

**NOTIFICATION OF A REFERRAL UNDER ARTICLE 31 OF DIRECTIVE 2001/83/EC**

**FAX NUMBER -44 20 75237051**

This notification is an official referral under Article 31 of Directive 2001/83/EC made by Denmark

Product Name(s), if appropriate, Strength(s) and Pharmaceutical Form(s)	
Active Substance(s)/Therapeutic class	Nicotinic acid and related substances (acipimox, xantinol nicotinate and other nicotinic acid analogues) indicated for the treatment of lipid disorders.

Marketing Authorisation Holder In the referring Member State: Pfizer

DK finds that it is in the interests of the Union to initiate a referral under article 31 of Directive 2001/83/EC to review the benefit-risk balance of authorised medicinal products containing acipimox, xantinol nicotinate and other nicotinic acid analogues indicated for the treatment of lipid disorders.

The European network was in December 2012 made aware of preliminary results from the HPS2-THRIVE (Heart Protection Study 2-Treatment of HDL to Reduce the Incidence of Vascular Events) randomized clinical outcome study, designed to investigate the long-term clinical effects of raising HDL cholesterol with extended release nicotinic acid/laropiprant and to assess the incremental benefit of nicotinic acid/laropiprant versus placebo on top of simvastatin 40 mg, with or without ezetimibe, in 25,000 high-risk patients in the UK, Scandinavia, and China.

These data showed that the study did not meet its primary endpoint of reduction of major vascular events. In addition, there was a statistically significant higher incidence of non-fatal serious adverse events in the nicotinic acid/laropiprant group compared to the placebo group. These imbalances occurred in several System Organ Classes (SOC), some of which reflect anticipated risks based on the known profile of nicotinic acid or earlier safety analyses of this trial (e.g. myopathy, new onset diabetes) and others which were unanticipated (e.g. infections).

In light of these data, a review of products containing this fixed combination (centrally authorised in the EU as Tredaptive, Trevaclyn and Pelzont) was conducted. Following an assessment by the Pharmacovigilance Risk Assessment Committee (PRAC), the Committee for Medicinal Products for Human Use (CHMP) adopted an opinion on 17 January 2013, concluding that the benefit-risk balance of nicotinic acid/laropiprant is affected adversely by the results from the HPS2-THRIVE study and recommending the suspension of the marketing authorisations of Tredaptive, Trevaclyn and Pelzont.

The data from the HPS2-THRIVE study suggests that nicotinic acid was the driver for the observed excess of adverse events. Further, the concerns regarding the efficacy of the combination product may also be of relevance for the mono-component products containing nicotinic acid or related substances (acipimox, xantinol nicotinate and other nicotinic acid analogues) indicated for the treatment of lipid disorders. Based on these concerns Denmark has decided to initiate a referral under article 31 of Directive 2001/83/EC to review the benefit-risk of these products.

PRAC is requested to assess the impact of the newly-available data as mentioned above and other relevant data on the benefit-risk balance for products containing nicotinic acid and related substances (acipimox, xantinol nicotinate and other nicotinic acid analogues) indicated for the treatment of lipid disorders and to give its recommendation on whether the marketing authorisations for these products should be maintained, varied, suspended or revoked.

Signed

  
Vagn Nielsen  
Director

Danish Health and Medicines Authority

Date

27/02-2013