29 November 2012
EMA/PRAC/74483/2012

PRAC List of questions

To be addressed by the marketing authorisation holder(s) for Short Acting Beta Agonists (SABAs) containing medicinal products authorised in obstetric indication(s)

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

Procedure number: EMEA/H/A-31/1347

INN/active substance: terbutaline, salbutamol, hexoprenaline, ritodrine, fenoterol, isoxsuprine

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The marketing authorisation holders MAH(s) for short acting beta agonists (SABAs) (terbutaline, salbutamol, hexoprenaline, ritodrine, fenoterol, isoxsuprine) containing medicinal products authorised in obstetric indication(s) are requested to provide the following:

Question 1

Concerning the SABA containing medicinal product(s) available on the EU market, the MAH is requested to provide the following information:

a. obstetric indications, posology and method of administration, contraindications, warnings and precautions, drug interactions, pregnancy and lactation, undesirable effects included in the Summary of Product Characteristics (SmPC). Please tabulate the main differences between the SmPCs in the different countries in the EU.

b. worldwide marketing status by product and by year since authorisation in the obstetric indication(s).

Question 2

The MAH should provide information on estimated patient exposure for the use of SABA for the authorised obstetric indications by product and by year in different EU member states since authorisation, using available sources of hospital and prescription data, where possible.

Question 3

The MAH should provide evidence of the therapeutic benefit of the product(s) for all authorised obstetric indications considering all available published and unpublished data from clinical trials and other sources. Separate analysis should be performed for all available formulations, particularly parenteral and oral formulations.

The analysis should also consider how therapeutic benefit (including pregnancy outcome) is influenced by:

a. duration of treatment;
b. period of gestation;
c. route of administration (if applicable)

Where data comparing the efficacy of SABAs for the obstetric indications is available this should be included.

Question 4

The MAH should provide an analysis of all available safety data relevant for the obstetric indication of the product(s) for women and for newborns/fetuses. Separate analysis should be performed for all available formulations, particularly parenteral and oral formulations. The analysis should cover data from spontaneous reports, clinical trials and all other published and unpublished sources and provide an overview and critical summary of the reported risks, including causality.

In addition, the analysis should pay particular attention to:

a. cardiovascular adverse events;
b. SABA-associated QT-prolongation and its underlying mechanism (e.g. possibly due to SABA-induced hypokalaemia)
c. risks associated with use of concomitant tocolytic agents
d. comparative risks between SABA products

The analysis should also consider how the safety profile is influenced by

i. duration of treatment;
ii. period of gestation;
iii. route of administration (if applicable).

Question 5

In light of the responses to Question 3 and 4, the MAH is requested to discuss the benefit/risk of their product(s) in its authorised obstetric indications. For parenteral formulations this evaluation should consider the effect of method of administration (infusion versus bolus) and route of administration (intravenous, intramuscular etc.)

a. The MAH should provide a critical appraisal of the efficacy and safety of their product(s) in an emergency obstetric indication such as uterine hyperactivity. This review should examine all potential obstetric emergency indications authorised for the product, or identified off-label emergency obstetric uses.

b. The MAH should specifically provide critical appraisal of the efficacy and safety of the product(s) for use in external cephalic version (ECV).

Question 6

In addition, where appropriate, the MAH should provide proposals and justification with supportive evidence for any measures to further minimise the risks of SABAs containing medicinal products authorised in obstetric indication(s) including changes to the SmPC and package leaflet.