EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

31 October 2012
EMA/PRAC/718095/2012

PRAC List of questions

To be addressed by the marketing authorisation holder(s) for codeine containing medicinal products used for pain in children

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

Procedure number: EMEA/H/A-31/1342

INN/active substance: codeine

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The marketing authorisation holders MAH(s) for codeine containing medicinal products used for pain in children are requested to provide the following:

Question No. 1

Regarding the use of codeine-containing products in children please provide:

a) Information about the formulation, approved indication(s), doses, age restrictions, treatment duration, contraindications, warnings and precautions, serious undesirable effects included in the Summary of Product Characteristics (SPC) and Patient Information Leaflets (PLs) for codeine-containing products.

b) Information on the present authorisations and marketing status in the different Member States for codeine-containing products indicated for in children and information on sales figures and estimated patient exposure, stratified by age <18 and ≥18 if possible, for each approved indication.

Question No. 2

Please provide a critical appraisal of the clinical efficacy of codeine in all authorised analgesic indications, specifically with regard to:

a) the impact of pharmacokinetics and pharmacogenomics, with a particular focus on CYP2D6 ultra-rapid metabolisers;
b) the effect of age.

Question No. 3

Please provide a detailed evaluation of available data from all sources including:

- Pre-clinical studies;
- Clinical trials (include both MAH sponsored and non- sponsored studies);
- Post-marketing spontaneous reports (please specify case definitions employed);
- Pharmacoepidemiological studies;
- Published literature.

In relation to the risk of opiate toxicity, please provide a critical appraisal of the effect of:

a) pharmacokinetics and pharmacogenomics, with a particular focus on CYP2D6 ultra-rapid metabolisers;
b) codeine dose and formulation;
c) age (under 2 years, 2 - <6 years, 6-<12 years and 12-<18 years);
d) clinical setting and in particular i) use in post-operative pain, including tonsillectomy, adenoidectomy, ii) any other surgery where respiratory function may be compromised, including any use off-label and iii) post-operative care setting ie in-patients *versus* day cases

Question No. 4

Please provide a risk:benefit evaluation of codeine in all authorised analgesic indication(s) in children. Based on the responses to the above questions, this should consider how the risk-benefit balance differs according to:

a) phenotype for CYP2D6 metabolism;
b) age;
c) dose and formulation;
d) clinical setting.

This should include proposals and justification with supportive evidence for any measures including changes to the SPC/PL which may improve the benefit/risk of codeine and how their impact should be monitored. Please provide a full proposal for a harmonised SPC, Labelling and PL for codeine-containing products indicated for use in pain in children.

Question No.5

Please provide a Risk Management Plan (RMP) for codeine in the management of pain that is in line with current EU guidelines, include appropriate risk minimisation measures and proactive Pharmacovigilance measures, reflecting your answers to the questions above. The RMP should include:

- Proposals for studies to further investigate the effectiveness of the proposed risk minimization measures

If the responses to previous questions indicate an unacceptable risk in unauthorised indications, proposals to minimise this risk should also be provided.