10 April 2014
EMA/PRAC/180085/2014

PRAC List of questions

To be addressed by the marketing authorisation holder(s) for codeine containing medicinal products for the treatment of cough and/or cold in paediatric patients

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

Procedure number: EMEA/H/A-31/1394

INN/active substance(s): codeine

7 Westferry Circus ● Canary Wharf ● London E14 4HB ● United Kingdom
Telephone +44 (0)20 7418 8400 **Facsimile** +44 (0)20 7418 8668
E-mail info@ema.europa.eu **Website** www.ema.europa.eu
An agency of the European Union

Question 1

Regarding the use of codeine-containing products for treatment of cough and/or cold in the paediatric population please provide

a) Information about the formulation, on approved indication(s), doses, age restrictions, treatment duration and contraindications included in the Summary of Product Characteristics (SmPC) and Package Leaflet (PL).

Please include the information in a table with the following structure:

Product name	Formulation	Indication	Age restrictions	Doses	Treatment duration	Contraindication

b) Information on sales figures and estimated patient exposure, stratified by age <12 and 12-18 if possible and by country.

c) Information on marketing and legal status in different EU Member States.

Question 2

What is the evidence of efficacy of codeine when used for cough and/or cold in the paediatric population?

Please provide a critical appraisal of the clinical efficacy of codeine in all authorised cough and/or cold indications, specifically with regard to:

- the impact of pharmacokinetics and pharmacogenomics, with a particular focus on CYP2D6 metabolism,
- the effect of age.

Question 3

What is the evidence for the risks of opiate toxicity associated with the use of codeine when used for cough and/or cold in the paediatric population?

Please provide a detailed examination of available data (including pre-clinical studies, clinical trials, epidemiological studies, published literature and post-marketing spontaneous reports). In relation to the risk of opiate toxicity, please provide a critical appraisal of the effect of:

- pharmacokinetics and pharmacogenomics, with a particular focus on CYP2D6 metabolism;
- dose and formulation;
- age,

including any off-label use and overdose.

Question 4

Please provide an evaluation of the balance of benefits and risks of use of codeine in cough, addressing the different underlying conditions, and an evaluation of the balance of benefits and risks of use of codeine in cold in the paediatric population.

Based on the responses to the above questions, this should consider how the benefit- risk balance differs according to:

- phenotype and genotype for CYP2D6 metabolism
- age
- dose and formulation

Question No. 5

Are there further studies and risk minimisation measures necessary and if yes, which measures? Are changes of the SmPC/PL required? Please provide a proposal for a harmonised SmPC and Package Leaflet. This proposal should take into consideration that as a consequence of the recent referral procedure codeine for the treatment of pain is not recommended for use in the paediatric population, for which breathing might be compromised, including children with upper respiratory or lung infections.