Solvay Healthcare Limited
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Clinical Expert Statement – Addendum

on

Lipantil 67, 140, 200, 267 mg capsules

Fenofibrate

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1. INTRODUCTION

This report supports the Type II variations to update section 4.4 "Special Warnings and precautions for use" of the Specific Product Characteristics (SmPC) for Lipantil 67, 140, 200 and 267 mg capsules.
During the previous years, several procedures conducted under the Mutual Recognition Procedure have been completed on other strengths/formulations of fenofibrate. During these procedures, some modifications of the safety sections of the SmPC have been proposed and approved. As a consequence the CCSI for fenofibrate was modified.
Consequently and in order to have all fenofibrate SmPC aligned on the fenofibrate CCSI, as proposed in the latest PSUR, we are proposing the following updates.

2. CHANGES TO THE SUMMMARY OF PRODUCT CHARACTERISTICS TO REFLECT THE POST MARKETING EXPERIENCE

2.1 Special Warnings and Precautions for Use

2.1.1 General statements

During registration of film-coated tablets containing 145 mg fenofibrate nanoparticles in Europe, (Mutual Recognition Procedure (DE/H/0497-498-500/01) with Germany as RMS and 15 CMS (Austria, Belgium, Czech republic, Finland, France, Greece, Hungary, Ireland, Italy, Luxembourg, Poland, Portugal, Slovakia, Spain and UK), modifications of the following safety sections of the SmPC have been requested by the RMS and/or CMS. This was reflected in the CCSI presented in fenofibrate PSUR n°8 (November 4, 2004 to May 3, 2005).
These changes are described hereunder.

1. The wording of the following statement, initially mentioned in section 4.2 "Posology and method of Administration" of Lipantil micro 200 mg
"Response to therapy should be monitored by determination of serum lipid values. Rapid reduction of serum lipid levels usually follows Lipantil Micro 200 treatment, but treatment should be discontinued if an adequate response has not been achieved within three months."
has been modified as follows and moved to section 4.4: "***Response to therapy should be monitored by determination of serum lipid values (total cholesterol, LDL-C, triglycerides). If an adequate response has not been achieved after several months (e.g. 3 months), complementary or different therapeutic measures should be considered***"

2. In addition, it has been requested to add in the SmPC the following statement:
"Secondary cause of hypercholesterolemia, 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 initiated."

3. In section 4.4 and to be consistent with the CCSI, we propose to replace the titles of the different subsections as follows:

"Transaminase" to be replaced by "Liver function".

"Renal impairment" to be replaced by "Renal function"

"Pancreatitis" to be replaced by "Pancreas"

"Myopathy" to be replaced by "Muscle"

2.1.2 Muscle

The section related to muscle toxicity is updated in order to be in alignment with the section from fenofibrate CCSI.
This change is the consequence from a request of BfArM following the assessment of fenofibrate PSURs n°4 and 5 (November 4, 2001- November 3, 2002). The rational from authorities was:

2. With regard to the recently finalised class review on statins by the Pharmacovigilance Working Party and CPMP, the warning section of the SPC for fenofibrate should be extended in order to include all patient conditions associated with an increased risk of myopathy/rhadomyolysis:
- age above 70 years old
- renal impaiment
- personal or familial history of hereditary muscular disorders
- alcohol abuse
- hypothyreoidism

Those of the above mentioned patient conditions already included in the current SPC (e.g. renal insufficiency) must not be included into the requested variation.
In addition, a wording should be included that for patients with predisposing risk factors for myopathy, doctors should carefully outweigh the putative benefits and risks of fenofibrate therapy.

The fenofibrate CCSI was modified accordingly and we now propose to update the current text of the Lipantil micro SmPC as follows (changes are highlighted in the following text).

In addition and to be in line with the updated frequency of rhabdomyolysis, as proposed in section 4.8, the term very rare has been changed to rare.

The new text should read as follows:

Muscle

Muscle toxicity, including ~~very~~ rare cases of rhabdomyolysis, has been reported with administration of fibrates and other lipid-lowering agents. The incidence of this disorder increases in case of hypoalbuminaemia and previous renal insufficiency.

Patients with pre-disposing factors for ***myopathy*** *and/or rhabdomyolysis, including* ***age above 70 years, personal or familial history of hereditary muscular disorders,*** *renal impairment, hypothyroidism and high alcohol intake, may be at an increased risk of developing rhabdomyolysis.* ***For these patients, the putative benefits and risks of fenofibrate therapy should be carefully weighed up****.*

2.1.3 Renal function

During renewal of fenofibrate 160 mg MRP (DE/H/235-236/R01) and evaluation of PSUR n°7 (May 4, 2003- November 3, 2003), it was requested by the RMS (Germany) to answer the following question: *"the MAH is requested to provide a cumulative review on previous cases of acute renal failure and cases of renal tubulopathies, which occurred in association with fenofibrate treatment."*.

Based on the available data presented at that time in the response document, whose conclusions were the following ones :
"The risk of acute renal failure is low and reversible after cessation of fenofibrate treatment, restoration of diuresis and management of other potential precipitating conditions.
Increase in creatinine levels by more than 50% is uncommon, observed within a few weeks of initiation of treatment in no more than 1% of patients in clinical studies. If such changes are observed with elevation of creatinine above the normal range, fenofibrate treatment must be withdrawn.
Measurement of creatinine levels is already required by current medical practice in patients at high risk of cardiovascular disease with or without existing renal dysfunction, thus additional monitoring is not required in these patients when they receive fenofibrate (except those on immunosuppressive therapy or existing renal dysfunction). Conversely, in patients with normal renal function (e.g. creatinine clearance > 90mL/min and low risk of cardiovascular disease), measurement of creatinine within the first 3 months after initiation of fenofibrate treatment may be considered."
the company proposed to amend the section relative to renal function of the fenofibrate SmPC. This proposal was further approved (FRAR dated Dec 2004) by authorities and implemented in the European fenofibrate SmPC and CCSI.

Renal function:
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.
Treatment should be interrupted in case of an increase in creatinine levels > 50% ULN (upper limit of normal).
It is recommended that creatinine is measured during the first 3 months after initiation of treatment and thereafter periodically (for dose recommendations see section 4.2).

3. OVERALL CONCLUSION

These changes to section 4.4 "Special warnings and precautions for use" of the SmPC of Lipantil 67, 140, 200 and 267 mg capsules reflect the current safety knowledge on fenofibrate and are in compliance with the CCSI presented in the latest version of the fenofibrate PSUR (n°14).

4. REFERENCES

Periodic Safety Update Report fenofibrate n°4 (Reference period November 4, 2001-May 3, 2002)

Periodic Safety Update Report fenofibrate n°5 (Reference period May 3, 2002-November 4, 2002)

Periodic Safety Update Report fenofibrate n°7 (Reference period May 4, 2003-November 3, 2003)

Periodic Safety Update Report fenofibrate n°8 (Reference period: November 4, 2004 to May 3, 2005)

Periodic Safety Update Report fenofibrate n°14 (Reference period: November 4, 2007 to November 3, 2008)