Annex II

Scientific conclusions and grounds for amendment of the summaries of product characteristics and package leaflets presented by the EMA

Scientific conclusions

Overall summary of the scientific evaluation of fenofibrate, bezafibrate, ciprofibrate and gemfibrozil containing medicinal products (see Annex I)

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 fibrates share a common mechanism of action and exert qualitatively similar effects on serum lipid triglycerides (decrease) and HDL-cholesterol concentrations (increase). In this regard, the Pharmacovigilance Working Party (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.

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 are available for ciprofibrate, but differences across the class in surrogate marker effects have not been shown.

Despite differences in methodology and study populations, the major fibrate trials have shown that treatment with fibrates may reduce coronary heart disease events but there is no clear evidence that they can reduce all cause mortality in the primary or secondary prevention of cardiovascular disease.

Overall the available evidence suggested that 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. Since therapeutic efficacy cannot be obtained from the data provided the use of fibrates as first line treatment for these indications is no longer justified 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, the effect of fibrates mainly on triglycerides but also 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.

Based on the above data, it was concluded that the product information for all fibrates should be updated to reflect the available evidence and current clinical practice, and define groups of patients that were more likely to derive benefit from fibrates such as patients with severe hypertriglyceridaemia with or without low HDL cholesterol or with mixed hyperlipidaemia when a statin is contraindicated or not tolerated.

Also recognizing that trials have provided evidence that gemfibrozil may differ from the rest of the class and may have a more favourable profile it was felt that a differentiation in the given indications for gemfibrozil was justified to also include treatment 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 positive recommendations for most fibrates. However, for certain doses of fenofibrate (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-analyses support 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 and this has been reflected in the given indications for this product.

Based on the above, the CHMP recommended the amendments of the marketing authorisations and concluded that the benefit risk profile of fibrates is still positive in the agreed indications.

Grounds for amendment of the summaries of product characteristics and package leaflets

Whereas

- The CHMP considered the referral under Article 31 of Directive 2001/83/EC, as amended, for medicinal products containing fenofibrate, bezafibrate, ciprofibrate and gemfibrozil.

- The CHMP 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 CHMP considered additional published data for the fibrates, including results of the ACCORD lipid trial which were supportive of the use of fenofibrate (100, 300, 67, 200, 250 mg capsules and 160 and 145 mg film coated tablets) as add on therapy to a statin in patients with mixed hyperlipidaemia at high cardiovascular risk when triglycerides and HDL cholesterol are not adequately controlled with a statin alone.

- 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 in severe hypertriglyceridaemia and certain dyslipidaemias where a statin cannot be used patients can still benefit from treatment with fibrates. Furthermore fenofibrate showed benefit as add on treatment to statins as detailed above.

the CHMP has recommended the variation of the marketing authorisation for which the relevant sections of the summaries of product characteristics and package leaflets are set out in Annex III for medicinal products containing fenofibrate, bezafibrate, ciprofibrate and gemfibrozil (see Annex I).