or induce the activity of some of these enzymes.

The effects of fenofibrate and fenofibric acid on selected CYP-dependent enzyme activities were evaluated using human liver microsomes.[3,4] At concentrations of 20 µM and 200 µM, neither fenofibrate nor fenofibric acid demonstrated significant (> 10%) inhibition of the CYP3A-dependent oxidation of terfenadine, the CYP2D6-dependent *O*-demethylation of dextromethorphan, the CYP1A2-dependent *O*-deethylation of phenacetin, or the CYP2E1-dependent 6-hydroxylation of chlorzoxazone. A small degree

of inhibition was demonstrated by fenofibrate (4.1% at 20µM and 20.4% at 200 µM) and fenofibric acid (12% and 25.5%) toward the CYP2C19-dependent 4-hydroxylation of *S*-mephenytoin. Both fenofibrate and fenofibric acid demonstrated concentration-dependent inhibition of the CYP2C9-dependent methylhydroxylation of tolbutamide. The concentrations at which fenofibrate and fenofibric acid inhibited 50% of the CYP2C9-dependent enzyme activity (IC_{50}) were 127µM and 139 µM, respectively. The IC_{50} values were between 4 and 6-times higher than the average circulating plasma concentrations of fenofibric acid in humans (20 to 30 µM). Overall, these results indicate that fenofibrate and fenofibric acid are unlikely to inhibit CYP3A-, CYP2D6-, CYP1A2-, CYP2E1-, CYP2C9- or CYP2C19-dependent metabolism at clinically relevant plasma concentrations (Table 1).

The effect of fenofibric acid on human hepatic microsomal paclitaxel 6α-hyrodroxylase activity, as a selective marker for CYP2C8, was investigated.[4] The calculated IC_{50} values for fenofibric acid were 293.1 µM and 153.3 µM, when the assay was performed in competitive and preincubation (10 min) modes, respectively. On the basis of these results, fenofibric acid is unlikely to inhibit CYP2C8-dependent metabolism at clinically relevant plasma concentrations (2 to 30 µM).

Table 1. Summary of Fenofibrate and Fenofibric Acid Effects on Selected CYP Activators in Human Liver Microsomes

CYP Isoform	Assay	% Control Activity[a]			
		[Fenofibrate]		Fenofibric Acid	
		20 µM	200 µM	20 µM	200 µM
1A2	Phenacetin *O*-deethylation	99.9 ± 1	115 ± 18	102 ± 2	110 ± 23
2A6	Coumarin 7-hydroxylation	92.8 ± 3	87.5 ± 2	90.1 ± 3	85.5 ± 1
2C9	Tolbutamide hydroxylation	81.7 ± 1	42.0 ± 1	78.8 ± 10	32.6 ± 6
2C19	S-Mephenytoin 4'-hydroxylation	95.9 ± 6	79.6 ± 6	88.0 ± 2	74.5 ± 7
2D6	Dextromethorphan *O*-demethylation	101 ± 1	101 ± 3	103 ± 3	101 ± 3
2E1	Chlorzoxazone 6-hydroxylation	95.7 ± 6	92.6 ± 3	98.5 ± 1	98.3 ± 10
3A	Terfenadine hydroxylation/	97.3 ± 1	102 ± 2	96.0 ± 5	103 ± 3

a. Data presented as Mean ± SD.

On the basis of the above data, the probability that fenofibrate leads to a clinical drug-drug interaction at the CYP450 level is very unlikely. This information is important for the prescriber and we recommend to add the following paragraph in Section 4.5.

> *Cytochrome P450 enzymes: In vitro studies using human liver microsomes indicate that fenofibrate and fenofibric acid are not inhibitors of cytochrome (CYP) P450 isoforms CYP3A4, CYP2D6, CYP2E1, or CYP1A2. They are weak inhibitors of CYP2C19 and CYP2A6, and mild-to-moderate inhibitors of CYP2C9 at therapeutic concentrations.*
>
> *Patients co-administered fenofibrate and CYP2C19 and CYP2A6, and especially CYP2C9 metabolised drugs with a narrow therapeutic index should be carefully monitored and, if necessary, dose adjustment of these drugs is recommended.*

2.5.5.4 Undesirable Effects

Section 4.8, *Undesirable effects*, is modified according to the Guideline on Summary of Product Characteristics – Revision 2, September 2009. Adverse reactions with specific wording including Medical Dictionary for Regulatory Activities (MedDRA) coding as well as their respective frequencies are presented as a single table.

The frequency categories were derived from the internal integrated safety database with 3,273 patients participating in placebo-controlled studies overall (fenofibrate n = 2,344; placebo n = 929). Data from the FIELD study, a randomized placebo-controlled trial performed in 9,795 patients with type 2 diabetes mellitus were considered for thromboembolic complications and pancreatitis (PSUR FENO 14 - November 2007 - November 2008).

This table is in line with the CCSI as provided in the latest version of the PSUR FENO 16 - August 2009 - July 2010).

Globally, all events previously described in the undesirable effects sections have been reported in the tabulated data. The proposed table is provided below.

Additional amendment concerns the conclusion drawn from the signal evaluation described in the previous PSUR.

2.5.5.4.1 Hypersensitivity

Further to the identification of a number of effects reported as a variety of terms associated with hypersensitivity (S01_FENO_Hypersensitivity_14JAN2008 - PSUR FENO 14), the CCSI Section 4.8, *Undesirable effects*, was amended as follows:

> *Skin and subcutaneous tissue disorders: Cutaneous hypersensitivity (e.g. rashes, pruritus, and urticaria).*
>
> *Immune system disorders: hypersensitivity.*

To follow this recommendation, we propose to modify the SmPC in Section 4.8, *Undesirable effects* accordingly.

2.5.5.4.2 Other Changes

The *Undesirable effects* section was checked for concise and specific wording including MedDRA coding. The frequency categories were derived from the integrated safety database, with 3,273 patients participating in placebo-controlled studies overall (fenofibrate n = 2,344; placebo n = 929). Data from the FIELD study, a randomized placebo-controlled trial performed in 9,795 patients with type 2 diabetes mellitus were considered for thromboembolic complications and pancreatitis (PSUR 14 - Nov 2007 to Nov 2008).

System Organ Class of Skin and Subcutaneous Tissue Disorders

In this section, the event "photosensitivity" has changed frequency from "uncommon" (current SmPC) to "rare" (proposed SmPC). The CCSI version of the section, *Undesirable effects*, was changed in January 2008. It was checked for concise and specific wording including MedDRA coding. The frequency categories were derived from the integrated

safety database with 3,273 patients participating in placebo-controlled studies overall (fenofibrate n = 2,344; placebo n = 929). In this database, photosensitivity was "rare."

System Organ Class of Investigations

In this section, the event "increased in serum creatinine and urea" has been changed to "blood creatinine increased." Moreover, "blood urea increased" has changed frequency from "uncommon" (current SmPC) to "rare" (proposed SmPC). The CCSI version of the section, *Undesirable effects,* was changed in January 2008. It was checked for concise and specific wording including MedDRA coding. The frequency categories were derived from the integrated safety database with 3,273 patients participating in placebo-controlled studies overall (fenofibrate n = 2,344; placebo n = 929). In this database, increase in blood urea was rare.

System Organ Class of Hepatobiliary Disorders

In this section, the term "development of gallstones" has been replaced by "cholelithiasis."

> *The most commonly reported ADRs during fenofibrate therapy are digestive, gastric, or intestinal disorders.*
>
> *The following undesirable effects have been observed during placebo-controlled clinical trials (n = 2344) with the frequencies indicated in the table below:*

MedDRA SOC	Common > 1/100, < 1/10	Uncommon > 1/1000, < 1/100	Rare > 1/10,000, < 1/1000	Very Rare < 1/10,000, incl isolated reports	Not known[a]
Blood and lymphatic system disorders			Haemoglobin decreased White blood cell count decreased		
Immune system disorders			Hypersensitivity		
Nervous system disorders		Headache			
Vascular disorders		Thromboembolism (pulmonary embolism, deep vein thrombosis)*			
Respiratory, thoracic, and mediastinal disorders					Interstitial pneumopathies[a]
Gastrointestinal disorders	Gastrointestinal signs and symptoms (abdominal pain, nausea, vomiting, diarrhoea, flatulence) Moderate in severity	Pancreatitis*			
Hepatobiliary disorders	Transaminases increased (see Section 4.4)	Choletlihiasis	Hepatitis, jaundice, complications of cholelithiasis (e.g., cholecystitis, cholangitis, biliary colic)		

Table continues on next page.

MedDRA SOC	Common > 1/100, < 1/10	Uncommon > 1/1000, < 1/100	Rare > 1/10,000, < 1/1000	Very Rare < 1/10,000, incl isolated reports	Not known[a]
Skin and subcutaneous disorders		Cutaneous hypersensitivity (e.g., rashes, pruritus, urticaria)	Alopecia Photosensitivity		
Musculoskeletal, connective tissue and bone disorders		Muscle disorder (e.g, myalgia, myositis, muscular spasms, and weakness)			Rhabdomyolysis[a]
Reproductive system and breast disorders		Sexual dysfunction			
Investigations		Blood creatinine increased	Blood urea increased		

* *In the FIELD study, a randomized placebo-controlled trial performed in 9,795 patients with type 2 diabetes mellitus, a statistically significant increase in pancreatitis cases was observed in patients receiving fenofibrate versus patients receiving placebo (0.8% versus 0.5%; P = 0.031). In the same study, a statistically significant increase was reported in the incidence of pulmonary embolism (0.7% in the placebo group versus 1.1% in the fenofibrate group; P = 0.022) and a statistically nonsignificant increase in deep vein thromboses (placebo: 1.0% [48/4,900 patients] versus fenofibrate 1.4% [67/4,895 patients]; P = 0.074).*

a. *In addition to those events reported during clinical trials, the following side effects have been reported spontaneously during postmarketing use of fenofibrate. A precise frequency cannot be estimated from the available data and, therefore, is classified as "not known."*
- Respiratory, thoracic and mediastinal disorders: Interstitial lung disease.
- Musculoskeletal, connective tissue and bone disorders: Rhabdomyolysis.

2.5.5.4.3 Hepatobiliary Disorders

In July 2009, a signal evaluation of complications of gallbladder disease resulting from mid-term and long-term use of fenofibrate (S13_FENO_Gallbladder Disease 07JUL2009 – see PSUR 16) resulted in the recommendation to add the following data to the CCSI under the postmarketing section (unknown frequency):

> *Hepatobiliary Disorders: jaundice, complications of cholelithiasis (e.g., cholecystitis, cholangitis, biliary colic, etc.)*

2.5.5.5 Overdose

We propose to rephrase the overdose section as follow after reevaluation of data:

> ~~No case of overdosage has been reported.~~ *Only anecdotal cases of fenofibrate overdosage have been received. In the majority of cases no overdose symptoms were reported.*
>
> No specific antidote is known. If an overdose is suspected, treat symptomatically and institute appropriate supportive measures as required. Fenofibrate can not be eliminated by haemodialysis.

This is based on the following analysis:

Fifty-nine unique reports describing the adverse event of overdose were completed in the Adverse Event Global Information System (AEGIS) during the review period of this report (from 04 November 1974 to 19 August 2011). The gender distribution was 22 females, 29 males, and 8 unknown or not reported. The median age was 59 years, with an age range of 16 to 86 years (n = 36).

Of the 59 reports, 2 described fatal events/outcomes. Report [redacted] described the death due to heroin overdose of a [redacted] who received fenofibrate therapy for 116 days for extensive and severe coronary artery disease with multiple attempts at revascularization. Two weeks after stopping fenofibrate therapy, the patient was found dead in his sleep. An autopsy linked the principal cause of death to a heroin overdose.

Report [redacted] described a [redacted] who died of an overdose of unspecified drug(s) with a history of drug abuse, back pain, hypertension, and diabetes who was treated with fenofibrate for 5 years for dyslipidemia. Concomitant medications included diazepam, oxycodone HCl, metformin HCl, insulin, panadeine, irbesartan, and simvastatin. The investigator felt drugs other than fenofibrate were involved in the patient's death. It was unknown whether an autopsy was performed.

Of the reports of fenofibrate overdose, majority of the cases did not report symptoms or adverse events relating to the overdose. A number of reports were for overdose from other drugs during therapy with fenofibrate.

On the basis of this review, no trends or new safety signals were identified. The CCSI already states the following:

> Only anecdotal cases of fenofibrate overdosage have been received. In the majority of cases no overdose symptoms were reported.
>
> No specific antidote is known. If an overdose is suspected, treat symptomatically and institute appropriate supportive measures as required. Fenofibrate can not be eliminated by haemodialysis.

It is recommended that the above replace the current wording in the SmPC.

2.5.6 Benefits and Risk Conclusions

The profile of fenofibrate is not modified and, therefore, its benefit/risk ratio remains positive.

2.5.7 References

1. Keech A, Simes RJ, Barter P, Best J, Scott, Taskinen, et al; The FIELD study investigators. Effects of long-term fenofibrate therapy on cardiovascular events in 9795 people with type 2 diabetes mellitus (the FIELD study): randomised controlled trial. Lancet. 2005;366(9500):1849-61.

2. ACCORD Study Group; Ginsberg HN, Elam MB, Lovato LC, Crouse JR 3rd, Leiter LA, et al. Effects of combination lipid therapy in type 2 diabetes mellitus. N Engl J Med. 2010;362(17):1563-74.

3. Abbott. [redacted] Effect of Abbott-52799 (fenofibrate) and fenofibric acid on cytochrome-P-450-selective enzyme activities in human liver microsomes. January 1999.

4. Abbott. [redacted] Effects of fenofibrate and fenofibric acid upon human hepatic microsomal paclitaxel 6α-hydroxylase activity (a selective marker for CYP2C8). February 2004.