Annex II

Scientific conclusions

Scientific conclusions

Further to the evaluation of a Worksharing PSUR of ambroxol-containing medicinal products started in January 2012 and of follow-up submissions as well as signal detection activities, the Belgian national competent authority (FAMHP) identified an increase in reporting of hypersensitivity reactions over the years 2012-2014, reports of severe cutaneous adverse reactions (SCARs) and a benefit-risk evaluation in children below 6 years of age concluded that while there was no indication of a different safety profile, insufficient evidence of efficacy was available in secretolytic therapy in this age group, leading to a negative benefit-risk balance. As ambroxol is a metabolite of bromhexine and hypersensitivity reactions are not dependent on the dose of the allergenic substance absorbed, the FAMHP considered that any confirmed risk with ambroxol could also be found in bromhexine-containing medicinal products with regards to these reactions.

In light of the above, on 4 April 2014, the FAMHP informed the European Medicines Agency, of their decision to notify a referral procedure to ask for the PRAC's recommendation pursuant to Article 31 of Directive 2001/83/EC, on whether the balance of benefits and risks for these products is still positive in the approved indications, and whether the marketing authorisations for ambroxol- and bromhexine-containing medicinal products should be maintained, varied, suspended or withdrawn.

On 25 February 2015, the CMDh, having considered the PRAC recommendation, dated 9 January 2015, reached by majority the position that the marketing authorisations for the concerned medicinal products should be varied. The CMDh position was forwarded to the European Commission. During the decision making process, at a meeting of the Standing Committee on Medicinal Products for Human Use, some Member States raised new questions of technical nature which they considered had not been sufficiently addressed in the PRAC recommendation and CMDh position. In light of this, the PRAC recommendation and CMDh position was referred back to the Agency for further consideration.

Ambroxol- and bromhexine-containing medicinal products have first been registered in a European Union (EU) Member State (MS) in 1978 and 1963, respectively, and are currently authorised in all EU MSs (as well as in Norway and Iceland) except the United Kingdom. The authorised indications of ambroxol, as listed in the Company Core Data Sheet of the originator, are secretolytic therapy, prophylaxis and treatment of Infant Respiratory Distress Syndrome (IRDS), prophylaxis and treatment of post-operative bronchopulmonary complications (PPC) and pain relief in acute sore throat. The authorised indications of bromhexine, as listed in the Company Core Data Sheet of the originator, are secretolytic therapy, alteration in the production or elimination of mucus (acute and chronic sinusitis) and Sjögren's syndrome. All indications are not authorised in all EU MS. In addition, ambroxol and bromhexine have been approved in some EU MS in airway diseases indications in fixed dose combinations with various active substances. These products are contra-indicated in different subsets of the paediatric population in the EU MS. Ambroxol and bromhexine are marketed in several formulations for oral, nasal, oromucosal, intravenous or rectal administration under various invented names. Ambroxol- and bromhexine-containing medicines are available as over-the-counter (OTC) as well as prescription-only medicines (POM).

1 – Overall summary of the scientific evaluation by the PRAC

Safety issues

SCARs

The safety information submitted by the MAHs, from Eudravigilance and from the literature, comprises in total around 300 case reports of suspected SCARs, many of which have possible confounders. Four cases of SCARs retrieved from Eudravigilance and 3 others from the literature have been assessed as

related to ambroxol. The PRAC considered that there was a reasonable possibility that ambroxol and bromhexine are associated with serious delayed-type hypersensitivity reactions associated with SCARs. Hypersensitivity reactions are dose and formulation independent, therefore the possible risk of developing hypersensitivity reactions including SCARs is inherent to all ambroxol- and bromhexine-containing products. The PRAC noted that the worldwide estimated exposure of the originator's products alone is over 50 million patient-years and, in the EU over the last decade, around 6.8 million patient-years. The PRAC considered that the evidence of risk of SCARs associated with ambroxol and bromhexine is weak.

Many patients with SCARs receive various mucolytic or secretolytic agents in the relevant time period before the onset of their adverse event. Most often these patients receive a number of drugs concomitantly and causality assessment is difficult. As SCARs sometimes start with flu-like symptoms some patients might also start taking ambroxol or bromhexine to alleviate these symptoms whereas the typical skin reactions appear later and ambroxol or bromhexine might be considered as suspect drug. Of note, drugs started less than 4 days or more than 8 weeks before the onset of the reaction are unlikely to be responsible. Many drug reactions cannot be distinguished from naturally occurring or infection-induced eruptions, and thus misdiagnosis is common. However, prompt recognition of severe reactions and early withdrawal of the causative agent is the most important factor to minimise morbidity and mortality.

Hypersensitivity reactions

Analysis of the safety information submitted by the MAH, from Eudravigilance and from the literature, demonstrates that ambroxol and bromhexine formulations in their different indications have been associated with reports of serious immediate hypersensitivity reactions. In addition, ambroxol formulations indicated in secretolytic therapy and prophylaxis or treatment of IRDS and PPC have been associated with delayed-onset hypersensitivity reactions without severe skin injury. However, these adverse reactions are already listed in the product information of most ambroxol- and bromhexine-containing products and the analysis of the most frequently reported adverse events selected by the SMQ Hypersensitivity (broad) did not identify any new safety concerns. Based on these data it is considered that the susceptibility of all age groups (paediatric, adults and elderly) to putative hypersensitivity-related undesirable effects of ambroxol or bromhexine is likely similar.

An increase was observed in the reporting frequency of anaphylactic reactions over 2012-2014 linked to ambroxol. However, when looking at the date of the reports, 40 reports, out of the 119 reported in total for the originator since the first marketing authorisation, appear to have been sent in two batches by the Chinese health authority to the MAH of the originator of these products. This increase in reporting follows the implementation of a new pharmacovigilance regulation in China that might have influenced adverse reaction reporting and does not reflect a new safety concern.

Efficacy issues

The clinical studies performed during the development of bromhexine- and ambroxol-containing products between the 1950ies and 1980ies were considerably less standardised than would be necessary today, and would not completely fulfil contemporary requirements with regard to validated endpoints, statistical confirmation, or Good Clinical Practice (GCP). These constitute the majority of the available evidence, in particular in the indications that were first authorised (e.g. secretolytic indication). In addition, all studies conducted more recently submitted by the MAHs were also considered by the PRAC. Often a large placebo effect is seen in studies investigating respiratory conditions, particularly in non-serious, self-limiting conditions. Further, the definition of the relevant clinical endpoints and the measurement of symptoms in these conditions are challenging (Rubin, 2007). The PRAC considered all these elements in its review of the available data on the efficacy of ambroxol- and bromhexine-containing products. It is acknowledged that most of the indications are

supported by old studies presenting limitations and deficiencies. Some trials failed to show a significant difference between ambroxol or bromhexine and placebo and other only showed significant difference in some of the studied endpoints. Nevertheless, modest but positive results were reported for ambroxol and bromhexine. It is acknowledged that clinical evidence from studies in children is weak due to their heterogeneity and to the lower number of children enrolled. It is recognised also that the limitations and uncertainties attached to the dataset hinder the ability to draw robust conclusions on the efficacy. For these reasons studies conducted after the initial marketing authorisation do not provide new significant scientific data on the efficacy of the products.

Benefit-risk assessment

When considering data in support of the safety issues, the PRAC was of the view that ambroxol- and bromhexine-containing products are associated with case reports of immediate and delayed hypersensitivity including hypersensitivity reactions, anaphylactic reactions including anaphylactic shock, angioedema, pruritus, rash and urticaria. The PRAC however noted that the observed increase in reporting of anaphylactic reactions for ambroxol-containing products was likely an artefact resulting from the implementation of a new pharmacovigilance regulation in China and did not constitute a new safety concern. With regards to delayed hypersensitivity reactions associated with SCARs, a few cases have been assessed as certainly related to ambroxol. Based on the evaluation of the individual case reports, considering the nature of these events the PRAC was of the view that there is a reasonable possibility that all ambroxol and bromhexine-containing products are associated with an increased risk of SCARs including combination products. However, the overall reporting rate is very low when the estimated exposure is considered and many confounders are present in these cases, the evidence supporting this risk is therefore weak.

The PRAC was of the view that the possible risk of SCARs can be adequately addressed by the proposed amendments to the PI to inform caregivers and patients of the risk and allow early identification of signs of SCARs and immediate discontinuation of treatment should they occur. In addition the PRAC recommended harmonising the terms related to hypersensitivity reactions in the product information. Moreover SCARs cases should be analysed in details in future PSURs. Consequently the PSUR cycle should be shortened to a 3-yearly cycle in order to periodically review these analyses.

In relation to the efficacy of ambroxol- and bromhexine-containing products, the PRAC concluded that although modest positive results were reported, the evidence of efficacy of ambroxol and bromhexine suffered from a number of limitations and deficiencies. This is not unexpected considering the methodological challenges inherent to this therapeutic area and evidential standards and requirements at the time when these products were first developed.

Taking into account these limitations, together with the weak evidence of a safety issue from the pharmacovigilance data, the PRAC could not conclude from the available evidence that risks outweighed benefits in the different indications. The PRAC also considered the available data in the paediatric population. The level of evidence did not allow for further stratification by age group. Therefore the PRAC concluded that the evidence available did not justify the introduction of further age specific restrictions in the product information.

In addition, the PRAC discussed the need to conduct post-authorisation studies, and concluded that such studies would likely not generate new robust information towards more definite conclusions. However, a shorter PSUR cycle should be introduced to continue to review periodically data that becomes available on the benefit-risk balance of the products.

The PRAC took note of the advice of the paediatric committee (PDCO) that the use of ambroxol and bromhexine varies significantly in paediatric clinical practice across the EU. Based on its clinical

experience, the PDCO was of the view that there is no need for the use of these products 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 all of the above into consideration, the PRAC concluded that the data reviewed supported amendments of the product information to reflect the risk of severe cutaneous adverse reactions, and that further age restrictions to reflect the concerns about the benefit-risk balance of ambroxol- and bromhexine-containing products are not justified on the basis of the data available.

Overall conclusion and grounds for the revised PRAC recommendation

Whereas

- The PRAC considered the procedure under Article 31 of Directive 2001/83/EC resulting from pharmacovigilance data for ambroxol- and bromhexine-containing medicinal products.
- The PRAC reviewed the totality of the data submitted in support of the safety and efficacy of ambroxol- and bromhexine-containing products, including submissions from the marketing authorisation holders and expert input.
- The PRAC considered that there is a reasonable possibility of a risk of SCARs associated with ambroxol and bromhexine.
- The PRAC considered that ambroxol and bromhexine are associated with an increased risk of hypersensitivity reactions.
- The PRAC was of the view that the risk of SCARs should be addressed by its inclusion in the product information accompanied by a warning in order for patients and caregivers to recognise the prodromes of SCARs and discontinue treatment immediately in the event of such signs.
- The PRAC considered that the available data were insufficient to justify new age restrictions.

Therefore, the PRAC recommends the variation to the terms of the marketing authorisations, for all ambroxol- and bromhexine-containing medicinal products identified in Annex I and for which the relevant sections of the Summary of Product Characteristics and Package Leaflet are set out in Annex III of the revised PRAC recommendation.

The PRAC, as a consequence, concluded that the benefit-risk balance of of ambroxol- and bromhexine-containing medicinal products remains favourable, subject to the above detailed amendments to the product information.

2 – CMDh revised position

All the available data submitted, related to the safety and the efficacy of the medicinal products were reviewed by the PRAC to assess the potential impact of the new safety concerns identified on the established benefit–risk balance of the authorised medicinal products. The CMDh, having considered the revised PRAC recommendation, agrees with the overall scientific conclusions by the PRAC and reached the position that the marketing authorisations for ambroxol- and bromhexine-containing medicinal products should be varied. The CMDh considered the PRAC recommendation that the evidence available did not provide sufficient grounds to demonstrate a change to the established benefit-risk balance, provided the recommended amendments to sections 4.4 and 4.8 of the product

information, detailed in annex III, are implemented. Only these amendments, adopted and included in the CMDh position, are legally binding and must be implemented by the Member States.