NOTIFICATION OF A REFERRAL UNDER ARTICLE 31 OF DIRECTIVE 2001/83/EC

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This notification is an official referral under Article 31 of Directive 2001 /83/EC to the PRAC made by Germany - Federal Institute for Drugs and Medicinal Devices/BfArM.

Product Name(s), if appropriate,	Codeine- containing medicinal products for the treatment of cough in paediatric patients
Active Substance	Codeine- containing medicinal products
Marketing Authorisation Holder(s)	Various

The Pharmacovigilance Risk Assessment Committee (PRAC) has recently reviewed the benefit-risk of products containing codeine for the relief of pain in children within procedure EMEA/H/A-31/1342. The reason for this review were concerns resulting from evaluation of data relating to pharmacovigilance of these products, namely concerns about an increased risk of morphine toxicity, manifesting as fatal or life-threatening respiratory depression, when codeine is used in children after adenoidectomy/tonsillectomy for obstructive sleep apnoea. In June 2013 PRAC gave its final recommendation on the above mentioned procedure. It was concluded that a number of risk minimisation measures are necessary to ensure that only children for whom benefits are greater than the risks are given codeine containing medicinal products for pain relief, in particular:

- Codeine is indicated in children older than 12 years of age for the treatment of acute moderate pain which is not considered to be relieved by other analgesics such as paracetamol or ibuprofen alone.

- Codeine is contraindicated in patients known to be CYP2D6 ultra-rapid metabolisers.

- Codeine is not recommended for use in children in whom respiratory function might be compromised including neuromuscular disorders, severe cardiac or

respiratory conditions, upper respiratory or lung infections, multiple trauma or extensive surgical procedures. These factors may worsen symptoms of morphine toxicity.

Codeine is also widely used for the treatment of cough in children and adolescents below the age of 18 years. The posology is similar in both the pain and cough indication and a patient's CYP2D6 status is independent of the indication. Furthermore, according to the above mentioned PRAC recommendation codeine is not recommended for use in children in whom respiratory function might be compromised, which might be conflicting with the cough indication.

In light of the above, Germany considers that it is in the interest of the Union to refer codeine again to the Pharmacovigilance Risk Assessment Committee and requests that it gives its recommendation under Article 31 of Directive 2001/83/EC, on whether the balance of benefits and risks is positive in the treatment of cough in children and adolescents below the age of 18 years and whether the Marketing Authorisations for medicinal products containing codeine should be maintained, varied, suspended or withdrawn.

[redacted]

Prof. Dr. Walter Schwerdtfeger
President

ANNEX A

List of Questions

Question No. 1

Regarding the use of codeine-containing products for treatment of cough in children please provide

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

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

Question No. 2

What is the evidence of efficacy of codeine when used for cough in the paediatric population?

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

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

Question No. 3

What is the evidence for the risks of opiate toxicity associated with the use of codeine when used for cough 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 No. 4

What is your analysis of the balance of risks and benefits of the use of codeine when used for cough in children? Please provide a risk-benefit evaluation of codeine in all authorised cough indications in children.

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

- phenotype for CYP206 metabolism
- age
- dose and formulation

Question No. 5

Are there further studies and risk minimization measures necessary and if yes, which measures? Are changes of the SPC/PL required? Please provide a proposal for a harmonised SPC 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 children, whose breathing might be compromised, including children with upper respiratory or lung infections.