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Acipimox only to be used as additional or alternative treatment to reduce high triglyceride levels

CMDh endorses PRAC recommendation

On 18 December 2013, the Co-ordination Group for Mutual Recognition and Decentralised Procedures – Human (CMDh)[1] confirmed by majority that medicines containing acipimox should have their marketing authorisations amended to ensure that they are used across the European Union only as an additional or alternative treatment in type IIb and type IV hyperlipoproteinaemia. These are conditions involving hypertriglyceridaemia (high levels of triglycerides, a type of fat, in the blood), with or without increased cholesterol. Acipimox-containing medicines should be used when changes in lifestyle, including diet and exercise, and treatment with other medicines are not adequate.

These recommendations were originally made by the European Medicines Agency's Pharmacovigilance Risk Assessment Committee (PRAC) at its meeting of 5-8 November 2013. The original reason for the review of acipimox was HPS2-THRIVE, a large study which looked at the long-term effect of the combination of nicotinic acid (a substance related to acipimox) and another medicine, laropiprant, in treating lipid disorders. The study showed that adding this combination to treatment with statins (another class of medicines used to treat lipid disorders) did not lead to additional benefits in reducing the risk of major vascular events such as heart attack and stroke, but did result in a higher frequency of non-fatal but serious side effects. As a result, the European Medicines Agency recommended the suspension of medicines containing the combination of nicotinic acid and laropiprant across the EU[2]. Because acipimox was related to nicotinic acid and was marketed for lipid disorders in the EU, its benefit-risk balance was also then reviewed.

After looking at the available data on acipimox, including evidence from the literature, spontaneous reports of adverse effects and advice from a group of experts in the treatment of lipid disorders, as well as data from HPS2-THRIVE, the PRAC concluded that acipimox continues to have a role as an additional or alternative treatment to reduce triglycerides in those forms of hyperlipoproteinaemia that involve high triglyceride levels (with or without increased cholesterol), in patients in whom lifestyle changes and use of other medicines such as fibrates and statins are not adequate. The results from HPS2-THRIVE could not be applied directly to acipimox since the study investigated the effect of the combination with laropiprant, whose effects were not established, and possible differences between

[1] The CMDh, a body representing EU Member States, is responsible for ensuring harmonised safety standards for medicines authorised via national procedures across the EU.
[2] More information can be found on the Agency's website: ema.europa.eu/Find medicine/Human medicines/Referrals/Tredaptive, Pelzont and Trevaclyn.

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nicotinic acid and acipimox were also identified. However, findings from the HPS2-THRIVE study were used to expand the warnings in the acipimox product information concerning a possible increased risk of painful muscle damage when acipimox is used together with a statin.

The CMDh endorsed the PRAC recommendations by majority at its meeting of 16-18 December 2013 and its position was sent to the European Commission which endorsed it and issued an EU-wide legally binding decision on 20 February 2014.

Information to patients

- Acipimox is a medicine used to treat disorders related to high levels of fat in the blood. Its uses and safety have been reviewed because of a study showing that a related medicine, nicotinic acid, increased the side effects and gave no additional benefit when it was taken together with other treatments for these disorders.
- The review has shown that acipimox can be useful as an additional or alternative treatment to lower high levels of triglycerides (a particular type of fat) in the blood of patients with high levels of these fats (with or without high cholesterol), who cannot be treated by means such as diet, exercise, or other medicines.
- Most patients taking acipimox are already using it in this way, but the product information is being updated to clarify the recommended use.
- Patients taking acipimox should have their treatment re-evaluated at their next regular appointment.
- Patients who have any questions should ask their doctor or pharmacist.

Information to healthcare professionals

- Acipimox is indicated for the treatment of hypertriglyceridaemia with or without hypercholesterolaemia (Fredrickson type IIb or type IV hyperlipoproteinaemia).
- 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. Patients receiving acipimox should have their treatment reviewed at their next regular appointment.
- The main role of acipimox is to prevent the non-cardiovascular complications of hypertriglyceridaemia and acipimox should not be used for the prevention of cardiovascular disease in the absence of convincing LDL-C or outcome data.
- Although the review of acipimox-containing medicines was originally triggered by concerns arising from the HPS2-THRIVE study, the extended release nicotinic acid/laropiprant combination used in that study cannot be regarded as the same as mono-component acipimox and the concerns can therefore not be extrapolated to acipimox, in particular due to the possible confounding effect of laropiprant.
- However, based on the results from HPS2-THRIVE and the chemical similarity of acipimox and nicotinic acid, prescribers should be aware of the potential increased risk of myopathy when acipimox is used in combination with a statin.

The review of acipimox was based on the limited available efficacy and safety data on acipimox as well as data from the scientific literature relating to the structurally related compound nicotinic acid. In addition, the PRAC consulted an ad-hoc expert group of European experts on the use of acipimox.

- 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.
- 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.
- 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. Flushing, rash and gastrointestinal 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. 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 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. This was endorsed by the CMDh.

More about the medicine

Acipimox is a substance closely related to nicotinic acid that has been available since 1984 as Olbetam and other trade names for the treatment of lipid disorders. In the EU, acipimox-containing medicines are currently marketed in Austria, Belgium, Denmark, Hungary, Italy, Luxembourg, the Netherlands and the United Kingdom.

Medicines containing nicotinic acid or related substances have been authorised in the EU via national procedures since the mid-1950s. Nicotinic acid is a naturally occurring substance used in low doses as a vitamin (known as niacin or vitamin B3). In higher doses, it reduces the levels of fat in the blood. Nicotinic acid was also authorised in combination with laropiprant. Laropiprant has no effect on cholesterol but it reduces flushing, which is a known side effect of nicotinic acid.

More about the procedure

The review of nicotinic acid and its related substances acipimox and xantinol nicotinate was initiated on 27 February 2013 at the request of the Danish Health and Medicines Authority, under Article 31 of Directive 2001/83/EC. In July 2013 it was established that nicotinic acid and the related substance xantinol nicotinate were not currently marketed in the EU to treat lipid disorders (xantinol nicotinate is authorised in some EU countries for oral use as a vasodilator, a medicine that widens the blood vessels used to treat blood circulation problems) and the review was therefore restricted to acipimox only.

A review of these data was first conducted by the Pharmacovigilance Risk Assessment Committee (PRAC). The PRAC recommendations were sent to Co-ordination Group for Mutual Recognition and Decentralised Procedures – Human (CMDh), which adopted a final position.

As the CMDh position was adopted by majority vote, it was sent to the European Commission, which endorsed it and issued an EU-wide legally binding decision on 20 February 2014.

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