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**2.5 CLINICAL OVERVIEW- ADDENDUM**

**SAFETY UPDATE**

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**LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS**

T2DM            Type 2 diabetes

## **2.5 CLINICAL OVERVIEW – ADDENDUM**

### **2.5.1 Product Development Rationale**

Not applicable

### **2.5.2 Overview of Biopharmaceutics**

Not applicable

### **2.5.3 Overview of Clinical Pharmacology**

Not applicable

### **2.5.4 Overview of Efficacy**

Not applicable

### **2.5.5 Overview of Safety**

#### **2.5.5.1 Posology and method of administration**

##### **2.5.5.1.1 Patients with renal impairment**

#### **Background**

Fenofibrate is rapidly and completely converted after administration to its active form (and major metabolite) fenofibric acid. Fenofibric acid is excreted predominately in the urine as fenofibric acid and fenofibric acid glucuronide. The plasma half-life of fenofibric acid is prolonged in patients with impaired renal function and, therefore, fenofibrate requires dose adjustment according to renal function. Renal function is not usually measured directly, but rather estimated but estimated with formulas such as the MDRD equation (which estimates glomerular filtration rate) or the Cockcroft-Gault formula (which estimates creatinine clearance). These formulas use serum creatinine, gender, age, and weight to estimate renal function.

In an early pharmacokinetic study of fenofibrate, patients with severe renal impairment ( $\text{CrCl} \leq 20 \text{ ml/min}$ ) demonstrated a 2.7-fold increase in exposure to fenofibric acid during repeated dosing compared to volunteers with normal renal function. Compared to healthy volunteers, patients with mild to moderate renal impairment ( $\text{CrCl} 30\text{-}80 \text{ ml/min}$ ) had similar fenofibric acid exposure but an increase in the half-life of fenofibric acid.

In a placebo-controlled, double-blind, 6-month study reported by A Levin et al [1], 28 patients with hypertriglyceridemia and moderate renal insufficiency (average  $\text{CrCl} \sim 45 \text{ ml/min}$ ), received fenofibrate dosed according to lipid response and safety. Patients received a starting dose of 67mg fenofibrate for 2 months and in a stepwise fashion, the dose was increased to 134 and 201 mg at 2-month intervals. Six patients ended the study receiving 67mg, 7 were receiving 134 mg

and 3 were receiving 201mg fenofibrate. An average reduction in CrCl of 8% was observed along with a mean (median?) 150mg/dL decrease in triglycerides.

Reversible increases in serum creatinine have been observed with fenofibrate administration and account for the reduction in calculated estimates of renal function observed while patients are receiving fenofibrate.

Based upon this information, different recommendations for dose adjustment have been included in the labeling of fenofibrate.

The UK labeling provides the following recommendation

In renal dysfunction, the dosage may need to be reduced depending on the rate of creatinine clearance, for example:

<b>Creatinine clearance (ml/min)</b>	<b>Dosage</b>
<60	Two 67mg micronized capsules
<20	One 67mg micronized capsule

#### *Fenofibrate Dosing in Renal Impairment—Clinical Trials*

ACCORD Lipid was a 5-year, placebo-controlled, intervention study in patients with type 2 diabetes (T2DM) on statin treatment conducted in the US and Canada to assess the effect of fenofibrate on cardiovascular events. In this trial, patients with CrCl <50mL/min received a reduced dose of the masked study medication (one third of the standard dose). The reduced fenofibrate dose was being utilized at the last study visit in 15.9% and 7.1% of participants in the fenofibrate and the placebo groups, respectively [2]. Only 3.1% of patients in the fenofibrate group and 1.1% of patients in the placebo group were not on blinded medication for low GFR or increased creatinine. Thus, the study results were reported independently from the dose received.

No dose adjustment for fenofibrate was used in the FIELD Study, another 5-year placebo-controlled study in T2DM patients. This study included participants with reduced baseline renal function (GFR 30-60 ml/min) who received 200mg micronized fenofibrate or placebo. The patients with reduced renal function who were randomized to receive fenofibrate had a significantly reduced risk of cardiovascular events (HR 0.68, 95% CI 0.47-0.97 p=0.035) and of cardiovascular mortality (HR 0.51 95% CI 0.28-0.93 p=0.028). Adverse safety signals were not different between categories of baseline GFR [3].

Measured creatinine levels tend to increase more in patients with reduced renal function. Thus it is preferable to update and harmonize the recommendations for dose reduction in the different labelings without excessively limiting the possibility for patients with chronic kidney disease, who are at high risk of cardiovascular events, to get benefit from fenofibrate treatment.

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### **New proposed labeling**

Chronic kidney disease is now classified in five stages according to estimated glomerular filtration rate [4]:

- Stage 1 kidney damage with normal or raised eGFR ( $> 90$  ml/min/1.73m<sup>2</sup>)
- Stage 2 kidney damage with mild decrease in eGFR (60-90 ml/min/1.73m<sup>2</sup>)
- Stage 3 moderate decrease in eGFR (30-59 ml/min/1.73m<sup>2</sup>)
- Stage 4 severe decrease in eGFR (15-29 ml/min/1.73m<sup>2</sup>)
- Stage 5 kidney failure with eGFR ( $<15$  ml/min/1.73m<sup>2</sup>)

Chronic kidney disease is defined as an eGFR  $<60$  ml/min/1.73m<sup>2</sup> for at least 3 months.

With this classification of chronic kidney disease, the same categories apply to eGFR or CrCl. Thus, the early cut points of 20, 50 or 80 used for CrCl should now be replaced by 30, 60 and 90 and a new category of kidney failure (including those on dialysis) has been created. As the eGFR results are generally given in laboratory reports together with the actual serum creatinine levels, this classification can be introduced in the labeling for prescriber guidance and, thus, should be harmonized.

- There is no need for reduction of fenofibrate dosage in patient without chronic kidney disease, namely in those with normal eGFR or mild eGFR reduction ( $> 60$  ml/min/1.73m<sup>2</sup>).

- In patients with moderate chronic kidney disease (Stage 3), who often present with an abnormal lipid profile, in particular with hypertriglyceridemia, and are likely to benefit from fenofibrate treatment, dose reduction is needed. It is recommended to initiate fenofibrate treatment with one third of the usual dose for 2 to 3 months and to assess the effect of fenofibrate on lipids and creatinine levels.

- In patients with Stage 4 chronic kidney disease, fenofibrate treatment is not recommended except if the anticipated benefit on lipids exceeds the risks of a potential increase in creatinine levels. In such case, treatment should be reserved to a specialist and not described in the labeling. Further reduction in dose could be considered in this circumstance, by increasing the interval between administration, e.g. twice or once a week.

### **Section 4.2: Posology and method of administration**

The proposed wording for the posology and method of administration should read as follows

#### Renal impairment

In renal dysfunction, the dosage may need to be reduced depending on the rate of creatinine clearance, for example:

<b>Creatinine clearance (ml/min)</b>	<b>Dosage</b>
30 - 59	One 67mg capsule
<30	Contra-indicated

### **Section 4.3: Contraindications**

The proposed wording in the contraindication section should be maintained as: *Severe chronic kidney disease*. This includes patient on dialysis as the product is not cleared by hemodialysis and no data are available in patients on peritoneal dialysis.

### **2.5.6 Benefits and Risks Conclusion**

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

### **2.5.7 Literature References**

1. Levin A, Duncan L, Djurdjev O, Shapiro RJ, Frolich J, Belanger A, Dumas R, Ross S. A randomized placebo-controlled double-blind trial of lipid lowering strategies in patients with renal insufficiency: diet modification with or without fenofibrate. *Clin Nephrol* 2000;53:140-146.
2. Ting R, Donoghoe M, Jenkins AJ, Hedley J, Rajamani K, Drury PL, Davis TME, Celermajer D, Simes RJ, Keech AC. Benefits and safety of long-term fenofibrate therapy in people with type2 diabetes and renal impairment –the FIELD study. *Eur Heart J* 2011;32 (Abstract Supplement Eur Soc of Cardiology, Paris 2011):323-324.
3. The ACCORD study group. Effects of combination therapy in type2 Diabetes Mellitus. *N Engl J Med* 2010;362:1563-1574.
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