

Anlage 1

PhVWP ASSESSMENT REPORT

on the benefit:risk of fibrates

EXECUTIVE SUMMARY

1. BACKGROUND

In the light of the established role of statins in the primary and secondary prevention of cardiovascular disease (CVD) and safety concerns arising from the use of fibrates, the CHMP Pharmacovigilance Working Party (PhVWP) agreed to undertake a benefit:risk assessment of this class of medicines. The objective was to establish the current place of fibrates in the treatment of cardiovascular and dyslipidaemic diseases, and in diabetes mellitus; also to provide recommendations regarding amendments of the Summary of Product Characteristics (SPC), as necessary.

Fibrates exert their effects mainly by activating the peroxisome proliferator-activated receptor-alpha (PPAR-alpha). Unique in this class, bezafibrate is an agonist for all three PPAR isoforms alpha, gamma, and delta. Fibrates have been shown to reduce plasma triglycerides 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%.

Today there are four licensed fibrates: bezafibrate, fenofibrate, gemfibrozil and ciprofibrate. Their currently approved indications are quite broad and in many cases still use the old Fredrickson classification for dyslipidaemias.

2. METHODOLOGY

In February 2006 a List of Questions was agreed by the PhVWP for the Marketing Authorisation Holders (MAHs) of medicinal products containing one of the four currently licensed fibrates (Annex 1). Other clofibrate-containing medicinal products (e.g. etofibrate, etofyllinclofibrate) were excluded from this class review, since these are available only in a few member states via national marketing authorisations.

In response to the List of Questions the MAHs submitted, among others, all available clinical data regarding the effects of the specific fibrate on cardiovascular mortality and morbidity, and data that might distinguish this fibrate from the rest of the class or support its potential use as second line therapy to statins in a given indication.

The assessment work of the submitted data was shared between four Members States acting as rapporteurs in this matter. The individual Assessment Reports on each of the four fibrates were presented to the PhVWP in March 2007. A Joint Assessment Report was discussed by the PhVWP at its meetings in July and September 2007, and finalised in February 2008.

3. CURRENT EVIDENCE

3.1. Clinical outcome

The long term efficacy and safety of the currently licensed fibrates were mainly examined in five large randomized, 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, and the most recent Fenofibrate Intervention in Event Lowering in Diabetes (FIELD) Study with fenofibrate. No randomized, controlled trial data are available for ciprofibrate. A summary table showing the main findings of the five trials can be found in Annex 2.

In most studies fibrate treatment achieved a significant lipid-modifying action which, however, did not appear to translate into a clear clinical benefit, with the exception of gemfibrozil. All studies showed a favourable trend in reducing non fatal cardiovascular events, which in

some cases reached statistical significance as in HHS and VA-HIT trials. However, there was an overall negative trend towards higher all cause mortality in patients on active treatment. Only VA-HIT trial, again with gemfibrozil, showed a small favourable effect on mortality, although not at a statistically significant level. The above findings, especially with bezafibrate and fenofibrate, appear to be generally consistent with the results of the older WHO trial with the now withdrawn from the market clofibrate, which showed a 47% excess mortality in the clofibrate treated group despite a significant reduction in the incidence of non-fatal myocardial infarction.

3.2. Differences between fibrates

There are no long term outcome data directly comparing the efficacy and safety of different fibrates. There are a number of smaller studies that compared lipid parameters and other surrogate markers between fibrates but the size of most of these studies, the variability in the design and methods, and inconsistencies in the findings make difficult to draw firm conclusions. Overall, in terms of their *pharmacodynamic* properties, it appears that there is little evidence to support any clinically relevant differences. It should be noted, however, that gemfibrozil has a different chemical structure from the rest of the class and the evidence suggests that it may be associated with a higher risk of drug-drug interactions. However, as mentioned above, the two clinical trials with gemfibrozil showed more positive results than the other fibrates.

3.3 Fibrates as second line treatment

One of the objectives of this class review was to investigate whether there are any data supporting the potential role of fibrates as second line therapy to statins for a specific indication. This included whether fibrates can be used in cases in which, for some reason, statins are not indicated or not tolerated, whether fibrates can offer some benefit in cases where statin therapy has failed to reach the predefined targets or whether there is any incremental benefit if fibrates are used as add-on therapy to statins.

Overall, there are no relevant long term data on cardiovascular hard endpoints, neither have there been any trials specifically designed to address these points. There are a number of small studies, examining surrogate markers that compared different fibrates with statins or examined the combination of a fibrate with a statin. In general, the results have shown a more potent effect of fibrates on triglycerides and HDL-C while statins are far superior in reducing total and LDL-cholesterol. The combination mainly showed a considerable decrease in triglyceride levels and in some cases further reduction in total and LDL-cholesterol, with an incremental increase in HDL-C.

These findings suggest that a group of special interest might be patients with combined (mixed) hyperlipidaemia. It should be noted here, that many statins are currently licensed as first line therapy for combined hyperlipidaemia and appear to be the initial treatment of choice especially when triglycerides are only moderately raised. Whether a fibrate can offer any additional benefit in terms of CVD morbidity and mortality, over and above that of a statin in this specific population or other patient groups, remains to be investigated. The currently ongoing ACCORD trial (Action to Control Cardiovascular Risk in Diabetes) which is testing, among others, the impact on cardiovascular events of a strategy involving combined therapy with a statin (simvastatin) plus a fibrate (fenofibrate) versus the statin alone, may provide in the future an insight into the clinical implications of such an approach.

When considering a statin-fibrate combination it is important to take into account the potential safety issues. The combination has been associated with a higher risk of myopathy/rhabdomyolysis and relevant warnings are included in the SPC of most products. The harmonised SPC for simvastatin as determined by the European Commission decision of 28/04/04 (CPMP/459/04) states that the risk of myopathy and rhabdomyolysis is increased by concomitant administration with fibrates and that the benefits of the combination should

be carefully weighed against the potential risks. The SPC further recommends a maximum dose of 10mg in case that simvastatin is co-administered with fibrates (except fenofibrate for which there is no evidence of excessive risk). A stronger warning is included about gemfibrozil because of a pharmacokinetic interaction resulting in increased simvastatin plasma levels and the SPC states that this combination should be avoided.

3.4. Specific subgroups

In an effort to identify potential subgroups of patients who might benefit more from treatment, a number of mainly post-hoc subanalyses were conducted on the results of some of the major fibrate trials with mixed results. A group of patients that has been suggested as most likely to benefit from fibrates are those with high triglycerides and/or low HDL cholesterol. Although there have been some positive results, there is no large trial specifically testing the long term safety and efficacy of fibrates in this patient group.

Another group of special interest are patients with diabetes. Several smaller studies looking at surrogate markers as well as subanalyses of the major trials provided evidence of a possible favourable effect of fibrates in this population. However, the largest and most recent randomised controlled trial in diabetic patients, the FIELD trial, failed to provide any clear evidence of a beneficial role of the treatment in this population, thus not allowing any positive recommendations.

3.5. Gender effects

No studies specifically investigating any possible gender effects on the potential benefits and risks associated with fibrate treatment have been identified. Most major trials with fibrates included either only men (HHS, VA-HIT, LEADER) or mostly men (in BIP women represented less than 9% of the study population). Only FIELD trial examined a considerable number of women (37 % of study population). The results showed no significant differences between men and women with regard to cardiovascular morbidity and mortality.

The relatively paucity of long term efficacy and safety data in women is of concern. However, the findings of the FIELD subgroup analysis suggesting no clinically relevant gender effects together with the lack of evidence from smaller studies to support an altered response of women to fibrates indicate that any specific recommendations for women may not be currently justified.

3.6. Subgroups or medical conditions associated with deleterious outcome

There are no robust epidemiological data suggesting that specific subgroups in terms of age, gender, exposure, concomitant therapies or medical conditions may be at increased risk of an adverse outcome when treated with fibrates.

3.7. Future studies – Risk management

No further clinical or epidemiological studies are ongoing or planned by MAHs for bezafibrate, ciprofibrate and gemfibrozil. However, the risk assessment is continuously being performed through pharmacovigilance and the Periodic Safety Update Reports.

For fenofibrate, a number of studies are currently in progress or planned aiming at investigating its effects, alone or in combination with other treatments, in various subgroups including patients with diabetes. These will form part of a Risk Management Plan proposed by the MAH.

4. CLINICAL GUIDELINES

Most current clinical guidelines on the treatment of dyslipidaemias and the prevention of

cardiovascular diseases agree that fibrates are the treatment of choice for severe hypertriglyceridaemia, although there is some disagreement on the precise triglyceride concentrations. All guidelines also agree that LDL-C reduction is the primary objective, and statins should always be used first as long as LDL-C needs to be reduced to the, predefined according to CVD risk, target levels. This apparently includes patients with mixed hyperlipidaemia as well as diabetic patients (following the FIELD trial results). Most guidelines recommend a statin-fibrate combination in cases where a statin alone has failed to reduce triglycerides (and/or increase HDL-C) to target levels. However, the lack of solid evidence to support such as strategy, and the potential risks are acknowledged. Finally, some guidelines recommend with caution, the use of a fibrate alone in cases of less severe hypertriglyceridaemia when LDL-C is controlled and there is increased CVD risk.

5. CONCLUSIONS

The fibrates share a common mechanism of action and have similar effects on serum lipids, mainly a decrease in triglycerides and a smaller increase in HDL-C concentrations. There are also some differences such as the distinct chemical structure of gemfibrozil but their clinical relevance is uncertain.

In most cases, the current indications for fibrates were first granted mainly on the basis of their effects on surrogate parameters. Recent trials, however, have provided evidence that a favourable action on lipid metabolism may not always translate into patient benefit. It was deemed, therefore, important to consider the current evidence on the effects of the different fibrates on cardiovascular morbidity and mortality, especially when considering the availability of alternative therapies, such as statins, with an overwhelming amount of data supporting a significant decrease in cardiovascular events and mortality in the primary and secondary prevention of CVD.

Despite differences in methodology and study populations, the major fibrate trials show 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). It needs to be noted, however, that 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 are available for ciprofibrate. Given, however, the similar mechanisms of action and effects on lipids, no considerable differences in terms of efficacy and safety should be expected.

This review tried to identify specific subgroups of patients who may benefit most from fibrate treatment. Clearly, patients with severe hypertriglyceridaemia are one subgroup, and this is also supported by most clinical guidelines. However, for most other dyslipidaemic patients with co-existing or isolated high cholesterol/ LDL-C, the body of evidence is inarguably in favour of statins as a first treatment choice. Nevertheless, fibrates can still have a role when statins cannot be used. As for diabetic patients, although the pathophysiology of action of fibrates provided a promising theoretical background, the current evidence, mainly from FIELD trial, is rather discouraging. With regard to the combination of statins with fibrates, the lack of robust data on the long term efficacy of such a therapy together with the potential risks do not allow any relevant recommendations.

In conclusion, despite the long presence of fibrates on the market, there is only limited evidence of a long term clinical benefit from their use 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 is no longer justified. However, the effects of

fibrates mainly on triglycerides, as well as a smaller but overall positive effect on HDL and LDL cholesterol suggest that there are subgroups of patients, who may still benefit from this therapy.

In this context, the overall benefit:risk of fibrates for specific indications is considered still positive. The SPC will be updated to reflect the available evidence and current clinical practice.

6. PhVWP DECISION

The following have been agreed by the PhVWP:

1. Changes to the SPC

Section 4.1

Section 4.1 of the SPC should be harmonised and updated as follows:

For bezafibrate, fenofibrate and ciprofibrate:

[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.*
- *Mixed hyperlipidaemia when a statin is contraindicated or not tolerated.*

For gemfibrozil:

[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.*
- *Mixed hyperlipidaemia when a statin is contraindicated or not tolerated.*
- *Primary hypercholesterolaemia when a statin is contraindicated or not tolerated.*

Section 5.1

The following statement should be included in section 5.1 of the SPC of all fibrates:

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

2. Risk Management Plan

A Risk Management Plan will be prepared for fenofibrate based on the initial proposal of the MAH and amended in line with the recommendations of the Rapporteur.

ANNEX 1

LIST OF QUESTIONS FOR BRAND-LEADERS OF GEMFIBROZIL (PFIZER), BEZAFIBRATE (ROCHE), FENOFIBRATE (FOURNIER) AND CIPROFIBRATE (SANOFI-AVENTIS)

CONTEXT

The fibrates were introduced into clinical practice at a time when the causative link between raised cholesterol, lipid metabolism and cardiovascular mortality were under intense investigation. The first to be introduced into clinical use was clofibrate in 1962 and was approved in the USA in 1967. There are currently 4 products (gemfibrozil, fenofibrate, bezafibrate and ciprofibrate) in clinical use; Clofibrate was withdrawn in the 1980s in the UK.

Fibrates were developed at the time when the classification of lipid abnormalities was evolving; hence the current indications for several products refer to the Fredrickson classification which is rarely used. The indications for the fibrates are quite diverse and reflect the results of clinical trials conducted to support the indications for individual products, the degree to which class action to support each new fibrate was accepted by the regulatory authorities, and to the emerging knowledge on the link between cholesterol and cardiovascular disease. Furthermore, whilst the pharmacology of statins is well understood, that for fibrates is more ambiguous. They stimulate lipoprotein lipase, hence increasing hydrolysis of TGs in chylomicron and VLDL particles, and liberate free fatty acids (FFAs) for storage in fat or metabolism in striated muscle. They also, probably, reduce hepatic VLDL production and increase hepatic LD uptake. Fibrates also reduce plasma fibrinogen and improve glucose tolerance. Whether these effects are clinically advantageous is unknown, but it has led to a recent surge of interest in linking them to the metabolic syndrome, possibly through activation of the peroxisome proliferators activated receptor activator type alpha (PPAR α). The British National Formulary (No 50) describes their action as decreasing serum TGs, with variable effects on LDL-cholesterol.

Their precise place in the treatment of coronary heart disease with the aim of reducing mortality and morbidity is also unclear. Though some SPCs have an indication for primary prevention of heart disease, others deny a specific beneficial effect on mortality or morbidity. The convincing demonstration of the significant effect of statins on total and CV mortality in large studies, has relegated fibrates to second line treatment at best; the current British National Formulary (No 50) states -

'Statins are drugs of first choice for treating hypercholesterolemia; statins or fibrates can be used, either alone or together to treat raised hyperlipidaemia.'

'Fibrates act mainly by reducing serum triglycerides; they have variable effects on LDL-cholesterol. Although a fibrate may reduce the risk of coronary heart disease events in those with low HDL-cholesterol or with raised triglycerides a statin should be used first.'

The Pharmacovigilance Working Party will undertake a risk:benefit assessment of the above four fibrates with the objective of establishing the place of fibrates in the treatment of cardiovascular and dyslipidaemic diseases; and in diabetes mellitus, in the statin era.

Marketing Authorisation Holders of medicinal products containing a Fibrate are requested to provide the CHMP with data regarding the following issues:

Regarding the clinical safety of your Fibrate containing medicinal product(s)

Please submit a **report summarising and critically reviewing**

1. All available clinical trial evidence for the effects of your fibrate on coronary heart disease (mortality and morbidity) and on all-cause mortality and stroke, in all users and in specific subpopulations, including patients with diabetes mellitus, (trials may be finalised or ongoing, published or unpublished). Study reports should be annexed. Additional meta-analyses of clinical trial data may be provided where appropriate.
2. Any trial data that might distinguish an individual fibrate from the rest of the class.
3. Trial evidence to support the use of your fibrates as second line therapy to statins in a given indication
4. Trial evidence for beneficial effect of treatment with your fibrate in a specific subgroup e.g. patients with raised TG and for low HDL. Surrogate and clinical outcomes should be provided.
5. Any evidence disproving gender effect in terms of increased benefit or risk by gender group.
6. Epidemiological data obtained from observational studies identifying factors such as age, gender, dose, duration of exposure, therapeutic indication, concomitant medication(s) and medical conditions which are associated with deleterious outcome may also be provided.

Regarding Risk Management plan of your Fibrate containing medicinal product(s)

1. Provide any plans/ protocols including ongoing and future clinical trials, epidemiological studies, with timelines to examine short, medium or long-term effects of fibrates on coronary heart disease (mortality and morbidity) and on all-cause mortality.
2. Provide details of data safety monitoring board reviews for all concerned trials (including ongoing and stopped), such as nature of review, timelines for interim analyses and assurance that any relevant analyses will be highlighted to Regulatory Authorities as soon as possible.
3. Provide plans for meta-analysis or pooled clinical trial analysis where appropriate.
4. Provide a table showing the timelines for all the above mentioned plans.

ANNEX 2

MAIN RESULTS OF MAJOR TRIALS WITH FIBRATES

| | HHS (1987) | VA-HIT (1999) | BIP (2000) | LEADER (2002) | FIELD (2005) |
|---|-----------------------|--------------------------|-----------------------|--------------------------|-------------------------------------|
| Active | Gemfibrozil | Gemfibrozil | Bezafibrate | Bezafibrate | Fenofibrate |
| N (men, %) | 4081 (men) | 2531 (men) | 3090 (91%) | 1568 (men) | 9795 (63%) |
| Population (prevention) | Primary | Secondary | Secondary | Secondary | Diabetics Primary & Secondary |
| Primary endpoint | CHD events | CHD events | CHD events | CVD events | CHD events |
| Lipid parameters | | | | | |
| TC (Δ %) | 6.96 (-11) | 4.51 (-4) | 5.47 (-5) | 5.60 (-8) | 5.03 (-7) |
| LDL-C (Δ %) | 4.88 (-10) | 2.95 (0) | 3.85 (-7) | 3.37 (-8) | 3.07 (-6) |
| TG (Δ %) | 1.98 (-43) | 1.7 (-31) | 1.63 (-21) | 2.11 (-23) | 1.95 (-22) |
| HDL-C (Δ %) | 1.21 (+9) | 0.85 (+6) | 0.89 (+18) | 1.11 (+8) | 1.10 (+1) |
| Endpoints | | | | | |
| Primary (Δ %) | -34 | -22 | -9 | -4 | -11 |
| p | 0.02 | 0.006 | 0.26 | 0.72 | 0.16 |
| All cause mortality (Δ %) | +6 | -11 | +5 | +5 | +11 |
| p | 0.36 | 0.23 | 0.62 | 0.81 | 0.18 |
| CHD: Coronary heart disease, CVD: Cardiovascular disease, TC: total cholesterol, LDL-C: low density lipoprotein cholesterol, TG: triglycerides, HDL-C: high density lipoprotein cholesterol | | | | | |