



EUROPEAN MEDICINES AGENCY  
SCIENCE MEDICINES HEALTH

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## Assessment report for fenofibrate, bezafibrate, ciprofibrate, and gemfibrozil containing medicinal products

pursuant to Article 31 of Directive 2001/83/EC, as amended

INN: fenofibrate, bezafibrate, ciprofibrate and gemfibrozil

Procedure number: EMEA/H/A-1238

Assessment Report as adopted by the CHMP with all information of a commercially confidential nature deleted.



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# 1. Background information on the procedure

## 1.1. Referral of the matter to the CHMP

On 20 October 2009, the United Kingdom triggered a referral under Article 31 of Directive 2001/83/EC, as amended (see enclosure 1). The CHMP was requested to give its opinion on whether the marketing authorisations for medicinal products containing fenofibrate, bezafibrate, ciprofibrate and gemfibrozil, and associated names should be maintained or varied.

The procedure described in Article 32 of Directive 2001/83/EC, as amended, was applicable.

## 2. Scientific discussion

### 2.1. Introduction

Fibrates (fenofibrate, bezafibrate, ciprofibrate and gemfibrozil) are a class of lipid-lowering drugs and exert their effects mainly by activating the peroxisome proliferator-activated receptor- $\alpha$  (PPAR- $\alpha$ ), apart from bezafibrate which is an agonist for all three PPAR isoforms  $\alpha$ ,  $\gamma$ , and  $\delta$ . Fibrates have been shown to reduce plasma triglycerides (TG) by 30% to 50% and raise the level of high density lipoprotein cholesterol (HDL-C) by 2% to 20%. Their effect on low density lipoprotein cholesterol (LDL-C) is variable, ranging from no effect to a small decrease of the order of 10%.

The Committee for Medicinal Products for Human Use (CHMP)'s Pharmacovigilance Working Party (PhVWP) undertook a benefit risk review of this class of medicines. The objective was to establish the current place of fibrates in the treatment of cardiovascular and dyslipidaemic diseases. Clinical data on the effect of the different fibrates on cardiovascular disease (CVD) mortality and morbidity, all cause mortality and stroke including subpopulations was considered. Data to support the potential use as second line therapy to statins in a given indication was requested. Information was also sought on evidence suggesting specific effects in subgroups in terms of gender, age, lipid profile, concomitant medication or other medical conditions including diabetes. In this regard, recommendations regarding amendments of the product information were expected, as applicable. This review was completed in 2008.

Further to the finalisation of the review of the available data, the conclusions and recommendations were communicated to the MAHs. The product information for all fibrates was to be updated to indicate that fibrates should be considered as first line treatment only in patients with severe hypertriglyceridaemia with or without low HDL-C. In patients with mixed hyperlipidaemia fibrates should be given only when statins are contraindicated or not tolerated. Based on the evidence that gemfibrozil may differ from the rest of the class and may have a more favourable profile, it was suggested that gemfibrozil's product information should also indicate that it could be considered in patients with primary hypercholesterolaemia, but again only when statins could not be administered. Finally, a statement was to be included in the product information of all products to indicate that treatment with fibrates may reduce coronary heart disease events but has no beneficial effect on all cause mortality in the primary or secondary prevention of cardiovascular disease.

As part of the implementation plan, in 2008 the national competent authorities (NCAs) contacted the brand leaders for the four fibrates requesting them to update their product's information in line with the PhVWP recommendations. However, as the full implementation of the proposed changes was not possible, it was thus considered in the interest of the Community to refer fenofibrate, bezafibrate, ciprofibrate and gemfibrozil to the CHMP/EMA and request a review of the benefit risk balance for all fibrates. The CHMP was asked in October 2009 to give its opinion under Article 31 of Directive 2001/83/EC, as amended, on whether the marketing authorisations for medicinal products containing the above mentioned active substances should be maintained or varied.

## 2.2. Clinical aspects

### 2.2.1. PhVWP recommendation

At the time of the PhVWP review, the long term efficacy and safety of the currently licensed fibrates had mainly been examined in five large randomised, placebo controlled trials: the Helsinki Heart Study (HHS)<sup>1</sup> and Veterans Affairs HDL Intervention Trial (VA-HIT)<sup>2</sup> with gemfibrozil, the Bezafibrate Infarction Prevention (BIP)<sup>3</sup> Study and the Lower Extremity Arterial Disease Event Reduction (LEADER)<sup>4</sup> Study with bezafibrate, and the Fenofibrate Intervention in Event Lowering in Diabetes (FIELD)<sup>5</sup> Study with fenofibrate. No randomised, controlled trial data were available for ciprofibrate. Despite differences in methodology and study populations, the major fibrate trials showed some noteworthy consistencies e.g. treatment appears to be associated with a lower risk of non fatal cardiac events but at the same time has an unfavourable effect on overall survival. This discrepancy, as yet unexplained, was observed for bezafibrate (BIP and LEADER trials), fenofibrate (FIELD trial) but also for gemfibrozil (HHS trial). However, in contrast to bezafibrate and fenofibrate trials, which failed in their primary endpoints, both gemfibrozil trials HHS and VA-HIT demonstrated a significant reduction in cardiovascular morbidity, and in the case of VA-HIT a positive trend in terms of all cause mortality, overall suggesting a more favourable profile compared to the rest of the class. No long term outcome data were available for ciprofibrate. Given, however, the similar mechanisms of action and effects on lipids, no considerable differences in terms of efficacy and safety were expected.

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<sup>1</sup> HHS: A large double blind study comparing gemfibrozil (600 mg twice daily) with placebo in 4081 men, 40 to 55 years of age with primary dyslipidaemia but no previous history of coronary heart disease (CHD). The primary endpoints were fatal and non fatal myocardial infarction (MI), sudden coronary death and unwitnessed coronary death during the 5 year follow-up period. The results showed that gemfibrozil significantly reduced non fatal MI and CHD death. A CHD risk related to triglycerides and/or HDL-C was present only when high triglycerides and low HDL-C were jointly present; and the presence of high triglycerides and low HDL-C was strongly associated with high blood pressure and glucose values. Gemfibrozil reduced CHD events mainly in overweight subjects with high glucose, high blood pressure, and dyslipidaemia. In addition, a non-significant trend towards an increase of different mortality-related parameters (non-cardiac mortality, overall mortality) was observed.

<sup>2</sup> VA-HIT: A double blind study comparing gemfibrozil (1200 mg per day) with placebo in 2531 men with CHD, HDL-C levels of < 40 mg/dl and normal LDL-C levels. The primary study outcome was non fatal MI or death from CHD, and the median follow-up was 5.1 years. Gemfibrozil significantly reduced the primary composite endpoint of non-fatal MI or death from coronary causes and produced a significant reduction in stroke. In addition, a trend towards an increased risk reduction for death from any cause was observed.

<sup>3</sup> BIP: A phase IV, multicentre, double blind, randomised placebo controlled trial with the main objective to investigate the effects of raising HDL-C or decreasing triglycerides with bezafibrate on the risk of cardiovascular events in coronary heart disease. The primary endpoint was a composite of fatal MI, non-fatal MI or sudden death within 24 hours of onset of symptoms. Overall, there were no statistically significant differences between bezafibrate and placebo in clinical outcome parameters. There was a trend in favour of bezafibrate with regard to the primary endpoint driven by non fatal MI. All cause mortality (not statistically significant) was higher in the bezafibrate group. Post-hoc analyses seem to demonstrate that patients with high triglycerides and low HDL-C, as well as patients fulfilling the criteria for metabolic syndrome benefited the most.

<sup>4</sup> LEADER: A multicentre, double blind, placebo controlled, randomised trial carried out with the objective to assess the effect of bezafibrate on the risk of CHD and stroke in men with lower extremity arterial disease. Median follow-up was 4.6 years. There was a statistically non-significant risk reduction of 4% on the primary endpoint for bezafibrate treated patients. Fatal and non-fatal CHD events showed a similar trend. A borderline statistically significant risk reduction was shown for non-fatal major coronary events. There was a non-significant excess of strokes with bezafibrate. All cause mortality was also slightly higher in the bezafibrate group.

<sup>5</sup> FIELD: A study which aimed to determine the effect of fenofibrate versus placebo on coronary events: fatal CHD plus non fatal MI. The study was restricted to 50-75 years old patients with type 2 diabetes and 9795 patients were randomised to fenofibrate or placebo and followed for over a period of at least 5 years (see also: Lancet. 2005 Nov 26;366(9500):1849-61). The primary total CHD was not significantly reduced, although for some morbidity related parameters (non fatal MI) and mixed morbidity/mortality related events (total cardiovascular events) a significant reduction of hazard ratios values due to fenofibrate treatment was observed. Co-therapy with other lipid lowering therapies (LLT; statins > 90%) was identified as an important potential confounding factor influencing the outcome to the disadvantage of fenofibrate. However even after adjustment for LLT, hazard ratios remained > 1, indicating a consistent trend towards an increased risk with fenofibrate.

Below is a summary of the conclusions and recommendations of the review:

### **Bezafibrate**

Effects on cardiac morbidity and mortality failed to show a significant effect on hard cardiovascular endpoints, despite overall favourable lipid modifying action of the therapy in both randomised placebo controlled secondary prevention trials with bezafibrate (BIP and LEADER).

The review concluded that there are limited clinical data on long term clinical benefit indicating that a first line treatment for the primary or secondary prevention of cardiovascular disease is no longer justified. However, the effect of bezafibrate on triglycerides and HDL cholesterol indicates that specific subgroups of patients might derive considerable benefit from bezafibrate therapy.

### **Ciprofibrate**

The data from literature sustaining the efficacy of ciprofibrate are limited and no randomised clinical trials on hard cardiovascular endpoints are available. However, ciprofibrate shares many of the pharmacodynamic properties of other fibrates showing potent hypolipidaemic effects and expected effects on triglycerides and HDL cholesterol as the rest of the class. There is no evidence to suggest that there are clinically significant differences between ciprofibrate and other fibrates.

Therefore, taking into account its activity on surrogate markers, the review concluded that specific subgroups of patients might derive considerable benefit from ciprofibrate therapy.

### **Gemfibrozil**

The review noted that gemfibrozil is molecularly different from the other fibrates, however available data do not suggest important differences between gemfibrozil and others in the class in terms of its pharmacodynamic effects.

In contrast with other fibrates, two long term outcome studies are available demonstrating consistently favourable results (HHS and VA-HIT). In addition, a subgroup analysis from the HHS trial showed that benefit was most pronounced in patients with hypertriglyceridaemia and mixed dyslipidaemia.

Therefore, it was also concluded that generally trials have provided evidence that the clinical effects of gemfibrozil may differ from the rest of the class and may have a more favourable profile; therefore, gemfibrozil could also be considered in primary hypercholesterolaemia and prevention of cardiovascular morbidity in males (as the outcome trials with gemfibrozil did not include women) when a statin is contraindicated or not tolerated.

### **Fenofibrate**

In the FIELD study, the primary outcome parameter "coronary events" (coronary heart disease, death, or non-fatal myocardial infarction) was reduced non significantly. The finding corresponded to a significant 24% reduction in non-fatal myocardial infarction and a non-significant increase in coronary heart disease mortality. At the time of the review, the FIELD study was the most relevant clinical trial on assessment of efficacy and safety of fenofibrate in diabetic patients. The co-therapy with a statin was identified as an important confounding factor influencing the outcome to the disadvantage of fenofibrate. However, patients with atherogenic dyslipidaemia (TG > 200 mg/dl; low HDL-cholesterol) profited from fenofibrate treatment as regards reduction of cardiovascular events.

Based on all evidence, the review concluded that although the data are insufficient for a first line treatment for the primary or secondary prevention of cardiovascular disease, specific subgroups of patients might derive considerable benefit from fenofibrate therapy.

During the review, the PhVWP was also aware of the ongoing ACCORD<sup>6</sup> Lipid trial which aimed to investigate the potential benefit of the co-medication of simvastatin and a fibrate (fenofibrate). The PhVWP acknowledged that the ACCORD study could provide important information with regard to benefits and risks resulting from the add-on of fibrate and a statin therapy. The study was to be available no earlier than 2010. The PhVWP urged the MAH for fenofibrate to report on the results and progress of this study in a timely manner.

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<sup>6</sup> ACCORD: Action to Control Cardiovascular Risk in Diabetes study was a randomised controlled National Heart, Lung and Blood Institute (NHLBI) sponsored study on 10 000 adults with type 2 diabetes. The study investigated major cardiovascular events in patients with intensively controlled blood sugar along with aggressive control of blood pressure and lipids. ACCORD Lipid was a component of the larger ACCORD trial that evaluated intensive versus standard management of blood pressure, lipids, and glycaemia in diabetic patients. Patients in the lipid-lowering arm were randomised to receive either simvastatin (20 mg) alone or simvastatin plus fenofibrate. See also 'The ACCORD study group. Effect of combination lipid therapy in type 2 diabetes mellitus. N Engl J Med 2010;10.1056/NEJMoa1001282'.

## Conclusions and Recommendations

The PhVWP noted that currently statins are the first line treatment for patients with lipid abnormalities where pharmacological intervention has been definitely associated with a beneficial outcome. Statins have shown convincing efficacy regarding both primary and secondary prevention of cardiac mortality and morbidity. The PhVWP concluded that based on all available information the current indications for fibrates were first granted mainly on the basis of their effects on surrogate parameters. Available trials had however provided evidence that a favourable action on lipid metabolism may not always translate into patient benefit. Data showed that there is only limited evidence of a long term clinical benefit from the use of fibrates in the primary or secondary prevention of cardiovascular disease. Considering the overwhelming evidence for statins in this area, the use of fibrates as a first line treatment was considered no longer justified. However, the effect of fibrates mainly on triglycerides but also a smaller but overall positive effect on HDL and LDL cholesterol suggested that there are subgroups of patients who may still benefit from this therapy.

Therefore, in the framework of its review, the PhVWP proposed the following wording **for both SPC and PL** of the different fibrates:

### 1. For bezafibrate, fenofibrate and ciprofibrate:

#### 1.1 SPC

Section 4.1 – Therapeutic indications (to replace current text)

*[Product name] is indicated as an adjunct to diet and other non-pharmacological treatment (e.g. exercise, weight reduction) for the following:*

- *Treatment of severe hypertriglyceridaemia with or without low HDL cholesterol.*
- *Mixed hyperlipidaemia when a statin is contraindicated or not tolerated.*

Section 5.1 – Pharmacodynamic properties (Additional text)

*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.*

#### 1.2 Patient Information Leaflet

*What [Product name] is and what it is used for*

*[Product name] belongs to a group of medicines, commonly known as fibrates. These medicines are used to lower the level of fats (lipids) in the blood. For example the fats known as triglycerides.*

*[Product name] is used, alongside a low fat diet and other non-medical treatments such as exercise and weight loss, to lower levels of fats in the blood.*

### 2. For gemfibrozil only:

#### 2.1 SPC

Section 4.1 – Therapeutic indications (to replace current text)

*[Product name] is indicated as an adjunct to diet and other non-pharmacological treatment (e.g. exercise, weight reduction) for the following:*

- *Treatment of severe hypertriglyceridaemia with or without low HDL cholesterol.*
- *Mixed hyperlipidaemia when a statin is contraindicated or not tolerated.*
- *Primary hypercholesterolaemia when a statin is contraindicated or not tolerated.*

*Primary prevention*

*Reduction of cardiovascular morbidity in males with increased non-HDL cholesterol and at high risk for a first cardiovascular event when a statin is contraindicated or not tolerated (see section 5.1).*

Section 5.1 – Pharmacodynamic properties (Additional text)

*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.*

*The VA-HIT study was a double-blind study comparing gemfibrozil (1200 mg per day) with placebo in 2531 men with a history of coronary heart disease, HDL-C levels of < 40 mg/dL (1.0 mmol/L), and*

normal LDL C levels. After one year, the mean HDL-C level was 6% higher and the mean triglyceride level was 31% lower in the gemfibrozil group than in the placebo group. The primary event of non-fatal myocardial infarction or cardiac death occurred in 17.3% of gemfibrozil-treated and 21.7% of placebo-treated patients (reduction in relative risk 22%; 95% CI, 7 to 35 %; P=0.006). Among secondary outcomes, patients treated with gemfibrozil experienced relative risk reductions of 25% (95% CI -6-47%, p=0.10) for stroke, 24% (95% CI 11-36%, p< 0.001) for the combined outcome of death from CHD, non-fatal myocardial infarction, or confirmed stroke, 59% (95% CI 33-75%, p< 0.001) for transient ischaemic attack, and 65% (95% CI 37-80%, p< 0.001) for carotid endarterectomy.

## 2.2 Patient Information Leaflet

*What [Product name] is and what it is used for*

*[Product name] belongs to a group of medicines, commonly known as fibrates. These medicines are used to lower the level of fats (lipids) in the blood. For example the fats known as triglycerides.*

*[Product name] is used, alongside a low fat diet and other non-medical treatments such as exercise and weight loss, to lower levels of fats in the blood.*

*[Product name] may also be prescribed to people who cannot be prescribed the more usual medicines for lowering blood cholesterol levels.*

### 2.2.2. CHMP review

The CHMP initially endorsed the PhVWP recommendations and proposal for product information update. The CHMP agreed that the use of fibrates as a first line treatment was considered no longer justified based on limited evidence of a long term clinical benefit from the use of these products in the primary or secondary prevention of cardiovascular disease. Notwithstanding this fact, the specific lipid lowering effects of fibrates, indicates there are subgroups of patients who may still benefit from this therapy, in particular patients with hypertriglyceridaemia or patients who cannot take statins. In the framework of the Article 31 a list of questions was sent to the MAHs of medicinal products containing one of the four authorised fibrates. All MAHs were requested to confirm agreement to update their product(s)' information in line with the recommendations of the PhVWP/CHMP or submit additional data to support a different position. In addition, the MAHs of fenofibrate-containing products were asked to submit information on the recently completed ACCORD Lipid trial.

#### **Bezafibrate**

All MAHs of bezafibrate containing medicinal products who responded to the list of questions indicated their agreement to implement the changes to their product information in line with the recommendations of the fibrates benefit risk review. No new data was submitted for consideration and assessment during this review.

#### **Ciprofibrate**

All MAHs of ciprofibrate containing medicinal products who responded to the list of questions indicated their agreement to implement the changes to their product information in line with the recommendations of the fibrates benefit risk review. No new data was submitted for consideration and assessment during this review.

#### **Gemfibrozil**

All MAHs of gemfibrozil containing medicinal products who responded to the list of questions indicated their overall agreement to implement the changes to their product information in line with the recommendations of the fibrates benefit risk review. No new data was submitted for consideration and assessment during this review however, small changes to the PL wording were proposed and agreed with by the CHMP as follows:

#### **PL**

*What [Product name] is and what it is used for*

*[Product name] belongs to a group of medicines commonly known as fibrates. These medicines are used to lower the level of fats (lipids) in the blood. For example the fats known as triglycerides.*

*[Product name] is used, alongside a low fat diet and other non-medical treatment such as exercise and weight loss, to lower levels of fat in the blood. [Product name] can be used when other medicines [statins] are unsuitable, to reduce the occurrence of heart problems in men who are at high risk and who have increased 'bad cholesterol'*

*[Product name] may also be prescribed to people who cannot be prescribed other lipid-lowering medicines for lowering blood cholesterol levels.*

### **Fenofibrate**

The majority of MAHs for fenofibrate products who responded to the list of questions indicated their agreement to implement the changes to their product information in line with the recommendations of the fibrates benefit risk review. The brand leader for fenofibrate submitted responses including results of the now finalised ACCORD Lipid trial (shown below), proposing further changes to section 4.1 of the SPC for the following strengths<sup>7</sup> of fenofibrate: 100, 300, 67, 200, 250 mg capsules and 160 and 145 mg film coated tablets. For the higher strengths of fenofibrate (267 mg capsules and 215 mg film coated tablets) the MAH indicated agreement to restrict the indication in line with the recommendation of the fibrates benefit risk review.

### **Efficacy**

#### **ACCORD Lipid trial**

The ACCORD Lipid was a randomised, controlled trial which aimed to evaluate whether adding fenofibrate to simvastatin could reduce cardiovascular risk beyond the risk reduction with simvastatin alone in type 2 diabetic patients.

The patient population of 5518 subjects with type 2 diabetes (mean age 62,3 years, 30,7 % women) who were at high risk for cardiovascular disease (36.5% with prior CV events) received in ACCORD lipid either fenofibrate (160 mg or equivalent dose) or matching placebo in addition to open label simvastatin 20 to 40 mg or less.

The primary outcome was the first occurrence of non-fatal myocardial infarction, non-fatal stroke, or death from cardiovascular causes. The mean follow-up was five years until death or the final visit that took place in early 2009. The annual rate of the primary outcome was 2.2% in the fenofibrate group and 2.4% in the placebo group (hazard ratio in the fenofibrate group 0.92; 95% confidence interval [CI] 0.79 to 1.08, p=0.32). There were also no significant differences between the two study groups with respect to any secondary outcome. Results for prespecified primary and secondary outcomes are presented below.

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<sup>7</sup> Fenofibrate was initially approved as standard formulations with 100 and 300 mg capsules. The bioavailability of the standard formulation was subsequently improved with a 250 mg capsule (sustained release formulation) and through a comiconisation process of the active substance leading to the development of the 200 mg micronised fenofibrate capsules, which was demonstrated to be bioequivalent to the 300 mg capsule. Then a 160 mg tablet formulation of micronised fenofibrate with a greater bioavailability than the capsule formulation was shown to be bioequivalent to the 200 mg capsule. In order to further reduce the dose administered to patients and to improve compliance, a no food effect formulation project was initiated. This led to the development of a 145 mg tablet, based on particle size reduction using nanoparticle technology, bioequivalent to the 160 mg tablet and the 200 mg capsule and without food effect. In the ACCORD Lipid study, 200mg capsules, 160 mg tablets and 145 mg tablets and their respective placebo were successively used.

In parallel, higher strengths of two formulations have been developed: 267 mg as a capsule and 215 mg as a tablet, which were bioequivalent to 400 (4x100) mg of standard fenofibrate, the highest posology initially approved. These were not used in the ACCORD Lipid study.



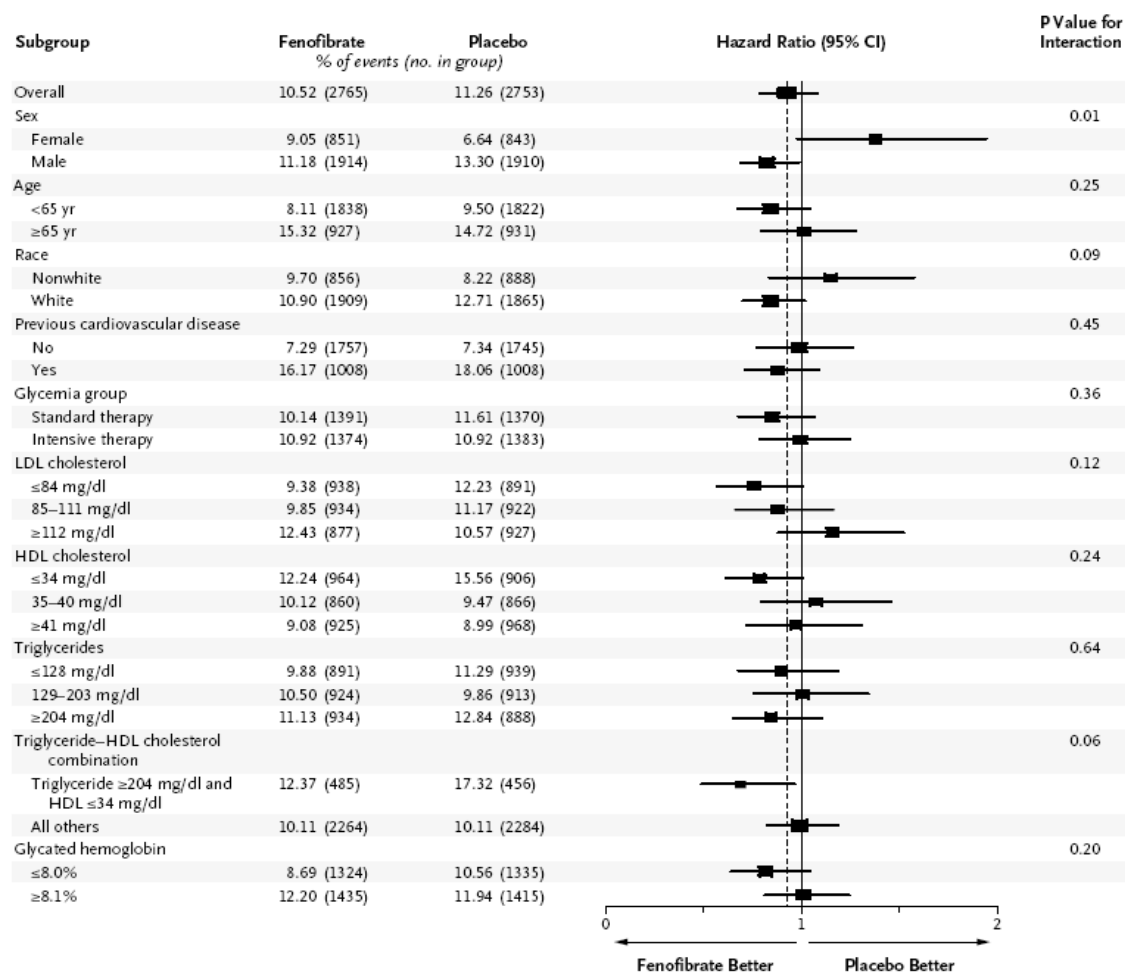
**ACCORD Lipid. Primary and Secondary Outcomes**

<b>Outcome</b>	<b>Fenofibrate (n=2765)</b>	<b>Placebo (n=2753)</b>	<b>Hazard Ratio (95% CI)</b>	<b>P value</b>
Primary outcome (major fatal or nonfatal cardiovascular event)	291	310	0.92 (0.79–1.08)	0.32*
Secondary outcomes				
Primary outcome plus revascularization or hospitalization for congestive heart failure	641	667	0.94 (0.85–1.05)	0.30
Major coronary disease event†	332	353	0.92 (0.79–1.07)	0.26
Nonfatal myocardial infarction	173	186	0.91 (0.74–1.12)	0.39
Stroke				
Any	51	48	1.05 (0.71–1.56)	0.80
Nonfatal	47	40	1.17 (0.76–1.78)	0.48
Death				
From any cause	203	221	0.91 (0.75–1.10)	0.33*
From cardiovascular cause	99	114	0.86 (0.66–1.12)	0.26
Fatal or nonfatal congestive heart failure	120	143	0.82 (0.65–1.05)	0.10

\* P values were adjusted for interim monitoring.

† A major coronary disease event was defined as a fatal coronary event, nonfatal myocardial infarction, or unstable angina.

Prespecified subgroup analyses were presented and statistical significant interactions were observed. Results are presented in the table below.

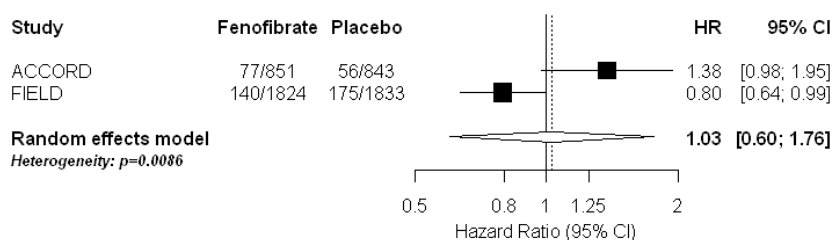


In particular results of interaction analysis by gender ( $p=0.01$ ) and by dyslipidaemic patients ( $p=0.06$ ) are discussed below.

#### ACCORD Lipid results by gender

A prespecified subgroup analysis based on gender in ACCORD Lipid identified a statistically significant treatment-by-gender interaction. Results in gender subgroups indicated a statistically significant treatment benefit of combination therapy in men and a potentially higher risk of primary endpoint in women treated with combination therapy compared to simvastatin monotherapy.

It was noted that this finding was not consistent with the monotherapy (fenofibrate only) study, FIELD, in which the treatment-by-gender interaction was not statistically significant ( $p=0.30$ ) and women who received fenofibrate had a lower rate of cardiovascular events than those receiving placebo (7.7% versus 9.5%;  $p=0.04$ ) (see below hazard ratio for major cardiovascular events in ACCORD Lipid and FIELD Women).



Furthermore, in the dyslipidaemic group the findings with regard to the gender effect were not consistent with those in the whole study population. In this group, there was a numerically lower rate

of major cardiovascular events in women treated with combination therapy compared to women treated with simvastatin monotherapy. Thus, the possible detrimental effect of the combination therapy seen in the overall population was not observed in women in the dyslipidaemic group but there was also no clear indication of benefit.

#### ACCORD Lipid results by dyslipidaemia

Overall, 17% (of ACCORD Lipid patients were defined as being dyslipidaemic (N=941), that is being simultaneously in the highest TG tertile and lowest HDL-C tertile at baseline (TG  $\geq$  204 and HDL-C  $\leq$  34). No statistically significant differences in baseline characteristics were observed between the two treatment groups. A difference in the primary outcome in favour of fenofibrate in dyslipidaemic patients, with high baseline triglyceride levels and low baseline HDL-C was observed compared to the rest of the study population, p-value for interaction 0.06. The tables below summarise the results in the dyslipidaemic population.

#### Primary and secondary outcomes in the ACCORD Lipid dyslipidaemic population

	Fenofibrate + Simvastatin (N = 485)		Simvastatin Monotherapy (N = 456)		Hazard Ratio	95% CI	P value
	Events	Rate/yr	Events	Rate/yr			
Primary Outcome <sup>a</sup>	60	2.63	79	3.69	0.692	(0.494, 0.969)	0.032
Composite Secondary Outcome <sup>b</sup>	130	6.15	158	8.58	0.706	(0.560, 0.891)	0.003
Major coronary disease event	64	2.79	90	4.45	0.627	(0.455, 0.864)	0.004
Non-fatal MI	37	1.59	48	2.30	0.695	(0.453, 1.068)	0.097
Stroke – Any	10	0.42	13	0.59	0.703	(0.308, 1.605)	0.403
Stroke – Non-fatal	10	0.42	10	0.45	0.910	(0.379, 2.187)	0.833
Death – Any Cause	37	1.50	50	2.21	0.670	(0.438, 1.025)	0.065
Death – CVD Cause	17	0.70	31	1.38	0.501	(0.277, 0.906)	0.022
Fatal or nonfatal CHF	33	1.40	32	1.48	0.918	(0.564, 1.493)	0.730

a. First occurrence of any of the following outcomes: CVD death, non-fatal MI or non-fatal stroke

b. Primary outcome + revascularization or hospitalization for Congestive Heart Failure

Major CV events (CV death, non-fatal MI and non-fatal stroke) were significantly reduced 31% (p=0.032) in the combination therapy with fenofibrate and simvastatin in the prespecified dyslipidaemic subgroup.

Significant decreases in the risk of a major coronary disease event (p=0.004) and cardiovascular death (p=0.022) were observed for combination therapy with fenofibrate and simvastatin compared to simvastatin monotherapy. In addition, compared to simvastatin monotherapy, combination therapy resulted in a non significant reduction of nonfatal MI and death from any cause.

The sample size of the dyslipidaemic group in ACCORD (N=941) was small but overall the results suggest an advantage of the fenofibrate treatment in this group, in co-administration with a statin.

#### Meta-analysis

Following the publication of the ACCORD Lipid results, a systematic review and meta-analysis of the effect of fibrates on cardiovascular outcomes was published by an independent group of researchers<sup>8</sup>.

This analysis included 18 fibrate outcome trials encompassing 45,058 patients. This meta-analysis evidenced a 10% relative risk reduction for major cardiovascular outcomes in five fibrate trials including 19,944 participants and 2,870 cardiovascular events (p=0.048) and a 13% relative risk reduction for coronary events in 16 trials including 44,667 participants in whom 4,552 events were reported (P < 0.0001) with no evidence of heterogeneity between studies. No effect of fibrate therapy

<sup>8</sup> Effects of fibrates on cardiovascular outcomes: a systematic review and meta-analysis (Jun Min et al; Lancet 2010; 375: 1875).

was noted on stroke, all-cause mortality, cardiovascular mortality, sudden death, or non-vascular mortality.

For coronary events, the benefit of fibrate therapy was larger in trials with a higher mean baseline TG level ( $p=0.030$ ). In addition, a correlation between the TG reductions and risk of coronary events was noted ( $p=0.026$ ), with larger risk reductions associated with larger TG decreases.

The results of ACCORD in the overall population are very similar to the results with all fibrates in the meta-analysis for all endpoints and for the major cardiovascular events. In particular, in the pooled analysis of fenofibrate trials ACCORD and FIELD, in the dyslipidaemic population the pooled hazard ratios for all the endpoints considered were consistently reduced by fenofibrate.

Although recognising the statistical limitations of comparison across trials, the table below looks at relative risk of cardiovascular events overall and in respective dyslipidaemic population across different trials where a lipid subgroup criterion was applied. Although it is noted that none of the previous trials specifically examined the effects of the add on therapy of fibrate to a statin, the results show consistency in the reduction of the overall relative risk for the primary endpoint in the dyslipidaemic population.

### Comparison of the ACCORD Lipid trial to earlier fibrate trials

Trial (Drug)	Primary Endpoint: Entire Cohort (P value)	Lipid Subgroup Criterion	Primary Endpoint: Subgroup (P value)
HHS (Gemfibrozil) <sup>a</sup>	-34% (0.02)	TG > 200 mg/dl LDL-C/HDL-C > 5.0	-71% (0.005)
BIP (Bezafibrate) <sup>b</sup>	-7.3% (0.24)	TG ≥ 200 mg/dl	-39.5% (0.02)
FIELD (Fenofibrate) <sup>c</sup>	-11% (0.16)	TG ≥ 204 mg/dl HDL-C < 40/50 mg/dl	-27% (0.005)
ACCORD (Fenofibrate) <sup>d</sup>	-8% (0.32)	TG ≥ 204 mg/dl HDL-C ≤ 34 mg/dl	-31% (0.032)

<sup>a</sup> HHS included only men.

<sup>b</sup> BIP study included 9% of women.

<sup>c</sup> FIELD study included 37% women.

<sup>d</sup> ACCORD Lipid included 30.7% women.

It is noted that a consistent increase in cardiovascular risk appears with a threshold of triglycerides of or above 200 mg/dl, i.e., the risk of cardiovascular event increases with the degree of dyslipidaemia. In this regard, the addition of fenofibrate to simvastatin seems to reduce the incremental risk due to dyslipidaemia.

## Safety

### ACCORD Lipid trial

The most common safety concerns for fenofibrate and statin combination therapy are renal, hepatic, and muscle-related adverse reactions. In general, the available data from the ACCORD Lipid trial did not suggest any new safety signals during the course of combination therapy with fenofibrate and simvastatin.

The tables below highlight the major serious adverse events (SAEs) reported for the overall population and its dyslipidaemic subgroup.

### Major Serious Adverse Events in ACCORD Lipid

	Fenofibrate + simvastatin (n=2765)	Simvastatin monotherapy (n=2753)	P value
Any severe muscle aches/pains regardless of CK	1110 (40.1%)	1115 (40.5%)	0.787*
Any non hypoglycemic SAE	54 (2.0%)	43 (1.6%)	0.269*
Any myopathy/myositis/rhabdomyolysis SAE	4 (0.1%)	3* (0.1%)	1.000
Any hepatitis SAE	3 (0.1%)	0	0.250
Any SAE attributed to lipid medications	27 (1.0%)	18* (0.7%)	0.183*

\* Value from the company analysis represents a minor discrepancy compared to the value presented in the published ACCORD Lipid article. The magnitude of the differences was such that no conclusions were affected by these discrepancies.

CK: creatinine kinase;

### Major serious adverse events in ACCORD Lipid dyslipidaemic population

	Fenofibrate + simvastatin (n=485)	Simvastatin monotherapy (n=456)	P value
Any severe muscle aches/pains regardless of CK	195 (40.2%)	191 (41.9%)	0.601
Any non hypoglycemic SAE	14 (2.9%)	8 (1.8%)	0.251
Any myopathy/myositis/rhabdomyolysis SAE	0	0	-
Any hepatitis SAE	2 (0.4%)	0	0.500
Any SAE attributed to lipid medications	7 (1.4%)	2 (0.4%)	0.114

In ACCORD lipid, there were 9% fewer deaths from any cause and 14% fewer CV deaths with fenofibrate plus simvastatin as compared to simvastatin alone. However, the results were not statistically significant.

Over five years average follow-up, the combination of fenofibrate 160 mg and simvastatin showed approximately the same incidence and types of adverse events as simvastatin monotherapy. There was no increase in the incidence of myositis or rhabdomyolysis in combination therapy with four cases in both groups. The incidence of increase in alanine transaminase (ALT) > 3 x upper limit of normal (ULN) was 1.9% in combination as compared to 1.5% for simvastatin with three cases of hepatitis with combination therapy versus none with simvastatin alone.

As noted in other fenofibrate trials, mean creatinine levels increased in the fenofibrate plus simvastatin group from 82 to 97 µmol/l within the first year and remained relatively stable thereafter. In the simvastatin alone group, creatinine level increased from 82 to 92 µmol/l during the course of the trial. In the fenofibrate plus simvastatin group, 15.9% of subjects received one third of the usual fenofibrate dose, i.e. 54 mg or equivalent, as requested by the protocol for those with reduced renal function (eGFR (glomerular filtration rate) < 50 ml/min/1.73 m<sup>2</sup>) at randomisation or on treatment. There was no difference in the incidence of haemodialysis or end stage renal disease between groups (75 cases in the fenofibrate plus simvastatin group and 77 cases in the simvastatin alone group). However, a higher incidence of renal complications compared to simvastatin alone was reported. Treatment was discontinued in twice as many patients (66, 2.4%) in the fenofibrate group than in the placebo group (30, 1.1%) because of a decrease in the estimated GFR.

There was no difference between the two groups in other safety results of interest (gallbladder related events, pancreatitis, venous thromboembolism and other non-hypoglycaemic serious adverse events).

Safety observations from the ACCORD trial were consistent with those in the FIELD, except for gender effect. Trends in gender effect observed (see also *ACCORD Lipid results by gender* above), showed that the increase in primary endpoint in women receiving fenofibrate and simvastatin (77/851) was not statistically significant as compared with those receiving simvastatin monotherapy (56/843).

### 2.2.3. Discussion

The fibrates share a common mechanism of action and exert qualitatively similar effects on serum lipid triglycerides (decrease) and HDL-cholesterol concentrations (increase). The PhVWP review of all available data on the benefit risk of fibrates in the treatment of cardiovascular (mortality and morbidity) and dyslipidaemic diseases, as initially endorsed by the CHMP, concluded that in most cases, the indications for fibrates had been granted mainly on the basis of their effects on these surrogate parameters and that little evidence was available on the effects of the different fibrates on cardiovascular morbidity and mortality. Statins have demonstrated a significant decrease in cardiovascular events and mortality in the primary and secondary prevention of cardiovascular disease, and it is noted that the body of data available from randomised clinical trials for different fibrates in this field is limited. Overall, there are no relevant long term data on cardiovascular hard endpoints. In addition, the major fibrate trials showed that treatment appears to be associated with a lower risk of non fatal cardiac events but at the same time has an unfavourable effect on overall survival. This discrepancy, which remains unexplained, was observed for bezafibrate (BIP and LEADER trials), fenofibrate (FIELD trial) but also for gemfibrozil (HHS trial).

Therefore, despite the long presence of fibrates on the market the use of fibrates as a first line treatment was considered no longer justified. However, specific subgroups of patients still benefit from fibrate treatment: patients with severe hypertriglyceridaemia are one subgroup, and this is also supported by most clinical guidelines; for mixed hyperlipidaemic patients, the body of evidence is in favour of statins as a first treatment choice. Nevertheless, fibrates can still have a role when statins cannot be used. A proposal for the update of the product information as endorsed by the Committee and agreed with MAHs for the different fibrates can be found at 2.4 Changes to the product information.

With regard to the combination of fibrates with statins, the lack of robust data on the long term efficacy of such a therapy together with the potential risks did not allow any recommendations for most fibrates. However, for certain strengths of fenofibrate (100, 300, 67, 200, 250 mg capsules and 160 and 145 mg film coated tablets), results from ACCORD lipid trial, a randomised placebo-controlled study of 5518 patients with type 2 diabetes mellitus treated with fenofibrate in addition to simvastatin showed that although the combination therapy did not show any significant differences compared to simvastatin monotherapy in the composite primary outcome of non-fatal myocardial infarction, non-fatal stroke, and cardiovascular death (hazard ratio [HR] 0.92, 95% CI 0.79-1.08, p=0.32; absolute risk reduction: 0.74%), in the pre-specified subgroup of dyslipidaemic patients, fenofibrate plus simvastatin therapy demonstrated a 31% relative reduction compared to simvastatin monotherapy for the composite primary outcome (hazard ratio [HR] 0.69, 95% CI 0.49-0.97, p=0.03; absolute risk reduction: 4.95%). This new data, taken together with previous outcome studies and fibrate trials meta-analysis confirm a benefit in the dyslipidaemic population, as the addition of fenofibrate to simvastatin seems to reduce the incremental risk in this population. Therefore, the CHMP considered that evidence exists to support the use of fenofibrate (100, 300, 67, 200, 250 mg capsules and 160 and 145 mg film coated tablets) in mixed hyperlipidaemic in patients at high cardiovascular risk together with a statin when triglycerides and HDL-cholesterol are not adequately controlled with a statin alone. The product information was updated accordingly (see 2.4 Changes to the product information).

No specific safety concern arose from the data provided. A statistically significant treatment-by-gender interaction (p = 0.01) was observed in ACCORD, indicating a possible treatment benefit of combination therapy in men (p=0.037) but a potentially higher risk for the primary outcome in women treated with combination therapy compared to simvastatin monotherapy (p=0.069). This finding was not consistent with the observed in other trials (FIELD) thus the product information was updated to reflect this (see 2.4 Changes to the product information).

### **2.3. Overall benefit/risk assessment**

Fibrates (fenofibrate, bezafibrate, ciprofibrate and gemfibrozil) are a class of lipid-lowering drugs and exert their effects mainly by activating the peroxisome proliferator-activated receptor-alpha (PPAR-alpha), apart from bezafibrate which is an agonist for all three PPAR isoforms alpha, gamma, and delta. Fibrates have been shown to reduce plasma triglycerides (TG) by 30% to 50% and raise the level of high density lipoprotein cholesterol (HDL-C) by 2% to 20%. Their effect on low density lipoprotein cholesterol (LDL-C) is variable, ranging from no effect to a small decrease of the order of 10%.

Currently statins are the first line treatment for patients with lipid abnormalities where pharmacological intervention has been definitely associated with a beneficial outcome. Statins have shown convincing efficacy regarding both primary and secondary prevention of cardiac mortality and morbidity. In comparison, there is only limited evidence of a long term clinical benefit from the use of fibrates in the primary or secondary prevention of cardiovascular disease. In fact, the long term efficacy and safety of the currently licensed fibrates has mainly been examined in six large randomised, placebo controlled trials: the Helsinki Heart Study (HHS) and Veterans Affairs HDL Intervention Trial (VA-HIT) with gemfibrozil, the Bezafibrate Infarction Prevention (BIP) Study and the Lower Extremity Arterial Disease Event Reduction (LEADER) Study with bezafibrate, the Fenofibrate Intervention in Event Lowering in Diabetes (FIELD) Study and the Action to Control Cardiovascular Risk in Diabetes study (ACCORD) with fenofibrate. No randomised, controlled trial data were available for ciprofibrate, but differences across the class in surrogate marker effects has not been shown.

Fibrates had been approved on the basis of their effects on surrogate parameters (mainly triglycerides and HDL cholesterol) but available trials provided evidence that a favourable action on lipid metabolism may not always translate into patient benefit. The previous major fibrate trials showed some noteworthy consistencies as treatment appeared to be associated with a lower risk of non fatal cardiac events but at the same time have an unfavourable effect on overall survival, with the possible exception of gemfibrozil. Thus overall 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. However, there are subgroups of patients such as those with severe hypertriglyceridaemia with or without low HDL cholesterol or with mixed hyperlipidaemia when a statin is contraindicated or not tolerated which could benefit from treatment with a fibrate.

Some differences in the available evidence across the class have been observed.

As discussed above, most trials (bezafibrate and fenofibrate) failed their primary endpoints, but both gemfibrozil trials demonstrated a significant reduction in cardiovascular morbidity, and in the case of VA-HIT a positive trend in terms of all cause mortality, overall suggesting a more favourable profile of gemfibrozil compared to the rest of the class. This merited a differentiation in the given indications for gemfibrozil and inclusion in addition of primary hypercholesterolaemia and primary prevention of cardiovascular morbidity in males when a statin is contraindicated or not tolerated.

Regarding co-administration of fibrates with statins, there are insufficient data on the long term efficacy of such a therapy to allow any recommendations for most fibrates. However, for fenofibrate at dose of 100, 300, 67, 200, 250 mg capsules and 160 and 145 mg film coated tablets, results from ACCORD lipid trial, taken together with previous outcome studies and fibrate trials meta-analysis confirm a benefit of add on therapy in the dyslipidaemic population, when triglycerides and HDL cholesterol are not adequately controlled with a statin alone. The addition of fenofibrate to simvastatin seems to reduce the incremental risk in this population therefore this has been reflected in the given indications for this product.

Based on the above, the CHMP recommended the amendments of the marketing authorisations (see 2.4 Changes to the product information) and concluded that the benefit risk profile of fibrates is still positive in the agreed indications.

### **2.4. Changes to the product information**

The CHMP agreed on the following amendments to the product information:

## **1. Bezafibrate, ciprofibrate and fenofibrate (267 mg capsules and 215 mg film coated tablets):**

### 1.1 SPC

Section 4.1 – Therapeutic indications (to replace current text)

*[Product name] is indicated as an adjunct to diet and other non-pharmacological treatment (e.g. exercise, weight reduction) for the following:*

- *Treatment of severe hypertriglyceridaemia with or without low HDL cholesterol.*
- *Mixed hyperlipidaemia when a statin is contraindicated or not tolerated.*

Section 5.1 – Pharmacodynamic properties (Additional text)

*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*

### 1.2 Patient Information Leaflet

What [Product name] is and what it is used for

*[Product name] belongs to a group of medicines, commonly known as fibrates. These medicines are used to lower the level of fats (lipids) in the blood. For example the fats known as triglycerides.*

*[Product name] is used, alongside a low fat diet and other non-medical treatments such as exercise and weight loss, to lower levels of fats in the blood.*

## **2. Gemfibrozil:**

### 2.1 SPC

Section 4.1 – Therapeutic indications (to replace current text)

*[Product name] is indicated as an adjunct to diet and other non-pharmacological treatment (e.g. exercise, weight reduction) for the following:*

- *Treatment of severe hypertriglyceridaemia with or without low HDL cholesterol.*
- *Mixed hyperlipidaemia when a statin is contraindicated or not tolerated.*
- *Primary hypercholesterolaemia when a statin is contraindicated or not tolerated.*

*Primary prevention*

*Reduction of cardiovascular morbidity in males with increased non-HDL cholesterol and at high risk for a first cardiovascular event when a statin is contraindicated or not tolerated (see section 5.1).*

Section 5.1 – Pharmacodynamic properties (Additional text)

*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*

*The VA-HIT study was a double-blind study comparing gemfibrozil (1200 mg per day) with placebo in 2531 men with a history of coronary heart disease, HDL-C levels of < 40 mg/dL (1.0 mmol/L), and normal LDL C levels. After one year, the mean HDL-C level was 6% higher and the mean triglyceride level was 31% lower in the gemfibrozil group than in the placebo group. The primary event of non-fatal myocardial infarction or cardiac death occurred in 17.3% of gemfibrozil-treated and 21.7% of placebo-treated patients (reduction in relative risk 22%; 95% CI, 7 to 35 %; P=0.006). Among secondary outcomes, patients treated with gemfibrozil experienced relative risk reductions of 25% (95% CI –6-47%, p=0.10) for stroke, 24% (95% CI 11-36%, p< 0.001) for the combined outcome of death from CHD, non-fatal myocardial infarction, or confirmed stroke, 59% (95% CI 33-75%, p< 0.001) for transient ischaemic attack, and 65% (95% CI 37-80%, p< 0.001) for carotid endarterectomy.*

### 2.2 Patient Information Leaflet

What [Product name] is and what it is used for

*[Product name] belongs to a group of medicines commonly known as fibrates. These medicines are used to lower the level of fats (lipids) in the blood. For example the fats known as triglycerides.*



*[Product name] is used, alongside a low fat diet and other non-medical treatment such as exercise and weight loss, to lower levels of fat in the blood. [Product name] can be used when other medicines [statins] are unsuitable, to reduce the occurrence of heart problems in men who are at high risk and who have increased 'bad cholesterol'*

*[Product name] may also be prescribed to people who cannot be prescribed other lipid-lowering medicines for lowering blood cholesterol levels.*

### **3. Fenofibrate (100, 300, 67, 200, 250 mg capsules and 160 and 145 mg film coated tablets):**

#### 1.1 SPC

##### Section 4.1 – Therapeutic indications (to replace current text)

*[Product name] is indicated as an adjunct to diet and other non-pharmacological treatment (e.g. exercise, weight reduction) for the following:*

- *Treatment of severe hypertriglyceridaemia with or without low HDL cholesterol.*
- *Mixed hyperlipidaemia when a statin is contraindicated or not tolerated.*
- *Mixed hyperlipidaemia in patients at high cardiovascular risk in addition to a statin when triglycerides and HDL cholesterol are not adequately controlled.*

##### Section 5.1 – Pharmacodynamic properties (Additional text)

*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.*

*The Action to Control Cardiovascular Risk in Diabetes (ACCORD) lipid trial was a randomized placebo-controlled study of 5518 patients with type 2 diabetes mellitus treated with fenofibrate in addition to simvastatin. Fenofibrate plus simvastatin therapy did not show any significant differences compared to simvastatin monotherapy in the composite primary outcome of non-fatal myocardial infarction, non-fatal stroke, and cardiovascular death (hazard ratio [HR] 0.92, 95% CI 0.79-1.08,  $p = 0.32$  ; absolute risk reduction: 0.74%). In the pre-specified subgroup of dyslipidaemic patients, defined as those in the lowest tertile of HDL-C ( $\leq 34$  mg/dl or 0.88 mmol/L) and highest tertile of TG ( $\geq 204$  mg/dl or 2.3 mmol/L) at baseline, fenofibrate plus simvastatin therapy demonstrated a 31% relative reduction compared to simvastatin monotherapy for the composite primary outcome (hazard ratio [HR] 0.69, 95% CI 0.49-0.97,  $p = 0.03$  ; absolute risk reduction: 4.95%). Another prespecified subgroup analysis identified a statistically significant treatment-by-gender interaction ( $p = 0.01$ ) indicating a possible treatment benefit of combination therapy in men ( $p=0.037$ ) but a potentially higher risk for the primary outcome in women treated with combination therapy compared to simvastatin monotherapy ( $p=0.069$ ). This was not observed in the aforementioned subgroup of patients with dyslipidaemia but there was also no clear evidence of benefit in dyslipidaemic women treated with fenofibrate plus simvastatin, and a possible harmful effect in this subgroup could not be excluded.*

#### 1.2 Patient Information Leaflet

What [Product name] is and what it is used for

*[Product name] belongs to a group of medicines, commonly known as fibrates. These medicines are used to lower the level of fats (lipids) in the blood. For example the fats known as triglycerides.*

*[Product name] is used, alongside a low fat diet and other non-medical treatments such as exercise and weight loss, to lower levels of fats in the blood.*

*[Product name] can be used in addition to other medicines [statins] in some circumstances when levels of fats in the blood are not controlled with a statin alone.*

### **3. Overall conclusion**

Having considered the PhVWP recommendations on the review of the benefit risk of fibrates in the treatment of cardiovascular (mortality and morbidity) and dyslipidaemic diseases, the overall data submitted provided by the MAHs in writing and in the oral explanation, the CHMP concluded that available trials provide evidence of a favourable action of fibrates on lipid metabolism.

The CHMP concluded from the data provided that there is a lack of therapeutic efficacy in the primary or secondary prevention of cardiovascular disease for all fibrates, with the exception of gemfibrozil which showed benefit on primary prevention of cardiovascular morbidity in males when a statin cannot be used. However patients can still benefit from treatment with fibrates in severe hypertriglyceridaemia and certain dyslipidaemias where a statin cannot be used.

Furthermore, data from a recent trial (ACCORD) supported a benefit in co-administration of some strengths of fenofibrate with a statin in patients with mixed hyperlipidaemic at high cardiovascular risk when triglycerides and HDL cholesterol are not adequately controlled with a statin alone.

Therefore, the CHMP recommended the variation to the terms of the marketing authorisation for the medicinal products referred to in Annex I, for which the relevant sections of the summary of product characteristics and package leaflet are set out in Annex III to the opinion.

### **4. Annexes**

The list of the names of the medicinal products, marketing authorisation holders, pharmaceutical forms, strengths and route of administration in the Member States are set out Annex I to the opinion.