Annex II

Scientific conclusions and grounds for revocation or variation to the terms of the marketing authorisations and detailed explanation for the differences from the PRAC recommendation

Scientific conclusions

The CMDh considered the below PRAC recommendation dated 13 June 2013 with regards to codeine-containing medicinal products indicated in the management of pain in children.

1. PRAC recommendation

Codeine-containing products are authorised nationally in Europe and are indicated for the management of pain in adults and children. They are commonly used in combination with other analgesics such as non-steroidal anti-inflammatory drugs and non-opioid analgesics. The analgesic properties of codeine stem from its conversion to morphine by the cytochrome P450 enzyme CYP2D6 and the toxicity of codeine is mainly due to its opioid effects. It has been established that CYP2D6 is subject to extensive polymorphism, and 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 efficacy.

A number of cases of opioid toxicity in children treated with codeine have been described in the literature, some with a fatal outcome. These children underwent tonsillectomy for obstructive sleep apnoea and experienced respiratory depression after using codeine as an analgesic at a therapeutic dose. In addition, a published case report described respiratory depression resulting in death in a breastfed newborn whose mother was a CYP2D6 ultra-rapid metaboliser. The Pharmacovigilance Risk Assessment Committee (PRAC) discussed this issue during its September 2012 meeting and raised concerns regarding the potential for serious opioid toxicity associated with the use of codeine as an analgesic in the paediatric population. A referral under Article 31 of Directive 2001/83/EC was therefore initiated, to review the benefit-risk balance of codeine in the management of pain in children.

Having reviewed the totality of the available data on the efficacy and safety of codeine-containing medicinal products indicated in the management of pain in children, including responses submitted by the marketing authorisation holders (MAHs), the PRAC noted that there is more limited information on the pharmacokinetics of codeine metabolism in children than is available for adults. The available data suggests that the maturity of the renal system and the drug metabolising enzymes, body weight or composition and the ontogeny of enzymes involved in the metabolism and pharmacology of codeine may be determinant for its analgesic or toxic effect and therefore result in pharmacokinetic differences in children compared to adults and between different age groups of children (neonates, infants).

Regarding efficacy, having reviewed the available efficacy data, the PRAC was of the opinion that the analgesic profile of codeine is not superior to that of other analgesics, such as non-steroidal anti-inflammatory drugs and non-opioid analgesics, in the management of post-operative pain in children. Nevertheless, the PRAC concluded that codeine still has a place in the treatment of acute pain in the paediatric population but given the concerns about its risks, it should only be used when in the management of acute moderate pain which is not considered to be relieved by other analgesics. It was also recommended that it should be used at the lowest effective dose for the shortest period of time.

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. In order to adequately minimise this risk, the PRAC considered that codeine should only be used in children above 12 years of age, since 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. In addition, CYP2D6 is subject to extensive polymorphism, with poor metabolisers likely to exhibit lower response to treatment, while extensive and ultra-rapid metabolisers are at risk of serious and fatal adverse events of opioid toxicity. The PRAC noted that performing genotype/phenotype screening of patients before prescribing codeine is unfeasible in practice, therefore, adequate warnings to highlight these risks were

recommended, including signs and symptoms of opioid toxicity and estimates of the prevalence of ultra-rapid metabolisers in different populations.

The PRAC noted that the six published cases of opioid toxicity (including three with fatal outcomes) in children taking codeine at recommended doses after tonsillectomy or/and adenoidectomy for obstructive sleep apnoea occurred in children. Three were subsequently found to be either ultra-rapid or extensive metabolisers of codeine and their underlying breathing problems may have made them more sensitive to develop respiratory depression when codeine converts to high levels of morphine in ultra-rapid metabolisers. Therefore, the PRAC considered that in children below 18 years of age that undergo tonsillectomy and/or adenoidectomy for Obstructive Sleep Apnoea Syndrome, the use of codeine should be contraindicated. In addition, the PRAC recommended caution in the specific subpopulation of patients who might already have a compromised airway and require post-operative pain relief and adequate warnings were reflected in the product information.

The PRAC also noted the published case of respiratory depression resulting in death in a breastfed newborn whose mother was a CYP2D6 ultra-rapid metaboliser. It was acknowledged that this was due to the presence of codeine metabolites in breast milk and the PRAC therefore raised concerns regarding the risk of opioid toxicity to the infant, which may be fatal, when the mother is an ultra-rapid metaboliser. To date, at least 44 cases of neonatal respiratory depression in breastfeed infants of codeine-using mother have been published. In view of these data, the PRAC recommended to contraindicate the use of codeine in women during breastfeeding. The use of codeine should also be contraindicated in patients of all ages who are known to be CYP2D6 ultra-rapid metabolisers.

The PRAC also concluded that the available data shows that codeine has a ceiling effect at higher doses, above which there is a marked increase in the incidence of adverse drug reactions and that these are dose dependent. The PRAC therefore considered a paediatric dose range of 0.5 to 1mg/kg to be appropriate, with accurate dosing based on body weight where feasible, with a duration of use limited to three days.

Benefit-risk balance

Having noted all of the above, the PRAC concluded that the benefit-risk balance of codeine-containing products indicated in the management of acute moderate pain in children remains favourable, subject to the agreed indication, contraindications, warnings and other changes to the product information as set out in Annex III to the opinion.

Grounds for PRAC recommendation

Whereas,

- The PRAC considered the procedure under Article 31 of Directive 2001/83/EC resulting from pharmacovigilance data, for codeine-containing products indicated in the management of pain in children (see Annex I).
- The PRAC considered the totality of the data available for codeine-containing products indicated in the management of pain in children in relation to the risk of opioid toxicity. This included the MAH responses and published literature data which became available since the initial granting of the marketing authorisations.
- The PRAC concluded that the available data indicates that codeine remains an effective analgesic for the treatment of acute moderate pain which is not considered to be relieved by

other analgesics. However, the PRAC also considered that its use can be associated with serious adverse events of opioid toxicity, in particular in the paediatric population below 12 years of age.

- The PRAC considered that serious adverse events of opioid toxicity are of particular concern in paediatric patients undergoing tonsillectomy and/or adenoidectomy for obstructive sleep apnoea syndrome and in patients with compromised respiratory function.
- The PRAC also determined that polymorphisms in the cytochrome P450 CYP2D6 system impact the metabolism of codeine, which can result in serious adverse events of opioid toxicity in ultra-rapid or extensive codeine metabolisers. The PRAC considered this risk to be of relevance to breast-fed infants whose mothers are ultra-rapid metabolisers.
- The PRAC therefore considered that in view of the available data and in order to maintain a favourable benefit-risk balance, codeine-containing products indicated in the management of pain should only be indicated in children above 12 years of age and 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. Moreover, codeine-containing products should be used at the lowest dose for the shortest duration possible.

The PRAC, as a consequence, concluded that subject to the agreed indication, contraindications, restrictions, warnings and other changes to the product information, the benefit-risk balance for codeine-containing products indicated in the management of acute moderate pain in children above 12 years of age remains favourable.

Therefore, in accordance with Articles 31 and 32 of Directive 2001/83/EC, the PRAC recommends the variation of the marketing authorisations for all medicinal products referred to in Annex I and for which the amendments to the product information are set out in annex III of the recommendation.

2 – Detailed explanation for the 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 changes were necessary to the wording proposed in Section 4.2 of the SmPC and Section 3 of the PL, in order to facilitate the practical implementation at the national level, taking into account the range of combination products included in the procedure.

The CMDh therefore reworded these sections, as follows:

Section 4.2 of SmPC - Posology and method of administration

Note: For products containing codeine-only, the text below should be used.

“Codeine should be used at the lowest effective dose for the shortest period of time. This dose may be taken, up to 4 times a day at intervals of not less than 6 hours. Maximum daily dose of codeine should not exceed 240 mg.”

Note: For combination products, the posology should be reviewed nationally and adapted to reflect the specific requirements of the product in view of the other active substances. The maximum daily dose of codeine should not exceed 240 mg.

“The duration of treatment should be limited to 3 days and if no effective pain relief is achieved the patients/carers should be advised to seek the views of a physician.”

“Paediatric population:

Children aged 12 years to 18 years:

Note: For products containing codeine-only, the text below should be used but should be reviewed nationally and adapted to reflect the specific requirements of the product in terms of the dosage range. The recommended approximate range is 30 to 60 mg.

"The recommended codeine dose for children 12 years and older should be [Dose range to be completed nationally] every 6 hours when necessary up to a maximum dose of codeine of 240 mg daily. The dose is based on the body weight (0.5-1mg/kg)."

Note: For combination products, the posology should be reviewed nationally and adapted to reflect the specific requirements of the product in view of the other active substances.

Children aged less than 12 years:
"Codeine should not be used in children below the age of 12 years because of the risk of opioid toxicity due to the variable and unpredictable metabolism of codeine to morphine (see sections 4.3 and 4.4)."

Section 3 of the PL - How to <take> <use> [Product Name]

"Children aged 12 years of above should take [To be completed nationally] every 6 hours, as needed. Do not take more than [To be completed nationally and see note below] in 24 hours.

Note: The posology should be reviewed nationally and adapted to reflect the specific requirements of the product, if necessary to take into account the other active substances in combination products. The maximum daily dose of codeine should not exceed 240 mg.

This medicine should not be taken for more than 3 days. If the pain does not improve after 3 days, talk to your doctor for advice.

[Product Name] should not be taken by children below the age of 12 years, due to the risk of severe breathing problems".

In addition, the CMDh considered that in view of the above restrictions to the posology, as well as the restrictions of the use of codeine in the management of pain to children above 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.

CMDh agreement

The CMDh, having considered the PRAC recommendation dated 13 June 2013 pursuant to Article 107k(1) and (2) of Directive 2001/83/EC, reached an agreement on the revocation or the variation, as applicable of the marketing authorisations of codeine-containing medicinal products indicated in the management of pain in children.

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