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. We consider 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.

The Paediatric Committee (PDCO) was consulted regarding the current use of ambroxol and bromhexine as secretolytics in the paediatric population in clinical practice. It was recognised that the use of ambroxol and bromhexine varies significantly in paediatric clinical practice across the EU. Based on its clinical experience, the committee was of the view that there is no need for these products to be used in this indication in children below 2 years of age. The PDCO was also of the view that these products are no longer the preferred treatment option in IRDS.

Taking the PDCO opinion into account, as well as the available efficacy data and all potential risks, we came to the conclusion that ambroxol/bromhexine as expectorant in children below 2 years of age should no longer be used, as the benefits of these medicines do not outweigh the risks in this population (negative outcome of the re-evaluation of the benefit-risk balance of ambroxol in the indication of secretolytic therapy in all paediatric populations below 2 years of age). Therefore, we believe this issue would only be fully addressed if a contra-indication is included in all medicinal

products containing ambroxol and bromhexine at least for paediatric populations below 2 years of age, not neglecting further restrictions in each Member State if considered needed.

Overall, it is considered that the newly identified safety risk of SCARs, along with the numerous other demonstrated hypersensitivity reactions significantly change the safety profiles of ambroxol and bromhexine. Moreover, this new safety information represents a new important identified risk associated with the use of ambroxol and bromhexine and is considered to represent "*solid and convincing evidence which, while not resolving the scientific certainty, may reasonably raise doubts as to the safety and/or efficacy of the medicinal product*" (EU General Court, decision of 26 November 2002 in Cases T-74/00 Artegodan).

It is also considered that the risk minimisation measures proposed in the PRAC recommendation are likely insufficient to prevent the risks of immediate and delayed-type hypersensitivities associated with ambroxol and bromhexine.

Regarding the benefits of ambroxol and bromhexine, we consider that the current scientific knowledge demonstrates that they are questionable and/or marginal in most indications, often greatly outweighed by the important safety risks detailed above.

As a consequence, we reached the following conclusions regarding the benefit-risk balances of ambroxol and bromhexine in their different indications, which are divergent from the conclusions of the revised CMDh position:

Benefit-risk balance for ambroxol-containing medicinal products

- Secretolytic therapy in acute and chronic Broncho-pulmonary disorders associated with abnormal mucus secretion and impaired mucus transport: The benefit-risk balance of all formulations of ambroxol hydrochloride is negative for patients aged 0-<2 yo or <12 Kg. Uncertainties persist concerning efficacy in the remaining paediatric age groups and in adults. More robust data, from a post authorization efficacy study, are needed for a proper evaluation of the risk benefit balance concerning efficacy in these age groups to confirm the benefit/risk as positive.

- 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 hydrochloride for the indication of postnatal treatment of IRDS is negative in the target population of patients (premature infants and neonates). It should not be recommended before new trials can prove efficacy for this therapeutic indication. PDCO has provided their opinion regarding this indication, being the general opinion that ambroxol products are no longer used as the preferred treatment option for IRDS.

- Prophylaxis of IRDS and stimulation of foetal lung maturation in pregnancies with threatening preterm delivery: The benefit-risk balance of antenatally administered ambroxol in order to reduce emergence of RDS 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). This view has been agreed upon by the MAH that has products for this indication.

- Prophylaxis of postoperative pulmonary complications in the adult population: Considering the limited evidence of efficacy of ambroxol in this indication and the important safety risks associated with the use of ambroxol, further data are needed in order to assess the benefit-risk profile of ambroxol in this indication. It should not be recommended before new trials can prove efficacy for this therapeutic indication. Therefore, the benefit-risk ratio must be considered negative until further data is provided.

Benefit-risk balance for bromhexine-containing medicinal products

- Secretolytic therapy in acute and chronic Broncho-pulmonary disorders associated with abnormal mucus secretion and impaired mucus transport: The benefit-risk balance of all formulations of bromhexine hydrochloride with a secretolytic indication is negative for age groups of patients 0-<2 yo or <12 Kg. Uncertainties persist concerning efficacy in the remaining paediatric age groups and in adults. More robust data, from a post authorization efficacy study, are needed for a proper evaluation of the risk benefit balance concerning efficacy in these age groups to confirm the benefit/risk as positive.

- Sjögren's syndrome (Keratoconjunctivitis sicca): 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.

Benefit-risk balance for ambroxol-containing combinations

- Combination of ambroxol-clenbuterol:

Considering the negative benefit of ambroxol-clenbuterol in this indication and the important safety risks associated with the use of ambroxol and clenbuterol, the benefit-risk balance of all formulations of ambroxol-clenbuterol with the indication "*Acute (and chronic) airways diseases associated with spasmodic constrictions, impaired formation and clearance of secretions, in particular spastic bronchitis, chronic obstructive lung disease associated with emphysema and bronchial asthma"* is negative in all age groups of patients (0-<12 yo, 12-adult) for which it is indicated.

- Combination of ambroxol-doxycycline:

Considering the negative benefit of ambroxol-doxycycline by default in this indication and the important safety risks associated with the use of ambroxol and doxycycline, the benefit-risk balance of all formulations of ambroxol-doxycycline with the indication "*Acute attacks of chronic bronchitis with accompanying pathological thickening of mucus, when these are caused by doxycycline-susceptible organisms*" is negative in the age population 12-adult for which it is indicated.

- Combination of ambroxol-theophylline:

Considering the negative benefit of ambroxol-theophylline in this indication and the important safety risks associated with the use of ambroxol and theophylline, the benefit-risk balance of all formulations of ambroxol-theophylline with the indication "*Treatment and prevention of shortness of breath due to narrowing of the airways (bronchoconstriction) in patients with persistent asthma or medium to severe obstructive pulmonary disease (e.g. chronic bronchitis and emphysema) with pathological secretion or impaired mucociliary clearance*" is negative in the age population 12-adult for which it is indicated.

CMDh member expressing a divergent opinion:

Sandra Petraglia (IT)	18 November 2015	Signature: .....