10 April 2014
EMA/PRAC/189078/2014

PRAC List of questions

To be addressed by the marketing authorisation holder(s) for ambroxol and bromhexine containing medicinal products

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

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

INN: ambroxol and bromhexine

7 Westferry Circus ● Canary Wharf ● London E14 4HB ● United Kingdom
Telephone +44 (0)20 7418 8400 **Facsimile** +44 (0)20 7418 8416
E-mail info@ema.europa.eu **Website** www.ema.europa.eu

The marketing authorisation holders (MAHs) for ambroxol-containing medicinal products and/or bromhexine-containing medicinal products are requested to provide the following:

Question 1

How is/are ambroxol and/or bromhexine used?

Please provide:

a) Information on the currently authorised ambroxol and/or bromhexine-containing products in the different Member States and their current marketing and legal (i.e. prescription vs. non-prescription) status, including information about the indication(s), doses, contraindications, warnings and precautions, and undesirable effects included in the Summary of Product Characteristics (SmPC) and the package leaflet (PL). Please tabulate the main differences between the SmPCs/PL in the different EU Member States (see tabulation attached).

   The information about treatment duration and the maximum daily dose present in the SmPC should be specified.

b) Information on sales figures and estimated patient exposure for ambroxol and/or bromhexine.

   When possible, the information on exposure should be stratified:

   - by age: populations of 0-6 years old, 6-12 years old and 12 years of age and older.
   - by Member State: exposure data should also include a yearly breakdown of sales and exposure over the last 10 years for each Member State.
   - by indication: the exposure to the formulations that have a specific indication (e.g. pain relief from sore throat) should be clearly identified.

c) Data on the way ambroxol and/or bromhexine is/are actually used in clinical practice including information on daily dose and duration of treatment for each indication.

Question 2

Please provide evidence of the therapeutic benefit(s) of ambroxol and/or bromhexine-containing products in all currently authorised indications. When applicable, this information should be stratified by age (populations of 0-6 years old, 6-12 years old and 12 years of age and older).

Question 3

Regarding the following risks:

- Immediate hypersensitivity (including anaphylactic reactions)
- Delayed-type hypersensitivities associated with severe cutaneous adverse events (SCARs)

Please provide all available information regarding these risks since the launch of medicinal products containing ambroxol and/or bromhexine. This should include non-clinical, clinical data as well as epidemiological studies and cases reported in the literature. A cumulative review of all cases reports (serious and non-serious) should also be provided. For this purpose, all the MedDRA Preferred Terms (PTs) within the SMQ Hypersensitivity (broad), reported for the selected suspected or interacting ambroxol and/or bromhexine -containing products should be provided. Causality assessment should be performed for serious cases. Of note, the PTs potentially linked to delayed-type hypersensitivities associated with severe cutaneous adverse events (Acute generalized exanthematous pustulosis (AGEP), Stevens Johnson Syndrome (SJS), Toxic Epidermal Necrolysis (TEN), Erythema Multiforme

(EM), dermatitis exfoliative, dermatitis bullous, rash macula-papular, etc) should be discussed separately.

Question 4

Please provide a benefit/risk balance evaluation of ambroxol and/or bromhexine-containing medicinal products, in each of their licensed indications. Based on the responses to the above questions, this should consider how the benefit risk balance may differ according to age, separating the populations of 0-6 years old, 6-12 years old and 12 years of age and older.

Question 5

Please provide proposals and justifications with supportive evidence for any risk minimisation measures (including changes to the SmPC/PL) which may improve the benefit/risk balance of ambroxol and/or bromhexine-containing products and how their effectiveness should be monitored.

TABULATION

Question 1

a)

INN	Product name	Marketing status	Legal Status	Indications	Strength	Pharmaceutical form

Maximum daily dose (SmPC)	Treatment duration (SmPC)	Contra-indications (SmPC)	Warnings and precautions (SmPC)	Undesirable effects (SmPC)	Contra-indications (PL)	Warnings and precautions (PL)	Undesirable effects (PL)	Main differences between the SmPC/PIL in the different EU Member States

b)

INNs	Product name	Country	Sales figures	Indication	Sales figures	Estimated patient exposure (in number of treatment per year)	Estimated target population (0-6 years old, 6-12 years old, 12 years of age and older)