SVD 66579o

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 Belgium-FAMHP

Product Name(s), if appropriate, Strength(s) and Pharmaceutical Form(s)	All ambroxol hydrochloride- and bromhexine hydrochloride-containing products and strengths
Active Substance(s)/Therapeutic class	R05CB06 and R05CB02
Marketing Authorisation Holder(s)	Various

Ambroxol hydrochloride is commonly used across Europe. Since 2000, Belgium is the Reference Member State (RMS), (PSUR)-RMS and lead Member State for the innovator products Mucosolvan and Mucoangin.

Ambroxol hydrochloride (C12H18Br2N2O) is one of the major active metabolites of bromhexine hydrochloride, and is a mucoactive agent belonging to the family of expectorants (molecules that increase secretion of mucus and increase mucus hydration). Many biological actions have been attributed to ambroxol hydrochloride, including mucokinetic properties and increase of respiratory fluids volume, stimulation of mucocilliary activity, surfactant activities, anti-inflammatory properties and local anaesthetic activities.
Ambroxol-containing medicinal products exist in various formulations (tablets, pastille, modified-release capsule, syrup, solution for infusion, lozenge…) and dosages.

Ambroxol hydrochloride has 2 main indications:
- Secretolytic therapy in acute and chronic bronchopulmonary disease associated with abnormal mucus secretion and impaired mucus transport.
- Pain relief in acute sore throat (restricted to the lozenge formulations).

Additionally, injectable formulations have 2 other indications:
- To enhance pulmonary surfactant production in premature infants and newborns with infant respiratory distress syndrome (IRDS) (sol. for injection).
- To enhance prenatal lung maturation and as prohylaxis of IRDS (sol. for infusion).

In November 2011, the MAH of the ambroxol-containing innovator products Mucosolvan/Mucoangin submitted a Periodic Safety Update Report (PSUR) in the frame of the worksharing procedure BE/H/PSUR/0003/002. Taking into consideration the data submitted during whole PSUR WS assessment procedure (initial submission and questions/answers), as well as recent evaluations in the context of signal detection based on electronic Reactions Monitoring Report, the below-listed conclusions and points of disagreements with the MAH were reached at the end of the PSUR WS assessment procedure (March 2014):

1) Immediate hypersensitivity, including anaphylactic reactions, is an identified risk associated with the use of ambroxol hydrochloride. However, over the last 2 years, a significant increase in the reporting rate of these reactions and in the proportional reporting ratio (PRR) associated with these reactions was observed in Eudravigilance. Indeed, 43% of the 132 cases of anaphylactic reactions registered in Eudravigilance were collected during 2012-2014.

2) Accumulating evidence from case reports, statistical detection methods from Eudravigilance (PRR) and recent publications demonstrate that ambroxol hydrochloride is responsible of severe cutaneous adverse reactions (SCARs) resulting from delayed-type hypersensitivities. There is indeed 210 case reports of SCARs associated with ambroxol administration in Eudravigilance (DLP 28 February 2014), with at least 9 entries in which the causality to ambroxol is considered as likely to definite due to positive immune testing (patch tests or lymphocyte stimulation tests). This information should be correctly mentioned in the safety documents of all ambroxol-containing products and constitutes an important safety concern associated with the use of ambroxol. Despite the evidence, the MAH denies any implication of ambroxol in such reactions and refuses to list these adverse events in the product information.

3) Nearly 35% (312/893) of the adverse events collected during the period of the last PSUR (2008-2011) concerned the paediatric population (under 18 years-old), with 27% (246/893) just for the paediatric population below 6 years old. A re-evaluation of the benefit-risk (B/R) balance of ambroxol hydrochloride-containing products indicated in secretolytic therapy in all paediatric subpopulations below 6 years-old was thus requested during the PSUR WS

assessment procedure and was concluded negative in these populations. The negative B/R balance was justified by insufficient evidence of the efficacy of ambroxol in the indication of secretolytic therapy in these populations, while the risks were equivalent to those observed in adult patients. The same analysis performed by the MAH concluded to a positive B/R balance. In Belgium, ambroxol hydrochloride is contraindicated/not recommended under 12 years of age in all indications.

Therefore, considering:

- the identification of immediate and delayed-type hypersensitivity issues that significantly impact on the safety profile of ambroxol hydrochloride;
- the negative outcome of the reevaluation of the benefit-risk balance of ambroxol in the indication of secretolytic therapy in all paediatric populations below 6 years of age;

Belgium came to the conclusion that the benefit-risk balance of ambroxol hydrochloride is questionable in all its currently approved indications and that a thorough reevaluation of the benefit-risk balance of ambroxol hydrochloride-containing medicinal products is necessary.

Moreover, as hypersensitivity-related AEs are not dependent on the dose of the allergenic substance and that ambroxol is a well-known metabolite of bromhexine, Belgium considers that the scope of the referral should also be extended to all medicinal products containing bromhexine hydrochloride.

In light of the above, Belgium considers that it is in the interest of the Union to refer ambroxol hydrochloride and bromhexine hydrochloride-containing medicinal products to the Pharmacovigilance Risk Assessment Committee and requests that it gives its recommendation under Article 31 of Directive 2001/83/EC on whether the balance of benefits and risks is positive for these products in the approved indications and whether the marketing authorisations for medicinal products containing ambroxol hydrochloride should be maintained, varied, suspended or withdrawn.

A draft list of questions to be submitted to the MAHs is annexed.

Signed 

Date 04/04/2014