EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Pharmacovigilance Risk Assessment Committee (PRAC)

PRAC referral assessment report

Substances related to nicotinic acid (acipimox) indicated for the treatment of lipid disorders

INN: acipimox

Procedure number: EMEA/H/A-31/1366

Procedure under Article 31 of Directive 2001/83/EC resulting from pharmacovigilance data

Note

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

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1. Background information on the procedure

On 27 February 2013, further to evaluation of data resulting from pharmacovigilance activities, the Danish Health and Medicines Authority informed the European Medicines Agency, pursuant to Article 31 of Directive 2001/83/EC, of their consideration that the benefit-risk balance of substances related to nicotinic acid indicated for the treatment of lipid disorders may have been impacted by recent clinical trial data and that it was therefore in the interest of the Union to refer the matter to the PRAC.

2. Scientific discussion

2.1. Introduction

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 as add-on therapy to simvastatin, with or without ezetimibe, in over 25,673 high-risk patients. Nicotinic acid/laropiprant (a combination product centrally authorised in the EU as Tredaptive, Trevaclyn and Pelzont) was indicated for the treatment of dyslipidaemia. The preliminary results of HPS2-THRIVE 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. On 10 January 2013, the PRAC concluded that the failure of HPS2-THRIVE to meet the primary efficacy endpoints raised serious concerns regarding the efficacy of nicotinic acid/laropiprant. The statistically significant increase in the incidence of serious adverse events observed in the nicotinic acid/laropiprant group compared to the placebo group was also of concern. As a patient population in which nicotinic acid/laropiprant had a clear favourable benefit-risk balance could not be identified, the PRAC concluded that the benefit-risk balance of nicotinic acid/laropiprant was affected adversely by the HPS2-THRIVE results and could no longer be considered favourable. The PRAC therefore recommended the suspension of the marketing authorisations, which was subsequently endorsed by the Committee for Medicinal Products for Human Use on 17 January 2013[1].

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 therefore discussed whether nicotinic acid, its related substances and laropiprant were affected by the new data on the combination products.

The PRAC noted that laropiprant has no effect on cholesterol and is instead used to reduce the incidence and severity of the known side effect of nicotinic acid-induced flushing. After confirmation that laropiprant is not authorised in the EU as a mono-component product, the PRAC concluded that no further review of laropiprant was necessary. However, mono-component products containing nicotinic acid or related substances indicated in the treatment of lipid disorders are authorised in the European Union. The Danish Health and Medicines Authority therefore initiated a review under Article 31 of Directive 2001/83/EC resulting from pharmacovigilance data 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.

Nicotinic acid has several derivatives (including acipimox and xantinol nicotinate) used at different doses for different indications. High dose (500–2000 mg/day) formulations can be used as lipid lowering products, while medium dose (50-150 mg/day) formulations are mainly used for vasodilatation in different syndromes e.g. intermittent claudication, memory disorders or loss of concentration. Lower dose (2-20 mg/day) formulations are mainly categorised as vitamins or food supplements, to prevent B3 vitamin deficiency or to aid smoking cessation. Taking into account the nature of the concerns raised by the data from HPS2-THRIVE, only high dose products indicated in lipid disorders were considered in the procedure. Having reviewed the list of EU products containing

[1] European Medicines Agency confirms recommendation to suspend Tredaptive, Pelzont and Trevaclyn - http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2013/01/news_detail_001694.jsp&mid=WC0b01ac058004d5c1

nicotinic acid or related substances, the PRAC noted that EU marketing authorisations for nicotinic acid-containing mono-component products had already been withdrawn and that xantinol nicotinate, a vasodilatator with anti-platelet and fibrinolytic effects, is prescribed primarily for various brain disorders and to patients with peripheral arterial obliterative disease. Having established that acipimox is the only high-dose substance indicated in lipid disorders still authorised in the EU, the PRAC decided to restrict the scope of the procedure to acipimox-containing products. Consequently, only the marketing authorisation holder (MAH) for acipimox submitted responses to the PRAC list of questions. In its responses to the PRAC list of questions, the MAH stated that there is very little data on the safety and efficacy of acipimox and also provided data from scientific literature on clinical trials performed with nicotinic acid as acipimox is structurally related to nicotinic acid. The PRAC took into account data all data submitted in its assessment. Only relevant information is discussed hereinafter.

2.2. Clinical efficacy

Medicines containing nicotinic acid (also known as vitamin B3, niacin or nicotinamide) have been authorised in the EU via national procedures since the mid-1950s in the treatment of cardiovascular disease although their use in Europe has largely been superseded by better-tolerated drugs. Nicotinic acid has complex effects on lipoprotein metabolism, decreasing levels of triglycerides and of low density lipoprotein cholesterol (LDL-C) through partial inhibition of lipolysis from the adipose tissue, resulting in a decreased flux of free fatty acids to the liver, reducing the very low density lipoprotein (VLDL) production rate. Nicotinic acid also increases levels of high-density lipoprotein cholesterol (HDL-C) by reducing hepatic removal, increasing the flux of cholesterol from cells to HDL particles and inhibiting the cholesterylester transfer protein-mediated lipid exchange, which leads to cholesterol-enriched HDL particles. Nicotinic acid also reduces lipoprotein(a) levels by about 25%.

Acipimox is a nicotinic acid derivative first authorised in Italy in 1984 and is currently authorised in eight EU member states as Olbetam. Acipimox inhibits lipolysis and the release of fatty acids from the adipose tissue hence lowering free fatty acid availability for hepatic production of VLDL and LDL with a subsequent overall reduction in triglyceride and cholesterol levels. Acipimox also has a favourable effect on HDL levels, which increases during treatment. The approved indications are the treatment of lipid disorders characterised by elevated plasma levels of triglycerides (hypertriglyceridaemia or Fredrickson type IV hyperlipoproteinaemia) or by elevated plasma levels of both triglycerides and cholesterol (mixed hyperlipidaemia or type Fredrickson IIb hyperlipoproteinaemia), with slight variations in the actual wording of the nationally authorised summary of product characteristics (SmPCs), such as reference to the severity of the condition in certain member states.

2.2.1. Efficacy data on acipimox

During clinical development, acipimox was tested for effectiveness in lowering blood lipids, primarily in double-blind trials, in a total of 1,118 patients with various forms of hyperlipiproteinaemia (types IIa, IIb, III, IV and V). The studies were conducted mostly in the 1980s and showed that acipimox proved significantly superior to placebo in reducing (between 26% and 43%) the triglyceride levels of patients with hypertriglyceridaemia. In patients with hypercholesterolaemia, acipimox reduced blood cholesterol (between 7% and 17%), which was significantly superior to placebo. Two studies were designed to evaluate the efficacy of acipimox in reducing the atherogenicity of the plasma lipid and lipoprotein profile in type IIb and IV patients. They showed that acipimox increases the size of LDL and HDL particles towards a less atherogenic pattern and restores the binding capacity of LDL with their receptors. Acipimox showed similar effectiveness to other lipid lowering agents, such as nicotinic acid, clofibrate and bezafibrate in lowering plasma lipids. Only one open, parallel group study compared acipimox 750 mg/day to nicotinic acid 3000 mg/day in 57 patients with combined hyperlipidaemia. Mean decreases in total and LDL-cholesterol of 8% and 13% were observed with acipimox compared to decreases of 9% and 16% with nicotinic acid. No statistical difference was found between the two treatment groups during the randomised phase. Overall, hypolipidemic effectiveness was demonstrated, with reductions of cholesterol assays between 10% and 27%, reduction of blood triglycerides between 26 and 68%, and increases of HDL-C between 18% and 24%. The PRAC also noted additional, smaller studies, specifically conducted in the treatment of Fredrickson type IV hyperlipoproteinaemia or type IIb hyperlipoproteinaemia.

<u>HDL-C elevating theory</u>

The PRAC also discussed the impact of the recent on the validity of the HDL-C elevating theory, according to which there is an association between elevated HDL-C levels and a reduced risk of cardiovascular disease, thereby making HDL-C elevation a rational target for lipid intervention. This

association was considered established for several decades, supported by animal studies and some post-hoc analysis of randomised controlled clinical trials. Treatment guidelines also recommended lifestyle changes and the use of HDL-C increasing medicines. However, having reviewed the data from the prematurely terminated AIM-HIGH and HPS2-THRIVE trials, the PRAC was of the view that the current data fails to confirm the HDL-C elevating theory. According to the consensus statement of National Lipid Association, published on 23 August 2013, elevating HDL-C is not a therapeutic target at the present time and LDL-C and non HDL-C should remain the first and secondary targets in the therapy of patients at elevated risks for cardiovascular disease. However, as acipimox is not indicated for increasing HDL-C and that consequently no statement on cardiovascular prevention is included in the SmPC, the PRAC was of view that the data casting doubts on the HDL-C elevating theory does not impact the terms of the marketing authorisations for acipimox.

2.2.2. Efficacy data on nicotinic acid

As acipimox is a related substance to nicotinic acid, the PRAC also reviewed efficacy data on nicotinic acid, to complement the review of the limited data on acipimox. The PRAC reviewed a number of studies conducted with nicotinic acid, as well as a number of meta-analysis conducted with these studies. The PRAC considered some trials to be difficult to interpret due to possible confounding effects and because the trials only investigated a relatively modest number of patients over a relatively short treatment period and were therefore not powered statistically to detect the effects of treatment on clinical outcome. Nevertheless, the PRAC considered that convincing evidence of the beneficial effects of ERN as an add-on therapy in patients already on statin treatment was provided by the ARBITER (Arterial Biology for the Investigation of the Treatment Effects of Reducing Cholesterol), HATS (HDL Atherosclerosis Treatment study) and the Coronary Drug Project trials, which demonstrated clear benefits in terms of reduced incidences of various cardiovascular events and mortality. This was supported by two meta-analysis conducted by Lavigne and Karas (2013) and the MAH for acipimox, respectively, which showed that ERN was associated with a significant reduction in the composite endpoints of any CVD and major coronary heart disease event. However, no significant association was observed between ERN therapy and stroke incidence and the PRAC considered that a number of factors made it difficult to interpret these meta-analyses.

The PRAC also reviewed the AIM-HIGH (Atherothrombosis Intervention in Metabolic Syndrome with Low HDL/High Triglyceride and Impact on Global Health Outcomes) study, conducted in 3,414 patients from 2006 to 2010. It was a double-blind, randomised, controlled clinical trial with the primary end point being the first event of the composite of death from coronary heart disease (CHD), non-fatal myocardial infarction (MI), ischemic stroke, hospitalisation for an acute coronary syndrome, or symptom-driven coronary or cerebral revascularisation. The trial was stopped 18 months early after a mean follow-up period of three years due to lack of efficacy, as the interim results showed no difference between the two treatment groups regarding the primary endpoints.

Finally, the PRAC reviewed the results from HPS2-THRIVE, which assessed the long-term effects of ERN/LRPT vs. placebo on the time to first major vascular event, defined as a composite of non-fatal MI, coronary death, stroke, or arterial revascularisation. Prior to randomisation, 42,424 patients were given simvastatin plus, if required, ezetimibe to standardise their LDL-lowering therapy. After withdrawals, a total of 25,673 remaining patients were randomised between ERN/LRPT daily vs. placebo (10,932 from China, 8,035 from the UK, and 6,706 from Scandinavia) and were followed for a median of 3.9 years. The PRAC considered that the efficacy findings from HPS2-THRIVE were generally consistent with those in AIM-HIGH, with no significant benefit of ERN/LRPT on the primary outcome of major vascular events observed. ERN/LRPT demonstrated no significant effect on mortality and the combination of ERN/LRPT and statin therapy did not further reduce the risk of the combination of coronary deaths, non-fatal heart attacks, strokes or revascularisations, compared to statin therapy, although trends favoured ERN/LRPT for patients with higher baseline LDL-C and lower baseline HDL-C. Although the differences in primary efficacy outcomes between treatments were small and not clinically or statistically significant, the trial follow-up of 4 years may not have been of sufficient duration, especially against a background of statin therapy, and substantive treatment differences may not have had time to develop. Additionally, the PRAC noted that the patients enrolled in HPS2-THRIVE had low levels of total cholesterol, non-HDL-C, and LDL-C and that patients with higher lipid values who are more likely to be treated with ERN and who are expected to benefit the most from ERN therapy were excluded.

Overall, the PRAC considered that while the efficacy data on nicotinic acid cannot be directly extrapolated to acipimox, the most recent data suggests that nicotinic acid is not associated with beneficial effects on the reduction of cardiovascular events. This is however not considered to impact the benefit-risk balance of acipimox, which is not indicated in cardiovascular protection.

2.2.3. Overall discussion on efficacy

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 statin or fibrates or who do not achieve triglyceride goals with statin or fibrate 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.

2.3. Clinical safety

2.3.1. Safety data on acipimox and nicotinic acid

Based on the available data, the PRAC noted a number of clinical differences between acipimox and nicotinic acid, with acipimox having a longer duration of action and non-clinical studies showing that acipimox is consistently less potent than nicotinic acid as an agonist of the HCA2 receptor. The PRAC carried out a comparative review of the main adverse events observed for acipimox and nicotinic acid, including the results obtained from HPS2-THRIVE, as presented by the HPS-2-THRIVE Collaboration Group.

The PRAC considered the safety profile of acipimox to be well characterised, with generally mild or moderately severe side effects. Flushing, rash and gastrointestinal (GI) effects (nausea, dyspepsia, diarrhoea and upper abdominal pain) are the most frequently reported adverse effects for acipimox and are listed in the acipimox product information, together with pruritus, erythema, urticaria and angioedema.

In the absence of safety data on nicotinic acid submitted by the MAH, the PRAC reviewed a search in the EudraVigilance database which resulted in 2,869 individual case safety reports obtained worldwide. Forty two fatal cases have been reported without any definitive causality with nicotinic acid and the reported adverse drug reactions were in line with those identified in the nicotinic acid SmPC. The main System Organ Classes (SOCs) affected were investigations, GI, musculoskeletal and connective tissue disorders, nervous system disorders, skin and subcutaneous tissue disorders, and vascular disorders. Reported adverse effects included mild increases in uric acid and of liver enzymes, hypotension, nausea, vomiting, diarrhoea, and precipitation of angina in patients on vasodilators.

Regarding HPS2-THRIVE, the PRAC noted that a statistically significant higher incidence of non-fatal serious adverse events (SAEs) was observed in the ERN/LRPT group compared to the placebo group. Adverse events associated with ERN/LRPT included expected side effects based on the known profile of nicotinic acid (diabetic complications in diabetics, new onset diabetes, skin reactions and GI disturbances) as well as unexpected infection and bleeding related events not previously associated with nicotinic acid. This was in contrast with studies which have shown that acipimox does not adversely affect blood glucose metabolism and may even improve metabolic profiles and insulin sensitivity in patient with diabetes. As neither acipimox nor nicotinic acid are associated with increased risks of infection or bleeding, the PRAC considered it possible that these events can be attributed to the pharmacological activity of laropiprant, whose full spectrum of effects, including long-term effects on CV outcomes is not known. The PRAC could therefore not conclude on a causal relationship between nicotinic acid and infections or bleedings.

<u>Skin events</u>

Skin events are recognised nicotinic acid adverse effects and were the main reason for subject withdrawal during HPS2-THRIVE. In the main study, 5.4% of patients discontinued due to skin related adverse effects, with serious skin adverse events occurring in 0.7% patients (versus 0.4% in controls). Several studies have demonstrated that flushing is the major reason why patients discontinued nicotinic acid therapy. Flushing in elderly patients can be associated with postural hypotension and increased risk of fall and may also be associated with pruritus and rash. The PRAC noted a meta-analysis of 30 trials using nicotinic acid, which found that 66% of subjects on extended release

nicotinic acid experienced flushing compared with 22% of subjects taking acipimox and therefore considered that acipimox is associated with flushing to a lesser degree than nicotinic acid. In clinical trials with acipimox ranging from 1 month to 24 months, the rate of any skin event ranged from 6.9% to 12.5% (versus 6.8% controls) which is similar to the rate of 7.7% reported in a phase IV study of acipimox in 3,009 patients with Type 2 diabetes. The PRAC noted that pruritus, rash, erythema, urticaria and angioedema are listed events in the acipimox product information and concluded that the main skin effects associated with acipimox were flushing and pruritus and were of short duration.

Gastrointestinal effects

In HPS2-THRIVE, GI effects were the reason for discontinuation in 3.9% of patients (versus 1.7% in controls) and serious adverse effects, including GI bleeding and peptic ulcer, were reported in 4.8% patients (versus 3.8% in controls). In contrast, GI effects reported in clinical trials with acipimox (mainly gastralgia, nausea and dyspepsia) were mild or moderate in severity. In clinical trials with acipimox, the rate of any GI event ranged from 7.4% to 13.1% (versus 8.3% controls) with a lower rate of 3.5% reported in a phase IV trial of acipimox in 3,009 diabetic patients. Because of the known risks of nicotinic acid, and the somewhat high incidence of GI disorders in patients that are likely to be prescribed acipimox, the product is contraindicated in patients with peptic ulcer disease. Dyspepsia, upper abdominal pain, abdominal pain, nausea and diarrhoea are listed GI adverse reactions in the acipimox product information. A cumulative search of the MAH's safety database for GI events was conducted for acipimox up until 15 March 2013 and returned 14 cases, the majority of which were consistent with the acipimox product information. The EudraVigilance database contains 328 adverse drug reactions in the SOC "Gastrointestinal disorders" for nicotinic acid but only four reactions for acipimox. The PRAC noted that GI disorders are already an identified potential risk for acipimox and therefore considered that this data did not identify new safety information which impacts the benefit-risk balance of acipimox.

Musculoskeletal effects

HPS2-THRIVE reported serious musculoskeletal adverse events in 3.7% patients (versus 3.0% in controls). ERN/LRPT added to statin increased the risk of any definite myopathy compared to the placebo arm (75 events vs. 17), of which 7 and 5 respectively were rhabdomyolysis. The increased risk of muscle-related adverse events in HPS2-THRIVE was potentially influenced by the inclusion of large numbers of participants from China, who may be at greater risk of statin induced muscle toxicity. This theory is supported by the fact that the relative excess risk of myopathy in the ERN/LRPT treatment group compared to placebo was greater among participants from China than Europe (relative risk 5.2 vs. 1.5) with any myopathy being more common among Chinese participants (138 vs. 27 in the placebo group) than among Europeans (17 vs. 11 in the placebo group). The PRAC had raised concerns regarding the concomitant use of acipimox and statins but noted that data from clinical trials indicate that combination therapy is generally safe and effective in the treatment of mixed dyslipidaemia and that neither nicotinic acid nor acipimox has been associated with increased risk of muscle toxicity when administered as mono-component treatments. A meta-analysis of nicotinic acid and acipimox trials did not find any evidence of an excess of muscle adverse effects in the absence of a statin and an analysis of the FDA adverse event database over the period 1999-2005 by Alsheikh-Ali and Karas (2007) indicated that the safety of combination therapy with extended release nicotinic acid and a statin is comparable to the safety of each of the drugs alone. Multiple clinical trials of nicotinic acid in combination with statins have shown no increase in muscle adverse effects over statins alone and in a large, open-label study of 4,499 patients treated with ERN/lovastatin, no cases of myopathy were reported. Cases of myopathic reactions or clinically significant myalgia (enough to limit statin doses) while taking nicotinic acid-statin combination therapy were usually associated with other contributors to myopathy. The PRAC also noted a cumulative search of the MAH's safety database for musculoskeletal events received up until 31 July 2013 for acipimox which identified a total of 15 cases reporting 21 relevant events. The PRAC noted that the current product information for nicotinic acid includes a warning against concomitant use with statins.
However, based on the results from HPS2-THRIVE and the chemical similarity of acipimox and nicotinic acid, the PRAC considered that a warning on the potential increased risk of myopathy when used in combination with a statin should be added to the acipimox product information, to inform prescribers of current data and to strengthen the already existing warning (see section 2.5 of this report).

Infection

HSP2-THRIVE identified an increased risk of infection-related serious adverse events, including lower respiratory, urinary tract, abdominal/GI and skin infections (8.0% versus 6.6% in controls). In the EudraVigilance database, 62 reactions were found in the SOC "Infections" (8 cases of eye infections staphylococcal, 5 cases of herpes zoster and 4 Staphylococcus infections). The PRAC noted that a cumulative search of the MAH's safety database for infection events for acipimox up until 15 March

2013 returned 4 cases. The PRAC therefore considered that this data did not identify new safety information which impacts the benefit-risk balance of acipimox.

Bleeding

HPS2-THRIVE showed an increased risk of bleeding, including intracranial bleeding and an increased risk of haemorrhagic stroke. A cumulative search of the MAH's safety database for bleeding events for acipimox up until 15 March 2013 returned 4 cases. No new risk was identified upon review of these cases. The PRAC considered it possible that laropiprant contributed to the excess case of bleeding in patients treated with ERN/LRPT combination.

Discontinuation

The PRAC noted that by the end of the HPS2-THRIVE study, 25.4% of participants allocated to the active ERN/LRPT group (12,838 patients) had discontinued study treatment, compared to 16.6% of participants allocated to the placebo group (12,835 patients). The most common medical reasons for ERN/LRPT discontinuation were known side effects related to skin, GI, diabetes and musculoskeletal events. A difference was also observed between the Chinese and Caucasian populations in terms of excess of discontinuation for medical reason in ERN/LRPT group. The PRAC also noted that nicotinic acid clinical trials are associated with a high drop-out rate due to adverse effects, with a meta-analysis of 30 trials using nicotinic acid showing that 19.7% (versus 10.2% placebo) of subjects withdrew due to adverse effects with flushing being the primary reason. In contrast, clinical trials with acipimox using no run-in period ranging from 1 month to 24 months showed discontinuation rates ranging from 3.8% to 6.5% (versus 2.3% with placebo) and in a meta-analysis of clinical trials, the acipimox discontinuation rate was reported to be 4.3% (versus 4.6% with placebo). While the PRAC considered the comparison of tolerability between nicotinic acid and acipimox to be complicated by the fact that they are administered at different dosages, acipimox in high doses up to 2250 mg/d has been shown to be well tolerated except for initial gastric complaints and flushing. The PRAC therefore considered that acipimox has been shown to be better tolerated than nicotinic acid.

2.3.2. Overall discussion on safety

Having reviewed the available safety data, including data on nicotinic acid obtained from HPS2-THRIVE, the PRAC considered the safety profile of acipimox to be 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 associated with the concomitant use of acipimox with statins, which was addressed by adding a warning to the product information.

The PRAC also noted that some events adverse events observed in HPS2-THRIVE could possibly be attributed to the pharmacological activity of laropiprant and that in the absence of a laropiprant arm in HPS2-THRIVE, it is not possible to separate out adverse events attributable with laropiprant from the ones attributable to nicotinic acid.

2.4. Consultation of an Ad-Hoc *expert group*

In the context of its assessment, the PRAC sought input from European experts on the clinical use of acipimox. An Ad Hoc expert group was convened on 6th September 2013 to discuss questions raised by the PRAC. Experts were screened for conflicts of interest in accordance with the EMA policy on conflicts of interests and the list of participating experts was endorsed by the PRAC prior to the meeting.

The experts agreed that the use and availability of acipimox across the EU is limited and variable and also noted the very limited data available on acipimox and that the clinical development programme only included 1,118 patients. The experts however confirmed that acipimox is currently seen as a useful option in the treatment of hypertriglyceridaemia but that for both the Fredrickson type IIb and type IV indications, it would be used as a second or third line treatment, after fibrate or statin and/or fatty acids. The experts were therefore of the view that there may be a role for acipimox in the treatment of severe hypertriglyceridaemia but only in second/third line indications (for example in statin- or fibrate-intolerant patients).

The experts then discussed the relevance of the outcome of recent studies (HPS2-THRIVE and AIM-HIGH) on the benefit-risk balance of acipimox. The experts considered that while HPS2-THRIVE showed safety concerns, the extended release nicotinic acid/laropiprant combination cannot be regarded as the same as the mono-component acipimox and the concerns can therefore not be extrapolated to acipimox, in particular due to the possible confounding effect of laropiprant. Regarding

AIM-HIGH, the experts noted the absence of bioequivalence data comparing acipimox with nicotinic acid but considered that the study showed no new or serious safety concerns. In addition, the experts noted that as the studies investigated the elevating of HDL-C levels, which is not an approved indication for acipimox, they were not considered of relevance to acipimox. The experts also noted the lack of data to support HDL-C level elevating as a therapeutic strategy. The experts therefore considered that the main role of acipimox is to prevent the non-cardiovascular complications of hypertriglyceridaemia and that acipimox should not be used in cardiovascular disease prevention indications, in the absence of convincing LDL-C or outcome data.

Finally, the experts noted that there is extremely limited data on the risk of myopathy with acipimox, due to the small patient numbers enrolled in the existing studies, with none performed on a background of statin therapy. The experts were however reassured by the lack of evidence of potential harm from pharmacovigilance data but did consider that prescribers should be made aware of the potential risk of the combination treatment, through appropriate risk minimisation measures. The experts heard a proposal from the MAH to include new information in the product information on the increased risk observed with nicotinic acid in combination with statin, highlighting higher incidence observed in the Chinese population, and were supportive of this addition. The experts concluded that given the limited role of acipimox, used as second or third line therapy for severe hypertriglyceridaemia, there are no further patient subsets where the risk of myopathy would preclude the use of acipimox treatment.

In conclusion, the experts unanimously agreed that acipimox has a role in well-defined settings and indications, such as the treatment of severe hypertriglyceridaemia but only as a second or third line agent. There is currently not sufficient data to support a role for acipimox in cardiovascular protection or risk modification. The current data available did not have any major impact on the safety profile and no changes to the current authorised indications or SmPCs for acipimox were considered warranted, beyond the restriction of use to second or third line treatment and the strengthening of the warning regarding the concomitant use of acipimox with statins.

2.5. Changes to the product information

The PRAC considered that based on the available data, the indications for acipimox should be restricted to alternative or adjunct treatment in patients who have not responded adequately to other treatments such as statin or fibrate treatment and consequently adopted the following indications for Section 4.1:

"[Product name] is indicated as alternative or adjunct treatment to reduce triglyceride levels in patients who have not responded adequately to other treatments such as statin or fibrate treatment for:

- *hypertriglyceridaemia (Fredrickson type IV hyperlipoproteinaemia);*
- *hypercholesterolaemia and hypertriglyceridaemia (Fredrickson type IIb hyperlipoproteinaemia).*

[Product name] should be used after other measures have been taken such as dietary changes and other non-pharmacological treatment (e.g. exercise, weight reduction).

It has not been shown that treatment of hyperlipoproteinaemia with acipimox leads to a reduction of cardiac morbidity or mortality."

The PRAC also considered that a a warning on the potential increased risk of myopathy when used in combination with a statin should be added to Section 4.4 of the acipimox SmPC, to inform prescribers of current data and to strengthen the already existing warning:

"*Acipimox is structurally related to nicotinic acid. The risk of muscle toxicity is increased when nicotinic acid is administered concomitantly with a statin (i.e. a 3-hydroxy-3- methylglutaryl coenzyme A [HMG-CoA] reductase inhibitor). In one study, Chinese patients taking* nicotinic acid *plus laropiprant concomitantly with simvastatin were reported to have a higher incidence of myopathy and rhabdomyolysis compared to Caucasians."*

Corresponding changes were also made to the package leaflet.

2.6. Overall benefit-risk assessment

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 associated with the concomitant use of acipimox with statins, 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 revised the indication accordingly.

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.

3. Overall conclusion and grounds for the 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 divergent position is appended to the PRAC recommendation.

Appendix 1

Divergent position to PRAC recommendation

Article 31 Directive 2001/83/EC resulting from pharmacovigilance data

Procedure No: EMEA/H/A-31/1366

Substances related to nicotinic acid (acipimox) indicated for the treatment of lipid disorders

Divergent statement

The undersigned member of PRAC did not agree with the PRAC's opinion recommending that the marketing authorisations of acipimox-containing products should be varied as stated by the PRAC.

The reasons for this divergent opinion were as follows:

For most patients with dyslipidaemia, the therapeutic needs are theoretically covered by the use of statins. For patients who are insufficiently controlled by statins or who cannot tolerate them, there are treatment alternatives.

Before the HPS2-THRIVE results, in the absence of morbidity/mortality data, acid nicotinic was to be considered under the category of symptomatic treatment for dyslipidaemia.

The HPS2-THRIVE trial results were very awaited especially as the AIM-HIGH trial, which compared the combined nicotinic acid/simvastatin with simvastatin alone, failed to demonstrate additional cardiovascular benefit of acid nicotinic among patients with ischemic heart disease.

In the light of HPS2-THRIVE results, the role of nicotinic acid in prevention of cardiovascular disease appears strongly questionable and could not be raised in the absence of data from cardiovascular prevention trials documenting adequately the safety and the efficacy of nicotinic acid.

Taking all these aspects and the safety profile of the product into account, the member considered that the benefit/risk of acipimox-containing products is negative, even in a restricted indication.

PRAC member expressing a divergent position:

Isabelle Robine (FR)	7 November 2013	Signature: ……