Annex II

Scientific conclusions and grounds for the variation to the terms of the marketing authorisations

Scientific conclusions and grounds for the variation to the terms of the marketing authorisations

The CMDh considered the below PRAC recommendation dated 7 November 2013 with regard to substances related to nicotinic acid (acipimox) indicated for the treatment of lipid disorders.

PRAC recommendation

On 19 December 2012, the European Medicines Agency was made aware of preliminary results from a large randomised clinical study (Heart Protection Study 2-Treatment of HDL to Reduce the Incidence of Vascular Events - HPS2-THRIVE) designed to assess the incremental benefit of extended release nicotinic acid (ERN)/laropiprant (LRPT) versus placebo in over 25,673 high-risk patients. The preliminary results of the HPS2-THRIVE study showed that the study did not meet its primary endpoint (reduction of the risk of major vascular events such as heart attack and stroke) as well as a statistically significant increase in the incidence of non-fatal but serious adverse events in the nicotinic acid/laropiprant group compared to the placebo group. A review of all available data was undertaken by the Pharmacovigilance Risk Assessment Committee (PRAC) to assess the above safety concerns and their impact on the benefit-risk balance of the centrally authorised combination products Tredaptive, Trevaclyn and Pelzont. As a result of the review, the PRAC recommended the suspension of the marketing authorisations of these products. Following the conclusion of these procedures, the PRAC was of the view that the concerns regarding the combination products may also be of relevance for the mono-component products and the Danish Health and Medicines Authority therefore initiated a review under Article 31 of Directive 2001/83/EC to assess the impact of the HPS2-THRIVE data on the benefit-risk balance of these products and to give its recommendation on whether their marketing authorisations should be maintained, varied, suspended or revoked and if the supply of the medicinal product should be prohibited. Having reviewed the list of EU products containing nicotinic acid or related substances, the PRAC noted that acipimox is the only high-dose substance indicated in lipid disorders still authorised in the EU and the scope of the procedure was therefore restricted to acipimox-containing products.

The PRAC considered that the clinical development data on acipimox was very limited and noted that no clinical outcome studies were conducted. Nevertheless, the PRAC considered that the efficacy of acipimox in lowering blood lipids in patients with some forms of hyperlipoproteinaemia is demonstrated. Based on the available data, acipimox was considered to be efficacious in reducing triglyceride levels in patients with hypertriglyceridaemia (Fredrickson type IV hyperlipoproteinaemia) and significantly superior to placebo in patients with hypercholesterolaemia and hypertriglyceridaemia (Fredrickson type IIb hyperlipoproteinaemia). It was noted that acipimox was of particular use in patients who either do not tolerate a statin or do not achieve triglyceride goals with statin therapy alone and could therefore be used as an alternative or adjunct treatment to reduce triglyceride levels in these patients. The PRAC also agreed that acipimox should not be indicated for increasing HDL-C or for cardiovascular prevention in line with the recent data casting doubts on the association between elevating HDL-C levels and reducing the risk of cardiovascular disease. This was reflected in the product information in order to adequately inform healthcare providers and patients.

The safety data available for acipimox, including data on nicotinic acid obtained from HPS2-THRIVE, showed that the safety profile of acipimox is well characterised. Most identified adverse events are already reflected in the acipimox product information and the PRAC considered that the available data did not identify any new safety information which impacts the benefit-risk balance of acipimox, with the exception of a potential risk of muscle toxicity, which was addressed by adding a warning to the product information.

The PRAC also took into account the views of the European experts consulted in an Ad-Hoc expert meeting, according to which acipimox has a role as lipid-lowering therapy in well-defined settings and indications, such as the treatment of severe hypertriglyceridaemia but only as a second or third line agent. The PRAC also noted that according to the experts, the current data available did not have any major impact on the safety profile of acipimox.

Having reviewed all the available data, including studies and publications on acipimox as well as data on the related substance nicotinic acid, including the AIM-HIGH and HPS2-THRIVE studies, the PRAC considered the efficacy of acipimox in the treatment of certain well-defined lipid disorders to be demonstrated and that acipimox therefore remains a treatment alternative in the management of lipid disorders characterised by elevated plasma levels of triglycerides (Fredrickson type IV hyperlipoproteinaemia), or both triglycerides and cholesterol (Fredrickson type IIb hyperlipoproteinaemia). However, taking into account the available data as well as the current use of

the product and on the basis of expert advice, the PRAC was of the opinion that acipimox should only be used to reduce triglyceride levels in patients who either do not tolerate statin or fibrates or who do not achieve triglyceride goals with statin or fibrate therapy alone and should therefore be used as an alternative or adjunct treatment to reduce triglyceride levels in these patients. The PRAC therefore revised the indication accordingly.

Overall conclusion

The PRAC concluded that the benefit-risk balance of acipimox-containing products remains favourable under normal conditions of use, subject to the agreed changes to the product information.

Grounds for PRAC recommendation

Whereas

- The PRAC considered the procedure under Article 31 of Directive 2001/83/EC resulting from pharmacovigilance data for nicotinic-acid and related substances initiated by Denmark and decided to restrict the scope of the procedure to products containing acipimox, the only high-dose nicotinic acid-related substance indicated in lipid disorders authorised in the EU;
- The PRAC reviewed the totality of the available data, including studies and publications on acipimox, the MAH responses as well as relevant data on nicotinic acid, including the AIM-HIGH and HPS2-THRIVE studies;
- The PRAC considered that acipimox is efficacious in reducing triglyceride levels in patients with hypertriglyceridaemia (Fredrickson type IV hyperlipoproteinaemia) and with hypercholesterolaemia and hypertriglyceridaemia (Fredrickson type IIb hyperlipoproteinaemia) but only, on the basis of available evidence including current medical knowledge on the use of acipimox, as a second or third line agent in patients who have not responded adequately to other treatments such as statin or fibrate treatment;
- The PRAC considered that the available safety data identified a potential risk of muscle toxicity, for which a warning was added to the product information.

The PRAC, as a consequence, concluded that the benefit-risk balance of the medicinal products containing acipimox identified in Annex I remains favourable, subject to the agreed changes to the product information. Having considered the matter, the PRAC therefore recommended the variation of the marketing authorisations for acipimox-containing medicinal products.

The CMDh, having considered the PRAC recommendation pursuant to article 107k of Directive 2001/83/EC dated 7 November 2013, reached a position on the variation to the terms of the marketing authorisations of acipimox for which the relevant sections of the summary of product characteristics and package leaflets are set out in Annex III.