2.5 CLINICAL OVERVIEW- ADDENDUM

CCDS UPDATE 2016

Redacted under Section 40 of the Freedom of Information Act.

AUTHOR: [redacted]

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

SmPC	Summary of Product characteristics
CCDS	Company Core Data Sheet
COA	Clinical Overview Addendum

2.5 CLINICAL OVERVIEW – ADDENDUM

This addendum to the fenofibrate clinical overview is supportive of various changes to the current Summary of Product Characteristics (SmPC), submitted as a type II variation, to harmonize the various SmPCs of fenofibrate (different strengths and formulations) in line with the most recent version of the Company Core Data Sheet (CCDS).

2.5.1 Product Development Rationale

Not applicable.

2.5.2 Overview of Biopharmaceutics

Not applicable.

2.5.3 Overview of Clinical Pharmacology

2.5.3.1 Proposed update to Section Posology and Method of Administration

2.5.3.1.1 Patients with Renal Impairment

Current wording:

Dosage reduction is required in patients with renal impairment.

In mild to moderate chronic kidney disease start with one capsule of 100 mg standard or 67 mg micronized once daily.

In patients with severe chronic kidney disease, fenofibrate is not recommended.

Proposed wording:

Dosage reduction is required in patients with renal impairment.

In ~~mild to~~ moderate chronic kidney disease ***(creatinine clearance 30 to 60 mL/min) and if a low dose is available***, start with one capsule of 100 mg standard or 67 mg micronized once daily.

If no low dose is available, then fenofibrate is not recommended. In patients with severe chronic kidney disease ***(creatinine clearance < 30ml/min)***, fenofibrate is ***contraindicated*** ~~not recommended~~.

Justification for the change:

See specific Clinical Overview Addendum provided with this submission.

2.5.4 Overview of Efficacy

Not applicable.

2.5.5 Overview of Safety

2.5.5.1 Nonclinical Information Related to Safety

Not applicable.

2.5.5.2 Clinical Information Related to Safety

Not applicable.

2.5.5.3 Post Marketing Experience

Proposed update to Section Fertility, Pregnancy and Lactation

Proposed wording:

Pregnancy

[…]

Lactation

[…]

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:

This section was modified to introduce information relative to fertility as recommended in the SmPC guidance. See specific Nonclinical Overview Addendum submitted with this application, also supporting related update in section 5.3.

Proposed update to Section Undesirable Effects

Nervous System Disorders

Current wording

In the fenofibrate CCDS, the two adverse events: Fatigue and Vertigo are listed with a rare frequency.

Proposed wording:

Nervous system disorders: Fatigue

Justification for the change:

A signal evaluation of "fatigue" event resulted in the recommendation to add fatigue under the postmarketing section (unknown frequency). See specific COA submitted with this application.

It is proposed to list the adverse event "Fatigue" with side effects reported spontaneously during postmarketing use and for which a precise frequency cannot be estimated from the available data and therefore classified as "not known".

Further to an in depth evaluation of the event Vertigo, it is concluded that, that there is no justification to list vertigo as side effect for fenofibrate.

As a consequence this event will be either removed or not added in the corresponding SmPCs.

Investigations

Proposed wording:

Investigation: Blood homocysteine level increased (common frequency)***

****** In the FIELD study the average increase in blood homocysteine level in patients treated with fenofibrate was 6.5 µmol/L, and was reversible on discontinuation of fenofibrate treatment. The increased risk of venous thrombotic events may be related to the increased homocysteine level. The clinical significance of this is not clear.***

Justification for the change:

Increase in homocysteine blood levels is as a potential risk in the fenofibrate Risk Management Plan (Edition 3 - July 2015).

Table 39. Potential Risk: Increased Risk of Increased Homocysteine Blood Levels

Identified risk	Homocysteine levels increase by an average of 6.5 µmol/L in patients treated with fenofibrate from a baseline mean value of 9.5 µmol/L. Baseline increases of homocysteine levels have been associated with increased risk of venous thromboembolic events (Hermann et al, 2012 [1]), and to a lesser degree with cardiovascular risk. The homocysteine blood level increase observed with fenofibrate therapy contributes less to the risk of venous thromboembolism than does an increased baseline homocysteine level.
Seriousness/outcomes	Abnormal laboratory finding.
Severity and nature of risk	Abnormal laboratory finding.
Frequency	Almost all patients tested.
Background incidence/prevalence	Slightly or modestly increased baseline homocysteine blood levels most likely are more important determinants of risk than the change induced by fenofibrate. How frequently slight to moderate increases of baseline levels occur in the target population is unknown.

Table 39. Potential Risk: Increased Risk of Increased Homocysteine Blood Levels

Risk groups or risk factors	With the inborn error of metabolism homocysteine levels increase approximately 10-fold and this inborn error of metabolism is known to be associated with venous thrombosis. Much more limited increase by up to 1.5-fold are seen due to many different causes, including renal failure, use of various medications including estrogen containing oral anticonceptives, fenofibrate, methotrexate. Such modest rises have been associated in some studies and meta-analyses with some level of increased risk of dementia, Alzheimer's disease, hypertension, atherosclerosis, myocardial infarction and stroke and neurodegenerative disorders in retrospective studies and various meta-analyses. Other studies have not always confirmed such risks.
Potential mechanisms	Unknown.
Preventability	Unknown.
Potential public health impact of safety concern	The treatment with statins and fenofibrate is considered to be beneficial in respect to reducing the increased risk of cardiovascular complications. The abnormal laboratory value could result in unnecessary investigations if physicians are insufficiently aware of this effect. For this reason mention of blood homocysteine increased is mentioned as abnormal investigation result in the RSI.
Evidence source	Literature, including Herrmann et al 2012 [1].
Regulatory action taken	Labeled undesirable effect

As a planned regulatory action, it is recommended to include "Increased blood homocysteine level" under Investigations in section 4.8 in the fenofibrate SmPC with a footnote adding information reported in the FIELD study.

2.5.6 Benefits and Risks Conclusion

The benefits and risks conclusion is not altered and remains favorable.

2.5.7 Literature References

1. Herrmann M, Whiting MJ, Veillard AS, Ehnholm C, Sullivan DR, Keech AC, for the FIELD study investigators. Plasma homocysteine and the risk of venous thromboembolism: insights from the FIELD study. Clin Chem Lab Med 2012;50:2213-2219.