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Pharmacovigilance Risk Assessment Committee (PRAC)

Assessment report

Pelzont

Procedures under Article 20 of Regulation (EC) No 726/2004

International non-proprietary name: nicotinic acid and laropiprant

Procedure no: EMEA/H/C/903/A-20/0038

Note

Assessment report as adopted by the PRAC and considered by the CHMP with all information of a commercially confidential nature deleted.

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1. Background information on the procedure

On 19 December 2012, the European Medicines Agency was made aware of the availability of preliminary results from a randomised clinical study (HPS2-THRIVE[1]) designed to assess the incremental benefit of nicotinic acid/laropiprant (as extended release formulation), versus placebo as add-on to simvastatin 40mg, with or without ezetimibe, in over 25,673 high-risk patients in the UK, Scandinavia and China. 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 follow-up of this study was part of the risk management plan agreed by the CHMP at the time of the authorisation and therefore part of the pharmacovigilance activities of the marketing authorisation holder (MAH).

The preliminary results of the HPS2-THRIVE study showed that the study did not meet its primary endpoint of reduction of major vascular events. In addition, there was a statistically significant increase in the incidence of non-fatal serious adverse events in the nicotinic acid/laropiprant group compared to the statin group.

In view of the above, the European Commission initiated procedures under Article 20 of Regulation (EC) No 726/2004 on 20 December 2012, requesting the European Medicines Agency to assess the above safety concerns and their impact on the benefit/risk for Tredaptive, Trevaclyn and Pelzont, and to give its opinion on whether the marketing authorisation for these products should be maintained, varied, suspended or withdrawn. As the request results from the evaluation of data resulting from pharmacovigilance activities, the Pharmacovigilance Risk Assessment Committee (PRAC) should issue a recommendation to be transmitted to the Committee for Medicinal Products for Human Use (CHMP).

After reviewing all the available data submitted by the MAH to address the concerns discussed, the PRAC adopted recommendations on 10 January 2013.

2. Scientific discussion

Nicotinic acid/laropiprant 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 20mg of laropiprant and 1000mg of nicotinic acid.

As part of the pharmacovigilance activities included in the adopted risk management plan, the MAH agreed to report on a randomised clinical study (HPS2-THRIVE) 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. The preliminary results submitted were deemed relevant for this review[2].

2.1. Clinical aspects

HPS2-THRIVE was a large trial designed to assess the effect of nicotinic acid/laropiprant on a composite endpoint of major vascular events, which included the combination of coronary death, non-fatal heart attack, stroke or revascularisation. The study started in 2007 and was included in the risk management plan in order to address the following identified risks: myopathy, glucose intolerance and abnormal liver function. The study was also used to address concerns over missing information, including monitoring of long-term safety (exposure greater than 12 months) and effects on bleeding and thrombotic cardiovascular events.

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

[2] The results referred in this report are preliminary and may include duplicates; thus minor differences between the values cited and future publications can be expected. All results are reported as nicotinic acid/laropiprant compared to placebo.

Patients enrolled in the HPS2-THRIVE study were at high risk of coronary heart disease (CHD) due to a history of occlusive vascular disease and were treated with simvastatin 40mg or simvastatin 40mg and ezetimibe 10mg to achieve a total cholesterol level of less than 3.5 mmol/L prior to randomisation to nicotinic acid/laropiprant or placebo. The inclusion criteria were patients from 50 to 80 years of age and at high risk of CHD due to a history of myocardial infarction, cerebrovascular disease, peripheral artery disease, or stable coronary disease in the presence of diabetes mellitus. The major exclusion criteria included medical conditions that were likely to be a problem with extended release nicotinic acid or statin therapy. Patients were followed for a median of 3.9 years.

2.1.1. HPS2-THRIVE preliminary results

The HPS2-THRIVE study enrolled 25,673 patients considered to be at high risk for cardiovascular events. Over the 3.9 years median follow-up, treatment with nicotinic acid/laropiprant (N=12,838) compared to placebo (N=12,835) resulted in a non-significant 4% proportional reduction in major vascular events (HR 0.96 (0.90-1.03); p=0.29); therefore the HPS2-THRIVE study did not achieve its primary endpoint. The results of the components of the primary endpoint (e.g. major coronary events, non-fatal heart attack, and stroke) were generally consistent with the results of the composite primary endpoint.

Regarding safety, results available in those patients who tolerated the run-in period and were randomised showed that approximately 16% and 8% stopped treatment for medical reasons in the nicotinic acid/laropiprant and placebo groups respectively. The majority of the differences between groups were due to skin and gastrointestinal adverse events.

There was a statistically significant increase in the incidence of non-fatal serious adverse events in the nicotinic acid/laropiprant group compared to the placebo group, with a risk ratio of 1.12 (1.08-1.16, p=0.0001) driven by differences in the following system organ classes:

a. blood and lymphatics 1.58 (1.13-2.21) p = 0.0075,
b. gastrointestinal 1.29 (1.14-1.45) p<0.0001,
c. infections 1.22 (1.11 – 1.33) p <0.0001,
d. metabolism 1.39 (1.27-1.53) p <0.0001,
e. musculoskeletal 1.23 (1.07 -1.41) p = 0.0033,
f. respiratory 1.18 (1.01-1.38) p= 0.04 and
g. skin 1.70 (1.22-2.39) p = 0.0019.

The observed adverse events data currently available revealed an elevation of hepatic transaminases in patients treated with nicotinic acid/laropiprant compared to placebo. Abnormal liver function tests, including elevations in transaminases, are a known identified risk, included in the product information and in the risk management plan.

The review also revealed an increase in gastrointestinal and intracranial bleeding, new onset diabetes, infections, skin reactions and myopathy in those patients on nicotinic acid/laropiprant compared to placebo. These adverse events of concern are discussed in further detail hereinafter.

Gastrointestinal and intracranial bleeding

According to the results available for review, the risk of blood and lymphatic disorders was greater among those allocated to nicotinic acid/laropiprant compared to placebo (84 vs. 53 patients, respectively; HR 1.58 [95% CI 1.13-2.21]; p = 0.0075). The difference appeared to be attributed largely to anaemia. There was an increased risk for gastrointestinal bleeding (109 vs. 71) and intracranial bleeding (139 vs. 119) among those allocated to nicotinic acid/laropiprant compared to placebo. The increase in any intracranial bleeding was mainly driven by an increase in haemorrhagic stroke. Overall, statistically increased numbers of gastrointestinal adverse events were observed with nicotinic acid/laropiprant compared to placebo (HR 1.29 [95% CI 1.14-1.45]; p < 0.001), in particular due to haemorrhages, ulcerations and other gastrointestinal signs and symptoms.

Infections

The risk of infection was increased among those allocated to nicotinic acid/laropiprant compared to placebo (for any infection, HR 1.22 [95% CI 1.11 – 1.33]; p <0.0001). Based on the information available, there was an increase in both bacterial (82 vs. 54) and mycobacterial (16 vs. 3) infections

observed in patients treated with nicotinic acid/laropiprant compared to placebo. Where the pathogen was not specified, there was also a higher number of serious adverse events observed in patients treated with nicotinic acid/laropiprant compared to placebo (885 vs. 745). There were increases in the risk of urinary tract and abdominal infections and significant increases in the risk of lower respiratory tract (519 vs. 446, HR 1.17 [95% CI 1.03 – 1.33]; p = 0.01), skin (67 vs. 40, HR 1.66 [95% CI 1.14 – 2.43]; p =0.0085) and other infections.

Diabetes
New onset diabetes was reported for those without diabetes at randomisation. Based on the preliminary results available for review, there was an increase in the risk of new onset diabetes with treatment with nicotinic acid/laropiprant compared to placebo (780 vs. 620, respectively; HR 1.28 [95% CI 1.15 – 1.42]). It was noted that nicotinic acid medicinal products have been associated with increases of fasting blood glucose levels and impaired glucose tolerance and the product information reflects this.

Myopathy
During the open-label run-in period in 2008 (first annual safety report of the HPS2-THRIVE study), the study safety committee identified a higher than expected incidence of myopathy in Chinese patients taking nicotinic acid/laropiprant and simvastatin 40mg. These findings were reflected in the risk management plan as well as in the product information. The results now available for review from the HPS2-THRIVE study confirmed an increased risk of myopathy (excluding rhabdomyolysis) in patients treated with nicotinic acid/laropiprant compared to placebo (68 vs. 12, respectively). The results seemed to be mainly driven by the events in patients from China.

Skin reactions
The risk of skin disorders, in particular epidermal and dermal disorders, was greater among those allocated to nicotinic acid/laropiprant compared to placebo (86 vs 50, HR 1.70 [95% CI 1.22 – 2.39]; p = 0.0019).

Death
The results showed an unfavourable trend in total mortality in patients treated with nicotinic acid/laropiprant compared to placebo, due to vascular and non-vascular causes.**2.1.2 Other studies**

Available safety information from the MAH pooled safety database, which included three randomised controlled pivotal phase II/III studies and six additional post-authorisation studies, was considered in this review. A total of 5,782 patients were exposed to laropiprant/nicotinic acid.

Based on the data available, there was no excess of bleedings, infections, myopathy and skin reactions among patients treated with laropiprant/nicotinic acid. The data suggest treatment with nicotinic acid/laropiprant increases blood glucose levels and this might lead to development of diabetes.
It was noted that serious cardiac disorders occurred more often in the nicotinic acid/laropiprant group compared to placebo. Adverse events with the highest incidence were myocardial infarction, angina pectoris, palpitations, tachycardia and atrial fibrillation. However, these studies were not designed to evaluate cardiac effects, had small sample sizes and short study durations.

2.2. Risk management plan

A tabular summary of the risk management plan, adapted from version 7 (dated June 2011) is presented below. No new information was provided by the MAH for this review, and no additional minimisation or mitigation measures were proposed to address the newly identified safety concerns.

Safety concern	Proposed Pharmacovigilance Activities (routine and additional)	Proposed Risk Minimisation Activities (routine and additional)
Identified Risks		
Abnormal liver function tests	Routine pharmacovigilance Monitor reports of abnormal liver function tests in ongoing and planned clinical trials	Wording to address this risk included in current labelling
Myopathy/rhabdomyolysis in combination with an HMG CoA reductase inhibitor	Routine pharmacovigilance to include evaluation of reports in Asian patients. Monitor reports of Myopathy/rhabdomyolysis in	Wording to address this risk included in current labelling

Safety concern	Proposed Pharmacovigilance Activities (routine and additional)	Proposed Risk Minimisation Activities (routine and additional)
	combination with an HMG CoA reductase inhibitor in ongoing and planned clinical trials	
Impaired glucose tolerance	Routine pharmacovigilance Monitor reports of impaired glucose tolerance in ongoing and planned clinical trials	Wording to address this risk included in current labelling
Important Missing Information		
Use during pregnancy and lactation	Routine pharmacovigilance Pregnancy registry (US based)-on hold. Swedish Medical Birth Registry GPRD: analysis of pregnancy exposures	Wording to address this included in current labelling
Use in patients below 18 years of age	Routine pharmacovigilance Monitor reports of use in patients below 18 years of age in ongoing and planned clinical trials including a paediatric study (P071)	Wording to address this included in current labelling
Use in patients greater than or equal to 65 years of age	Routine pharmacovigilance Monitor reports of use in patients greater than or equal to 65 years of age in ongoing and planned clinical trials **including HPS2-THRIVE**	Wording to address this included in current labelling
Long term exposure (greater than 12 months)	Routine Pharmacovigilance Monitor reports of long term exposure (greater than 12 months) in ongoing and planned clinical trials **including long-term safety data from HPS2-THRIVE**	
Concomitant therapy with lipid lowering drugs other than statins	Routine pharmacovigilance	Wording to address this included in current labelling
Patients on long term therapy exposure - Effects on Platelet Reactivity (Inhibition)- bleeding events	Routine pharmacovigilance Monitor reports of patients on long term therapy exposure - Effects on Platelet Reactivity (Inhibition)- bleeding events in ongoing and planned clinical trials **including long-term safety data from HPS2- THRIVE**	
Patients on long term therapy exposure - Effects on Platelet Reactivity (Activation) - thrombotic cardiovascular events.	Routine pharmacovigilance Monitor reports of patients on long term therapy exposure - Effects on Platelet Reactivity (Activation) - thrombotic cardiovascular events in ongoing and planned clinical trials including **long-term safety data from HPS2-THRIVE**	
Use in Chinese patients on ER niacin/laropiprant in combination with statins other than simvastatin	Routine Pharmacovigilance	Wording to address this included in current labelling
Use in non-Chinese Asian patients	Routine Pharmacovigilance	Wording to address this included in current labelling

3. Overall discussion and benefit/risk assessment

Overall discussion

The PRAC considered the available evidence provided by the MAH in writing and at an oral explanation, including the preliminary data from the HPS2-THRIVE study.

Reference was made to data previously available on nicotinic acid/laropiprant, which included nine studies where a total of 5,782 patients were exposed to nicotinic acid/laropiprant. 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 preliminary results of the HSP2-THRIVE study that started in 2007 are now available. This 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 results of the components of the primary endpoint (e.g. major coronary events, non-fatal heart attack, stroke) were also generally consistent with the results of the composite 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. An increase in intracranial bleeding was observed, and this seemed to be mainly driven by an increased risk of haemorrhagic stroke. A statistically increased number of gastrointestinal adverse events was observed in the study drug group compared to the placebo group, in particular due to haemorrhages, ulcerations and other gastrointestinal signs and symptoms. The risk of infection was also increased in the study drug group compared to the placebo group.
It was also noted that there was a trend towards increased overall mortality (both vascular and non-vascular) in the study drug group compared to the placebo group.

The PRAC noted that 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 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.

No additional risk minimisation measures were identified or proposed by the marketing authorisation holder to minimise the newly identified safety concerns.

Benefit risk balance

Having noted all of the above, the PRAC 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.

Given the new risks identified, and that no risk minimisation measures are available to healthcare professionals and patients to address these concerns, the PRAC therefore considers that provisional measures are needed and recommends that the marketing authorisation, the marketing and the supply of nicotinic acid/laropiprant be suspended forthwith in all concerned EU member states awaiting the adoption of the final measures.

4. Communication plan

The PRAC considered that a Direct Healthcare Professional Communication (DHPC) was needed to communicate on the preliminary results from the HPS2-THRIVE study and the resulting regulatory measures.

Relevant European healthcare professional organisations were consulted and provided input on the draft DHPC.

The MAH should agree the translations and local specificities of the DHPC with national competent authorities. The DHPC should be sent to physicians who treat patients with lipid disorders (e.g. general practitioners, internal medicine physicians, cardiologists) and pharmacists.

5. Conclusion and grounds for the recommendation

Whereas,

- The PRAC 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 PRAC 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 and the discussions within the PRAC,
- The PRAC 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 PRAC 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 PRAC noted that no additional risk minimisation measures could be recommended at this point in time,
- The PRAC 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 PRAC 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 PRAC 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).

Given the new risks identified, and that no risk minimisation measures are available to healthcare professionals and patients to address these concerns, the PRAC therefore considers that provisional measures are needed and recommends that the marketing authorisation, the marketing and the supply of nicotinic acid/laropiprant be suspended forthwith in all concerned EU member states awaiting the adoption of the final measures.