Annex I

Scientific conclusions and grounds for suspension of the marketing authorisation presented by the European Medicines Agency

Scientific conclusions

Overall summary of the scientific evaluation of nicotinic acid/laropiprant

Nicotinic acid/laropiprant (authorised in the EU as Tredaptive, Trevaclyn and Pelzont) is indicated for the treatment of dyslipidaemia, particularly in adult patients with combined mixed dyslipidaemia and in adult patients with primary hypercholesterolaemia in combination with HMG-CoA reductase inhibitors (statins), when the cholesterol lowering effect of HMG-CoA reductase inhibitor monotherapy is inadequate. It can be used as monotherapy only in patients in whom HMG-CoA reductase inhibitors are considered inappropriate or not tolerated. The product is authorised as modified release tablets containing 1000mg of nicotinic acid and 20mg of laropiprant.

As part of the pharmacovigilance activities included in the adopted risk management plan, the marketing authorization holder (MAH) agreed to report on a randomised clinical study (HPS2-THRIVE[1]) designed to assess the incremental benefit of nicotinic acid/laropiprant versus placebo as add-on to simvastatin 40mg, with or without ezetimibe. The HPS2-THRIVE study was conducted by the Clinical Trial Service Unit at the University of Oxford and funded by the MAH. Preliminary results of this study became available and were submitted by the MAH for review end of December 2012. The available evidence provided by the MAH in writing and at an oral explanation was reviewed by the Pharmacovigilance Risk Assessment Committee (PRAC).

Previously available data on laropiprant/nicotinic acid included nine studies where a total of 5,782 patients were exposed to the medicine. The studies were not designed to evaluate cardiac effects but it was noted that serious cardiac disorders occurred more often in the nicotinic acid/laropiprant group compared to placebo. Identified risks were reflected in the product information and the risk management plan and included myopathy, glucose intolerance and abnormal liver function. Important missing information, such as the effects of long-term exposure, bleeding and thrombotic cardiovascular events was expected to be clarified through routine pharmacovigilance and through monitoring of patients in clinical trials, in particular the HPS2-THRIVE study.

The HSP2-THRIVE study was a very large randomised trial, enrolling 25,673 patients considered to be at high risk of cardiovascular events. Over the 3.9 years median follow-up, treatment with nicotinic acid/laropiprant compared to placebo did not achieve its primary endpoint. The PRAC therefore considered that the results demonstrate that nicotinic acid/laropiprant has no additional efficacy in terms of cardiovascular outcome as an add-on treatment to statins.

With regards to the risks observed, there were also strong new unfavourable safety signals. There was a statistically significant increase in the incidence of non-fatal serious adverse events in the nicotinic acid/laropiprant (study drug) group compared to the placebo group. This increase was driven by differences observed in the system organ class blood and lymphatic, gastrointestinal, infections, metabolism, musculoskeletal, respiratory and skin, which all favoured placebo. Based on the known safety profile of the product, some adverse events were expected, such as elevations in transaminases, myopathy, some skin and gastrointestinal events and impaired glucose tolerance. However, the new unexpected higher incidence of bleeding and infections in the study drug group compared to the placebo group was of concern. The risk of blood and lymphatic disorders was greater in the study drug group compared to the placebo group.

Although the population studied in HPS2-THRIVE was not selected based on high LDL cholesterol levels, the safety results observed in the 25,673 patients were considered to be of relevance to the current approved indication as there is no evidence to suggest that patients currently indicated for treatment with nicotinic acid/laropiprant would be protected from the adverse events observed in

[1] HPS2-THRIVE: Hearth Protection Study 2 – Treatment of HDL (high density lipoprotein) to Reduce the Incidence of Vascular Events.

HPS2-THRIVE study. In addition, the failure of the HPS2-THRIVE study to meet the primary efficacy endpoints raised serious concerns regarding the efficacy of nicotinic acid/laropiprant in the indicated patient population, as overlap between this and the study populations is expected.

The PRAC concluded that data from the HPS2-THRIVE study has confirmed the previously known safety profile of nicotinic acid/laropiprant and additionally revealed new safety concerns. Considering the lack of clinically relevant efficacy and the negative safety profile (including the newly identified serious safety concerns) associated with the use of nicotinic acid/laropiprant, the PRAC considered that the benefit-risk balance has shifted towards a negative balance. Furthermore, no additional risk minimisation measures were identified or proposed by the marketing authorisation holder to minimise the newly identified safety concerns.

The PRAC issued a recommendation to the CHMP on 10 January 2013.

Overall conclusion

Having noted all of the above, the CHMP considers that the benefit-risk balance for nicotinic acid/laropiprant is not favourable in the approved indication and recommends the suspension of the marketing authorisation of the products containing laropiprant/nicotinic acid.

For the suspension to be lifted, the MAH would need to provide convincing data to identify a patient population in which the efficacy of nicotinic acid/laropiprant can be demonstrated, and in which the benefit clearly outweighs the risks, taking into account the new risks identified by the HPS2-THRIVE study.

Grounds for CHMP opinion

Whereas,

- The CHMP considered the notification under Article 20 of Regulation (EC) No 726/2004 for nicotinic acid/laropiprant (approved in the EU as Tredaptive, Trevaclyn and Pelzont) initiated by the European Commission,
- The CHMP considered the totality of the data available for laropiprant/nicotinic acid, including the emerging preliminary data from the HPS2-THRIVE study, which was not available at the time of the original marketing authorisation, the MAH responses, the PRAC assessment and the discussions within the CHMP,
- The CHMP considered that the failure of the HPS2-THRIVE study to meet the primary efficacy endpoints raises serious concerns regarding the efficacy of laropiprant/nicotinic acid,
- The CHMP concluded that the statistically significant increase in the incidence of serious adverse events observed in the nicotinic acid/laropiprant group compared to the placebo group of the HPS2-THRIVE study raises serious concerns,
- The CHMP noted that no additional risk minimisation measures could be recommended at this point in time,
- The CHMP therefore considered that a patient population in which nicotinic acid/laropiprant has a clear favourable benefit-risk cannot be identified based on the current data.

The CHMP therefore concluded that the benefit-risk balance of nicotinic acid/laropiprant is affected adversely by the results from the HPS2-THRIVE study and is considered no longer favourable.

Following the provisions under Article 20 of Regulation (EC) No 726/2004, the CHMP recommends the suspension of the marketing authorisations for nicotinic acid/laropiprant (see Annex A).

To lift the suspension, the MAH would need to provide convincing data to identify a patient population in which the efficacy of nicotinic acid/laropiprant can be demonstrated, and in which the benefit clearly outweighs the risks, taking into account the new risks identified by the HPS2-THRIVE study (see Annex II).

Annex II

Conditions for lifting the suspension

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For the suspension to be lifted, the marketing authorisation holder for nicotinic acid/laropiprant shall provide the following:

Convincing data to identify a patient population in which the efficacy of nicotinic acid/laropiprant can be demonstrated, and in which the benefit clearly outweighs the risks, taking into account the new risks identified by the HPS2-THRIVE study.