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2.5 CLINICAL OVERVIEW- ADDENDUM

TO MODIFY THE POSOLOGY SECTION FOR PATIENTS WITH RENAL IMPAIRMENT IN THE COMPANY CORE DATA SHEET (CCDS) OF FENOFIBRATE

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

CCDS	Company Core Data Sheet
T2DM	Type 2 diabetes

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The current document provides supporting information to modify the posology section for patients with renal impairment in the Company Core Data Sheet (CCDS) of fenofibrate.

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 (CrCl≤20ml/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 (CrCl 30-80 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 CrCl ~45 ml/min), received

fenofibrate dosed according to lipid response and safety. Patients received a starting dose of 67 mg 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 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.

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 of the dose received.

Of interest, in ACCORD Lipid, the composite primary endpoint of fatal CVD, non-fatal myocardial infarction and non-fatal stroke was reduced by 16% in those with an early increase in creatinine levels (at 4 months) as compared with those without such a change (HR 0.84 95% confidence interval 0.63;1.15 p=0.30). The numbers of subjects with a primary cardio vascular endpoint in the combination arm were the following: 117/1212 (9.7%) in those who raised creatinine, 143/1311 (10.9%) in those who did not and 291/2765 (10.5%) in the entire fenofibrate plus simvastatin arm [3] [4]. Over five years in ACCORD Lipid, the number of subjects reaching end stage renal disease or needing hemodialysis was 75 (2.7%) in the fenofibrate plus simvastatin group and 77 (2.8%) in the simvastatin monotherapy group.

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 [5].

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.

New proposed labeling

Chronic kidney disease is now classified in five stages according to estimated glomerular filtration rate [6]:

- Stage 1 kidney damage with normal or raised eGFR (> 90 ml/min/1.73m2)
- Stage 2 kidney damage with mild decrease in eGFR (60-90 ml/min/1.73m2)
- Stage 3 moderate decrease in eGFR (30-59 ml/min/1.73m2)
- Stage 4 severe decrease in eGFR (15-29 ml/min/1.73m2)
- Stage 5 kidney failure with eGFR (<15 ml/min/1.73m2)

Chronic kidney disease is defined as an eGFR<60 ml/min/1.73m2 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 or terminal chronic kidney disease 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. The preference is given to the expression as "creatinine clearance" for historical reason in labeling information.

- 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).

- 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

Dosage reduction is required in patients with renal impairment.

In moderate chronic kidney disease (creatinine clearance 30 to 59 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.

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. The ACCORD study group. Effects of combination therapy in type2 Diabetes Mellitus. N Engl J Med 2010;362:1563-1574.

3. 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. Diabetes Care 2012;35:218-225.

4. Mychaleckyj JC, Craven T, Nayak U, et al. Reversibility of fenofibrate therapy-induced renal function impairment in ACCORD type 2 diabetic participants. Diabetes Care 2012;35:1008-1014.

5. Bonds DE, Craven TE, Buse J, Cruse JR, Cuddihy R, Elan HN, Ginsberg HN et al. Fenofibrate-associated changes in renal function and relationship to clinical outcomes among individuals with Type 2 Diabetes: the action to control cardiovascular risks in diabetes (ACCORD experience). Diabetologia 2012;55:1641-1650.

6. Levey AS, Eckardt KU, Tsukamoto Y, Levin A, Coresh J, Rossert J, deZeeuw D, Hostetter TH, Lameire N, Eknoyan G. Definition and classification of chronic kidney disease: A position statement from Kidney Disease : Improving Global Outcomes (KDIGO). Kidney International 2005;67:2089-2100.