Annex II

Scientific conclusions

and detailed explanation of the scientific grounds for the differences from the PRAC recommendation

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Codeine, also known as methylmorphine, binds to μ-opioid receptors to produce analgesia and euphoria, as well as respiratory depression, miosis, and reduced gastric motility. Apart from its use as an analgesic for relief of pain, it is also used for the symptomatic treatment of cough and/or cold.

Codeine was subject of an Article 31 referral to the PRAC in 2013[1], when used for pain relief in the paediatric population (hereafter refer as "children") due to concerns regarding opioid toxicity and the lack of consistent risk minimisation measures raised following cases described in the literature of fatal or life-threatening respiratory depression, when codeine was given to children after adenoidectomy/tonsillectomy for obstructive sleep apnoea.

Further to consideration of all data available at that time, the PRAC concluded that codeine remained an effective analgesic for the treatment of acute moderate pain in children above 12 years of age which is not considered to be relieved by other analgesics. The PRAC further concluded that codeine should be contraindicated in paediatric patients below 18 years of age undergoing tonsillectomy and/or adenoidectomy for obstructive sleep apnoea syndrome as well as in women during breast-feeding and in patients known to be CYP2D6 ultra-rapid metabolisers. The PRAC also considered that the use of codeine in pain relief could be associated with serious adverse events of opioid toxicity due to the variable and unpredictable metabolism of codeine to morphine, in particular in the paediatric population below 12 years of age and therefore codeine should not be used in this population. Similarly, it was not recommended to use codeine in children whose breathing could be compromised including children with neuromuscular disorders, severe cardiac or respiratory conditions, upper respiratory or lung infections, multiple trauma or extensive surgical procedures. The symptoms of morphine toxicity may be increased in these settings.

The present referral under Article 31 of Directive 2001/83/EC concerns the use of codeine in paediatric patients for the cough and/or cold indications as triggered on 02 April 2014 by the German National Competent Authority (BfArM) due to the applicability of the above risk measures also to these indications.

The PRAC initiated a review of the benefit-risk balance of codeine in the treatment of cough and/or cold in paediatric patients. All codeine containing medicinal products approved for the treatment of cough and/or cold in paediatric population, including single and combination products authorised in the European Union are included in this review.

The PRAC reviewed all available data from different sources: clinical trials, observational studies, meta-analyses, post-marketing data and further published literature data on the use of codeine containing products in children for treatment of cough and/or cold. The PRAC also considered data from the European Pharmacovigilance database (Eudravigilance), a drug utilisation study of the patterns of prescription of codeine and performed a consultation with European healthcare professional organisations and with the Paediatric Committee (PDCO).

Cough is a reflex response to mechanical, chemical, or inflammatory irritation of the tracheobronchial tree. Cough serves as a physiologic function to clear airways of obstructive or irritating material or to warn of noxious substances in inspired air.

Codeine suppresses the cough reflex through a direct effect on the cough centre in the medulla. However, there is little clinical data in the medical literature to support the efficacy of codeine in the

[1] Article 31 pharmacovigilance referral for codeine used for management of pain in paediatric patients (EMA/H/A-31/1342) http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/referrals/Codeine-containing_medicines/human_referral_prac_000008.jsp&mid=WC0b01ac05805c516f

symptomatic treatment of cough and/or cold as current evidence does not find codeine to be more effective than placebo for acute cough in children.

Overall, only four published studies investigating the use of codeine-containing medicines for the treatment of cough in children could be identified. Two studies (Kelly et al, 1963 and Jaffe et al, 1983), which did not include a placebo control group, suggested that efficacy was no greater for codeine than the other antitussives but that the incidence of side effects in the codeine group was higher than in the comparator group. A randomised clinical trial (Jaffe G et al, 1983) and an epidemiological study (De Blasio F et al, 2012) did not show a significant effect of the treatment with codeine in cough and/or cold in children. In addition, another randomised clinical trial (Taylor et al, 1993) in children with codeine, dextromethorphan as an active comparator, and a placebo group showed that neither codeine nor dextromethorphan were significantly better then placebo for the symptomatic treatment of cough in children under 12 years of age. In 2012, the Taylor et al study was included in a Cochrane review of non-prescription/over-the-counter (OTC) medications for acute cough in children and adults in ambulatory settings; this review additionally identified two randomised controlled trials where codeine was tested in adults (Eccles et al, 1992; Freestone C, 1997): codeine was found to be no more effective than placebo.

Efficacy data is therefore limited, with no recent and well-established controlled scientific studies to clearly support the benefit of codeine in the approved indications for cough and/or cold for the paediatric population.

Codeine is converted into morphine in the body by cytochrome P450 2D6 (CYP2D6), an enzyme which shows genetic polymorphism. Individuals are normally classified as poor (PM), extensive (EM) or ultra-rapid metabolisers (UM), depending on the activity of the enzyme. Whereas EMs or UMs are at risk of morphine toxicity, PMs may be at an increased risk of a lack of therapeutic effect. The unpredictable and variable metabolism of codeine in children, governed by CYP2D6 polymorphism, may cause some children to exhibit morphine-related serious adverse events such as breathing difficulties or respiratory depression even within the recommended doses. Therefore, this continues to represent a variable safety risk across all paediatric age groups. A review of serious and fatal cases in paediatric patients from the literature, global pharmacovigilance databases and regulatory authorities suggests that the respiratory depressant effects of codeine may influence the occurrence of respiratory complications. The risk of opioid toxicity is especially pronounced among UMs due to its serious consequences of respiratory depression.

In total, fourteen reports of codeine intoxication in children related to the treatment of cough and respiratory infection were identified in the published literature. A review of these cases indicated that, four cases had a fatal outcome. The remaining cases were all life-threatening but resulted in full recovery. The children's age ranged from 17 days to 6 years. Data analyses from the Eudravigilance database identified a total of 50 case reports that could be related to opiate toxicity, of which 31 cases were in those younger than 6 years (including 4 fatal cases), 7 cases in older than 6 years and younger than 12 years (including 1 fatal case) and the remaining 12 cases were on those older than 12 and younger than 18 years (including 1 fatal case). Overall, the majority (38/50) of the cases were in patients younger than 12 years of age and 6 were fatal cases.

While acknowledging that uncertainties remain regarding the identification of particular paediatric populations at higher risk and the impact of age on codeine metabolism, the PRAC was of the opinion that neonates, toddlers and young children may be more vulnerable to opioid toxicity and therefore at special risk of life-threatening respiratory depression. The PRAC took into account that the enzymatic systems responsible for the metabolism of codeine in children older than 12 years of age can be considered comparable to that of adults.

The PRAC also noted that cough associated with upper respiratory tract infections is the dominating cause of cough in children. The large majority of childhood respiratory infections with cough are caused by viral infections, which are self-limiting and only last for a few days whereas in the case of chronic cough, treatment should be directed at the underlying disease[2,3] (American Academy of Paediatrics Committee on Drugs 1997, American Academy of Paediatrics, AAP publications retired or reaffirmed 2006). In such clinical settings it is not expected that codeine use brings any significant benefit, while the risks identified can be of serious consequences. Based on all the above, the PRAC recommended restrictions of the use of codeine for cough and/or cold in the paediatric population. The PRAC considered that children below 12 years are at special risk of life-threatening respiratory depression and therefore, contraindicated the use of codeine in children below 12 years. The PRAC further considered that in children aged 12 years to 18 years for whom respiratory function might be compromised including those with neuromuscular disorders, severe cardiac or respiratory conditions, upper respiratory or lung infections, multiple trauma or extensive surgical procedures, codeine is not recommended as these conditions may worsen symptoms of morphine toxicity.

In addition, the PRAC also recommended that the relevant risk minimisation measures from the previous referral should also apply to the use of codeine in the symptomatic treatment of cough and/or cold. This included contraindication in patients of any age known to be CYP2D6 ultra-rapid metabolisers and in women of all ages who are breastfeeding. In this regard the PRAC noted that all codeine containing products approved for adults regardless of the indication, should have these contraindications included in their labelling. Therefore, the PRAC suggests that National Competent Authorities of the EU Members States to take the necessary actions to have the labelling of codeine products approved only for adults updated with the contraindications.

The PRAC also considered that the risk of accidental overdose (four cases identified) could be minimised by the use of child resistant containers (CRC). Therefore, the PRAC recommends child resistant containers (CRC) for all oral liquid codeine containing medicinal products.

Having noted all of the above, the PRAC concluded that the benefit-risk balance of codeine-containing products indicated in cough and/or cold in children remains favourable, subject to the agreed restrictions, contraindications, warnings and other changes to the product information as set out in Annex III to the opinion.

Overall conclusion and grounds for the variation to the terms of the marketing authorisations

Whereas

- The PRAC considered the procedure under Article 31 of Directive 2001/83/EC resulting from pharmacovigilance data for codeine containing medicinal products for the treatment of cough and/or cold in children.
- The PRAC considered available data on the safety and the efficacy of the codeine containing medicinal products for the treatment of cough and/or cold in children in relation to the risk of opioid toxicity. This included MAH responses, published literature data which became available since the initial granting of the marketing authorisations and consultation of healthcare professionals and other experts.

[2] American Academy of Pediatrics Committee on Drugs 'Use of codeine- and dextromethorphan-containing cough remedies in children', Pediatrics 1997;99:918-20.
[3] American Academy of Pediatrics. AAP Publications Retired or Reaffirmed, October 2006. Pediatrics 2007;119(2):405.

- The PRAC considered that there is limited evidence that support the efficacy of codeine in cough and cold and that these are generally self-limiting conditions. Treatment guidelines recommend treatment of persistent chronic cough in paediatric patients based on aetiology.
- The PRAC having reviewed the available evidence and in particular the risk of serious adverse reactions of opioid toxicity in children, the nature of the condition and the views of clinical experts considered that the use of codeine containing medicinal products for the treatment of cough and/or cold in the paediatric population is not recommended.
- In addition, the PRAC considered that the current evidence suggests that children below 12 years are at special risk of life-threatening respiratory depression and therefore, concluded that the use of codeine containing medicinal products for the treatment of cough and/or cold is contraindicated in children below 12 years. The PRAC further considered that in children aged 12 years to 18 years with compromised respiratory function the use of codeine is not recommended.
- The PRAC, in line with the restrictions introduced during the codeine referral for pain relief in children, also concluded that all codeine containing medicinal products for the treatment of cough and/or cold should be contraindicated in women when breastfeeding, as well as in patients known to be CYP2D6 ultra-rapid metabolisers.

The PRAC, as a consequence, concluded that the benefit-risk balance of the medicinal products containing codeine for cough and/or cold in children remains favourable, subject to the inclusion of the restrictions, warnings and other agreed changes to the product information.

Therefore, the PRAC recommended the variation to the terms of the marketing authorisation for medicinal products containing codeine for cough and/or cold in children referred to in Annex I, for which the relevant sections of the summary of product characteristics and package leaflet are set out in Annex III of the PRAC recommendation.

2 – Detailed explanation of the scientific grounds for differences from the PRAC recommendation

Having reviewed the PRAC recommendation, the CMDh agreed with the overall scientific conclusions and grounds for recommendation.

However, the CMDh considered that in view of the recommended contra indication of the use of codeine for cough and/or cold in children below 12 years of age, some marketing authorisations may have to be revoked. Therefore, in addition to the PRAC recommendation to vary the marketing authorisations, the CMDh also agreed that if a marketing authorisation cannot be varied in line with the terms of the CMDh agreement, member states may consider the revocation of that marketing authorisation.

In addition, the CMDh considered that a minor change was necessary to the wording proposed in Sections 4.2 and 4.6 of the Summary of Product Characteristics (SmPC) and Section 2 of the Package Leaflet (PL), in order to facilitate the practical implementation at the National level, taking into account the range of combination products included in the procedure. Therefore, whenever reference to codeine is made in these SmPC sections and the product is a combination of codeine and other active substances, the wording is amended to include the invented name of these products instead of the INN “codeine”.

Moreover, the CMDh noted as advised by the PRAC that the contraindication in women of all ages who are breastfeeding should also apply to all codeine containing products approved for adults and regardless of the indication. Therefore, consideration should be given at National level for this contraindication to be included in the labelling of codeine products approved only for adults via variation application submitted by the respective marketing authorisation holders.

The CMDh also considered that the risk of accidental overdose (four cases identified) could be minimised by the use of child resistant containers (CRC) for all oral liquid codeine containing medicinal products. Therefore, the marketing authorisation holders of codeine containing medicinal products in oral formulations should discuss with the National Competent Authorities in the Member States the applicability of this minimisation measure in their territory.

CMDh agreement

The CMDh, having considered the PRAC recommendation, agrees with the overall scientific conclusions by the PRAC and agreed that the marketing authorisation(s) for should be revoked or varied, as applicable.

The timetable for the implementation of the agreement is set out in Annex IV.