NOTIFICATION OF A REFERRAL UNDER ARTICLE 31 OF DIRECTIVE 2001/83/EC
FAX NUMBER –44 20 75237051

This notification is an official referral under Article 31 of Directive 2001/83/EU made by the United Kingdom

Product Name(s), if appropriate,	Codeine containing medicinal products
Active Substance	Tablets, suppositories and syrup
Marketing Authorisation Holder(s)	Various

Codeine is a very commonly used analgesic across Europe with a well recognised safety profile. It is also has a number of other indications across Europe.

Codeine is metabolised by O- and N-demethylation in the liver to morphine, norcodeine, and other metabolites including normorphine and hydrocodone. Its metabolism to morphine is mediated by the cytochrome P450 isoenzyme CYP2D6, which shows genetic polymorphism. The clinical implications of this genetic polymorphism are undisputed as it leads to uncertainty regarding codeine's efficacy (in poor metabolisers) and an increased risk of morphine toxicity (in ultra-rapid metabolisers).

Recent concerns have arisen about an increased risk of morphine toxicity, manifesting as fatal or life-threatening respiratory depression, when codeine is used in children after tonsillectomy and/or adenoidectomy for obstructive sleep apnoea (Ciszkowski C. et al N Engl J Med 2009 and Kelly LE et al Pediatrics 2012). These children were subsequently found to be CYP2D6 ultra-rapid or extensive metabolisers, which will have increased the risk of adverse effects following the use of therapeutic doses. It is also recognized that obstructive sleep apnoea is often related to adenotonsillar hypertrophy and children suffering from sleep apnoea are at increased risk of developing acute airway maintenance difficulties after tonsillectomy. Furthermore, paediatric tonsillectomy and/or adenoidectomy are often routinely day case surgical procedures and therefore the subsequent post-operative care is in the home environment.

Overall these cases raise concerns that phenotype, clinical setting (use post-operatively in those with compromised airways) and post-operative care setting (day case surgery versus in patients) may also influence the risk of morphine toxicity, particularly opioid induced respiratory depression in children. Further review to ensure that appropriate risk minimization measures are in place to help optimize safe use of codeine when used for pain in children is therefore warranted.

The urgency for further review needs to take account of the small number of cases, the very wide usage of codeine within Europe and existing clinical guidance, which suggests that codeine is not the first choice for pain relief post-operatively in children and only used if simpler analgesics had been shown to be ineffective.

In light of the above the UK therefore considers that it is in the interest of the Community to refer codeine to the Pharmacovigilance Risk Assessment Committee and requests that it gives its recommendation under Article 31 of Directive 2001/83 EEC, as amended, on whether the balance of benefits and risks is positive in the management of pain in children and whether the Marketing Authorisations for medicinal products containing codeine-containing medicines should be maintained, varied, suspended or withdrawn.

Signed [redacted] Date 22th October 2012

ANNEX A

List of Questions

Question No. 1

What is the authorised use of codeine in the paediatric population in the European Union?

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

A), Information about the formulation, indication(s), doses, age restrictions, treatment duration, contraindications, warnings and precautions, serious undesirable effects included in the Summary of Product Characteristics (SmPC) and Patient Information Leaflets (PILs).

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

Question No. 2

What is the evidence of efficacy for the use of codeine for analgesia in the paediatric population?

Please provide a critical appraisal of the clinical efficacy of codeine in all authorized 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

What is the evidence for the risks of opiate toxicity associated with the use of codeine in analgesia in the paediatric population?

Please provide a detailed examination 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

What is your analysis of the balance of risks and benefits of the use of codeine in analgesia in children?

Please provide a risk:benefit evaluation of codeine in all authorized analgesic indications 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

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This should include proposals and justification with supportive evidence for any measures including changes to the SPC/PIL 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 Package Leaflet for codeine.

Question No.5

What further studies and risk minimization measures are required?

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 unauthorized indications, proposals to minimize this risk should also be provided.