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SCIENCE MEDICINES HEALTH

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Pharmacovigilance Risk Assessment Committee (PRAC)

## Revised assessment report

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

Ambroxol and bromhexine containing medicinal products

INN: ambroxol and bromhexine

Procedure number: EMEA/H/A-31/1397

### Note

Assessment report as adopted by the PRAC and considered by the CMDh with  
all information of a commercially confidential nature deleted.



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# 1. Background information on the procedure

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 - indeed 43% of the 132 cases of anaphylactic reactions registered in Eudravigilance (EV) were collected over that period. In addition the Belgian national authority was of the view that accumulating evidence from case reports and the literature demonstrated that ambroxol is responsible for severe cutaneous adverse reactions (SCARs). As of the 28<sup>th</sup> of February 2014 there were 210 case reports of SCARs in EV, including at least 9 with a causal relationship to ambroxol assessed as likely to definite. Finally the FAMHP conducted a benefit risk evaluation in children below 6 years of age after having observed a relatively high proportion of AEs reported in children below 6 years of age (27%) over the reporting period 2008-2011. This evaluation concluded that, while this was not indicative 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, pursuant to Article 107k(1) and (2) of Directive 2001/83/EC, the CMDh, having considered the PRAC recommendation dated 9 January 2015 with regards to ambroxol- and bromhexine-containing medicinal products, 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 EU 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 were referred back to the Agency for further consideration.

## 2. Scientific discussion

### 2.1. Introduction

Ambroxol, a substituted benzylamine, is the active N-desmethyl metabolite of bromhexine, which itself is a synthetic derivative of vasicine, the active principle of *Adhatoda vasica*. The pharmacological properties of ambroxol are claimed to be:

- secretolytic (mucolytic) agent: decreasing mucus viscosity through depolymerisation of acidic polysaccharide fibres in the bronchial secretion and stimulation of neutral polysaccharide production by glandular cells
- mucokinetic agent: stimulation of cilia activity and mucociliary clearance (MCC)

- enhancement of availability of surfactant (through its stimulating effect on the synthesis and release of surfactant by type II pneumocytes)
- antioxidant actions
- anti-inflammatory actions
- anti-viral and anti-bacterial properties
- local anaesthetic (through inhibition of the neuronal sodium channels)

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 MS (as well as in Norway and Iceland) except the United Kingdom. Ambroxol- and bromhexine-containing products were first authorised in secretolytic therapy. Additional indications were authorised in some EU MS at a later point in time.

The authorised indications of ambroxol, as listed in the Company Core Data Sheet of the originator, are presented below:

- Secretolytic therapy (oral, inhalative, rectal and intravenous administration)
- Prophylaxis and treatment of Infant respiratory distress syndrome (IRDS) (intravenous administration)
- Prophylaxis and treatment of postoperative bronchopulmonary complications (PPC) (intravenous administration)
- Pain relief in acute sore throat (oromucosal administration in adult and children >12)

The authorised indications of bromhexine, as listed in the Company Core Data Sheet of the originator, are presented below:

- Secretolytic therapy (oral, inhalative and intravenous administration)
- Alteration in the production or elimination of mucus – acute sinusitis, chronic sinusitis (oral and inhalative administration)
- Sjögren's syndrome (oral administration)

In addition, ambroxol and bromhexine have been approved in some EU MS in airway diseases indications in fixed dose combinations with various active substances (e.g. ambroxol/doxycycline, ambroxol/clenbuterol, ambroxol/theophylline and bromhexine/amoxicillin). These products are contraindicated 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).

As mentioned above, one of the triggers for this review was the identification of severe cutaneous adverse reactions (SCARs) reports, possibly linked to ambroxol. SCARs comprise Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN) and the overlapping condition, erythema multiforme (EM) especially when mucous membranes are involved (EM majus: EMM), acute generalised exanthematous pustulosis (AGEP) and drug reaction (hypersensitivity) with eosinophilia and systemic symptoms (DRESS). EM and EMM may also result from several underlying causes, mostly infections (herpes virus, mycoplasma pneumonia, upper respiratory tract infections and influenza-like illness) but

can also be drug-induced. SJS, TEN, AGEP and DRESS are most often drug-induced and, in more rare cases, of infectious aetiology.

SJS and TEN present with a prodromal period with influenza-like symptoms such as fever, aching body, malaise, headaches, rhinitis, pharyngitis, sore throat, myalgia, arthralgia, nausea and/or diarrhoea that may last up to 14 days. Then the eruption starts, it is usually distributed symmetrically on the face, upper trunk and proximal extremities. However, the exanthema can rapidly extend to the entire body. Nikolsky's sign is positive, flaccid blisters develop and detachment of necrotic epidermis on slight pressure reveals large areas of denuded skin. The principal difference is the extent of detachment, limited in SJS and more widespread in TEN. Mucous membrane involvement is noted in around 85% of patients with erythema and painful erosions of the buccal, ocular, nasal and genital mucosa.

## **2.2. Clinical aspects**

In its assessment, the PRAC considered all the data submitted from different sources. A summary of the most relevant data is included below. The marketing authorisation holders provided estimates of the patient exposure derived from sales data. As sales are measured per formulations, patient exposure in each indication cannot be differentiated. For the originator, the worldwide patient exposure was estimated to be 31,881,769 patient-years for ambroxol-containing products indicated in secretolytic therapy, IRDS and PPC, 364,223 patient-years for products indicated in pain relief in sore throat and 20,737,760 patient-years for bromhexine-containing products. When looking only at the last decade (2004-2013) in the EU, the exposure was estimated to be 4,356,482 patient-years for ambroxol-containing products indicated in secretolytic therapy, IRDS and PPC, 248,267 patient-years for products indicated in pain relief in sore throat and 2,185,404 patient-years for bromhexine-containing products.

### **2.2.1. Safety**

#### **Severe cutaneous adverse drug reactions (SCARs)**

Spontaneous reports of SCARs (data lock point (DLP) 31 March 2014)

A search with the standard MedDRA query (SMQ) severe cutaneous adverse reaction (SCARs) in the database of the MAH of the originator products containing ambroxol indicated in secretolytic therapy, IRDS and PPC retrieved 131 cases. The most reported events were SJS (54), EM (34), TEN (20) and dermatitis bulbous (12). Considering the estimated exposure the reporting rate is 4.1 per million patient-years corresponding to 0.16 cases reported per million patients exposed.

A search with the SMQ severe cutaneous adverse reaction (SCARs) in the database of the MAH of the originator products containing ambroxol indicated in pain relief in acute sore throat retrieved 3 cases: 1 SJS, 1 dermatitis exfoliative and one skin eruption. Considering the estimated patient exposure this translates into a reporting rate of 8.2 per million patient-years corresponding to 0.07 cases reported per million patients exposed. The SJS case was assessed as possibly related to ambroxol.

A search with the SMQ SCARs in the database of the MAH of the originator products containing bromhexine indicated in secretolytic therapy retrieved 19 cases. Reported terms were SJS (7), TEN (6), EM (3), Dermatitis bullous (2), Dermatitis exfoliative (1), Exfoliative rash (1) and Toxic skin eruption (1). Considering the estimated exposure the reporting rate is 0.92 per million patient-years,

corresponding to 0.035 cases reported per million patients exposed. Eight cases were assessed as possibly related to ambroxol and the remaining eight were unassessable.

Eudravigilance analysis of severe cutaneous adverse drug reactions (DLP 26 June 2014)

A search in Eudravigilance with the SMQ SCARs (broad) and ambroxol reported as a suspected or interacting medicinal products retrieved 360 AEs corresponding to 265 cases reports. Age analysis was similar to that observed for the terms retrieved with the SMQ hypersensitivity (broad) detailed further below.

For cases corresponding to product indicated in secretolytic therapy, IRDS and PPC the causal relationship was assessed as certain in 4 cases, probable in 4 cases, possible in 32 cases (including 4 fatal cases, 1 adult with SJS, 2 adults with TEN and 1 child with EM) and for 78 cases, the causality was not assessable. The 4 cases assessed as certainly related to ambroxol included 1 case of SJS in an adult, 1 cases of AGEP in a paediatric patient, 1 cases of EM in a paediatric patient and one case of drug eruption in an adult patient). Among the cases assessed as probably related to ambroxol 1 SJS and 1 EM and 1 were reported in adults. Of note one case of dermatitis bullous and of stomatitis was included in the preferred terms from the SMQ SCARs and assessed as probably related to ambroxol but were in fact respectively an immediate hypersensitivity reaction and a delayed hypersensitivity reaction without skin injury and therefore not SCARs. Regarding age distribution, among the 40 cases assessed as certainly, probably or possibly related to ambroxol, 28 cases (70%) concerned adults, 6 cases (15%) paediatric patients aged 0 to <6, 5 cases (13%) patients aged 6 to <12 and 1 cases (2%) patient aged 12 to <18 years old.

For cases corresponding to products indicated in pain relief in acute sore throat the causal relationship was assessed as certain for none of the cases, as probable in 2 cases (mouth ulceration and oral mucosa blistering) and as possible in 2 cases (SJS and dermatitis exfoliative).

Literature cases of SCARs

Additional cases were retrieved from the literature including 3 cases assessed as certainly related to ambroxol used in secretolytic therapy, IRDS or PPC, one maculopapular erythematous eruption with mucosal involvement, one case of facial vesicular erythema, and one generalised maculopapulous rash (Saad N, 2006 [1]; Mancuso G, 1989 [2]; Terasaki K, 2002 [3]).

Epidemiological studies on background incidence of SCARs

Several epidemiological studies in Germany, France, the EU and the US estimate the incidence of SJS, SJS/TEN overlap and TEN to be 1-2 per million (Rzany, 1996 [4]; Mockenhaupt, 2009 [5]; Roujeau, 1990 [6]; Fritsch, 2000 [7]; Schoepf, 1991 [8]). The incidence of AGEP has been estimated to 1-5 per

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<sup>1</sup> Saad N, Guillot I, Vautrin C, Freymond N, Catelain A, Kerhoas A, Nicolas JF. [Ambroxol-induced toxicoderma]. *Ann Dermatol Venereol*. 2006 Feb;133(2):181-2

<sup>2</sup> Mancuso G, Berdondini RM. Contact allergy to ambroxol. *Contact Dermatitis*. 1989 Feb;20(2):154.

<sup>3</sup> Terasaki K et al: A case of skin eruption due to ambroxol hydrochloride except for the site of radiation therapy. *Environ Dermatol* 9 : 70-73, 2002

<sup>4</sup> Rzany B, Mockenhaupt M, Baur S, Schroeder W, Stocker U, Mueller J, Hollaender N, Bruppacher R, Schoepf E. Epidemiology of erythema exsudativum multiforme majus, Stevens-Johnson syndrome, and toxic epidermal necrolysis in Germany (1990 - 1992): structure and results of a population-based registry. *J Clin Epidemiol* 49 (7), 769 - 773 (1996)

<sup>5</sup> Mockenhaupt M. Severe cutaneous adverse drug reactions. In: Burgdorf WHC, Plewig G, Wolff HH, Landthaler M, editors. *Braun-Falco's dermatology*. 3rd ed. Heidelberg: Springer, 473 - 484 (2009)

<sup>6</sup> Roujeau JC, Guillaume JC, Fabre JP et al. Incidence and drug aetiology in France, 1981-1985. *Arch Dermatol* 1990; 126 (1): 37-42

<sup>7</sup> Fritsch PO, Sidoroff A. Drug-induced Stevens-Johnson syndrome/toxic epidermal necrolysis. *Am J Clin Dermatol* 1 (6), 349 - 360 (2000)

<sup>8</sup> Schoepf E, Stuehmer A, Rzany B, Victor N, Zentgraf R, Kapp JF. Toxic epidermal necrolysis and Stevens-Johnson syndrome: an epidemiologic study from West Germany. *Arch Dermatol* 127, 839 - 842 (1991)

million (Fernando, 2012 [9]). As patients with EM are often not hospitalised, the occurrence of this event cannot be reliably estimated.

## Hypersensitivity reactions

### Spontaneous reports of hypersensitivity reactions

A search with the SMQ hypersensitivity (broad) in the database of the MAH of the originator product containing ambroxol, indicated in secretolytic therapy, IRDS and PPC retrieved 1,879 cases. Taking into account the estimated patient exposure the reporting rate is 58.7 per million patient-years. The majority of case reports containing an event of the SMQ hypersensitivity (broad) is related to the system organ class (SOC) subcutaneous tissue disorders (78.7%), followed by immune system disorder (11.9%), respiratory thoracic and mediastinal disorder (6.8%), gastrointestinal disorder and mediastinal disorder (3.2%), general disorder and administration site conditions (2.6%), eye disorder (2.1%) and infection and infestation (1.7%).

Excluding the SCARs cases, 256 serious cases were retrieved, 234 of which were confirmed by a healthcare professional and 20 had a fatal outcome. Among the 256 serious cases, the causal relationship to ambroxol was assessed as certain in 3 cases, probable in 20 cases, possible in 164 cases, unlikely in 34 cases and 35 cases were unassessable. Five of the fatal cases were assessed as possibly related to ambroxol and none as probably or certainly related. Of the 3 cases for which causality was assessed as certain, the reported events were angioedema, laryngeal oedema, suffocation sensation in one case (age not provided), photosensitivity reaction and eosinophilia in the second (82 year-old) and dermatitis contact, rash maculopapular and pruritus in the third (79 year-old). Of the 20 case reports assessed as probably related the most frequently reported preferred terms were anaphylactic reaction (6), dyspnoea (4), anaphylactic shock (3), rash (3), urticaria (3) and hypersensitivity (3). The serious reports on paediatric patients represented 18.3% of the total, split across the age range as follow: 14.8% for the population below 6 years of age, 2.7% for the children aged 6-12 years old and 0.8% for older children. The age was not reported in 8% of the reports. For 14.8% (38 cases) of the paediatric cases the causal relationship to ambroxol was assessed as possible or probable.

A search with the SMQ hypersensitivity (broad) in the database of the MAH of the originator product containing ambroxol indicated in pain relief in acute sore throat retrieved 292 adverse events (AEs) corresponding to 234 cases which translate into an estimated reporting rate of 642 per million patient-years. The majority of case reports containing an event of the SMQ hypersensitivity (broad) is related to the SOC skin and subcutaneous tissue disorders (33%), respiratory, thoracic and mediastinal disorder (23%), immune system disorders (19%) and gastrointestinal disorders (18%), this is globally in line with what was reported for other formulations.

Excluding the SCARs cases 33 serious cases were retrieved, 30 of them were confirmed by a healthcare professional and none had a fatal outcome. Among the 33 cases the causal relationship was assessed as probable in 4 cases, possible in 22 cases and was not assessable in 2 cases. No cases were assessed as certainly related to ambroxol. The most frequently reported events in the 5 cases assessed as probable are dyspnoea (3), pharyngeal oedema incl. pharyngeal disorder (3), angioedema (2) and anaphylactic shock (2). Only one case was reported in the paediatric population in a 13 year old which was rated as possibly related to ambroxol; age was not provided in 18 reports.

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<sup>9</sup> Fernando SL. (2012) Acute generalised exanthematous pustulosis. *Australas J Dermatol.*;53(2):87-92

A search with the SMQ hypersensitivity (broad) in the database of the MAH of the originator product containing bromhexine, indicated in secretolytic therapy retrieved 588 cases, 398 (68%) of them health-care professional confirmed. Taking the patient exposure into account the estimated reporting rate is 28.35 per million patient-years. The majority of case reports containing an event of the SMQ Hypersensitivity (broad) is related to the SOC skin and subcutaneous tissue disorders (67.5%), followed by immune system disorders (15.65%), respiratory, thoracic and mediastinal disorders (15.35%), gastrointestinal disorders (6.85%), eye disorders (3.65%) and general disorders and administration site conditions (2.4%).

Excluding the SCARs cases, 85 serious cases were retrieved, 75 of them were confirmed by a healthcare professional and five cases had a fatal outcome. The causal relationship in these cases was assessed as possible in 2 cases, unlikely in 2 cases and unassessable in 1 case. Among the 85 cases the causal relationship was assessed certain in 1 case, as probable in 11 cases, as possible in 43 cases and 19 cases were unassessable. Events reported in the case assessed as certain are tongue oedema, oedema of the mouth, angioedema, dyspnoea, obstructive airways disorder. The most frequently reported events in the 11 cases assessed as probable are anaphylactic shock (4), bronchospasm (3) and angioedema and oedema concerning various locations (5). The age range for these cases was 1 - 83 years. Only 15 cases were reported in the paediatric population (up to 6 years: 7 cases, 6 – below 12 years: 2 cases, 12 – below 18 years: 6 cases) and the age was not provided in 11 cases.

In the safety database of the originator product, only 4 hypersensitivity reactions and no SCAR cases could be identified where bromhexine use was reported for treatment of sinusitis and no case could be identified where it was used for treatment of Sjögren's syndrome.

With regards to the concerns around an increased reporting of anaphylactic reactions, a search was conducted in the database of the MAH of the originator and retrieved 119 cases for ambroxol-containing products indicated in secretolytic therapy, IRDS and PPC of which nearly half originated from China and 7 cases for originator product indicated in pain relief in acute sore throat. No increase in reporting of this reaction was found for bromhexine-containing products. When looking at the reporting date of reports two peaks corresponded to two batches of case reports sent by the Chinese health authority to the MAH of these products. This increase in reporting follows the implementation of a new pharmacovigilance regulation in China that might have influenced adverse reaction reporting.

#### Eudravigilance analysis of hypersensitivity reactions (DLP 26 June 2014)

In Eudravigilance 1,351 cases were retrieved corresponding to 823 case reports (562 when excluding SCARs cases) with ambroxol reported as suspected or interacting medicinal product. These were predominantly spontaneous reports from healthcare professionals (HCP) (91%) and originated mostly from Europe (66%) and Asia (30%). Analysis of the case reports demonstrated that 23% of the reports concerned paediatric patients (11% in 0-6, 8% in 6-12 and 4% in 12-18 years old children or adolescents) and 69% adults (of which 25% were older than 65 years of age), no age was specified in the remaining cases. Slightly more cases were reported in the younger and older patients, however this effect could be explained by a more frequent use of these medications partially linked to an increased susceptibility to respiratory tract infections in these populations. It was therefore considered that the susceptibility of all age groups to putative ambroxol-related hypersensitivity reactions is likely to be similar.



Excluding SCARs, 530 cases corresponded to ambroxol-containing products indicated in secretolytic therapy, IRDS and PPC. Causal relationship was assessed as certain in 4 cases, probable in 64 cases, possible in 134 cases (including 6 fatal cases further to anaphylactic shock) and 195 cases were not assessable. The 4 cases for which the causality was assessed as certain corresponded to two cases of rash (one in an adult, one in a child below 6 years of age), one case of hypersensitivity and one case of delayed onset hypersensitivity without severe skin reactions, both in adults. Most preferred terms reported in these serious cases assessed as certainly, probably or possibly related to ambroxol were anaphylactic reactions, anaphylactoid reactions, hypersensitivity, rash, urticaria and angioedema. Of note 28 cases corresponded to delayed onset hypersensitivity reactions but not SCARs as they involved no or moderate skin injury but occurred between 3 and 32 days after treatment initiation. When comparing age groups, 145 cases (71%) concerned adults, 35 cases (17%) paediatric patients aged under 6 years old, 12 cases (6%) paediatric patients aged between 6 and 12 years old and 6 cases (3%) paediatric patients older than 12 years old.

For products indicated in pain relief in acute sore throat, 15 cases were assessed as probably related to ambroxol and 17 as possibly related, no fatal cases were reported and one case was retrieved in the paediatric population, in a 13 year old. The cases assessed as probably related corresponded to angioedema, hypersensitivity, anaphylactic reaction, rash and mouth oedema.

### Paediatric populations

Additional safety analyses were conducted focusing on the paediatric population (0-12 years old) in comparison with the adolescent/adult population based on case reports belonging to the secretolytic indication of ambroxol and bromhexine.

In total 3,876 case reports were retrieved in the secretolytic indication in the safety database of the MAH of the originator product containing ambroxol. Of these, 383 (9.9%) case reports were serious and 2,927 (75.5%) health professional confirmed (HPC). A fatal outcome was reported in 32 (0.8%) cases. For 371 (9.6%) case reports the age was not provided.

**Table 1.** Total case count and case characteristics per age group for originator products containing ambroxol

	≥ 12	6 to <12	2 to <6	0 to <2
Number of cases	2,627	196	370	312
Number of cases in % of total cases with reported age	74.9%	5.59%	10.55%	8.9%
Serious cases in %*	10.62%	13.27%	8.11%	10.9%
Health Professional confirmed cases in %*	83.87%	71.97%	54.01%	53.2%
Cases including hospitalisation in %*	7.2%	9.18%	4.86%	6.09%
Life-threatening cases in %*	1.64%	3.57%	2.7%	1.28%
Fatal cases in %*	0.88%	0.51%	0%	1.92%

\* Of total cases reported per age group

In total 2,036 case reports were retrieved in the safety database of the MAH of the originator product containing bromhexine. Of these, 174 (8.5%) case reports were serious and 1 174 HPC (57.7%). A fatal outcome was reported in 17 (0.8%) cases. For 840 (41.3%) case reports the age was not provided.

**Table 2.** Total case count and case characteristics per age group for originator products containing bromhexine

	≥ 12	6 to <12	2 to <6	0 to <2
Number of cases	825	64	170	137
Number of cases in % of total cases with reported age	68.98%	5.35%	14.21%	11.45%
Serious cases in %*	14.91%	7.81%	4.71%	3.65%
Health Professional confirmed cases in %*	63.15%	40.63%	30.59%	29.93%
Cases including hospitalisation in %*	9.46%	4.69%	2.94%	2.19%
Life-threatening cases in %*	3.15%	1.56%	0%	0%
Fatal cases in %*	1.21%	1.56%	0%	0%

\* Of total cases reported per age group

No significant differences were seen in the percentages of the presented case characteristics between the different paediatric age groups and patients aged 12 and above. Due to the relatively low numbers in the paediatric age groups, a certain variation can be expected however no tendency was identified towards a higher severity of events in the paediatric population. The only other obvious difference is seen in the proportion of health professional confirmed cases.

A further analysis including only terms of the SMQ hypersensitivity (narrow) was conducted and revealed a similar distribution of cases. Erythema multiforme however occurred more frequently with ambroxol in children from 6 to below 12 years of age (4.08% compared to 0 to 1.08% in the other age groups in table 1 and 2). The same holds true for Stevens-Johnsons-Syndrome with 2.55% of occurrence in this age group, compared to between 0.81% and 0.98% in the other age groups. In contrast to the broad selection of cases presented in tables 1 and 2, the rate of health professional confirmed cases is higher, especially in the smaller children.

### Clinical data

*Non-injectable formulations of ambroxol-containing products indicated in secretolytic therapy:* the clinical safety database of the originator pooled the subjects of six randomised placebo controlled trials identified as suitable out of the 33 studies evaluated. In these six trials 1,528 patients were treated with doses ranging from 60 to 180 mg daily for duration ranging from 12 days to a year and were matched to 948 patients receiving placebo. In these trials, the event nausea was reported with the frequency "common", while dyspepsia, vomiting, diarrhoea, and abdominal pain were reported with the frequency "uncommon" and rash and urticaria with the frequency "rare". Dry mouth, dysgeusia and pruritus were also reported but not classified as related to ambroxol.

*Ambroxol-containing solution for infusion:* one post-marketing surveillance study sponsored by the MAH of the originator and 3 published studies (Salzer, 1986 [10], Wolff, 1987 [11] and Laoag-Fernandez, 2000 [12]) were identified to constitute the clinical safety database of the originator.

<sup>10</sup> Salzer H, Weidinger H, Simbruner G, Vytiska-Binstorfer E. Ambroxol versus betamethasone for stimulation of prenatal pulmonary maturity – a multi-centre study. Z Geburtshilfe Perinatol 190, 49 - 59 (1986)

<sup>11</sup> Wolff F, Ponnath H, Wiest W. Induction of fetal lung maturation under the action of ambroxol and betamethasone. Results of an open open multi-centre trial. Geburtshilfe Frauenheilkd 47, 19 - 25 (1987)

<sup>12</sup> Laoag-Fernandez JB, Fernandez AM, Maruo T. Antenatal use of ambroxol for the prevention of infant respiratory distress syndrome. J Obstet Gynaecol Res 26 (4), 307 - 312 (2000)

Hypersensitivity, dizziness, headache and abdominal pain were reported in this pooled data set of 1,154 patients.

*Ambroxol-containing solution for injection:* three clinical trials sponsored by the MAH or the originator and two published studies (Marini, 1986 [13]; Wauer, 1992 [14]) were pooled for the clinical safety data set of the originator and none of the listed AEs were reported in these 270 premature babies and newborns.

*Ambroxol-containing lozenge and spray formulations:* eight double blind placebo controlled trials were pooled for the originator's clinical safety database. In these 1226 patients treated with ambroxol for one to three days, dysgeusia, pharyngeal hypoaesthesia, upper abdominal pain, diarrhoea, dry mouth, dry throat, dyspepsia, hypaesthesia oral and nausea were reported with common and uncommon frequencies. Hypersensitivity, angioedema, rash and vomiting were also reported but not classified as related to ambroxol.

*Bromhexine:* cumulatively, approximately 650 adult patients and 450 paediatric patients have been treated with bromhexine in clinical trials initiated with the originator product. In the clinical safety data set which covers clinical study reports with sufficient evaluable quantitative data on AE reporting to serve for frequency estimation, the only suspected cutaneous allergic reaction was described as allergic exanthema.

## **Discussion**

### **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

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<sup>13</sup> Marini A, Arosio A, Chirico G, Console V, Episcopi E, Farina C, Flauto U, Franzetti M, Giancola A, Maccabruni M, Magni L, Pelti M, Rondini G, Schioppa F, Tomasini G, Zavattini G. Treatment of idiopathic RDS with Ambroxol: final report on neonatal data of a double-blind multicentre study versus placebo. 10th Eur Cong of Perinatal Med, Leipzig 12-16 Aug 1986

<sup>14</sup> Wauer RR, Schmalisch G, Boehme B, Arand J, Lehmann D. Randomised double blind trial of ambroxol for the treatment of respiratory distress syndrome. Eur J Pediatr 151 (5), 357 - 363 (1992)

reactions and early withdrawal of the causative agent is the most important factor to minimise morbidity and mortality. Stevens-Johnson syndrome and TEN are rare, but are the most severe drug-induced skin reactions. The background incidence of SJS and TEN together has been calculated to be 1-2 per million in several epidemiological studies. While these rates put into context indicate relatively low reporting rates of SCARs linked to ambroxol and bromhexine (from 0.92 per million patient-years for bromhexine to 4.1 to 8.2 per million patient-years for ambroxol) the two sets of figures cannot be directly compared.

Delayed-type hypersensitivity reactions associated with SCARs (EM, SJS/TEN and AGEP) should be reflected in the product information with the frequency "unknown". In addition, a warning should be introduced in the product information in order for caregiver and patients to be aware of the first symptoms of SCARs and to be advised to discontinue treatment immediately and seek medical advice should they occur. Moreover SCARs cases should be analysed in detail in future PSURs. Consequently the PSUR cycle should be shortened to a 3-yearly cycle in order to periodically review these analyses.

### **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 PI of most ambroxol- and bromhexine-containing products. Based on the clinical safety dataset and spontaneous reporting, the frequencies and listing of events should nevertheless be harmonised: hypersensitivity reactions, rash and urticaria should be listed with the frequency "rare" and anaphylactic reactions including anaphylactic shock, angioedema and pruritus should be listed with the frequency "not known". The analysis of the most frequently reported adverse events selected by the SMQ Hypersensitivity (broad) did not identify any new safety concerns.

While slightly more cases were reported in the older and younger patient populations, the number of cases is not considered sufficient to allow for a definite conclusion. This effect may be explained by increased susceptibility to respiratory tract infections and therefore more frequent use of these medications in these younger and older populations (see also detailed analysis in the paediatric population below) as well as more systematic reporting. 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.

### **Paediatric populations**

The safety profile for ambroxol and bromhexine when stratified by age groups does not show major differences regarding most frequently observed adverse reactions, including mild to moderate hypersensitivity reactions. The number of reports of EM and SJS is slightly higher in patients aged 6 and below 12 years of age, however, this may be explained by a higher incidence of infections especially with *Mycoplasma pneumoniae*. Of note, children and adolescents of <17 years of age account for 45% of EMM patients (mostly from infectious aetiology) and for SJS 13% (more often drug

induced) (Mockenhaupt, 2012 [15]). However, as mentioned above, protopathic bias which occurs when a pharmaceutical or other therapeutic agent is inadvertently prescribed for an early manifestation of a disease that has not yet been diagnostically detected could also play a significant role.

### 2.2.2. Efficacy

As part of this referral procedure, the MAHs were requested to provide all available data on the efficacy of ambroxol and bromhexine, including in combination with other active substances, in their approved indications and when applicable stratified by age (populations between 0-2, 2-6, 6-12 and above 12 years of age). The PRAC considered all available data submitted and a summary is presented hereinafter.

#### ***Secretolytic therapy***

This indication is very broad and may refer to several sub-indications such as acute bronchitis, chronic bronchitis and chronic obstructive pulmonary disease (COPD), for which ambroxol and bromhexine are administered as mono-component or in fixed dose combinations. While the physiopathology of these diseases differs, the therapeutic effect of ambroxol and bromhexine in the different sub-indications is thought to be mediated by a similar mechanism of action. A large number of placebo, active-control and open studies were provided. They were conducted between 1965 and 2009 in a specific single condition or in patients with different types of respiratory diseases associated with increased mucus production.

#### **Ambroxol**

##### *Adult population*

##### Matthys

In this study 676 outpatients with acute bronchitis of recent onset with a forced expiratory volume in 1 second (FEV<sub>1</sub>) value of 75% of the predicted value and without evidence of chronic pulmonary disease were randomly assigned to double-blind treatment with a phytotherapeutic extract (Gelomyrtol 1,200 mg/day for 14 days), cefuroxime (500 mg/day for 6 days), ambroxol (90 mg/day for day 1-3 and 60 mg/day for days 4-14), or placebo (Matthys, 2000 [16]). Treatments were matched by the use of placebo capsules. Concomitant medications were only allowed if they did not interfere with the eligibility criteria or the evaluation of the study endpoints. Efficacy variables included the responder rate (non-responders were patients whose symptoms did not improve or deteriorated to such extent that discontinuation was indicated) as assessed by the investigators, diary cards on coughing fits during the day, disturbances of sleep by cough, type of cough, and general well-being (verbal rating scales), clinical signs, overall efficacy, bronchial hyperreactivity as assessed by coughing when exposed to temperature changes, noxious substance and/or during exercise, and lung function parameters. The responder rate after two weeks was 63.4% in the placebo, 88.2% in the Gelomyrtol, 83.6% in the cefuroxime, and 82.2% in the ambroxol group in the intention-to-treat (ITT) population. In the two comparators and ambroxol group, less patients had coughing fits (about 70% vs. 50% at nights and

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<sup>15</sup> Mockenhaupt M. Epidemiology of cutaneous adverse drug reactions. Chem Immunol Allergy 97, 1 - 17 (2012)

<sup>16</sup> Matthys H, de Mey C, Carls C, et al. Efficacy and tolerability of myrtol standardised in acute bronchitis. A multi-centre, randomised, double-blind, placebo-controlled parallel group clinical trial vs. cefuroxime and ambroxol. Arzneimittelforschung 2000 Aug; 50(8): 700-11

50% vs. 30% at day time) and felt good or very good compared to placebo. The statistical significance of those results was not provided in the publication. Responder rate, which was the primary end-point in this study, is not considered relevant for self-limiting conditions such as acute bronchitis.

#### Heinrich-Nols

In this double-blind trial, 1,080 patients with acute bronchitis were randomised to receive one of three doses of ambroxol tablets (120, 240 or 480 mg/day) or placebo for 12 days (Heinrich-Nols, 1997 [17]). Antibiotics were allowed to be administered, however patients requiring an antibiotic later than 72 hours into the trial, were considered to be a drop-out/withdrawal from the study. Efficacy was primarily assessed by means of a "total average score" calculated as the mean value from 4-point scales on frequency of cough, nocturnal cough, intensity of cough and difficulty of expectoration. The proportion of responders (total average score  $\leq 2$ ) at day 6 was defined as primary efficacy parameter. None of the ambroxol doses was superior to placebo with regard to the primary and secondary efficacy endpoints (proportion of responders at day 12 and parameters documented in the patients diary). The significance of this study is limited as high placebo response rates were reported (50% on day 6, 80% on day 12).

#### Benedikter

The effect of 45 mg/day ambroxol inhaled for 4 days was compared against placebo in 188 outpatients (mean age of 45 years, range: 18-74 years) suffering from an acute attack of chronic bronchitis in a double-blind multicentre randomised trial during the winter 1993-1994 (Benedikter, 1996 [18]). In the ambroxol group 34% of the patients were taking co-medication (chronic treatment with glucocorticosteroids and antibiotics) at baseline and 4% during the trial (35% and 5% respectively in the placebo group). The acute attack of chronic bronchitis was defined according to the World Health Organisation definition. Difficulty of expectoration, intensity of cough, frequency of cough and consistency of mucus were assessed on severity scales ranging from 0 to 4 points (0 to 6 for difficulty of expectoration). For inclusion in the study the patients had to have a total score of at least 11 points. 183 patients were included in the ITT analysis and 139 in the exploratory analysis (49 patients were excluded due to incomplete record forms or diary). At the end of a mean treatment period of 4 days the difference in the total symptom score between the two treatment groups was 1.2 score points ( $p < 0.05$ ). No statistically significant difference was observed for the frequency of cough and viscosity of mucus. The relief of the symptoms is observed about after 2 days of treatment.

#### Ericsson

Ambroxol (60 and 120 mg/day for 2 weeks) or matched placebo tablets were given to 97 patients with simple chronic bronchitis in a randomised, double-blind controlled trial using 3 parallel groups (Ericsson, 1986 and 1987 [19]). The study period lasted 6 weeks, the two middle weeks being the actual treatment period. Of the 97 patients starting the study, 92 completed the trial satisfactorily. Possible therapeutic effects were evaluated by means of interviews on subjective drug effects and current respiratory symptomatology, patient diary cards and lung function tests. Comparison with the placebo group at the end of the treatment period showed that significantly more subjects in the 120 mg group reported improvement in respiratory symptoms ( $p < 0.05$ ), mainly due to improved

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<sup>17</sup> Heinrich-Nols J. A double-blind, randomised, multicentre, parallel group comparison of 3 oral doses of Ambroxol (120, 240, 480 mg) versus placebo in patients with acute lower respiratory tract disease (acute bronchitis). Unpublished, December 1997

<sup>18</sup> Benedikter L, Wemmer M, Blohm W, et al. Efficacy and tolerance of ambroxol inhalation a parallel group comparison in outpatients with an acute attack of chronic bronchitis. Unpublished, September 1996

<sup>19</sup> Ericsson CH, Juhász J, Jönsson E, Mossberg B. Ambroxol therapy in simple chronic bronchitis: effects on subjective symptoms and ventilatory function. *Eur J Respir Dis* 1986 Oct; 69(4):248-55. And: Ambroxol and simple chronic bronchitis. Effects on subjective symptoms and ventilatory function. *Respiration* 1987; 51 Suppl 1: 33-6



expectoration ( $p < 0.05$ ). Subjects in the 120 mg group tended to prefer the treatment period when compared to placebo but the diary cards did not indicate significant changes. Lung function values were mainly normal and did not change during treatment. A similar trend but no statistical difference was observed in the 60 mg group compared to placebo.

#### Guyatt

A 4 weeks double-blind randomised controlled trial was conducted in 90 adult patients with chronic bronchitis receiving 120 mg/day ambroxol or placebo (Guyatt, 1987 [20]). Patients were stratified based on FEV<sub>1</sub> percentage of predicted FEV<sub>1</sub> and FEV<sub>1</sub>/ventilatory capacity (VC) ratio (above or below 70% and/or 0.7). End points were peak flow, FEV<sub>1</sub>, forced vital capacity (FVC), mid-expiratory flow rates (FEF<sub>25-75</sub>), and symptom score (7 point symptom questionnaire). Despite a small deterioration in mean FEV<sub>1</sub> in both groups (0.004L in the ambroxol group, 0.021L in the placebo group), and essentially stable FEF<sub>25-75</sub> (increase of 16 ml/s in the ambroxol group, deterioration of 123 ml/s in the placebo group), questionnaire scores improved in the major areas in which benefit with ambroxol was anticipated. This improvement was maintained over the four weeks of the trial, but was closely comparable in the two groups. There were no statistically significant differences between active and placebo, nor were there substantial trends.

#### Kempthorne-Rawson

A twelve-week multicentre double-blind parallel trial was conducted in 107 patients with chronic bronchitis randomised to receive 60 mg/day or 90 mg/day ambroxol or placebo (Kempthorne-Rawson, 1988 [21]). Antibiotics or steroids were administered to treat exacerbation. One or more protocol violation (rated as minor) occurred in 74% of the patients. No statistical difference was reported between either doses of ambroxol and placebo on the frequency and severity of exacerbations, time to first exacerbation, alleviation of symptoms, distance walked during the 12 minute walking test, functional capacity, or spirometry measurements. Of note a low numbers of exacerbations was reported compared to the three previous years ( $< 0.32$  vs.  $> 2$ ). The quality and significance of this trial was limited due to low numbers of exacerbations and missing power considerations.

#### Michnar

In this double blind study 70 patients were randomly allocated to receive treatment with either ambroxol or a placebo for 2 months (Michnar, 1996 [22]). The physician and the patient assessed the following points using a scoring system: the general well-being, the symptoms of a cold and of fever, the need for treatment with antibiotics, the amount, viscosity and colour of sputum, the difficulty in expectoration, the severity of coughing and any changes in breathlessness while at rest. Breathlessness while at rest and the rate of exacerbation was significantly lower in the ambroxol group after 2 weeks of therapy. Similarly, sputum viscosity, difficulty in expectoration and severity of coughing were reduced in this group after 4 or 8 weeks. Limited information was available on this study and the primary end point appears not to have been assessed. Further, comparison of the frequency of exacerbations over 1 year is considered more appropriate, in order to take into account seasonal fluctuations.

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<sup>20</sup> Guyatt GH, Townsend M, Kazim F, Newhouse MT. A controlled trial of ambroxol in chronic bronchitis. *Chest* 1987 Oct; 92(4): 618-20

<sup>21</sup> Kempthorne-Rawson J, Huyck S, Marmaras S. A 12 week multicentre double-blind parallel placebo-controlled pilot study with 60 mg, 90 mg of ambroxol in patients with chronic bronchitis. Unpublished, May 1988

<sup>22</sup> Michnar M, Milanowski J: Assessment of efficacy and tolerability of the oral treatment of ambroxol in patients with chronic bronchitis. *Pneumonol Alergol Pol* 1996; 64 (Suppl 1): 90-7

Olivieri

In a long-term, double-blind, placebo-controlled, multicentre trial, 240 patients (range: 40 - 80 years of age) with chronic bronchitis were treated with 75 mg/day ambroxol or placebo for 6 months (Olivieri, 1987 [23]). Ambroxol was found to significantly reduce the incidence of exacerbations compared to placebo (45.5% of patients treated with ambroxol and 14.4% of patients receiving placebo had no episodes of exacerbation,  $p < 0.01$ ). This protective effect was observed already after 2 months of treatment ( $p < 0.05$ ); however the difference between the mean of improvement in each group was not calculated. Patients in the ambroxol group lost significantly fewer working days due to illness (442 versus 837,  $p < 0.01$ ) and had fewer days when they needed antibiotic therapy (371 versus 781,  $p < 0.01$ ). Treatment with ambroxol also induced a statistically significant improvement of symptoms (difficulty of expectoration, cough, dyspnoea and auscultatory signs) compared with placebo ( $p < 0.01$ ). Physicians assessed the efficacy as being excellent or good in 76% of patients treated with ambroxol and 34% of the patients treated with placebo ( $p < 0.01$ ). In a recent review this study was found to have high risk of attrition bias and unclear risks of reporting and selection bias (Poole, 2012). In addition a study-duration of a year is considered necessary to evaluate the influence of a medicinal product on the frequency of exacerbations in order to exclude the influence of seasonal fluctuations. Measuring only during winter season as was the case for this study (October-December 1983 to March-May 1984) may tend to overestimate the number of exacerbations per year and lead to an overestimation of the effect on the frequency of exacerbations.

Cornelissen

Between September 1986 and June 1987, 200 patients with chronic bronchitis (32-80 years, mean age: 59 years) were treated with either ambroxol given at a dose of 120 mg/day or placebo for 6 months, in a double-blind, randomised, parallel study (Cornelissen, 1987 [24]). In the 140 patients who completed the study no difference was observed in lung function measurements, symptoms and number of exacerbations between both treatment groups. No alteration was identified in laboratory analysis of blood and urine. No beneficial effect was demonstrated regarding the symptoms of chronic bronchitis by using a questionnaire. However more patients discontinued the study due to lack of efficacy (sticky sputum and difficulty in expectoration) in the placebo arm ( $n=23$ ) than in the ambroxol arm ( $n=10$ ) ( $P < 0.009$ ). The investigators stated that due to the extremely low number of exacerbations during this trial (approximately 0.5 exacerbations per patient over the 6-month period) no definite conclusion could be drawn concerning the effect of 120 mg ambroxol daily on the frequency of exacerbations.

Cornelissen

This double-blind, randomised, parallel-group study compared 120 mg/day ambroxol and placebo for 6 months (between September 1987 and July 1987) in 242 patients with chronic bronchitis (Cornelissen, 1988 [25]). Number of exacerbations, symptom scores, functional capacity plus pulmonary function tests ( $FEV_1$  and inspiratory VC), pulse rate and blood pressure, and adverse events were recorded. The assessment of the 200 patients who completed the 6 months treatment period revealed no statistical significant difference between the 2 groups regarding the number of exacerbations, pulmonary function, functional capacity and symptoms. Of note the exacerbation rate per patient was rather low

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<sup>23</sup> Olivieri D, Zavattini G, Tomasini G, et al. Ambroxol for the prevention of chronic bronchitis exacerbations: long term multicentre trial. Protective Effect of ambroxol against Winter Semester Exacerbations: A Double-Blind Study versus Placebo. *Respiration* 51 (Suppl 1), 42 - 51 (1987)

<sup>24</sup> Cornelissen PJG, Smeets JJ, Mijnstreek O, Maesen FPV. Safety and efficacy of ambroxol 60 mg b.i.d. on the frequency and severity of exacerbations and symptoms of chronic bronchitis. Unpublished, October 1988

<sup>25</sup> Cornelissen PJG, Bantje TA, Beumer HH, et al. Efficacy of ambroxol 60 mg b.i.d. on the frequency and severity of exacerbations and symptoms of chronic bronchitis. Unpublished, November 1988



(1.3 and 1.4 during the 6 months of the study in the placebo and ambroxol group respectively) compared to the previous year (4.3 and 4.4 in the placebo and ambroxol group respectively). In addition, the inclusion criteria concerning the baseline FEV<sub>1</sub> (which had to be between 45 and 75% of their predicted normal value) was violated for approximately half of the patients. Furthermore, bronchodilators were frequently used within the 8 hours preceding lung function testing.

#### Cegla

A long-term double blind trial was conducted in 180 adult patients with chronic bronchitis treated with 75 mg/day ambroxol or placebo for 2 years (Cegla, 1988 [26]). At baseline there were no significant differences between the groups with regard to severity of disease and clinical symptoms.

Co-medication with antibiotics, bronchodilators, glucocorticosteroids and antitussives were allowed. In addition use of additional secretolytic drugs was permitted in cases of absolute necessity and had to be recorded. Of the 167 patients who completed the trial, those treated with ambroxol were found to have significantly fewer lost working days due to their bronchopulmonary disease: 1,216 versus 1,789 days (ambroxol vs. placebo:  $p < 0.01$ ). In the ambroxol group the lung function parameters significantly improved ( $p < 0.05$ ) which was not the case for placebo, however no direct comparison of the mean improvement in both groups was conducted and the difference between the values at the end of treatment was not statistically significant. A tendency towards improvement of dyspnoea and less frequent consumption of antibiotics in the ambroxol group was reported, though not statistically significant. There were no differences between both groups with regards to hospital admissions, expectoration and sputum. Overall assessment of therapeutic efficacy by the investigator after 2 years of treatment was significantly better for the patients treated with ambroxol ( $p < 0.05$ ). Of note however, in a recent review (Poole, 2012) it was found to have unclear risks of selection, attrition and reporting bias. Further the concomitant use of antibiotics, bronchodilators, glucocorticoids or antitussives was not considered in sensitivity analyses.

#### Cornelissen

In this double-blind study 115 patients with chronic bronchitis were randomly allocated to treatment with either ambroxol 60 mg/day or placebo for a 6-month period (Cornelissen, 1989 [27]). Assessment of the patients who completed the trial ( $n=92$ ) revealed no significant difference between the treatment groups regarding the number of exacerbations ( $p=0.90$ ; mean  $\pm$  s.d.: ambroxol:  $0.63 \pm 0.79$ ; placebo:  $0.67 \pm 0.85$ ). The survival analysis, taking patients with an exacerbation or drop-out due to lack of efficacy as endpoint, yielded no significant difference. Analysis of the FEV<sub>1</sub>, FVC and peak expiratory flow rate (PEFR) measurements before and during the trial, as well as the daily PEFR recordings (morning and evening values) revealed no significant difference between the two groups. However, the stepwise discriminant analysis of the symptom questionnaire showed that ambroxol facilitated the expectoration of sputum ( $p=0.017$ ) and slightly improved the patients' ability to exercise ( $p=0.04$ ). The quality and significance of this trial was limited due to the very low numbers of exacerbations and missing power considerations.

#### Malerba

In a prospective, randomised, double blind, placebo controlled, multicentre, parallel group trial investigating 242 outpatients (age range 38-76 years) with COPD treated for 1 year with 150 mg/day

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<sup>26</sup> Cegla UH Long-term Treatment of Chronic Bronchitis for Two Years with Ambroxol (Mucosolvan (R)) Retard Capsules. Results of a Double-blind Trial Including 180 Patients. *Prax Klin Pneumol* 42, 715 - 721 (1988)

<sup>27</sup> Cornelissen PJG, Maesen FPV, Smeets JJ. Efficacy of oral ambroxol 30 mg b.i.d. on the frequency and severity of exacerbations and symptoms of chronic bronchitis. A double-blind, randomised, placebo controlled study. Unpublished, December 1989

ambroxol (n = 118) or placebo (n = 123), the percentage of patients free from exacerbation at 6 months was 63% with ambroxol and 60% with placebo (p=0.366) and at 12 months 56% with ambroxol and 53% with placebo (p=0.363) (Malerba, 2004 [28]). Patients enrolled had a value of FEV<sub>1</sub> between 60% and 80% of predicted value (stage IIA GOLD), pathological chest auscultatory findings, and positive history for at least one episode of bronchitis exacerbation in the previous 12 months. A post-hoc analysis revealed that in a subset of 45 patients with more severe baseline symptoms, ambroxol therapy was associated with a significant higher percentage of patients free from exacerbation compared to placebo: 63 vs. 38% (p=0.038). The significance of this study is limited as in addition to the high placebo response observed, in a recent review (Poole, 2012) the risk of selection bias was assessed as unclear. Of note, the dose used in this study was higher than that recommended in the PI (150 mg daily instead of 120 mg).

#### Heinrich-Nols

In this double-blind study 692 patients with COPD were randomised to be treated with either 180 mg/day ambroxol or placebo for 8 weeks in parallel-groups (Heinrich-Nols, 1998 [29]). Antitussive expectorant and mucolytics were not allowed during the study; however antibiotics were administered when required for the treatment of exacerbations. Efficacy was primarily assessed by means of the quality of life (QOL) parameters of the St. George's Respiratory Questionnaire (SGRQ), the changes in clinical symptoms of the disease (evaluated by the sub-scores "symptoms", "activity", "impacts" of SGRQ, daily diary records of quality and quantity of sputum, frequency and intensity of cough, ease of expectoration, breathlessness, chest discomfort), symptomatic bronchodilator usage, improvement of lung function, enhancement of exercise tolerance, and global assessment of efficacy. No difference was identified between ambroxol and placebo in this regard. Of note after considering the number of patients randomised and available for the ITT and per protocol analysis, it became apparent that approximately 20% of patients were lost at baseline for the per-protocol analysis and more than 30% were lost in the per-protocol population for the assessment of the primary endpoint after week 8 which indicates problems with monitoring.

#### Kölher

A total of 1,577 patients with chronic obstructive pulmonary disease were randomised in double-blind fashion to treatment with 0.04 mg/60 mg per day of ambroxol/clenbuterol or 0.04 mg/day clenbuterol alone over 14-16 days (Kölher, 2004 [30]). Improvement of FEV<sub>1</sub> was observed in both groups (29.7% and 28.4% respectively for the combination and clenbuterol alone) without a statistically significant difference. No significant difference was seen either in the efficacy assessment by the investigator and the final visit, no other endpoints were studied.

#### Thomae

In a randomised double-blind trial the influence on the tracheal clearance velocity of a combination of 60 mg/0.04 mg daily ambroxol/clenbuterol compared with the same dose of the single components and placebo for 14 days was assessed in 66 out patients after operation for tracheostenosis

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<sup>28</sup> Malerba M, Ponticello A, Radaeli A, Bensi G, Grassi V. Effect of twelve-months therapy with oral ambroxol in preventing exacerbations in patients with COPD. Double-blind, randomised, multicentre, placebo-controlled study (the AMETHIST trial). *Pulm Pharmacol Ther* 17 (1), 27 - 34 (2004)

<sup>29</sup> Heinrich-Nols J, Sigmund R, Bibby R, et al. A multi-centre, double-blind, placebo-controlled, randomised, parallel-group study to assess the effect of ambroxol on the quality of life of patients with chronic obstructive pulmonary disease. Unpublished, November 1998

<sup>30</sup> Kölher M, Schumacher H, Straka A, Efficacy and tolerability of a clenbuterol/ambroxol combination in a randomised, double-blind, parallel-group comparison with clenbuterol in out-patients with reversible respiratory tract obstruction. Unpublished, January 2004

(Thomae, 1985 [31]). Co-medication that could affect tracheal clearance velocity had to be discontinued at least a day before treatment initiation. Increase in tracheal clearance velocity after 14 days of treatment for placebo was 17%, combination 93%, clenbuterol 38% and ambroxol 24%. Statistically significant increase from baseline was seen after 3 days of treatment; however no statistical comparison between groups was conducted. Significant increases from baseline were also observed in peak expiratory flow for the combination and clenbuterol alone. Difficulty in breathing also improved in the combination and clenbuterol groups while the sputum quantity and quality improved in the combination and ambroxol groups, however no statistical analysis was provided.

Fraschini

In this study 60 patients suffering from COPD with a purulent sputum were divided into three groups and given amoxicillin, erythromycin, or cefuroxime (all 1,500 mg/day) associated under double-blind conditions with placebo or 90 mg/day ambroxol, for seven days (Fraschini, 1988 [32]). Levels of the antibiotics were measured in serum and in bronchial secretion on the first and seventh day and after one and eight hours, and four and eight hours, respectively. Compared with placebo the combination with ambroxol significantly increased the levels of the antibiotics in the bronchial secretion ( $p < 0.05$ ) but not in the serum.

Perez-Neria

The response to the combination of ambroxol/amoxicillin (ambroxol: 90 mg/day, amoxicillin: 1,500 mg/day) versus amoxicillin alone by the oral route for at least 10 days was compared in a randomised blind study in a group of 40 adult patients who presented with bacterial infections of the lower respiratory tract (mainly acute bronchitis (>40% in each group)) (Perez-Neria, 1992 [33]). Antibiotic levels in plasma and mucus were determined in all patients by bioassay using cultures of *Sarcina lutea*. A comparison using the Wilcoxon test revealed significant differences in favour of the ambroxol/amoxicillin combination for concentrations of the antibiotic in plasma and mucus ( $p = 0.00021$ ), and for subsidence of fever ( $p = 0.00036$ ). Using this method, a marginal difference was found in baseline leukocyte counts in favour of the patients treated with ambroxol/amoxicillin ( $p = 0.02$ ). Using a linear regression model, the only variable which adequately fitted with the subsidence of fever was the level of antibiotic in the mucus.

Poole

A Cochrane review including three studies on ambroxol found that mucolytics may produce a small reduction in acute exacerbations however no effect was seen on lung function or quality of life (Poole, 2012 [34]). It was also noted that treatment effect was larger in earlier studies than that observed in more recent studies. The authors suggested that this difference may be due to a higher risk of publication bias with the earlier smaller trials and therefore the benefits may not be as large as suggested by previous evidence. The review concludes that mucolytics could be considered a treatment option in patients with frequent exacerbations who cannot take other types of therapies.

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<sup>31</sup> Thomae K, Retiene K, Clinical trial on tablets of the combination clenbuterol + ambroxol for the assessment of its effects on the tracheal clearance velocity. Unpublished, August 1985

<sup>32</sup> Fraschini F, Scaglione F, Scarpazza G, Marchi F, Calzavara M. Effects of a Mucolytic Agent on the Bioavailability of Antibiotics in Patients with Chronic Respiratory Diseases. *Curr Ther Res* 1988; 43(4): 734-742

<sup>33</sup> Perez-Neria J, Garcia Rubi E Ambroxol-amoxiciline fixed combination vs. amoxiciline in acute infectious respiratory conditions - Comparative study of antibiotic levels in bronchial mucus and blood. *Compend Invest Clin Lat Am* 12, 5 - 10 (1992)

<sup>34</sup> Poole P, Black PN, Cates CJ. Mucolytic agents for chronic bronchitis or chronic obstructive pulmonary disease. *Cochrane Database Syst Rev*. 2012 Aug 15

## Paediatric population

### Caredu

A trial was carried out in 60 children (45 children were aged 2 to 5 years and 15 children were aged 6 to 12) with an acute respiratory disease accompanied by catarrh and cough (bronchitis, asthmatic bronchitis or tracheobronchitis) (Caredu, 1984 [35]). The patients were randomised to receive either ambroxol syrup (45 mg/day to 60 mg/day depending on the age) or N-acetylcysteine granules (600 mg/day) for 6 to 8 days. Patients with fever, leucocytosis or a raised erythrocyte sedimentation rate were given concomitant antibiotics. From the fourth day onwards, all bronchial symptoms (severity and frequency of cough, discomfort caused by catarrh) improved to a much greater extent in the ambroxol group than in the comparator group ( $p < 0.02$ ). The quality of the sputum gradually changed from mucopurulent to mucous to serous and, by the end of the treatment period, sputum volume had decreased to zero. The changes in sputum viscosity between the start and the end of treatment were significant ( $p < 0.001$ ) with no differences between the two groups (tested in 10 patients  $> 6$  years of age, in each group). There was a statistically significant change in maximal expiratory flow<sub>25</sub> (MEF<sub>25</sub>), forced expiratory volume<sub>1</sub> (FEV<sub>1</sub>) and total airway resistance between the start and the end of treatment in both groups (tested in 10 patients  $> 6$  years of age, in each group) ( $p < 0.001$ ). The physician's ratings of treatment efficacy, based on the improvement in clinical symptoms, were favourable in 100% of the patients receiving ambroxol and in 68% of the patients receiving the comparator ( $p < 0.01$ ). However it should be noted that no information was available on blinding and that co-medications were not considered in sensitivity analyses. Further, the doses used were higher than that recommended in the PI.

### Weinmann

Several doses and formulations were evaluated in an open multi-centre trial performed in children aged between 2 months and 14 years with various airways diseases (e.g. acute and chronic bronchitis, rhinopharyngitis, sinobronchitis, tracheobronchitis, asthmatic bronchitis, bronchopneumonia and bronchial asthma) (Weinmann, 1981 [36]).

**Table 1.** Age distribution in the clinical trials with the different pharmaceutical forms

	Tablets	Syrups	Drops	Solution for inhalation	Solution for injection	Total
Total	32	340	99	37	109	617
< 2 years	6	101	12	9	51	179
2-5 years	11	115	23	18	24	191
> 5 years	15	124	64	10	34	247

The average daily doses were 15 mg, 20-30 mg and 30-60 mg in the respective age groups. Co-medication was administered to 12/32 children in the tablet study (antibiotics and bronchodilator), 148/229 children in one of the two studies with the syrups (bronchodilator, corticosteroids, antibiotics or rhinologic agents) (the information was not provided for the other study), 76/136 children with the drops and solution for inhalation (antitussive or antibiotics) and 66/109 children in the study with the

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<sup>35</sup> Careddu P, Zavattini G. Mucosolvan (R) (ambroxol) in paediatric use - Controlled clinical trial vs. acetylcysteine. *Asthma Bronch Empphys* 4, 23 - 26, passim (1984)

<sup>36</sup> Weinmann HM Ambroxol (Mucosolvan) in paediatrics. Clinical results with different forms of administration. *Therapiewoche (Karlsruhe)* 31, 7940 - 7947 (1981)

solution for injection (bronchodilator, antitussive/expectorant or antibiotics). Improvement of symptoms (abnormal sputum, cough, dyspnoea) was observed after 2-3 days of treatment in most children. After 5-7 days of treatment, symptoms were usually found to be either completely resolved or markedly improved in all age groups. No analysis was conducted per age group.

#### Munoz Carbajal

In this open-label, observational trial, 103 children with acute or chronic bronchitis, tracheobronchitis or common cold, were treated with ambroxol syrup for 8 days (Munoz-Carbajal, 1984 [37]). The age distribution was as follow: 25 patients aged 0-2, 54 aged 2-6 and 24 children were 7-14 years old. Doses in the respective age groups were 15 mg/day, 22.5 mg/day and 30-45 mg/day. The best efficacy was observed in children 0–2 months old, with total disappearance of bronchial symptoms after 4–6 days of treatment. For this reason, the authors decided to score efficacy of treatment according to the time when improvements became apparent: day 4 = excellent, day 5 = very good, day 6 = good, day 8 = moderate. Those patients who failed to exhibit any result were characterised as poor. Efficacy was rated as “excellent” in 70, “very good” in 15, “good” in 13, “acceptable” in 1 and “absent” in 4 subjects, the data was not presented per age groups.

#### Thomae

A combination of clenbuterol and ambroxol was administered to 64 children (mean age 4.7 years) with obstructive diseases of the respiratory tract. A total of 43 children were in the age group 0-6 years, 19 were in the age group 6-12 years and 2 in the age group > 12 years (Thomae, 1983 [38]). Daily dosages ranged from clenbuterol/ambroxol 0.005 mg/7.5 mg to 0.04 mg/60 mg depending on age and weight of the children. After a 2-week treatment period, the initial symptoms disappeared in 69% and improved in 29% of patients. Bronchospasmodic attacks no longer occurred in 74% of patients and were less frequent in 24% of patients. Dyspnoea was no longer present in 86% and improved in 8% of patients. Further, expectoration was normalised in 61% and improved in 37% of patients. Information on efficacy was not specified according to age.

### ***Bromhexine***

#### *Adult population*

#### Jirou-Najou

In this double-blind study 90 adult patients with acute or chronic bronchopulmonary disease and acute episodes of bronchial congestion were randomised to receive a treatment of 48 mg/day bromhexine or placebo for 10 days (Jirou-najou, 1988 [39]). Concomitant treatment with amoxicillin was administered to all patients as well as physiotherapy. Primary efficacy parameters were changes in sputum volume, sputum viscosity and difficulties in expectoration on day 10 compared to day 0. Secondary efficacy criteria were daily changes in dyspnoea and cough (semi-quantitative scores), peak expiratory flow and safety. Albeit sputum volume increased until day 5 more rapidly in the placebo group and showed thereafter a more rapid decrease, these differences between groups did not reach statistical significance. No improvement in sputum viscosity, difficulties in expectoration and clinical scores for dyspnoea and cough were observed in either group. Of note the statistical analysis revealed that both groups were not comparable at study entry concerning mean age (bromhexine:

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<sup>37</sup> Munoz-Carbajal P. Ambroxol in paediatric practice. Unpublished, March 1984

<sup>38</sup> Thomae K, Efficacy and tolerability of the syrup form of a new combination preparation (Clenbuterol, 0.005 mg, and ambroxol, 7.5 mg/5ml) in children with obstructive diseases of the respiratory tract. Unpublished, July 1983

<sup>39</sup> Jirou-Najou JL. Study on the efficacy and safety of bromhexine in acute episodes of bronchial congestion in the course of bronchopulmonary disease. Unpublished, April 1988

62.95±8.32 years, placebo: 58.35±10.63 years,  $p=0.02$ ) and clinical score (sum of dyspnoea and cough scores), which was higher in the bromhexine group ( $p=0.015$  vs. placebo).

#### Jirou-Najou

In a double-blind study 60 patients with acute bronchopneumopathy with cough and expectoration were randomised to receive 96 mg/day bromhexine or placebo for 7 days. Antibiotic treatment and physiotherapy were also administered to all patients (Jirou-Najou, 1986 [40]). The endpoints measured were difficulty and frequency of expectoration and cough, dyspnoea, sputum volume and spirometry was investigated. All investigated variables improved during the course of the study, but differences between groups could not be detected. Of note, significantly more smokers were included in the bromhexine group ( $p<0.01$ ).

#### Stark

In a double-blind, controlled trial, 51 patients with chronic bronchitis were randomised to a sequence of 4 treatment periods of 3 weeks each, during two periods the patients received 48 mg/day bromhexine and during the two others a placebo (Stark, 1973 [41]). Patients were asked to summarise their symptoms during the previous treatment period by recording the extent of improvement or deterioration of breathlessness, expectoration and stickiness and physical characteristics of sputum compared with their usual state. A trend in favour of bromhexine in "increased number of good days" and "decreased number of bad days" in term of breathlessness when compared with placebo was observed, however this was not statistically significant. No difference was observed in the physician assessment of symptomatic benefits or in other patient-reported symptoms (stickiness of sputum, difficulty of expectoration or time taken to clear the chest in the morning).

#### Takishima

The efficacy of a week-long treatment with inhalations of 15 ml/day of a 40% solution of bromhexine or of 6 ml/day of acetylcysteine solution was compared in a double blinded randomised study in 112 patients with chronic bronchitis and difficulty with sputum clearance (Takishima, 1989 [42]). At the end of the first week of treatment, if the patient showed a poor response and a dose increase was possible, the dose was doubled and inhalation was continued for another week. Sputum volume and clinical symptoms were then compared in the two groups. Globally 79.2% of patients in the bromhexine group and 59.6% of patients in the comparator group improved moderately or markedly. The usefulness rating showed that the drug was moderately or very useful in 75.0% of patients in the bromhexine group and 53.6% of patients in the comparator group. These differences between the two groups were not statistically significant.

#### Mirsa

A double-blinded, placebo-controlled cross-over study in 40 adults with COPD evaluated the effect of a 7-day bromhexine 48 mg/day treatment against placebo (Mirsa, 1984 [43]). The two treatment phases were separated by a 7-day washout period. All patients were also given 1 g/day erythromycin estolate. Compared to pre-values and placebo, bromhexine was found to significantly increase sputum volume ( $p<0.01$ ) and decreased sputum viscosity ( $p<0.001$ ). Of the 33 patients for whom the

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<sup>40</sup> Jirou-Najou JL, Dy NR. Clinical study of the efficacy of bromhexine's adjunction in high posology (96 mg/d) in the treatment of acute broncho-pneumopathies. Unpublished, February 1986

<sup>41</sup> Stark J.E. A controlled trial of the effects of bromhexine on the symptoms of out-patients with chronic bronchitis. A report to the Research Committee of the British Thoracic and Tuberculosis Association. *Br J Dis Chest* 1973 Jan; 67(1): 49-60

<sup>42</sup> Takishima T. Clinical effect of inhalation therapy with NA 247 (bromhexine hydrochloride) solution on sputum expectoration in patients with chronic bronchitis. *Ther Res* 1989; 10(3):1063-85

<sup>43</sup> Misra MP, Tiwari UC, Chahal CC, Galhotra R. Double Blind Crossover Randomised Study of Bromhexine in Chronic Obstructive Airway Disease. *J Assoc Physicians India* 32 (5), 423 - 425 (1984)



information was available, 22 could expectorate easily following bromhexine therapy. No significant changes in pulmonary function (FEV<sub>1</sub>) were observed in either group. The authors hypothesised that this may be due to irreversible nature of the airway obstruction in the patients included. However, 72% of the patients felt better with bromhexine whereas this improvement was only seen by 9% of patients with placebo.

#### Iaia

In this study patients with chronic obstructive lung disease in an acute stage were randomised to bromhexine (48 mg/day, n=16) or to sobrerol (1,800 mg/day, n=16) for 10 days (Iaia, 1990 [44]). The study medication was blinded to the evaluator. The therapeutic efficacy was evaluated by monitoring the following clinical parameters using a semi-quantitative scale: cough, breathlessness, quantity and quality of expectorations, ease of expectoration. Clinical symptoms were improved in the bromhexine group compared to baseline ( $p<0.05$ ) and to the comparator group ( $p<0.01$ ). In accordance, the alleviation of cough and normalisation of expectoration (analysed separately) were less rapid with the comparator; the difference was statistically significant in favour of bromhexine ( $p<0.01$ ). Both treatments were rated effective and well tolerated. The physician rated the efficacy as excellent or good in 15 out of 16 patients for bromhexine and in 10 out of 16 patients for the comparator ( $p<0.05$ ). Concomitant treatments were similar in both groups.

#### Matts

In a double-blind trial 103 patients randomised to treatment with 32 mg/day bromhexine plus 1 g/day oxytetracycline or oxytetracycline 1 g/day for 10 days (Matts, 1974 [45]). Concomitant treatments were allowed as necessary. The overall assessment of the response to treatment showed that 35 (67%) had a good response to oxytetracycline with bromhexine and 26 (51%) to oxytetracycline alone while 11 patients (21%) on the combined treatment and 14 (27%) on oxytetracycline alone were withdrawn from the trial as treatment failures, no statistical comparison was provided. The mean duration of stay in hospital for the oxytetracycline with bromhexine group was 9.4 days (SD  $\pm$  1.79) compared with 11.2 days (SD  $\pm$  2.31) for the oxytetracycline alone group ( $p<0.001$ ).

#### Roa

A multicentre double-blind trial was performed in 392 adult patients with clinical diagnosis of acute bronchitis or pneumonia of bacterial aetiology randomised to treatment with 1 g amoxicillin plus 32 mg bromhexine daily or 1 g/day amoxicillin alone (Roa, 1995 [46]). Clinical response, improvement in symptom scores using a visual analogue scale and bacteriologic response were monitored at days 3, 5 and 7 of treatment. Results showed that although similar number of patients had favourable clinical response at the end of treatment in the combination and the amoxicillin group (94% and 93%, respectively), the infection was completely resolved for 46% of patients given the combination 34% of patients given amoxicillin alone ( $p=0.022$ ). Patients given the combination of active substances had significant ( $p<0.001$ ) greater reduction of their symptom scores at Day 3 for symptoms of cough discomfort, cough frequency, ease of expectoration and sputum volume. The difference remained significant until end of treatment for cough discomfort only. No significant difference was observed for difficulty in breathing and chest pain. Among the subset of patients with pneumonia the cure rates for patients receiving both active substances and those receiving only amoxicillin were 24/50 (47%) and

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<sup>44</sup> Iaia E, Marengo G. Efficacy and tolerability of a new bromhexine granulate formulation versus sobrerol granulate in patients with chronic obstructive bronchopneumopathies. *Med Torac* 1990;12:215-8

<sup>45</sup> Matts SG. A comparative trial of bromhexine HCl and oxytetracycline in acute and chronic bronchitis. *Br J Clin Pract* 1974 Dec; 28(12):403-5

<sup>46</sup> Roa CC Jr, Dantes RB. Clinical effectiveness of a combination of bromhexine and amoxicillin in lower respiratory tract infection. A randomised controlled trial. *Arzneimittelforschung* 1995 Mar;45(3):267-72

11/50 (22%) respectively ( $p=0.008$ ). Insufficient information on bacteriologic response was available in patients infected with other pathogens. Of note, in a recent review (Chang, 2014 [47]) this study was found to have unclear risks of selection and attrition bias.

#### *Paediatric population*

##### Rubaltelli

Bromhexine (24 mg/day) was compared to N-acetylcysteine (600 mg) in an open randomised trial in 32 children (outpatients) with acute bronchitis (17 were aged 2-6 years and 15 were 6-12 years old) (Rubaltelli, 1984 [48]). The treatment administered was blinded to the evaluator. The following parameters were recorded: cough and dyspnoea, frequency, characteristics and ease of expectoration, fever and auscultatory findings. The mean values obtained with bromhexine did not differ significantly from those obtained with the comparator except for the symptom "facility of expectoration" for which a statistically significant trend was observed in favour of bromhexine. Improvement of symptoms was observed with both treatments compared to baseline ( $p<0.01$ ). The symptoms of cough, dyspnoea and ease of expectoration, improved sooner in the bromhexine group. Overall treatment with both products revealed comparable results, as judged by the physician, with very good or good efficacy in 13 patients treated with bromhexine and 7 patients treated with the comparator. There was a slight advantage for bromhexine, which was non-significant. Age-related analyses were not performed.

##### Azzollini

A randomised controlled clinical trial compared the efficacy of 6-12 mg/day bromhexine to 100-200 mg/day sobrerol in 40 children aged less than 5 years old (mean age bromhexine  $41\pm 16.3$  months), affected by acute hypersecretory bronchopulmonary disease (Azzollini, 1990 [49]). Both treatments revealed good efficacy with a significant improvement compared to baseline symptom scores (clinical conditions, dyspnoea, cough severity, sputum volume and viscosity ( $p<0.05$ )). In the bromhexine and comparator groups respectively 16/20 and 18/20 patients improved overall. No significant difference was observed between both groups.

### ***Ambroxol in prophylaxis and treatment of infant respiratory distress syndrome (IRDS)***

#### *IRDS prevention, in pregnant women*

##### Salzer

In this a multicentre, randomised double-blind study, the effect of betamethasone and ambroxol in prenatal prevention of IRDS was compared in 185 patients with premature labour or an induced termination of pregnancy between the 28<sup>th</sup> and 36<sup>th</sup> week of gestation (Salzer, 1986 [50]). Several patients were excluded as treatment was interrupted (16 patients in the ambroxol group and 7 patients in the comparator group) in most cases due to the impossibility to further delay delivery. Treatment groups showed no significant differences with regard to age, weight, history, rate of premature rupture of membranes, gestational age at beginning of therapy and at time of delivery, mode of delivery, rate of tocolytic therapy and prematurity. In both groups, most patients (approximately 80%) had a gestational age over 34 weeks. The difference in RDS morbidity

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<sup>47</sup> Chang CC, Cheng AC, Chang AB. Over-the-counter (OTC) medications to reduce cough as an adjunct to antibiotics for acute pneumonia in children and adults. Cochrane Database Syst Rev. 2014 Mar 10:3

<sup>48</sup> Rubaltelli M. Comparative clinical study between the new "granular" pharmaceutical form of Bisolvon and N-acetylcysteine. Unpublished, January 1984

<sup>49</sup> Azzollini E, Bosi M, Mantegazza M, Picci E, Careddu P. Sobrerol (Sobrepim) administered dropwise to children with acute hypersecretory bronchopulmonary disease - A controlled trial v. bromhexine. Clin Trials J 27 (4), 241-249 (1990)

<sup>50</sup> Salzer H, Weidinger H, Simbruner G, Vytiska-Binstorfer E. Ambroxol versus betamethasone for stimulation of prenatal pulmonary maturity – a multi-centre study. Z Geburtshilfe Perinatol 190, 49 - 59 (1986)



(established by a standardised evaluation of the infants considering X-ray, clinical and blood-gas analyses findings) between the two groups was not statistically significant (9% (7/79) in the ambroxol group and 6% (5/86) in the comparator group). Amniotic fluid analyses carried out in a total of 46 patients of both groups showed increased surfactant parameters after therapy as compared to initial values before therapy. There were no significant differences in favour of either group.

#### Wauer

A prospective double-blind clinical trial was carried out to determine whether ambroxol treatment (1000 mg/day for a period of 5 days) reduces the risk of RDS in 246 potentially premature infants born to 224 mothers compared to placebo (Wauer, 1982 [51]). Amniocentesis was performed before the first and 24 h after the last infusion to assess the development of the total phospholipid phosphorus content, the lecithin–sphingomyelin (L/S) ratio, the palmitin–stearic acid (P/S) ratio, and the properties of the surface tension of the amniotic fluid. Gestational time was 36 weeks or less for 56 infants in the ambroxol and 60 in the placebo group. No differences between groups occurred in risk factors for RDS (diabetes, asphyxia, male sex, caesarean section). The incidence of RDS was significantly reduced in the ambroxol group (23.2%) compared to the placebo group (41.7%;  $p < 0.05$ ). However this improvement was not observed in infants with a gestational age shorter than or equal to 32 weeks. The examined parameters for determining lung maturity reflected a stimulatory effect of ambroxol compared with the results of the placebo group, particularly before the 33<sup>rd</sup> week of gestation. Of note, the publication does not specify whether treatment allocation was randomised.

#### Csaba

A multicentre randomised, double-blind study compared the efficacy of 1000 mg/day ambroxol and 8 mg/day betamethasone in 392 pregnant women. The primary end-point being was the incidence of respiratory distress syndrome in the newborn (Csaba, 1990 [52]). In addition, follow-up examinations were conducted at ages of 4 weeks and 6, 12, and 24 months. Statistical analysis was carried out by the chi-squared test and the t-test, with calculation of 95% confidence intervals. The overall incidence of respiratory distress syndrome was 12.0% in the ambroxol group and 15.9% in the comparator group. When only patients who received treatment for more than 3 days were considered, the incidence of respiratory distress syndrome was 15.6% and 23.3%, respectively. In either case the difference observed was not statistically significant. The 95% confidence intervals, though, show a favourable trend in favour of ambroxol over the comparator. None of the other results, including the incidence of neurological or other paediatric disorders at 24 months (over 60% of infants were examined in both groups), revealed any statistically significant differences.

#### Laoag-fernandez

This was a prospective study in 80 pregnant patients with premature labour or with premature rupture of membranes at an estimated gestation time of 27 to 34 weeks (Laoag-fernandez, 2000 [53]). Based on their decision and the physician's decision, half the patients were administered 1,000 mg/day ambroxol by intravenous infusions (4 hours) for 3 days, while the other half was not administered ambroxol. Other medications administered included antibiotics, antihypertensives, tocolytics and vitamins supplements. Main measures included Apgar score (used to determine whether a newborn

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<sup>51</sup> Wauer RR, Schmalisch G, Menzel K, et al. The antenatal use of ambroxol (bromhexine metabolite VIII) to prevent hyaline membrane disease: a controlled double-blind study. *Int J Biol Res Pregnancy*, 84 - 91 (1982)

<sup>52</sup> Csaba IF, Lampe LG, Kovacs L, Zsolnai B, Kirchaessler KU. Clinical study with ambroxol and betamethasone to investigate antepartal stimulation of lung maturation and prophylaxis of the respiratory distress syndrome (RDS). Unpublished, February 1990

<sup>53</sup> Laoag-Fernandez JB, Fernandez AM, Maruo T. Antenatal use of ambroxol for the prevention of infant respiratory distress syndrome. *J Obstet Gynaecol Res* 26 (4), 307 - 312 (2000)

needs help breathing or is having heart trouble, scores around 7-10 are generally normal), clinical signs of one or more of the following: respiratory rate superior to 60 per minute, intercostal retraction, alar flaring, expiratory grunting, cyanosis on room air and radiological evidence of IRDS. Chi-square test was used to determine the statistical significance of the results. Incidence of IRDS, IRDS mortality, incidence of neonatal death and perinatal mortality were significantly lower in the treatment group ( $p < 0.01$ ). Profile of newborns and associated risk factors for IRDS (e.g. gestational age and weight at birth) were found to be similar in both groups, however more neonates had a low Apgar score ( $< 4$ ) in the control group (at 1 minute 17.5% vs. 28.5% and at 5 minutes 12.4% vs. 22.1%).

#### Kimya

In this study women at risk of pre-term delivery were given the choice to receive either 1300 mg/day ambroxol ( $n=24$ ) until delivery or no treatment for foetal lung maturation ( $n=58$ ). Tocolysis was applied to 17 patients in the ambroxol group and none in the control group (Kimya, 1995 [54]). There were no significant differences in mean maternal ages, mean gestational ages at delivery (mean  $34.7 \pm 3.1$  weeks in the ambroxol group and  $32.3 \pm 6.6$  weeks in the control group), the mean 10<sup>th</sup> minute Apgar scores and the mean birth weight between both groups. In the ambroxol group 1 (6%) male and 1 (12%) female infants developed RDS, while in the control group 5 (18%) males and 1 (3%) of the female did. Of those, only the male patient in the ambroxol group survived (rate of RDS perinatal mortality was 4% vs. 10% in favour of the ambroxol group). Mean treatment length was around 12 days. No information was given on the statistical significance of those differences in the publication.

#### Litta

In this study the occurrence of RDS in the infants of women who gave birth at or before 35 weeks of gestation was followed (Litta, 1990 [55]). The pregnant women were administered either 2 g/day ambroxol intravenously for 2 days ( $n=43$ ) and or no preventive therapy ( $n=383$ ). A trend was observed in favour of the ambroxol group which however did not reach significance less in the need for assisted ventilation ( $p=0.09$ ) and occurrence of RDS (27.9% in the ambroxol group and 33.7% in the control group;  $p=0.53$ ). Of note, several discrepancies were present in this publication, in particular between figures given in tables and in running text, and no information was given on treatment duration, blinding and randomisation.

#### *IRDS in newborn*

#### Elsayed

This clinical trial evaluated the effect of postnatal administration of ambroxol in the prevention of respiratory distress syndrome (RDS) in 120 preterm neonates (with gestational age of 28 to 34 weeks) at risk of RDS and on treatment of RDS in those neonates already suffering from it (Elsayed, 2006 [56]). The patients were randomised to receive intravenous ambroxol (20 mg/kg/day) or a placebo. All patients received routine care including, when needed, continuous positive airway pressure (CPAP) and mechanical ventilation by intubation in severe cases with hypoxia despite CPAP. In addition antenatal corticosteroids were given to all women. No significant difference was observed between both groups at baseline regarding respiratory and heart rate, temperature and oxygen saturation. Ambroxol decreased the incidence of respiratory distress syndrome (33.3% vs. 48.4%,

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<sup>54</sup> Kimya Y, Kucukkomurcu S, Ozan H, Uncu G. Antenatal ambroxol usage in the prevention of infant respiratory distress syndrome - beneficial and adverse effects. *Clin Exp Obstet Gynecol* 22 (3), 204 - 211 (1995)

<sup>55</sup> Litta P, Piermarocchi P, Cazzaro L, Marchetti M. Prevention of the respiratory distress syndrome with ambroxol - Report of our experience. *J Foetal Med* 10 (1-4), 33 - 35 (1990)

<sup>56</sup> Elsayed HF, Elkhaiouby MI, Elsharkawey SM, Elnemr MA. Evaluation of the role of postnatal ambroxol in the prevention and treatment of respiratory distress syndrome in preterm neonates. *Sultan Qaboos Univ Med J* 6 (2), 41 - 46 (2006)

$p < 0.05$ ), improved the gas exchange ( $p < 0.05$ ), and decreased continuous positive airway pressure ( $p < 0.001$ ), the length of mechanical ventilation ( $p < 0.001$ ) and also the mortality rate (18.3% vs. 35%,  $p < 0.05$ ). The mortality rate due to RDS however was slightly lower in the ambroxol group but the difference did not reach statistical significance (36.4% vs. 38.1%).

#### Wauer

A multicentre, randomised, placebo-controlled double-blind trial was conducted in 148 infants with a birth weight below 1,500 g and gestational age below 34 weeks treated with 30 mg/kg/day ambroxol (birth weight 1190 +/- 216 g; gestational age 29.1 +/- 1.9 weeks) or 74 placebo (birth weight 1168 +/- 216 g; gestational age 28.9 +/- 1.9 weeks) (Wauer, 1992 [57]). Intermittent mandatory ventilation was provided. There was no significant difference between both groups at baseline. In 28 day-survivors ambroxol was able to significantly improve the ratio of partial pressure arterial oxygen and fraction of inspired oxygen ( $\text{PaO}_2/\text{FiO}_2$  ratio) ( $p < 0.01$ ), mean airway pressure ( $p < 0.05$ ), phospholipid profile of tracheal effluent ( $p < 0.05$ ) and pulmonary mechanics of spontaneously breathing infants ( $p < 0.05$ ). In addition, in the 28 day-survivors, the incidences of bronchopulmonary dysplasia ( $p < 0.01$ ), intraventricular haemorrhage ( $p < 0.05$ ) and postnatally acquired pneumonia ( $p < 0.05$ ) were significantly reduced in the ambroxol group as compared to the control group. No significant difference was observed in the mortality rate during the first 150 days of life between the ambroxol and the placebo group (23 (31%) and 27 (37%) respectively), nor in RDS associated morbidity apart from grade I/II intracerebral haemorrhage (14.3 % vs. 28.4%,  $p < 0.05$ ).

#### Fan

In this study 61 premature infants born between the 28<sup>th</sup> and the 37<sup>th</sup> gestational week were randomly divided into an ambroxol high-dose group (30 mg/kg/day) and a conventional dose group (15 mg/kg/day) for 3 days, with the possibility to extend the treatment by a further 4 days as required (Fan, 2009 [58]). Half of the dose was nebulised and the other half was infused intravenously. Nasal tube was retained for continuous low flow oxygen inhalation (0.5-1 L/min), and recovery bag-mask was used for oxygen supply in patients with transcutaneous saturation ( $\text{TcSO}_2$ )  $< 0.85$  which could not be elevated. If this was ineffective, non-invasive nasal continuous positive airway pressure (CPAP) was used instead. There were no significant differences between both groups in gender, gestational age, weight and Apgar score. RDS occurred in 3.2% in the high dose group and in 23.3% in the conventional dose group ( $p < 0.05$ ). The incidence of type I respiratory failure was 19.4% in the high-dose group and 43.3% in the conventional dose group ( $p < 0.05$ ). The incidence of type II respiratory failure was 16.1% in the high dose group and 40% in the conventional dose group ( $p > 0.05$ ). Intracranial haemorrhage and pulmonary infection occurred significantly more frequently in children from the conventional dose group ( $p < 0.05$ ). The mortality was 3.2% in the high dose group and 20.0% in the conventional dose group ( $p < 0.05$ ). Of note however, the protocol and results were poorly described in this publication and no information was provided about dropped out patients.

#### Hu

This study aimed at comparing the efficacy of two different ways of administering ambroxol (i.e. intravenous injection and atomising inhalation), for the prevention of respiratory distress syndrome in preterm infants (Hu, 2006 [59]). A total of 125 preterm infants born between 28 to 37 weeks of

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<sup>57</sup> Wauer RR, Schmalisch G, Böhme B, et al. Randomised double blind trial of ambroxol HCl for the treatment of respiratory distress syndrome. *Eur J Pediatr* 1992; 151: 357-63

<sup>58</sup> Fan YZ, Wen ZL. Efficacy of different dosages of ambroxol hydrochloride in the prevention of neonatal respiratory distress syndrome. *Chin J Contemp Pediatr* 11 (9), 771 - 772 (2009)

<sup>59</sup> Hu Q, Lian JM, Li JQ. Efficacy of intravenous or atomising ambroxol for prevention of respiratory distress syndrome in preterm infants. Original in Chinese. *Chin J Contemp Pediatr* 8 (4), 301 - 303 (2006)

gestation were randomly assigned into 3 groups: intravenous and atomising ambroxol treatment groups (n=40 each) or control group (n=45). The intravenous group was injected with 15 mg/kg of ambroxol through the umbilical vein immediately after birth and then received 30 mg/kg/day ambroxol for 2 days by intravenous infusion. The atomising group was administered with 30 mg/kg of ambroxol daily for 2 days by atomising inhalation immediately after birth. The control group received no ambroxol treatment. The incidences of respiratory distress syndrome and complications as well as the blood gas results 6 hours after birth were compared among the 3 groups. The incidence of respiratory distress syndrome was 7.5%, 5.0% and 24.4% in the intravenous, atomising and control groups, respectively. The incidence of RDS in the two treatment groups was noticeably lower than in the control group ( $p < 0.05$ ). The blood gas results did not show significant differences between the two ambroxol treatment groups but both groups demonstrated improved blood gas results compared with the control group at 6 hours after birth ( $p < 0.05$ ). The incidence of complications, such as pulmonary haemorrhage, respiratory failure, intracranial haemorrhage, was similarly reduced in the two ambroxol treatment groups compared with the control group ( $p < 0.05$ ), but there were no differences between the two ambroxol groups.

### ***Ambroxol in prophylaxis and treatment of postoperative pulmonary complication (PPC)***

Gao

In this double blind study, 60 patients who underwent video-assisted thoracic surgery lobectomy for lung cancer were randomly assigned to 2 treatment groups: a group treated intravenously with 1000 mg/day ambroxol for 4 days, starting the day of the operation, or a group treated with placebo (Gao, 2014 [60]). Perioperatively, a second-generation cephalosporin antibiotic was administered for short-term prophylaxis and in the 72 hours after the procedure a non-opioid analgesic was administered intravenously to control postsurgical pain. The two groups were well matched for demographics and operative variables. The pulmonary function tests, arterial blood gases, incidence of perioperative morbidity, postoperative mechanical ventilation time, duration of intensive care unit (ICU) stay, length and costs of postoperative hospital stay were compared between the two groups. The ambroxol group showed better lung function parameters ( $p < 0.05$ ), including percent predicted FEV<sub>1</sub>, the ratio of FEV<sub>1</sub>/FVC, the percent predicted diffusing capacity of the lung for carbon monoxide, and arterial oxygen pressure compared to the control group. No statistical difference however was found between the two groups in arterial partial pressure of carbon dioxide. The postoperative pulmonary complications were significantly reduced ( $p < 0.05$ ), the duration of mechanical ventilation and the length of ICU stay were shortened ( $p < 0.05$ ). The length and costs of postoperative hospital stay were also significantly decreased in the ambroxol group compared to the control group ( $p < 0.05$ ). In the ambroxol treatment group, one patient had a lung infection. In the control group, four patients had lung infections, four patients had atelectasis, one patient had continuous air leaking postoperatively (>7 days), one patient had respiratory failure, and two patients had one or more pulmonary complications. No difference was observed between the two groups in other types of postoperative complications.

Refai

In this similar double blind study, 140 patients who underwent lobectomy for lung cancer, by lateral thoracotomy, were randomly assigned to 2 treatment groups: a group treated intravenously with 1000 mg/day ambroxol for 4 days, starting the day of the operation, or a group treated with placebo

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<sup>60</sup> Gao Y, Cheng Y, Dong S, He Z, Zhou W, Liang L, Zhang C. Effect of perioperative treatment with ambroxol on lung cancer patients after videoassisted thoracic surgery lobectomy. *J Cent South Univ (Med Sci)* 39 (8), 849 - 854 (2014)

(Refai, 2009 [61]). Bronchodilators were administered in case of an objective evidence of reversible obstruction after bronchodilator administration at the preoperative pulmonary function tests. The two groups were well matched for perioperative and operative variables. Groups were compared in terms of occurrence of postoperative complications, length of stay and costs. Short-term antibiotic prophylaxis with cefazolin was administered to all patients. Compared to the placebo group, the group treated with ambroxol had a reduction of postoperative pulmonary complications (6% vs. 19%,  $p < 0.05$ ). This difference was not observed for cardiac complications. A trend in favour of the ambroxol group was also observed for the frequency of unplanned ICU admission/readmission (1.4% vs. 8.6%,  $p = 0.1$ ). The postoperative stay and costs were reduced by 2.5 days (5.6 vs. 8.1,  $p = 0.02$ ) and 2765 Euro (2,499 Euro vs. 5,264 Euro,  $p = 0.04$ ), respectively. Blood gases were analysed. Two patients died in the placebo group, one due to respiratory failure and the other one due to cardiac arrest.

#### Liangqi

This study evaluated the efficacy of two doses of ambroxol on postoperative pulmonary complications in 40 patients at high risk of developing such complications, defined as having two or more of the following risk factors: long-term smoking, history of chronic lung disease (such as COPD or asthma), advanced age, obesity and prolonged bed rest) (Liangqi, 2011 [62]). Patients undergoing upper abdominal surgery (liver operations, bile duct operations, spleen operations and three other cases) were randomly divided into two groups to receive either 990 mg/day or 90 mg/day ambroxol in intravenous drip for 10 days. No changes were found at baseline for levels of white blood cells (WBC), pH, PaO<sub>2</sub>, partial pressure of carbon dioxide (PaCO<sub>2</sub>), total CO<sub>2</sub> (TCO<sub>2</sub>), and interleukin 10 (IL-10) in both groups. The infection of lung in the high dose group was 10% post-operation, which was significantly lower than that of the control group (40%) ( $\chi^2 = 8.107$ ,  $p < 0.05$ ). There were 8 cases of lung infections in the low dose group (coughing, expectoration, changes in lung infections as seen in X-rays) and in two cases an improvement was seen compared to baseline symptoms. In the high dose group 2 cases of lung infection were reported and 9 patients significantly improved after the surgery. Diagnostic of the pulmonary infections not described. The level of WBC in both groups started to significantly reduce at the 7<sup>th</sup> day of post-operation ( $p < 0.05$ ). Unlike the level of PaCO<sub>2</sub>, those of PaO<sub>2</sub> and TCO<sub>2</sub> in the high dose group were significantly superior to that of the low dose group from the third day of post-operation ( $p < 0.05$ ). The level of IL-10 increased in both groups following surgery and was significantly higher in the high dose group from the third day ( $p < 0.05$ ).

#### Huang

This study was conducted in 120 elderly patients (range 60-80; mean age: 72.1±7.8) undergoing colorectal surgery, in order to compare the efficacy of two doses of ambroxol in preventing postoperative pulmonary complications (Huang, 2012 [63]). Patients were randomised postoperatively to receive treatment with 45 mg/day intravenous and 45 mg/day inhaled ambroxol, 360 mg/day intravenous and 90 mg/day inhaled ambroxol for seven days or to a control group. These groups were comparable in sex constituent ratio, age, operation mode, pre-operative cardiac function, pulmonary function and concomitant diseases. Both regimens were found to significantly improve ease of expectoration as well as the sputum characteristics and quantity compared to placebo ( $p < 0.05$ ). However, while a trend was observed with the lower dose, the incidence of pulmonary infections and

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<sup>61</sup> Refai M, Brunelli A, Xiume F, Salati M, Sciarra V, Socci L, Nunzio L di, Sabbatini. A Short-term perioperative treatment with ambroxol reduces pulmonary complications and hospital costs after pulmonary lobectomy: a randomised trial. *Eur J Cardiothorac Surg* 35 (3), 469 - 473 (2009)

<sup>62</sup> Liangqi C, Shaomang L, Xuwei Y, et al. Clinical study on high dose of Mucosolvan in perioperative period in upper abdominal surgeries. *Clinical Medical Engineering* (2011), 18(3): 330-332

<sup>63</sup> Huang J, Chen J, Lei J, Ke C. Large doses of Mucosolvan in the prevention of the elderly colorectal postoperative pulmonary complications. *Chin J Gerontol* 32 (1), 28 - 29 (2012)

atelectasis was only significantly reduced compared to the control group with the higher dose ( $p < 0.05$ ). All the measured parameter except for incidence of atelectasis were also found significantly improved with the higher dose compared to the lower dose ( $p < 0.05$ ). The incidence rate of pulmonary infection was 32.5%, 22.5%, and 5% respectively in the control, low dose and high dose group while the rate of atelectasis was 15%, 7.5% and 0% respectively in these groups.

Li

A total of 61 acute cervical spinal cord injury (CSCI) patients admitted to the Intensive Care Unit were randomly divided into two groups: one group received intravenous ambroxol at 990 mg/day for 5 consecutive days after operation; the other group was treated with a placebo (Li, 2012 [64]). Short-term antibiotics piperacillin/sulbactam or cefminox were administered to all patients to prevent pulmonary infections. No significant differences were found in patient age, gender, ratio of smokers, the highest level, and the degree of CSCI (ASIA classification) between the two groups. The group treated with high-dose ambroxol showed a lower rate of postoperative pneumonia and hypoxemia within 5 days after operation ( $p < 0.05$ ). There were no significant differences in the rate of atelectasis. On the 3<sup>rd</sup> and 5<sup>th</sup> days, the oxygenation index in the high-dose ambroxol group ( $291.02 \pm 34.96$  and  $301.28 \pm 37.69$ ;  $p < 0.05$ ) was significantly higher than in the control group ( $230.08 \pm 26.25$  and  $253.82 \pm 26.26$ ;  $p < 0.05$ ), with significant differences between the two groups ( $p < 0.05$ ).

Fegiz

A double-blind multicentre study was carried out to evaluate the effectiveness of ambroxol in the prevention of postoperative bronchopulmonary complications (Fegiz, 1991 [65]). A total of 252 patients with stable chronic obstructive lung disease undergoing upper abdominal surgery were randomly allocated to receive either 1000 mg/day ambroxol intravenously for 6 consecutive days starting 3 days before surgery or placebo. The patients' basal characteristics, clinical signs, x-ray results, blood gas analysis and the duration of surgery were not significantly different in the 2 groups however 10% more smokers were in the placebo group. Clinical and x-ray examinations were conducted to diagnostic respiratory tract pathologic conditions. Blood gas analyses (PaO<sub>2</sub>, PaCO<sub>2</sub>, pH, SaO<sub>2</sub>, HCO<sub>3</sub>) were also carried out. There was a significant difference in atelectasis between the 2 groups (10.6% ambroxol vs. 23.9% placebo,  $p < 0.05$ ) and a trend in favour of the ambroxol group for infective complications which was not statistically significant (8.8% ambroxol vs. 12.4% placebo). There was no difference between the two groups in term of number of patients needing antibiotic therapy before and after surgery. Analysis of variance showed that the PaO<sub>2</sub> values of the ambroxol-treated group after surgery decreased less than those of the placebo-treated group ( $p < 0.05$ ) from the preoperative values, however the same effect was not seen for PaCO<sub>2</sub>, pH, SaO<sub>2</sub> and HCO<sub>3</sub>. The clinical chest evaluation (according to a classification in 4 composite categories reflecting the presence or absence of fever, cough, abundant secretions, chest sounds, hypoxemia, need for intubation and mechanic ventilation) and respiratory rate did not show any significant difference between the 2 groups of patients during the first week after surgery. It is however unclear whether the study was truly blinded as ambroxol was administered by infusion in 500 ml saline solution whereas the placebo is stated as being an "identical 50 ml solution" administered by infusion over the same period of time.

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<sup>64</sup> Li Q, Yao G, Zhu X. High-dose ambroxol reduces pulmonary complications in patients with acute cervical spinal cord injury after surgery. *Neurocrit Care* 16 (2), 267 - 272 (2012)

<sup>65</sup> Fegiz G. Prevention by ambroxol HCl of bronchopulmonary complications after upper abdominal surgery: double-blind Italian multicentre clinical study versus placebo. *Lung* 1991;169(2):69-76



Kranicke

In this study 40 patients undergoing general and accident surgery (including 19 patients above the age of 60) were given 60 mg/day ambroxol for 5 to 7 days postoperatively (Kranicke, 1978 [66]). Half of the daily dose was given intravenously and half by inhalation. Patient evaluation was based on chest X-rays, sputum viscosity, subjective symptoms and clinical examination (auscultation, percussion, expectoration, and cough). Improvement in the subjective symptoms was recorded during the first 3 days of treatment including ease of expectoration. Cough (reported in 9 patients at study entry) was resolved after the third day of treatment and the mucus viscosity decreased. In most of the patients the auscultation finding had improved by the 7<sup>th</sup> day of treatment.

Ulas

Fifty patients without known pulmonary disease were randomly assigned to receive a placebo or 480 mg/day ambroxol for 14 days starting a week prior coronary artery bypass grafting (Ulas, 2008 [67]). Groups were compared with respect to pulmonary function tests (PFTs), lecithin/sphingomyelin (L/S) ratio in the bronchoalveolar lavage fluid, arterial blood gases, and incidence of perioperative morbidity. Postoperative L/S was significantly lower than the preoperative values in both groups without significant differences between both groups. Although preoperative PaO<sub>2</sub> in both groups was similar, it was significantly lower in control group on postoperative second day (62.4 +/- 7.1 vs. 55.2 +/- 6.4 mm Hg, p<0.05). Postoperative FVC and FEV<sub>1</sub> were significantly lower than preoperative values with a more prominent decrease in control group. Perioperative morbidity was similar. Of note, a later review stated that the randomisation method was not clearly specified and the allocation concealment conditions could not be determined, and thus selective bias may have occurred in this study (Su, 2012 [68]).

### ***Ambroxol in pain relief in acute sore throat***

Seven multi-centre, randomised, placebo controlled, double-blind, parallel-group clinical trials studied the effect of ambroxol in 2,509 patients with acute, uncomplicated sore throat of recent onset. Of the patients enrolled 2,427 were evaluable in terms of efficacy (lozenges: 1,934; spray: 493 patients; 2,206 adults and 221 adolescents) (Aicher, 1996 [69]; Gund, 1997 [70]; Nel, 1998 [71]; Rensburg, 1998 [72]; Zabolotniy, 2007 [73]; Port, 2006 [74]; Patel, 2012 [75]). In the studies with the

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<sup>66</sup> Kranicke R. Results of a clinical trial with ambroxol as to postoperative therapy of bronchitis. *Arzneimittelforschung* 28, 934 - 935 (1978)

<sup>67</sup> Ulas MM, Hizarci M, Kunt A, et al. Protective effect of ambroxol on pulmonary function after cardiopulmonary bypass. *J Cardiovasc Pharmacol.* 2008 Dec; 52(6):518-23

<sup>68</sup> SU Na, WU Bin, LU Jing, XU Ting. Efficacy and Safety of Ambroxol for Lung Protection in Perioperative Period: a Systematic Review. *Chinese Pharmaceutical Journal (Beijing)* 2012, 47 14 1154-1157

<sup>69</sup> Aicher B, Sigmund R, Siebers U, et al. Double-blind, randomised, placebo-controlled dose finding study of the efficacy and tolerability of ambroxol lozenges (5, 10 and 20 mg) in the treatment of sore throat in patients with acute viral pharyngitis. Unpublished, July 1996

<sup>70</sup> Gund HJ, Cisar L, Aicher B, et al. Double-blind, randomised, placebo-controlled clinical trial of the efficacy and tolerance of ambroxol lozenges (20 mg) in the treatment of sore throat in patients with acute viral pharyngitis. Unpublished, September 1997

<sup>71</sup> Nel PR, Mare PD, Boshoff L, et al. Double-blind, randomised, placebo controlled clinical trial to investigate the efficacy and tolerability of ambroxol lozenges (30 mg and 20 mg) in the treatment of sore throat in patients with acute viral pharyngitis. Unpublished, June 1998

<sup>72</sup> Rensburg GSJ van, Bergh JS van den, Baraldi E, et al. Double-blind, randomised, placebo controlled trial to investigate the efficacy and tolerance of Ambroxol lozenges (30 mg and 20 mg) in the treatment of sore throat in patients with acute viral pharyngitis. Unpublished, June 1998

<sup>73</sup> Zabolotniy D, Ottillinger B, Peil H, Uvarova E, Vix JM. Efficacy and tolerability of Ambroxol Lozenges 20 mg in relieving pain of sore throat in patients with acute viral pharyngitis – A randomised, double-blind, placebo- and active-controlled parallel group study. Unpublished, February 2007

<sup>74</sup> Port, M, Jacovides A, Peil, H. Efficacy and tolerability of Ambroxol Lozenges 20mg in relieving the pain of sore throat in adolescent patients with acute viral pharyngitis – A randomised, double-blind, placebo controlled parallel group study. Unpublished, June 2006

lozenges, patient discontinued treatment mostly due to lack of efficacy (18 in the bromhexine group and 9 in the placebo group), protocol non-compliance (13), adverse events (19, including worsening or primary diagnostic or of co-morbidity in 8 cases and occurrence of other adverse events in 3 cases in the placebo group and 7 in the bromhexine group) or were lost to follow-up (24). Similar reasons were observed in the spray study. Baseline sore throat intensity was to be at least "severe" (4 studies) or "moderate" (1 study) scored by verbal rating scale. In the trial with the oromucosal spray (n=494), trial participants had to have acute sore throat of onset within the last 72 hours and with a baseline pain intensity of at least 6 points on an 11-point pain scale.

In the trials with ambroxol lozenges (6), investigational treatments consisted of a single 20 mg lozenge followed by pharmacodynamic pain evaluation for 3 hours, subsequently, up to 6 lozenges could be taken per day at a minimum interval of 0:30 h; treatments lasted 1-3 days. Other lozenges strength were investigated but did not show improvement over placebo (5 mg, 10 mg) or were not found superior to the 20 mg lozenge (30 mg). In all trials except for one (in which improvement was seen but did not reach statistical significance) the pain relief provided by the first lozenge was statistically significantly larger than for the placebo ( $p < 0.01$ ). A post-hoc analysis of these trials found that, the pooled effect after sucking a first lozenge containing 20 mg ambroxol represents a pain relieving effect over the first three hours that is 12% (95%CI: 9 to 15%) larger than for the placebo (expressed as percentage of the maximum achievable effect). During the ambulatory treatment phase subsequent to the in-depth analysis of the response to the first dose, the subjects recorded their evaluation of the overall treatment efficacy at the end of each day. In the adult patients, overall efficacy was consistently scored to be at least "good" by more patients in the ambroxol group (69% vs. 53% for the first day, 78% vs. 59% for the second day and 78% vs. 67% for the third day).

For the ambroxol spray, with a dose of 10 mg ambroxol per application, these effects tended to be faster but slightly smaller, although within the range of the pooled effects for lozenges containing 20 mg ambroxol.

The efficacy of ambroxol lozenge for pain relief during acute pharyngitis was studied in a recently published meta-analysis included five clinical trials (Chenot, 2014 [76]). Ambroxol lozenges were found slightly more effective for local pain reduction in adult patients with sore throat compared to a mint flavoured placebo lozenge within 3 hours. However, the additional benefits of ambroxol beyond 3 hours remain unclear as the quality of reporting of the studies was low and given that more than 50% of patients using placebo for pain relief reported good or very good efficacy after 1 day compared to 69% with ambroxol.

### ***Bromhexine in treatment of sinusitis***

Olsson

In this double-blind study 31 patients (mean age 35 years) with acute sinusitis were randomised to treatment with 48 mg/day bromhexine or placebo for 2 weeks (Olsson, 1970 [77]). All patients also received penicillin V and oxymetazoline. In the bromhexine group 68% of patients were cured completely after 2 weeks. The amount of secretion on the bromhexine group was initially higher than in the placebo group. At the end of treatment it had declined to almost the same value for the placebo

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<sup>75</sup> Patel J, Richter E, Waldhauser L. A multi-centre, randomised, double-blind, placebo controlled, parallel group dose finding study to assess the efficacy and safety of ambroxol spray (2.5mg, 5mg or 10mg) versus placebo for the temporary relief of sore throat pain in patients with acute sore throat. Unpublished, March 2012

<sup>76</sup> Chenot JF, Weber P, Friede T. Efficacy of Ambroxol lozenges for pharyngitis: a meta-analysis. BMC Fam Pract. 2014 Mar 13;15:45

<sup>77</sup> Olsson O. Clinical trial of Bisolvon in acute sinusitis. Unpublished, 1970.



group (9%). The patients in the bromhexine group experienced less days of pain (25 days compared to 55 days with the placebo group).

#### Tarentino

In a double blind study 30 paediatric patients aged between 3 and 12 years and suffering from acute sinus inflammation were randomised to receive a 8-day treatment with 48 mg/day bromhexine, or a placebo (Tarantino, 1988 [78]). Further stratification by age group was not given in the publication (average age bromhexine  $5.63 \pm 2.55$  years). All patients received concomitantly 150 mg/kg/day amoxicillin. There was a statistically significant difference ( $p < 0.01$ ) in favour of the group treated with bromhexine for the reduction of nasal secretion and rhinitis improvement. Hyperaemia of the nasal mucosa was evaluated as presence or absence of the clinical sign; there was a statistically significant difference ( $p < 0.01$ ) in favour of the bromhexine groups at the end of treatment. Of the 7 patients experiencing pain at the beginning of the study (2 in the bromhexine group and 5 in the placebo group), one was still in pain at the end of the study, in the placebo group. Temperature was no longer observed in either treatment group. Fewer days lost from school were reported in the bromhexine group than in the placebo group for the children of school age ( $n=11$ ).

#### Polakow

Treatment of chronic maxillary sinusitis by inhalation therapy with bromhexine was carried out, in an open study, when conventional methods of treatment had given unsatisfactory initial results; the patients had reached a stage where antrostomy and drainage would have been considered as the next method of treatment (Polakow, 1973 [79]). No acute infective cases were included in the random group of 44 patients studied. Following treatment with bromhexine solution 5 ml/day inhaled over 5 minutes for 5 days, the fluid levels in 17 patients had resolved completely. The remainder constituted a group of 27 with radiological diagnosis of "gross mucosal thickening" or "opaque maxillary antra"; 20 of these patients showed excellent improvement, 5 responded to a moderate extent, and 2 failed to show evidence of any improvement.

#### Kloosman

In an open study 450 patients with clinical sinusitis were randomly allocated to a 10-day treatment of 24 mg/day bromhexine against 300 mg/day mepyramine maleate, with adjunct antibiotic therapy (penicillin G procaine and streptomycin) (Kloosman, 1972 [80]). The average severity of sinusitis was considered identical in the two groups. The bromhexine group showed a 100% clinical cure rate over a period of 8 days, patient reported an initial increase in the flow of nasal and postnasal discharge for about 4 days combined with a relief of the other symptoms of sinusitis. In the comparator group there was a partial relief of symptoms but no complete cure. In the discharge, where the examination was conducted, bacterial cure was observed after 4 days in the bromhexine group and after 7 days in the comparator group.

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<sup>78</sup> Tarantino V, Stura M, Marengo G, Leproux GB, Cremonesi G. Advantages of treatment with bromhexine in acute infant sinus inflammation. Randomised double blind study vs. placebo. *Minerva Pediatr* 40 (11), 649-652 (1988)

<sup>79</sup> Polakow, E. S. The treatment of chronic maxillary sinusitis by inhalation therapy with Bisolvon. *South African Medical Journal* 1973, 47, 985-987

<sup>80</sup> Kloosman WLS. A comparative study of two treatment schemes in clinical sinusitis. *S Afr Med J* 46, 695 - 696 (1972)

## ***Bromhexine in treatment of Sjögren's syndrome***

### **Brophy**

The efficacy of 64 mg/day bromhexine for 3 weeks was compared to placebo in a randomised double-blind cross-over (two 3 weeks periods) study in 64 patients with keratoconjunctivitis sicca (KCS) (with or without the presence of Sjögren's syndrome or xerostomia) (Brophy, 1986 [81]). Withdrawals or protocol violations occurred with 19 patients, therefore 45 patients were included in the efficacy analysis. No difference was observed in any of the parameters observed i.e. time taken to eat a biscuit, tear break up time, Schirmer test (which measures tears production), maximum of the combined hyperaemia score, maximum of the combined mucus score and diary (ocular grittiness, stickiness, soreness, redness, severity of xerostonia, usage of hypromellose eye drops). No differences in side-effects, withdrawals or compliance between bromhexine and placebo were seen. Of note, the patients were experimenting lack of symptoms at study entry (over half of the patients were only diagnosed with "dry eye" 8 with "dry mouth", 3 with Sjögren's syndrome and about 20 with rheumatoid arthritis). Hypromellose eye drops were authorised, the amount needed and frequency was intended to be included in the analysis but the level of data available was insufficient.

### **Frost Larsen**

Twenty-nine patients with Sjögren's syndrome were assigned to two consecutive randomised double-blind crossover trials with bromhexine and placebo, each comprising two 2-week periods (Frost-Larsen, 1978 [82]). In the first trial bromhexine 24 mg/day was given and in the second the dose was increased to 48 mg/day. Concomitant treatment were allowed but were kept constant throughout the trials. Eighteen patients had primary Sjögren's syndrome, while in 8 the main diagnosis was systemic lupus erythematosus (SLE) and in 3, rheumatoid arthritis. Two patients took part only in the first (low-dose) trial. One of these two patients on bromhexine dropped out because one of the preparations used in the first trial caused such abundant lacrimation that she considered that any further increase would be unduly unpleasant. The other patient, who had been suffering from SLE for years, died of septicaemia. On the low-dose regimen there were no statistically significant differences in ophthalmological values between treatment with bromhexine and that with placebo, but with the high-dose regimen the Schirmer test values and the break-up times were higher after bromhexine than after placebo ( $p < 0.02$  and  $p = 0.06$  respectively). There was no difference between the Rose Bengal scores (which measures epithelial damage in the ocular surface) during the two treatments in either trial. There was no significant correlation between the duration of Sjögren's syndrome and the ophthalmological effects of bromhexine or placebo. Neither of the trials showed any significant differences between the effects of bromhexine and placebo treatment on biscuit eating time, patients' feeling of moistness in the eyes and mouth or the blood values.

### **Manthorpe**

A further randomised placebo-controlled trial assessed the efficacy of bromhexine 48 mg/day for 3 weeks on various ophthalmological and oral values in 32 patients with Sjögren's syndrome (Manthorpe, 1981 [83]). Schirmer test and break up time were significantly higher after treatment with the bromhexine compared to the placebo group ( $p < 0.05$  and  $p = 0.05$ , respectively). No improvement

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<sup>81</sup> Brophy; Harrop LM, Richards AB, Snell B, Easty, Logan P. Statistical report: Bromhexine in the treatment of keratoconjunctivitis sicca. Unpublished, December 1986

<sup>82</sup> Frost-Larsen K, Isager H, Manthorpe R. Sjogren's syndrome treated with bromhexine: a randomised clinical study. *Br Med J* 1, 1579 - 1581 (1978)

<sup>83</sup> Manthorpe, R. et al. Bromhexine treatment of Sjogren's syndrome: Effect on lacrimal and salivary secretion and on proteins in tear fluid and saliva. *Scand. J. Rheumatol.* 1981, 10, 177-180

however was seen on the Rose Bengal score or in the composition of the tear fluid. In contrast to other proteins in saliva, the IgM concentration decreased in patients with high values at study entry.

#### Prause

This study followed a group of 34 patients with primary Sjögren's syndrome (30 females and 4 males) for a mean period of 53 (range 27-76) months (Prause, 1989 [84]). The patients were divided according to their initial response to treatment with 48 mg/day bromhexine. The responder group included 22 females and one male (mean age was 53 (range 32-73) years and mean disease duration 9 (range 1-38) years). The non-responder group included eight females and three males (mean age was 52 (range 24-69) years and the mean duration of disease 8 (range 1-16) years). KCS parameters (Schirmer test, tear break up time and Rose Bengal score) and plasma cell activity (p-IgG, M and A) were measured repeatedly during the observation period. Patients responding to and continuously treated with bromhexine (60% of patients) improved significantly ( $p < 0.05$ ) in Rose Bengal score compared to the non-responders, but had increasing levels of p-IgG. Non-responders kept their low tear-production rate and had also increasing p-IgG levels. However, when subdivided according to p-IgG level, the group of patients with relatively low p-IgG improved in Rose Bengal score, compared to the high p-IgG-group increased in Rose Bengal score ( $p < 0.05$ ). The Schirmer test values remained unchanged in both groups, but the values of the non-responders were significantly lower than those of the responders ( $p < 0.02$ ). Break up time remained unchanged in the responder group, but improved in the non-responder ( $p < 0.05$ ); the difference between the two groups was not statistically significant.

#### Discussion

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. These historical aspects are coupled with the difficulty of operating in a therapeutic area where endpoints are poorly defined and there is a lack of scientific consensus as to the most appropriate clinical trial methodologies. According to a relatively recent publication (Rubin, 2007 [85]), there seem to be no consensus on endpoints to be used in clinical trials examining the efficacy of mucolytics as some correlate poorly with other measures of efficacy (lung volume and flow), others are insensitive to the acute or long-term effects of mucoactive therapy (spirometry) or highly variable (sputum volume due to patient reticence to expectorate, inadvertent swallowing of secretions, salivary contamination of secretions, and variability in cough). For long-term studies, epidemiologic data support the hypothesis that improved mucus clearance may affect the rate of decline in pulmonary function over time by reducing the number of pulmonary infections and exacerbations, however in order to evaluate the rate of change in pulmonary function over time, clinical trials with long observation times and large numbers of patients are needed. In the same publication, exercise capacity is suggested as more sensitive indicator of mucus clearance and it is hypothesised that mucus retention can be linked to dyspnoea when it has a measurable effect on pulmonary function. The assessment of symptoms of cough, sore throat, and dyspnoea are similarly difficult. The use of these attributes as clinical endpoints is difficult to measure and prone to large errors. Furthermore often a

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<sup>84</sup> Prause JU, Kriegbaum NJ, Manthorpe R, Oxholm P. Rose Bengal Score - A Possible Key Parameter when Evaluating Disease Level and Progression in Primary Sjogren's Syndrome. *J Autoimmun* 2 (4), 501 - 507 (1989)

<sup>85</sup> Rubin BK. Designing clinical trials to evaluate mucus clearance therapy. *Respir Care* 52 (10), 1348 - 1361 (2007)

large placebo effect is seen in studies investigating respiratory conditions, particularly in non-serious, self-limiting conditions.

The PRAC considered all these elements in its review of the available data on the efficacy of ambroxol- and bromhexine-containing products.

The secretolytic effect of ambroxol and bromhexine was studied as mono-component and in combination with other active substances, in a wide variety of studies, often not well documented, conducted as part of the development program and thereafter. In a number of studies these active substances were found superior to placebo or equivalent to comparators. Due to the high placebo effect in this therapeutic area, non-inferiority studies may not be considered appropriate to demonstrate an effect. In other studies, superiority to placebo was only seen in some endpoints or subgroups of the population studied. In addition, in some studies, no statistical difference was observed between placebo and bromhexine or ambroxol in the studied end points. Due to the known difficulties of conducting clinical trials in this area and the methodological issues identified in these studies, such conflicting results can be expected and the absence of statistical significance alone does not lead to the conclusion that the product is ineffective. Despite the methodological issues identified in those studies, the PRAC considered that taken altogether they constituted evidence of modest efficacy. In the paediatric population active-controlled and open studies together with a few placebo-controlled trials were submitted. Infants and children of all ages were included in those studies, although in most cases results stratified per age groups were not available, therefore they did not allow the discrimination of a paediatric population in which efficacy might be lower than that observed in adults. Similarly, for the fixed dose combinations, the studies available after the initial marketing authorisation do not provide new significant data on the efficacy of the products. The PRAC discussed the need to conduct a post-authorisation efficacy study in the paediatric population, in order to generate more robust data in the different subgroups of interest. However given the known methodological difficulties associated to this therapeutic area, it was considered unlikely that such initiative would be successful in providing more robust evidence.

Uncertainties are also attached to the results of the studies of ambroxol in IRDS, often due to their incomplete description. The conclusions of the authors however point to a preventive effect of ambroxol administered prenatally, which may depend on the gestational age at birth. This effect was found similar to that of corticosteroids in several studies. When administered postnatally, ambroxol also showed a protective effect on RDS, which however did not consistently translated in a significant reduction of mortality.

Inconsistent results were also reported in the studies evaluating the efficacy of ambroxol in preventing or treating postoperative bronchopulmonary complications, in some studies ambroxol effectively reduced the incidence of postoperative pulmonary complications, in others an effect was seen only in some types of pulmonary complications or an effect was seen in endpoints such a blood gases or ventilatory capacities but this did not translate in a reduction of pulmonary complications. The clinical context was often not correctly defined (e.g. information on co-medications, smoking cessation, respiratory exercise and physiotherapy) and therefore the assessment of the efficacy data is difficult. The authors concluded that ambroxol administered preoperatively at high doses showed moderate positive results in specific hospital settings in a few studies. While the high dose of ambroxol was found superior to a lower dose in several studies, lower intravenous doses of ambroxol also demonstrated limited efficacy. Having discussed the potential need to conduct a post-authorisation efficacy study in the prophylaxis and treatment of postoperative pulmonary complication indication, the PRAC considered it would likely not provide conclusive evidence to contribute to the overall knowledge of the product in this indication. It was noted that the MAH of the originator informed the PRAC that an

additional trial was already planned to be initiated in 2015 in this indication in patients above 60 years of age with COPD.

The indication pain relief in acute sore throat was developed more recently, which is reflected in the quality of the corresponding clinical trials. Those demonstrated the efficacy of ambroxol in short-term pain relief for patients suffering from sore throat due to acute viral pharyngitis. Ambroxol consistently achieved a modest but rapid reduction of pain intensity. The data however did not allow confirming the efficacy past the first three hours of treatment.

In sinusitis and Sjögren's syndrome, fewer studies, of poor quality, were available. The authors concluded that modest effects were observed in the different endpoints measured or recorded in the studies on sinusitis. In the treatment of Sjögren's syndrome, results were heterogeneous across studies; however the authors concluded that some beneficial effects were also observed, mostly on ophthalmological symptoms.

Overall, modest positive results were reported for ambroxol- and bromhexine-containing products. 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.

### **2.2.3. Consultation of the Paediatric Committee**

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 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.

### **2.3. Risk management plan**

The PRAC did not require the MAH to submit a risk management plan.

### **2.4. Overall 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.

In relation to the efficacy of ambroxol- and bromhexine-containing products, the PRAC concluded that although modest positive results were reported in secretolytic therapy, prophylaxis and treatment of respiratory distress syndrome and postoperative pulmonary complications, sinusitis and Sjögren's syndrome, the evidence of efficacy of ambroxol and bromhexine suffered from a number of limitations and deficiencies. In particular in sinusitis and Sjögren's syndrome, a limited number of studies, of simpler design were available. Overall for ambroxol and bromhexine as mono-component and in fixed dose combinations, in studies conducted in these indications, conflicting results were observed in the different endpoints measured, the level of details provided in the description of the studies was often insufficient and the design used, not to current standards. 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. Studies conducted after the initial development of the products suffered from limitations and did not provide new significant scientific data on the efficacy of the products.

With regards to the use of ambroxol in short term pain relief in acute sore throat, the PRAC concluded that more robust data supported the efficacy in this indication; however the effect past the first intake remains uncertain.

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 the benefit-risk balance of the products.

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.

## ***2.5. Changes to the product information***

The PRAC considered that routine risk minimisation measures in the form of updates to the product information would be necessary in order to address the potential risk of hypersensitivity and SCARs. These changes include amendments to sections 4.4 and 4.8 of the Summary of Product Characteristics and corresponding amendments of the package leaflet.

## **2.6. Communication plan**

The PRAC agreed on key messages that could be used for communication via preferred routes, to be decided nationally, e.g. bulletin, web-page or direct healthcare professional communication (DHPC). The information could be disseminated to healthcare professionals such as physicians and pharmacists (hospital and community), to inform them of the possible risk of SCARs linked to ambroxol- and bromhexine-containing products.

The following key elements for communication were agreed but the exact content and presentation is to be agreed with the national competent authority of the Member States where the product is marketed:

- Severe hypersensitivity reactions have been reported in patients receiving ambroxol. These include:
  - anaphylactic reactions
  - severe cutaneous adverse reactions (SCAR) including erythema multiforme, Stevens-Johnson syndrome/toxic epidermal necrolysis and acute generalised exanthematous pustulosis;
- Because ambroxol is a metabolite of bromhexine, the same risks are considered to apply to medicines containing bromhexine
- The product information will be updated with the current knowledge including a warning on the risk and a recommendation to patients to discontinue treatment immediately if symptoms of skin rash occur.

## **3. Conclusion and grounds for the revised 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 Committee, as a consequence, concluded that the benefit-risk balance of ambroxol- and bromhexine-containing medicinal products remains favourable subject to the agreed changes to the product information.



# Appendix 1

## **Article 31 of Directive 2001/83/EC**

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.

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 PRAC recommendation:

### **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:**

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.

**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.

**PRAC members expressing a divergent opinion:**

Jean-Michel Dogné (BE)	10 September 2015	Signature: .....
Marcel Bruch (LU)	10 September 2015	Signature: .....

## **Article 31 of Directive 2001/83/EC**

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.

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).

The proposed routine and additional risk minimisation measures with updating section 4.4 and 4.8 of the corresponding SmPCs of ambroxol and bromhexine with information on risks of immediate and delayed type hypersensitivities as well as further communication via preferred routes on national basis (e.g. DHPC, bulletin, web-page) are deemed sufficient at this moment.

Regarding the benefits of ambroxol and bromhexine, it is considered that the current scientific knowledge demonstrates that they are questionable and/or marginal in several indications.

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 PRAC recommendation:

### **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 non-proven efficacy 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 the age group of patients from 0-<2 years old. Subgroups can be justified on the basis of different pathophysiological conditions. The alveolar proliferation ends at the age of 3 years, however the microvascular proliferation lasts until the age of 4 years. Therefore, the benefit/risk for the 2-4 year old children is also considered as **negative**.

#### **- Treatment and Prophylaxis of IRDS in premature babies and neonates:**

Considering the non-proven efficacy 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:**

The **benefit-risk balance** of antenatally administered ambroxol in order to reduce emergence of IRDS is considered as **negative**, as there is no obvious evidence of efficacy.

#### **- Prophylaxis of postoperative pulmonary complications (PPC) in the adult population:**

Considering the non-proven efficacy 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 non-proven efficacy 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 non-proven efficacy 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 non-proven efficacy 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**

- Secretolytic therapy:

Considering the non-proven efficacy of bromhexine in this indication and the important safety risks associated with the use of bromhexine, the **benefit-risk balance** of all formulations of bromhexine with a secretolytic indication is **negative** in the age group of patients 0-4 years old.

- Sinusitis and Sjögren's syndrome:

Considering the non-proven efficacy of bromhexine in the 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 these indications is **negative** in all age groups of patients for which it is indicated.

**PRAC members expressing a divergent opinion:**

Martin Huber (DE)	10 September 2015	Signature: .....
Brigitte Keller-Stanislawski	10 September 2015	Signature: .....
Júlia Pallós (HU)	10 September 2015	Signature: .....

**Article 31 of Directive 2001/83/EC**

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

**Ambroxol- and bromhexine-containing medicinal products**

**Divergent statement**

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 in some indications and in some age groups, especially in light of poorly documented efficacy.

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 in 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.

**PRAC member expressing a divergent opinion:**

Kirsti Villikka (FI)	10 September 2015	Signature: .....
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## **Article 31 of Directive 2001/83/EC**

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 Artgodan).

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 PRAC recommendation:

### **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.

**PRAC member expressing a divergent opinion:**

Isabelle Robine (FR)	10 September 2015	Signature: .....
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## **Article 31 of Directive 2001/83/EC**

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.

**PRAC member expressing a divergent opinion:**

Marina Dimov Di Giusti (HR)	10 September 2015	Signature: .....
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## **Article 31 of Directive 2001/83/EC**

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 in 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 Artogodan).

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 PRAC recommendation:

#### **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 pediatric 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 pediatric 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.
- Sjogren's syndrome (Keratokonjunctivitis 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.*

**PRAC member expressing a divergent opinion:**

Carmela Macchiarulo (IT)	10 September 2015	Signature: .....
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**Article 31 of Directive 2001/83/EC**

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

**Ambroxol- and bromhexine-containing medicinal products**

**Divergent statement**

We support the PRAC updated AR and updated recommendations, but only for the following indications

- Bromhexine: Secretolytic indication for adults and children >2 years
- Ambroxol: Pain relief of mild to moderate symptoms of acute sore throat

The benefit/risk balance for these indications remains favourable provided that the SmPC will be updated according to the conditions set out in Annex III of the recommendation.

The benefit/risk balance is considered negative for all other indications and all bromhexine-combination as well as ambroxol-combination products.

**PRAC members expressing a divergent opinion:**

Sabine Straus (NL)	10 September 2015	Signature: .....
Marie Louise De Bruin	10 September 2015	Signature: .....

## **Article 31 of Directive 2001/83/EC**

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 in 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 Artogodan).

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 PRAC recommendation:

#### **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. For children between 2-6 yo, ambroxol should be used only under medical advice. The benefit-risk balance of all formulations of ambroxol hydrochloride is positive for 6-<-12 yo and 12-adult.
- Pain relief in acute sore throat: The benefit-risk balance of all formulations of ambroxol hydrochloride indicated in Pain relief in acute sore throat is positive 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: 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: The benefit-risk balance of ambroxol hydrochloride in this indication is not clear in all age groups of patients (0-<6 yo, 6-<-12 yo, 12-adult). 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. For children between 2-6 yo, bromhexine should only be used with medical advice. The benefit-risk balance of all formulations of bromhexine hydrochloride with a secretolytic indication is positive for 6-<-12 yo and 12-adult.
- Sjogren's syndrome (Keratokonjunctivitis 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 (SmPc Belgium and Luxembourg): Bromhexine as oral treatment or via nebulization is authorized in e.g. Belgium and Luxembourg for the treatment of acute and 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.



**PRAC members expressing a divergent opinion:**

Margarida Guimarães (PT)	10 September 2015	Signature: .....
Jana Mladá (CZ)	10 September 2015	Signature: .....