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 considers 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.

These safety risks associated with the use of ambroxol and bromhexine were found to be equivalent among genders and age groups (0-<6 yo, 6-<-12 yo, 12-adult).

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 bronchopulmonary disorders associated with abnormal mucus secretion and impaired mucus transport:

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 all formulations of ambroxol with a secretolytic indication is **negative** in all age groups of patients (0-<6 yo, 6-<-12 yo, 12-adult).

Pain relief in acute sore throat:

As the important risks associated with the use of ambroxol outweigh the slightly positive benefits in this indication, demonstrated only for 3 hours following the first intake, the **benefit / risk balance** of all formulations of ambroxol indicated in pain relief in acute sore throat is **negative** in the age population 12-adult for which it is indicated.

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

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 all formulations of ambroxol indicated in the postnatal treatment of IRDS is **negative** in the target population of patients (premature infants and neonates).

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

Efficacy data are not sufficiently demonstrative to consider that ambroxol have an effect in prophylaxis of IRDS, the **benefit / risk balance** of antenatally administered ambroxol in order to reduce emergence of IRDS is considered as **negative**.

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.

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.

Benefit-risk balance for bromhexine-containing medicinal products

Considering the negative benefit of bromhexine in the secretolytic, sinusitis and Sjögren's syndrome indications and the important safety risks associated with the use of bromhexine, the **benefit / risk balance** of all formulations of bromhexine (including the combination products) in all its indications is **negative** in all age groups of patients for which it is indicated.

CMDh member expressing a divergent opinion:

Virginie Bacquet (FR)	18 November 2015	Signature: ……