Redacted under Section 40, Section 41 and Secrtion 43 of the Freedom of Information Act.

2.5 CLINICAL OVERVIEW – ADDENDUM

FENOFIBRATE AND VERTIGO

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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

During the label alignment project it was identified, that the common SmPCs for Fenofibrate 145 and 160 mg (MRP with Germany as Reference Member State) do not contain the term vertigo as side effect. In contrast, in the common SmPC for fenofibrate 67, 200, 267 and 215 mg (MRP with Ireland as Reference Member State) vertigo is listed. However, although listed in the CCDS under 4.8 Undesirable effects, no supportive data was identified that would justify labeling of vertigo as side effect. A signal validation has investigated, whether there is reasonable evidence for a causal relationship between fenofibrate and vertigo.

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. Vertigo is a symptom characterized by a sensation of motion. It is defined as the illusory sense or hallucination of movement, either of oneself or the environment. This analysis presents a best-evidence assessment of all fenofibrate data and facts available on vertigo. Based on the current state of scientific knowledge it is not justified to list vertigo as an ADR.

Fenofibrate is a lipid regulating drug. Its effects are mediated via activation of Peroxisome Proliferator Activated Receptor type alpha (PPARα). PPARα controls the transcription of genes involved in the regulation of lipid metabolism. Fenofibric acid is the active metabolite of fenofibrate. Indications focus on treatment of lipid disorders.

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

The safety profiles of both fenofibrate and its metabolite fenofibric acid were evaluated in rats, dogs, and monkeys. No relevant neurological changes were noted.

2.5.5.2 Clinical Information Related to Safety

Table 1 presents reported incidence rates of adverse events as preferred terms (PTs) linked to vertigo in placebo-controlled clinical studies. In addition, the FIELD trial was a large randomized placebo-controlled trial performed in 9,795 patients with type 2 diabetes mellitus . The incidence rate of adverse events is reported in Table 2.

Table 1. Adverse events in placebo-controlled studies (FIELD trial not included).

	Adverse Event (MedDRA PT) n (%)	
	Fenofibrate (N=2,344)	**Placebo (N=929)**
Vertigo	16 (0.68 %)	17 (1.83%)
Vertigo positional	3 (0.13%)	3 (0.32%)

n = Number of subjects

Table 2 presents the incidence rates of PTs linked to vertigo in the five-year treatment phase of FIELD:

Table 2. Incidence rates of adverse events in the FIELD Trial

	Adverse Event (MedDRA PT) n (%) E	
	Fenofibrate (N=4,895)	**Placebo (N=4,900)**
Vertigo CNS origin	0 (0%) 0	1 (<0.1%) 1
Vertigo positional	7 (0.14%) 7	10 (0.20%) 10

n = Number of subjects
E = Number of events

In conclusion, placebo-controlled clinical studies including the large FIELD trial demonstrate that vertigo with fenofibrate was not more frequently reported than with placebo.

2.5.5.3 Post Marketing Experience

The Abbott global post-marketing safety database was searched for all fenofibrate or fenofibric acid ICSRs that were received from 01 January 1900 (per default) through 15 November 2015. The MedDRA (v. 18.1) search term used in selecting the reports was the preferred term Vertigo. A total of 77 spontaneous ICSRs were retrieved, of which one (case [redacted] was out of scope: The patient suffered from brain neoplasm with secondary epilepsy and in this case vertigo occurred more frequently after fenofibrate was discontinued.

Of the 76 ICSRs in scope, age was reported in 54 cases of which 30 were older than 60 years. Sixteen of the 76 ICSRs were not medically confirmed from consumers (none with fenofibric acid). Some consumer cases had confounding factors including concurrent hypertension/ vomiting (case [redacted] , concurrent visual impairment (case [redacted] , alcohol abuse (case [redacted]), maprotiline, zolpidem, and atenolol as concomitant drugs known to cause vertigo (case [redacted]). All remaining consumer reports had too limited information.

There were 60 medically confirmed ICSRs (seven with fenofibric acid). Of the 60 medically confirmed ICSRs 20 had too limited information for an assessment; these were mostly old cases dating back to the 1980s and 1990s. In 38 of the 40 remaining ICSRs (16 serious) the following confounding factors were identified during medical review. Many reports had more than one confounder and therefore appear in more than one category (case numbers in brackets):

18 ICSRs confounded by <u>medical history</u>:

- 14 with hypertension ([redacted])
- 3 with vertigo in the past ([redacted])
- 1 with past transitory ischemic attack/stroke ([redacted])

29 ICSRs with <u>co-suspect/concomitant drugs known to cause vertigo:</u>

- 8 with neuropsychotropic drugs: Benzodiazepines/central muscle relaxants ([redacted] , opioids ([redacted]), amitryptilin ([redacted] flupirtin ([redacted]), gabapentin ([redacted]), lamotrigin [redacted] , olanzapine ([redacted] venlafaxine [redacted] , zolpidem [redacted])
- 8 with antihypertensive calcium channel blockers: Amlodipine [redacted], [redacted]), diltiazem ([redacted]), 1 with nicardipine ([redacted] , 1 with efonidipine ([redacted] , 1 with nifedipine ([redacted]
- 7 with antihypertensive beta-blockers ([redacted], [redacted])
- 3 with antihypertensive ACE inhibitors/sartans [redacted])
- 2 with antihypertensive prazosin ([redacted])
- 1 each with urapidil [redacted]), dipyridamole [redacted])

27 ICSRs with concurrent diseases/conditions causing vertigo

- 4 alcohol use [redacted])
- 3 with hypoglycemia [redacted]
- 3 with migraine/headache [redacted])
- 2 with presyncope/syncope ([redacted]
- 2 with concurrent hypertension [redacted] not related as per reporter)
- 2 with primary nausea/vomiting ([redacted])
- 1 each with stroke [redacted] seizure [redacted] abasia [redacted]
- 1 each with tinnitus [redacted], unilateral hypacusis [redacted]
- 1 each with left bundle branch block [redacted]), tachycardia [redacted]
- 1 with attack of acute hypertension and nausea [redacted]
- 1 with extreme weakness [redacted]
- 1 with cardiomyopathy [redacted])
- 1 with duodenal ulcer hemorrhage ([redacted]

In many cases multiple confounding factors were present at the same time. Only one ICSR had no obvious confounders: In this report [redacted] a [redacted] with hypertriglyceridemia, obesity, and type 1 diabetes mellitus treated with fenofibrate experienced non-serious speech disorder and vertigo. The patient didn't want to stop fenofibrate because of [redacted] high triglycerides levels (no further information available). Speech disorder could have occurred due to several reasons (e.g. a transitory ischemic attack, not reported though) in light of the high cardiovascular risk in this patient.

2.5.5.4 Assessment of Other Relevant Information

2.5.5.4.1 Literature

A thorough literature search was performed. Neither fenofibrate nor any other fibrate has been causally linked with vertigo.

2.5.5.4.2 Review of competitor labels and information on drugs of the same, or related, classes

Two fenofibrate competitor labels (Actavis, Zentiva) list vertigo as side effect. However, vertigo is not labeled for fenofibrate by Genus Pharmaceuticals. Competitor labels of other fibrates (such as ciprofibrate, gemfibrozil, bezafibrate) were evaluated as well. Vertigo is labeled for ciprofibrate and gemfibrozil but not for bezafibrate (SmPCs accessed through eMC website http; // www . medicines . org . uk / emc / on 02 December 2015). Although some generic labels list vertigo as side effect, no supportive data are available.

2.5.5.4.3 Epidemiology

Per the overview by Neuhauser, 2007 [1] one-year prevalence estimates were 4.9% for vertigo and 1.6% for benign paroxysmal positional vertigo (BPPV). The one-year incidence of BPPV was 0.6%. Age, migraine, hypertension, hyperlipidaemia and stroke were independently associated with BPPV. The prevalence of Ménière's disease is approximately 0.51%.

2.5.5.4.4 Exposure data

Clinical trial FIELD

In the FIELD study the median duration of treatment with blinded study medication was 5 years. Total person-time of exposure to fenofibrate in the randomized, blinded setting was 22,658 person-years.

Post-marketing exposure

For fenofibrate and fenofibric acid the estimated cumulative post-marketing patient exposure until 31 July 2015 was approximately 45.5 and 1.7 million patient years respectively. Fenofibrate/simvastatin was only launched in May 2014; the estimated cumulative exposure since 01 March 2014 was only 6,400 patient years until 27 February 2015.

2.5.5.4.5 Conclusion

In conclusion, the number of spontaneous ICSRs with vertigo is low; all (except for one) are confounded by underlying/concurrent diseases and concomitant medications. Both the small number of ICSRs and the one ICSR with no obvious confounders reflect background incidence of vertigo in the patient population. In light of the high worldwide fenofibrate exposure over decades there is no evidence for vertigo being a fenofibrate side effect. Furthermore, neither the scientific literature nor placebo-controlled clinical trials provide reasonable evidence for a causal relation of fenofibrate with vertigo.

2.5.6 Benefits and Risks Conclusion

This Clinical Overview Addendum demonstrates that there is no justification to list vertigo as side effect for fenofibrate. 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. Neuhauser, H. (2007), Epidemiology Of Vertigo. Curr Opin Neurol(20), 40-46.