2.5 CLINICAL OVERVIEW ADDENDUM

(67/200/267 MG CAPSULES)

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

CCSI	Company Core Safety Information
CKD	Chronic Kidney Disease
CrCl	Creatinine Clearance
e-GFR	Estimated Glomerular Filtration Rate
GFR	Glomerular Filtration Rate
HDL-C	High Density Lipoprotein Cholesterol
HR	Hazard ratio
MDRD	Modification of Diet in renal Disease
MRP	Mutual Recognition Procedure
PSUR	Period Safety Update Report
QRD	Quality review of documents
SmPC	Summary of Product Characteristics
T2DM	Type 2 Diabetes Mellitus

2.5.1 INTRODUCTION

This addendum to the fenofibrate clinical overview is supportive of various changes to the current Summary of Product Characteristics (SmPC) of micronised formulations: 67, 200 and 267 mg capsules, submitted as a type II variation, to reflect:

1) The safety information coming from the most recent fenofibrate Periodic Safety Update Reports (PSUR), and

2) To harmonize the various SmPC of the different strengths and formulations in line with the most recent version of the CCDS/CCSI.

In addition, some editorial adaptations, changes for consistent wording and enhanced readability as well as revisions to meet the requirements of the revision of the guideline on Summary of Product Characteristics issued in September 2009 by the European Commission and the latest version of the QRD template are proposed for implementation.

2.5.2 BIOPHARMACEUTICS

2.5.2.1 Proposed update to Section Posology and Method of Administration

2.5.2.1.1 Response to therapy

Current wording:

Currently in section “Method of administration”: *The response to therapy should be monitored by determination of serum lipid values and the dosage may be altered within the range 2-4 capsules of <Tradename> 67mg daily*.

Proposed wording:

Response to therapy should be monitored by determination of serum lipid values. If an adequate response has not been achieved after several months (e.g. 3 months), complementary or different therapeutic measures should be considered

Justification for the change:

To be consistent with other fenofibrate SmPC and to give a clear recommendation we have moved the general statement from the section “Method of administration” to the beginning of the paragraph. The wording of the text is slightly modified but the given information is not altered. The second part of the statement related to the range of dose was removed as the information is already given in the “Posology” section.

2.5.2.1.2 Posology in adults

Current wording:

In adults, the recommended initial dose is 200 mg daily administered as 3 x 67mg capsules or 1x200 mg capsule.

For 67 mg and 267 mg: The dosage can be titrated up to 4 capsules (67 mg) or 1x267 mg capsule if required.

Proposed wording:

The recommended dose is 200 mg daily administered as three capsules <Tradename> 67 mg or one <Tradename> 200 mg.

The dose can be titrated up to 267 mg daily administered as 4 capsules <Tradename> 67 mg or one capsule *<Tradename 267 mg> if required*

Justification for the change:

The changes related to the Posology section are considered as editorial changes.

2.5.2.1.3 Method of administration

Current wording:

Capsule should be swallowed whole with water.

Fenofibrate should always be taken with food, because it is less well absorbed from an empty stomach. Dietary measures instituted before therapy should be continued.

Proposed wording:

Tablets should be swallowed whole during a meal.

Justification for the change:

The modification of this section is in line with the information given in other fenofibrate SmPCs.

2.5.2.1.4 Geriatric population

Current wording:

Elderly: In elderly patients without renal impairment, the normal adult dose is recommended.

Proposed wording:

In elderly patients, the usual adult dose is recommended.

Justification for the change:

This constitutes an editorial change.

2.5.2.1.5 Patients with Hepatic Impairment

Current wording:

Hepatic disease: Patients with hepatic disease have not been studied

Proposed wording:

Fenofibrate is not recommended for use in patients with hepatic impairment due to the lack of data

Justification for the change:

This constitutes and editorial change. The information given with the new wording is clearer for the prescriber.

2.5.2.1.6 Patients with Renal Impairment

Current wording:

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

Creatinine clearance (ml/min)	***Dosage***
20 - 60	*Two 67mg capsules*
10 - 20	*One 67mg capsule*

Proposed wording:

Dosage reduction is required in patients with renal impairment. In mild to moderate chronic kidney disease, start with one capsule of 67 mg micronized fenofibrate once daily. In patients with severe chronic kidney disease fenofibrate is not recommended.

Justification for the change:

Renal impairment, corresponding to chronic kidney disease, is classified in 5 stages according to estimated glomerular filtration rate (eGFR)[1]

Stage 4 corresponds to severe decrease in eGRF and stage 5 to kidney failure. As severe chronic kidney disease appears as a contra-indication, it was important to modify the wording above to reflect this change.

2.5.3 PHARMACOLOGY

2.5.3.1 Proposed update to Section Interactions

Current wording:

Oral anticoagulants:

Fenofibrate enhances oral anti-coagulant effect and may increase risk of bleeding. It is recommended that the dose of anticoagulants is reduced by about one-third at the start of treatment and then gradually adjusted if necessary according to INR (International Normalised Ratio) monitoring. Therefore, this combination is not recommended.

Proposed wording:

Oral anticoagulants:

Fenofibrate enhances oral anti-coagulant effect and may increase risk of bleeding. It is recommended that the dose of anticoagulants is reduced by about one-third at the start of treatment and then gradually adjusted if necessary according to INR (International Normalised Ratio) monitoring.

Justification for the deletion:

To be in line with the interaction section of the other formulations of fenofibrate, we propose to delete the last sentence of this section. This information is in contradiction with the recommendation on adjustment of the posology.

2.5.3.2 Proposed update to Section Pharmacokinetic properties

Current wording

The absorption of fenofibrate in the gastrointestinal tract is increased when taken with food. Steady state plasma concentration lies in the range of 10 to 15 µg/ml during a total daily dosage of 200mg of micronised fenofibrate.

After oral administration, fenofibrate is rapidly hydrolysed by esterases to the active metabolite fenofibric acid.

Unchanged fenofibrate is not recovered in the plasma. Fenofibric acid, the major plasma metabolite, is highly bound to plasma albumin (more than 99%) and can displace antivitamin K compounds from the protein binding sites with a potential for increasing their anti-coagulant effect.

Peak plasma concentration occurs after a mean period of 5 hours following administration.

The product is mainly excreted in the urine. 70% in 24 hours and 88% in 6 days, at which time total excretion in urine and faeces reaches 93%. Fenofibrate is mainly excreted as fenofibric acid (9 to 11%) and its derived glucuronoconjugate.

Kinetic studies after the administration of repeated doses show the absence of accumulation of the product.

Fenofibric acid is not eliminated during haemodialysis. The plasma elimination half-life of fenofibric acid is approximately 20 hours.

Proposed wording:

Absorption:

Maximum plasma concentrations (Cmax) occur within 4 to 5 hours after oral administration. Plasma concentrations are stable during continuous treatment in any given individual.

The absorption of fenofibrate is increased when administered with food.

Distribution:

Fenofibric acid is strongly bound to plasma albumin (more than 99%).

Metabolism and excretion:

After oral administration, fenofibrate is rapidly hydrolised by esterases to the active metabolite fenofibric acid.

No unchanged fenofibrate can be detected in the plasma. Fenofibrate is not a substrate for CYP 3A4. No hepatic microsomal metabolism is involved.

The drug is excreted mainly in the urine. Practically all the drug is eliminated within 6 days. Fenofibrate is mainly excreted ~~as~~ in the form of fenofibric acid and its glucuronoconjugate.

In elderly patients, the fenofibric acid apparent total plasma clearance is not modified.

Kinetic studies following the administration of a single dose and continuous treatment have demonstrated that the drug does not accumulate.

Fenofibric acid is not eliminated during haemodialysis. The plasma elimination half-life of fenofibric acid is approximately 20 hours.

Justification for the changes:

This section has been reworded as a sake of clarity and in order to be compliant with the most recently approved SmPC for fenofbrate (145 mg tablets). No new information is added. The data have either been reorganized to follow the the ADME scheme or reworded.

2.5.3.3 Proposed update to Section Pharmacodynamic properties

Current wording

The lipid-lowering properties of fenofibrate seen in clinical practice have been explained in vivo in transgenic mice and in human hepatocyte cultures by activation of Peroxisome Proliferator Activated Receptor type α (PPARα).

Through this mechanism fenofibrate increases lipolysis and elimination of triglyceride-rich particles from plasma by activating lipoprotein lipase and reducing production of apoprotein CIII. Activation of PPARα also induces an increase in the synthesis of apoproteins AI, AII and of HDL cholesterol.

.../...

Epidemiological studies have demonstrated a positive correlation between increased serum lipid levels and an increased risk of coronary heart disease. The control of such dyslipidaemias forms the rationale for treatment with fenofibrate. However, the possible beneficial and adverse long-term consequences of fibrates used in the hyperlipidaemias are still the subject of scientific discussion.

…/… Regression of xanthomata has been observed during fenofibrate therapy.

Patients with raised levels of fibrinogen and Lp(a) have shown significant reductions in these measurements during clinical trials with fenofibrate.

In addition, fenofibrate has a uricosuric effect.

Proposed wording:

Fenofibrate is a fibric acid derivative whose lipid modifying effects reported in humans are mediated via activation of Peroxisome Proliferator Activated Receptor type α (PPARα).

Through activation of PPARα, fenofibrate increases lipolysis and elimination of atherogenic triglyceride-rich particles from plasma by activating lipoprotein lipase and reducing production of apoprotein CIII. Activation of PPARα also induces an increase in the synthesis of apoproteins AI and AII.

.../...

Because of its effect on LDL cholesterol and triglycerides, treatment with fenofibrate should be beneficial in hypercholesterolaemic patients with or without hypertriglyceridaemia, including secondary hyperlipoproteinaemia such as type 2 diabetes mellitus.

.../...Extravascular deposits of cholesterol (tendinous and tuberous xanthoma) may be markedly reduced or even entirely eliminated during fenofibrate therapy.

Patients with raised levels of fibrinogen treated with fenofibrate have shown significant reductions in this parameter, as have those with raised levels of Lp(a). Other inflammatory markers such as C Reactive Protein are reduced with fenofibrate treatment.

The uricosuric effect of fenofibrate leading to reduction in uric acid levels of approximately 25% should be of additional benefit in those dyslipidaemic patients with hyperuricaemia.

Fenofibrate has been shown to possess an anti-aggregatory effect on platelets in animals and in a clinical study, which showed a reduction in platelet aggregation induced by ADP, arachidonic acid and epinephrine.

Justification for the changes:

This section has been reworded to be in line with the most recently approved SmPC for fenofbrate (145 mg tablets). No new information is added, when needed additional details are provided (see hereafter).

During the referral procedure on fibrates completed in Feb 2011, it was recommended to add in the section pharmacodynamic properties the following statement: "There is evidence that treatment with fibrates may reduce coronary heart disease events but they have not been shown to decrease all cause mortality in the primary or secondary prevention of cardiovascular disease." In order to give consistent information to the prescriber, we we propose to remove the following section "*Epidemiological studies have demonstrated a positive correlation between increased serum lipid levels and an increased risk of coronary heart disease. The control of such dyslipidaemias forms the rationale for treatment with fenofibrate. However, the possible beneficial and adverse long-term consequences of fibrates used in the hyperlipidaemias are still the subject of scientific discussion."*

Effects on Lipoprotein (a)

Lipoprotein(a) is a distinct lipoprotein among the LDL species which contains apoprotein (a). The description of the striking structural homology of apo (a) with plasminogen has attracted attention as a potential link between atherosclerosis and thrombosis. Elevated Lp(a) has been associated with an increased risk for the development of premature coronary heart disease in many populations [11, 12]. Levels above 20 - 30 mg/dl increase the risk of atherosclerosis by two to three times. In combination with hypercholesterolaemia the risk is even higher. Fenofibrate has been demonstrated to decrease Lp(a) levels from baseline (range -7% to -14%) in patients with type II dyslipidemia [7,8,9].

Action on inflammation

Fenofibrate decreased plasma fibrinogen levels in normolipidaemic patients [2] and in dyslipidaemic patients. The fibrinogen-lowering effect of fenofibrate was shown to be in the range -7% to -17% [3 to 7]. This effect was more pronounced in patients with type IIb dyslipidemia compared with type IIa (15% vs 7%) and was significantly greater than that of simvastatin 20 mg

and pravastatin 20 mg [8, 9, 10]. This reduction of fibrinogen was accompanied by a reduction in other acute phase proteins such as interleukine 6 and C Reactive Protein [10].

Hypouricemic effects

A hypouricemic effect of approximately 25% was demonstrated in patients with dyslipidemia who were treated with fenofibrate. This was explained by an increased fractional clearance of uric acid. It was demonstrated that fenofibrate enhanced uric acid reduction in patients with gout already treated with allopurinol and, in those patients who still have recurrent attack of gout on allopurinol, the addition of fenofibrate was associated with a long term remission [13, 14].

Effects on platelet aggregation

Patients with type II dyslipidemia showed increased platelet aggregation in response to ATP, adrenaline and arachidonic acid that was reduced by more than 50% with 300 mg fenofibrate treatment. After 1 to 18 months of treatment platelet aggregation was comparable to that of healthy controls. Conversely, thrombin induced aggregation was unchanged [15].

2.5.4 EFFICACY

This section is not applicable for this submission.

2.5.5 SAFETY

2.5.5.1 Clinical Information Related to Safety

2.5.5.1.1 Proposed update to Section Contraindications

2.5.5.1.1.1 Hepatic Insufficiency

Current wording:

Hepatic insufficiency (including biliary cirrhosis and unexplained persistent liver function abnormality .e. g. persistent elevations in serum transaminases)

Proposed wording:

Hepatic insufficiency (including biliary cirrhosis and unexplained persistent liver function abnormality)

Justification for the change:

The end of the statement « e.g. persistent elevation in serum transaminases » is not needed as persistent liver function abnormality covers a larger spectum of abnormal laboratory liver function tests which includes, but is not limited to « persistent elevation in serum transaminases ».

2.5.5.1.1.2 Gallbladder disease

Current wording:

Gallbladder disease

Proposed wording:

***Known** gallbladder disease*

Justification for the change:

Known was added as otherwise this would imply that a gallbladder ultrasound is required prior to initiate fenofibrate treatment. The contraindication thus applies to clinical evidence of gallbladder disease but asymptomatic gallbladder disease already diagnosed by ultrasound examination can be included.

2.5.5.1.1.3 Renal insufficiency

Current wording:

Renal insufficiency

Proposed wording:

Severe chronic kidney disease

Justification for the change:

In patients with severe CKD, fenofibrate treatment is not recommended. Consequently, we propose to update the wording related to patients with renal insufficiency as above. This includes patient on dialysis as the product is not cleared by hemodialysis and no data is available in patients on peritoneal dialysis.

2.5.5.1.2 Proposed update to Section Special Warnings and Precautions for Use

2.5.5.1.2.1 Secondary causes of hyperlipidemia

Current wording:

For hyperlipidaemic patients taking oestrogens or contraceptives containing oestrogen it should be ascertained whether the hyperlipidaemia is of primary or secondary nature (possible elevation of lipid values caused by oral oestrogen

The potential for fenofibrate/fenofibric acid to affect the metabolism of other drugs has not been fully investigated in vitro or in vivo. Interactions cannot be predicted, and therefore, caution is recommended if fenofibrate is combined with other drugs.

Proposed wording:

Secondary cause of hyperlipidemia, such as uncontrolled type 2 diabetes mellitus, hypothyroidism, nephrotic syndrome, dysproteinemia, obstructive liver disease, pharmacological treatment, alcoholism, should be adequately treated before fenofibrate therapy is considered. *For hyperlipidaemic patients taking oestrogens or contraceptives containing oestrogen it should be ascertained whether the hyperlipidaemia is of primary or secondary nature (possible elevation of lipid values caused by oral oestrogen).*

Justification for the change:

To be in line with the most recent text approved during the fenofibrate 145 mg MRP, we propose to introduce the new statement describing the causes of secondary hyperlipidemia which should be considered before any treatment is initiated.

In addition, we propose to delete the end of the paragraph, which is a very general statement.

2.5.5.1.2.2 Liver function

Current wording:

Moderately elevated levels of serum transaminases may be found in some patients but rarely interfere with treatment. However, it is recommended that serum transaminase should be monitored every 3 months during the first twelve months of treatment and thereafter periodically. Treatment should be discontinued if ASAT (SGOT) and ALAT (SGPT) levels increase to more than 3 times the upper limit of the normal range. When symptoms indicative of hepatitis occur (e.g. jaundice, pruritus), and are confirmed by laboratory testing, fenofibrate therapy should be discontinued.

Proposed wording:

As with other lipid lowering agents, increases have been reported in transaminase levels in some patients. In the majority of cases these elevations were transient, minor and asypmtomatic. It is recommended that transaminase levels are monitored every 3 months during the first twelve months of treatment and thereafter periodically. Attention should be paid to patients who develop increase in transaminase levels and therapy should be discontinued if AST (SGOT) and ALT (SGPT) levels increase to more than 3 times the upper limit of the normal range. When symptoms indicative of hepatitis occur (e.g. jaundice, pruritus), and diagnosis is confirmed by laboratory testing, fenofibrate therapy should be discontinued.

Justification for the change:

We propose to modify the wording of this paragraph in line with the most recent version of the SmPC (145 mg tablets). No major information is added or deleted. This should provide a better clarity of the information for the prescriber, as for the last sentence where more clear and precise recommendation is given to the practitioner on the procedure to follow in case symptoms of hepatitis occur.

2.5.5.1.2.3 Muscle

Current wording:

Muscle toxicity, including very rare cases of rhabdomyolysis, has been reported with administration of fibrates and other lipid-lowering agents. .../...

The risk of muscle toxicity may be increased if the drug is administered with another fibrate or an HMG-CoA reductase inhibitor, especially in case of pre-existing muscular disease. Consequently, the co-prescription of fenofibrate with a statin should be reserved to patients with severe combined dyslipidaemia and high cardiovascular risk without any history of muscular disease. This combination should be used with caution and patients should be monitored closely for signs of muscle toxicity.

Proposed wording:

Muscle toxicity, including rare cases of rhabdomyolysis, ***with or without renal failure****, has been reported with administration of fibrates and other lipid-lowering agents. …/…*

The risk of muscle toxicity may be increased if the drug is administered with another fibrate or an HMG-CoA reductase inhibitor, especially in case of pre-existing muscular disease. Consequently, the co-prescription of fenofibrate with a ***HMG-CoA reductase inhibitor or another fibrate*** should be reserved to patients with severe combined dyslipidaemia and high cardiovascular risk without any history of muscular disease. ***and with a close monitoring of potential muscle toxicity***

Justification for the change:

The frequency of rhabdomyolyse was modified from very rare to rare according to the new frequency presented in section 4.8 “undesirable effects”. In addition, the statement with or without renal failure was added to complete the definition of rhadomyolysis.

Referring to the last section of the paragraph, we propose to modify the statement to be in line with the most recent text approved during the fenofibrate 145 mg MRP. This change does not affect the recommendation made to the prescriber.

2.5.5.1.2.4 Renal function

Current wording:

In renal dysfunction, the dose of fenofibrate may need to be reduced, depending on the rate of creatinine clearance (see Section 4.2). Dose reduction should be considered in elderly patients with impaired renal function.

Proposed wording: -

Justification for the deletion:

We propose to align this section with the most recent text approved for fenofibrate 145 mg tablets. In addition, this information is already given in the section 4.2 Posology.

2.5.5.2 Post Marketing

2.5.5.2.1 Proposed update to Section Undesirable effects

2.5.5.2.1.1 Gastrointestinal Disorders

Current wording:

Gastrointestinal signs and symptoms (abdominal pain, nausea, vomiting, diarrhoea, flatulence) moderate in severity

Proposed wording:

Gastrointestinal signs and symptoms (abdominal pain, nausea, vomiting, diarrhoea, flatulence)

Justification for the change:

The statement "moderate in severity" was deleted in order to comply with guidance which recommend not to have any judgment on the event in the table.

2.5.5.2.1.2 Column "not known"in the table

Current wording:

Column "not known": Intersticial pneumopathies, rhabdomyolysis, jaundice, complications of cholelithiasis (e.g. cholecystitis, cholangitis, biliary colic)

Text provided under the table: *"In addition to those events reported during clinical trials, the following side effects have been reported spontaneously during postmarketing use of Lipantil Micro 67mg. A precise frequency cannot be estimated from the available data and is therefore classified as "not known".*

- *Respiratory, thoracic and mediastinal disorders: Interstitial lung disease.*
- *Musculoskeletal, connective tissue and bone disorders: Rhabdomyolysis."*

Proposed wording:

Text provided under the table: "In addition to those events reported during clinical trials, the following side effects have been reported spontaneously during postmarketing use of Lipantil Micro 67mg. A precise frequency cannot be estimated from the available data and is therefore classified as "not known".

- *Respiratory, thoracic and mediastinal disorders: Interstitial lung disease.*
- *Musculoskeletal, connective tissue and bone disorders: Rhabdomyolysis."*
- ***Hepatobiliary Disorders: jaundice, complications of cholelithiasis (e.g., cholecystitis, cholangitis , biliary colic, etc.)***

Justification for the change:

In the current version of the table undesirable effects, a column designated as "not known" describes the effects coming from the post-marketing and for which only an estimated frequency is available. This was in agreement with the recommendation in the guidance on SPC (rev 1).

In the last version of the same guidance (rev 2, Sept 2009), the column not known is no more recommended. As a consequence, we have removed the column which in fact presented the same information that the text provided after the table and related to side effects spontaneously reported during post-marketing use. This change does not cause any loss in the provided information.

2.5.6 OTHER CHANGES

2.5.6.1 Proposed update to Section Qualitative and Quantitative Composition

Current wording:

Excipients

Proposed wording:

Excipients ***with known effects***

Justification for the change:

This change is in line with the last version of the QRD template

2.5.6.2 Proposed update to Section Fertility, Pregnancy and Lactation

Current wording:

There are no adequate data from the use of fenofibrate in pregnant women. Animal studies have not demonstrated any teratogenic effects. Embryotoxic effects have been shown at doses in the range of maternal toxicity (see section Preclinical safety data of SmPC). The potential risk for humans is unknown. There are no data on the excretion of fenofibrate and/or its metabolite into breast milk. It is therefore recommended that fenofibrate should not be administeredto pregnant or to breast feeding women.

Proposed wording:

Pregnancy: *There are no adequate data from the use of fenofibrate in pregnant women. Animal studies have not demonstrated any teratogenic effects. Embryotoxic effects have been shown at doses in the range of maternal toxicity (see section Preclinical safety data of SmPC). The potential risk for humans is unknown. Therefore,"Trademark" should only be used during pregnancy after a careful benefit/risk assessment.*

Lactation: It is unknown whether fenofibrate is excreted in human milk. A risk to the newborns/infants cannot be excluded. Therefore fenofibrate should not be used during breast-feeding.

Justification for the change:

To comply with the QRD template, the title of section 4.6. was modify to ***Fertility***, P*regnancy and Lactation*. In addition, the paragraph was split to reflect the different subsections: Pregnancy and then Lactation.

For the lactation section, the text was modified to comply with the proposed statement of the CHMP/SWP guideline on reproduction and lactation. This does not modify the global recommendation.

2.5.7 BENEFIT AND RISK CONCLUSION

The changes as proposed in the SmPC do not modify the profile of fenofibrate and, therefore, its benefit/risk ratio remains positive.

2.5.8 REFERENCES

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2.5.9 APPENDICES