2.5 CLINICAL OVERVIEW – ADDENDUM

SMPC UPDATE FOR FENOFIBRATE

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

ADR	Adverse drug reaction
MedDRA	Medical Dictionary for Regulatory Activities
PT	MedDRA 'Preferred Term'
SmPC	Summary of Product Characteristics

2.5 CLINICAL OVERVIEW – ADDENDUM

This clinical overview addendum is intended to support an update in section 4.8 Undesirable effects of the Summary of Product Characteristics (SmPC) for fenofibrate. It concerns the adverse drug reaction (ADR) of fatigue. Fatigue is defined as the subjective sensation of having reduced energy, loss of strength or becoming easily tired. This analysis presents a best-evidence assessment of all data and facts available on the fenofibrate ADR fatigue. Based on the current state of scientific knowledge it is justified to place the MedDRA preferred term (PT) fatigue into the subsection of ADRs reported spontaneously during postmarketing use of fenofibrate.

2.5.1 Product Development Rationale

Not in the scope of this submission.

2.5.2 Overview of Biopharmaceutics

Not in the scope of this submission.

2.5.3 Overview of Clinical Pharmacology

Not in the scope of this submission.

2.5.4 Overview of Efficacy

Not in the scope of this submission.

2.5.5 Overview of Safety

2.5.5.1 Nonclinical Information Related to Safety

Not in the scope of this submission.

2.5.5.2 Clinical Information Related to Safety

In placebo-controlled clinical trials, fatigue was reported with fenofibrate at the same frequency rate as with placebo. The FIELD study was a large randomized placebo-controlled trial performed in 9,795 patients with type 2 diabetes mellitus. Table 1 presents the incidence rates of PTs linked to fatigue in the five-year treatment phase of FIELD:

Table 1. Incidence Rates in the FIELD Trial

	Adverse Event (MedDRA PT) n (%) E	
	Fenofibrate (N = 4,895)	**Placebo (N = 4,900)**
Fatigue	65 (1.3%) 70	95 (1.9%) 98
Chronic fatigue syndrome	1 (<0.1%) 1	1 (<0.1%) 1

n = Number of subjects. E = Number of events

In conclusion, the large placebo-controlled clinical trial FIELD demonstrates that fatigue with fenofibrate was not more frequently reported than with placebo.

2.5.5.3 Post Marketing Experience

4.8 Undesirable effects

In placebo-controlled clinical trials the incidence rate of fatigue was not higher with fenofibrate versus placebo. Therefore, fatigue is not an ADR solely based on placebo-controlled clinical trials. The clinical trial data reflect the high background incidence of fatigue. The categorization of fatigue as adverse fenofibrate drug reaction is based on postmarketing experience over decades. According to the most recent Fenofibrate PSUR (Fenofibrate PSUR 21, 2015) [1], fatigue was one of the most frequently reported spontaneous ADRs with 362 ADRs cumulatively. The vast majority of 318 ADRs (88%) were non-serious. In more than hundred cases of fatigue, there were no confounding factors identified documenting the causal relationship of fatigue with fenofibrate.

In conclusion, fatigue can be placed as ADR into the postmarketing section of SmPC Section 4.8 Undesirable Effects (additions marked in ***italic bold*** text):

"…In addition to those events reported during clinical trials, the following side effects have been reported spontaneously during postmarketing use of <Tradename>. A precise frequency cannot be estimated from the available data and is therefore classified as "not known";

- …

- ***Nervous system disorders: Fatigue***"

2.5.6 Benefits and Risks Conclusion

The proposed update of the SmPC reflects the most current state of knowledge on fenofibrate adverse drug reactions. It does not alter the benefit risk profile of fenofibrate.

2.5.7 References

1. Fenofibrate Periodic Safety Update Report 21; 01 August 2014 – 31 July 2015 ([redacted]).