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

Procedure No: EMEA/H/A-31/1397

Ambroxol- and bromhexine-containing medicinal products

Divergent statement

The safety profiles of ambroxol and bromhexine are considered indistinguishable, as ambroxol is an important metabolite of bromhexine.

A new important safety issue, namely delayed-type hypersensitivity events associated with severe cutaneous adverse reactions (SCARs – erythema multiforme, Stevens-Johnson syndrome/toxic epidermal necrolysis and acute generalised exanthematous pustulosis) has been highlighted for the active substances ambroxol and bromhexine. Though rare, SCARs are serious in 80% of the cases, leading to the hospitalisation of 65% of the patients, while these events are fatal in about 10% and disabling in 2% of the cases. It is considered that the causal association between SCARs and ambroxol has been indisputably demonstrated in 7 case reports (1 SJS, 1 AGEP, 1 EM, 4 (generalised) maculopapular eruptions with mucosal involvement and/or vesicles/skin desquamation) by positive rechallenge and exclusion of the confounding factors. Additionally, 4 SCAR cases were considered as probably related to ambroxol, and a causal association was assessed as possible in 32 other cases.

Aside from this risk of delayed-type hypersensitivity associated with SCARs, risks of immediate and delayed hypersensitivity reactions have also been demonstrated for ambroxol and bromhexine. These hypersensitivity reactions include a broad group of adverse events ranging from non-serious rash and pruritus to life-threatening angioedema, bronchospasm and anaphylactic shock. A causal association with ambroxol was assessed as certain in 4 case reports, probable in 79 case reports and possible in 151 cases from Eudravigilance.

Risks of hypersensitivity reactions, immediate and delayed-type including SCARs, have a major impact on the safety profile of ambroxol, as AEs collected within the SMQ hypersensitivity (broad) account for respectively 37% and 25% of the totality of AEs collected in Eudravigilance for ambroxol and bromhexine. Moreover, as most medicinal products containing ambroxol or bromhexine are distributed over-the-counter, the risk of hypersensitivity associated with these active substances is likely (way) underestimated.

It is considered that the risks of SCARs and other hypersensitivity reactions significantly influence the safety profile of ambroxol and bromhexine. Taking into account all the limitations of efficacy data, we are of the opinion that the benefit-risk is negative in some of the ambroxol and bromhexine indications, as described below.

AMBROXOL

Secretolytic therapy in acute and chronic bronchopulmonary disorders associated with abnormal mucus secretion and impaired mucus transport:

The benefit-risk balance of all formulations of ambroxol is negative for children aged 0-<2 years. For children aged 2-<6 and 6-<12 years, ambroxol should be used only under medical advice.

Considering the specific anatomic and functional characteristics of the immature respiratory system organs in children below 2 years of age, lack of adequate clinical studies in which efficacy is proven and the currently known safety profile (not only hypersensitivity reactions but also increased risk of bronchial obstruction by the mucus secretion and inability of children to cough up liquefied mucus), we are of the opinion that in this population ambroxol should be contraindicated. Moreover, this is in line with the Paediatric Committee's (PDCO) opinion related to this indication that there is no need for use of these products in children from birth to less than 2 years of age.

Pain relief in acute sore throat:

Studies supporting this indication showed that the product has a quick relief of sore throat pain until 3 hours, whilst the benefit beyond 3 hours is unclear. This modest benefit is not outweighed by the risk associated to ambroxol. Therefore, the benefit-risk balance of all formulations of ambroxol is negative for all age groups in this indication.

Additive therapy for stimulation of alveolar surfactant in premature babies and neonates with IRDS:

The benefit-risk balance of all formulations of ambroxol for the indication of postnatal treatment of IRDS is negative in the target population of patients (premature infants and neonates).

The PDCO was also of the view that these products are no longer the preferred treatment option in IRDS.

Prophylaxis of IRDS and stimulation of foetal lung maturation in pregnancies with threatening preterm delivery:

As the benefits outweigh the important risks in this indication, the benefit-risk balance of antenatally administered ambroxol in order to reduce emergence of IRDS is considered as positive, but only in a particular restricted population i.e. if corticosteroids are contraindicated for the pregnant mother (e.g. allergy to corticosteroids or systemic fungi disease).

Prophylaxis of postoperative pulmonary complications in the adult population:

Considering the negative benefit of ambroxol in this indication and the important safety risks associated with the use of ambroxol, the benefit/risk balance of ambroxol indicated in the prophylaxis of postoperative pulmonary complications is negative in the adult age group for which it is indicated.

BROMHEXINE

Secretolytic therapy in acute and chronic bronchopulmonary disorders associated with abnormal mucus secretion and impaired mucus transport:

The benefit-risk balance of all formulations of bromhexine is negative for children aged 0-<2 years. For children aged 2-<6 and 6-<12 years, bromhexine should be used only under medical advice.

Considering the specific anatomic and functional characteristics of the immature respiratory system organs in children below 2 years of age, lack of adequate clinical studies in which efficacy is proven and the currently known safety profile (not only hypersensitivity reactions but also increased risk of bronchial obstruction by the mucus secretion and inability of children to cough up liquefied mucus), we are of the opinion that in this population bromhexine should be contraindicated.

Moreover, this is in line with the Paediatric Committee's (PDCO) opinion related to this indication that there is no need for use of these products in children from birth to less than 2 years of age.

Sjögren's syndrome:

The benefit-risk balance of all formulations of bromhexine hydrochloride is negative in the age population 12-adult for which it is indicated.

Acute sinusitis, chronic sinusitis:

There is no clinical evidence at the present moment to support the minor bromhexine indication in the treatment of acute and chronic sinusitis, therefore we conclude on a negative benefit/risk ratio.

Combinations of ambroxol and bromhexine with other active substances:

We consider benefit-risk balance of ambroxol or bromhexine containing combination products negative.

CMDh member expressing a divergent opinion:

Sabina Uzeirbegović (HR)	18 November 2015	Signature: ……