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## Assessment report for codeine-containing medicinal products indicated in the management of pain in children

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

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

Assessment Report as adopted by the PRAC with all information of a confidential nature deleted.



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# 1. Background information on the procedure

Concerns regarding opioid toxicity and the lack of consistent risk minimisation measures were raised following cases described in the literature of morphine toxicity in children treated with codeine after undergoing tonsillectomy for obstructive sleep apnoea. A number of the children were subsequently found to be ultra-rapid or extensive codeine-to morphine metabolisers.

In light of the above, the United Kingdom initiated a procedure under Article 31 of Directive 2001/83/EC resulting from pharmacovigilance data and referred the matter to the Pharmacovigilance Risk Assessment Committee (PRAC), on 03 October 2012. On 22 October 2012, an amended notification was received from the United Kingdom, extending the scope of the referral to all types of pain. The PRAC was requested to give its opinion on whether the marketing authorisations for codeine-containing medicinal products indicated in the management of pain in children, should be maintained, varied, suspended or withdrawn. As the request results from the evaluation of data resulting from pharmacovigilance activities, the PRAC should issue a recommendation to the Co-ordination Group for Mutual Recognition and Decentralised Procedures (CMDh).

After reviewing all the available data to address the concerns discussed, the PRAC adopted its recommendation on 13 June 2013.

## 2. Scientific discussion

### 2.1. Introduction

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 with the aim of increasing the analgesic effect due to the different mode of action of the individual drugs. The main pharmaceutical form is tablets (60%) but codeine is also available as capsules, effervescent tablets, syrups, suppositories and solutions.

The Pharmacovigilance Risk Assessment Committee (PRAC) noted that in November 2007, the Medicines and Healthcare products Regulatory Agency (MHRA) issued a Drug Safety Update containing a communication on the “very rare risk of side-effects in breastfed babies” from maternal ingestion of codeine, following a 2006 published case report of respiratory depression resulting in death in a breastfed newborn whose mother was a CYP2D6 ultra-rapid metaboliser. The PRAC also noted that in August 2012 the United States (US) Food and Drug Administration (FDA) issued a communication concerning codeine use in children after tonsillectomy and/or adenoidectomy for obstructive sleep apnoea, following reports of rare but life-threatening adverse events, including death. The FDA identified three paediatric deaths and one non-fatal but life-threatening case of respiratory depression, documented in the medical literature (*Ciszkowski C. et al* N Engl J Med 2009 and *Kelly LE et al* Pediatrics 2012). The children ranged in age from two to five years old. The three deaths occurred in children who had evidence of being UMs and the life-threatening case occurred in a child who was an extensive metaboliser. All children received doses of codeine that were within the recommended posology; however the post-mortem morphine concentrations in the three children who died were substantially higher than the recommended therapeutic range. Following its review, the FDA concluded that there was a need to add a boxed warning and a contraindication to the product information of US products against the use of codeine for the post-operative pain management in children after tonsillectomy or adenoidectomy, regardless of the metabolic status.

The PRAC discussed this issue during its September 2012 meeting and concluded that since 2007, there were five cases of opioid toxicity in children treated with codeine after undergoing tonsillectomy for obstructive sleep apnoea, with a sixth, non-fatal case reported in 1997 (*Talbott et al*, 1997). Three of the children were subsequently found to be CYP2D6 extensive or ultra-rapid metabolisers. The PRAC therefore concluded that the issue of serious opioid toxicity and the lack of consistent risk minimisation measures should be evaluated fully in order to determine whether further risk minimisation measures should be introduced in order to ensure the safe use of codeine. In October 2012, a referral under Article 31 of Directive 2001/83/EC was therefore initiated. The PRAC was therefore specifically

requested to assess all available evidence of the efficacy and safety of codeine and thus review the benefit-risk balance of codeine-containing medicinal products (including combination products) indicated in the management of pain, including post-operative analgesia, in children.

The PRAC adopted a list of questions to be addressed by all marketing authorisation holders (MAHs) of codeine-containing medicinal products indicated in the treatment of pain in children. The MAH responses included searches of Medline (via Ovid or PubMed), Embase, Google Scholar and Cochrane reviews, summaries of relevant studies and data from pharmacovigilance databases. Following the review of the MAH responses, the PRAC noted differences across the member states with regard to the wording of the indication (details of the type and intensity of the pain), posology, contraindications and warnings and the mention of CYP2D6 genetic polymorphisms.

## **2.2. PRAC review of clinical efficacy**

### **2.2.1. Pharmacogenetics, pharmacokinetics and pharmacodynamics of codeine metabolism**

The analgesic properties of codeine stem from its conversion in the liver to its active metabolite morphine by the hepatic microsomal enzyme system cytochrome P450 enzyme CYP2D6. The toxicity of codeine is mainly due to its opioid effects and the most common adverse reactions to codeine include drowsiness, light-headedness, dizziness, sedation, shortness of breath, nausea, vomiting, and sweating, while serious adverse reactions include respiratory depression and, to a lesser degree, circulatory depression, respiratory arrest, shock, and cardiac arrest.

It has been established that CYP2D6 is subject to extensive polymorphism resulting from more than 100 different known allelic variants. This phenotypic variability is translated into a wide spectrum of metabolic capacity in terms of the capacity to metabolise codeine. Broadly speaking, CYP2D6 alleles are characterised as wild-type (normal function), reduced-function, or non-functional based on the expected activity level of the enzyme for which they encode. Two non-functional alleles result in poor metaboliser (PM) phenotype; at least one reduced functional allele in intermediate metaboliser (IM); at least one functional allele in extensive metaboliser (EM) and multiple copies of a functional allele, due to duplication or multi-duplications of the CYP2D6 gene, in ultra-rapid metaboliser (UM) phenotype (Somogyi *et al.*, 2007, Madadi P *et al.*, 2008; Ingelman-Sundberg M *et al.*, 2007). The clinical implications of this genetic polymorphism are not fully understood but have been reported in the literature to be linked to potentially serious events of opioid toxicity, as described in this report. Ultra-rapid codeine metabolism in UM patients may result in increased conversion of codeine to morphine resulting in toxic systemic concentrations of morphine even at low codeine doses. On the other hand, a lack of analgesic efficacy can occur in PM patients, even at high doses, making it impossible to predict treatment response and the risk of opioid intoxication, even if the patient's CYP2D6 status is known.

The PRAC noted that prevalence of the various phenotypes varies across individuals, based on ethnicity and has been determined for a number of ethnicities and nationalities. 7–10% of Caucasians are PMs, while the prevalence is 2% of Asians and 1% of Arabs. Regarding UMs, the overall prevalence in Caucasians is up to 10% but ranges from low in northern Europe (1-2% in Finland, Denmark, Norway and Sweden), Central Europe, North America (4-5%) and Asia (0.5-2.5%), to significantly higher in the Mediterranean countries (7-12% in Portugal, Spain, Greece and Italy), Saudi Arabia (21%) and Ethiopia (29%). Overall, it is estimated that the distribution of CYP2D6 phenotypes is the following: 1.9% UM, 6.5% IM, 8.3% PM, and 83.3% EM (Rideg *et al.*, 2011).

The PRAC noted the literature reviews carried out by the MAHs of studies which investigate the use of codeine as an analgesic, both in adults and in children, including studies investigating the route of administration. The vast majority of pharmacokinetic (PK) and pharmacodynamic (PD) data for codeine has been obtained from investigations in adults, very little information is available from studies in children or infants and no published work in neonates was identified. Overall PK and PD studies in children are lacking, particularly regarding the impact of the CYP2D6 genetic polymorphism on the efficacy of codeine in analgesia.

When considering the studies conducted in adults, the PRAC noted in particular the Clinical Pharmacogenetics Implementation Consortium (CPIC) systematic review relating to the interpretation

of CYP2D6 genotype test results to guide the dosing of codeine (*Crews KR et al 2012*). The resulting guidelines give a strong recommendation to avoid codeine use in patients with known CYP2D6 UM and PM phenotypes and to consider alternative analgesics such as morphine or non-opioids. CYP2D6 phenotypes can be predicted, although not fully, from CYP2D6 genotypes. In addition, the study by *Kirchheiner et al (2007)* investigated the PK differences of codeine between a group of UMs and EMs. A small group of PMs served as an additional reference group. A single dose of 30mg codeine was administered. Significant differences between the EM and UM groups were detected in areas under the plasma concentration versus time curves (AUCs) of morphine. The authors observed a strong correlation between the number of active CYP2D6 genes and plasma concentrations as well as urinary recovery ratios of codeine metabolites. The plasma concentrations and AUCs of morphine between UMs and EMs differed about 1.5-fold with a nearly exact linear gene-dose effect. CYP2D6 genotypes predicting UMs resulted in about 50% higher plasma concentrations of morphine and its glucuronides compared with the EMs. No severe adverse effects were seen in the UMs in the study, most likely because a low dose of only 30 mg was used for safety reasons.

The studies conducted in children were also reviewed. The PK/PD study conducted by *Williams DG et al (2002)* was considered to be of high relevance. It investigated genotype, phenotype and morphine production from codeine in 96 children aged from three to 12 years undergoing adenotonsillectomy, and compared analgesia from codeine or morphine combined with diclofenac. The study concluded that a reduced ability to metabolise codeine may be more common than previously reported and considerably higher than the prevalence described for the general population.

The PRAC concluded that as the inter-individual variability of response to codeine analgesia is related to functional polymorphisms in CYP2D6, PMs may suffer from poor analgesia with codeine but still experience some adverse effects, while UMs may experience exaggerated and even potentially dangerous opioid effects, although the variability of the analgesic effect which can be attributed to CYP2D6 genotypes has not been completely defined in the paediatric clinical settings. Assays are available to determine the genotype of the key pathways involved in codeine bioactivation but while it acknowledged that CYP2D6 genotyping prior to analgesic therapy is desirable where accurate testing is available, the PRAC considered that this is unlikely to happen in most clinical practice, particularly as the response to codeine is not directly correlated with phenotype. Close monitoring for signs of opioid toxicity is therefore of critical importance. The study by *Williams et al* on the implications of CYP2D6 polymorphisms on the analgesic effect of codeine found similar associations between serum metabolite concentrations and phenotypes, however no differences in pain scores or need for a rescue medication after codeine administration were identified for the different phenotypes in children.

### **2.2.2. Effect of age on the efficacy of codeine**

It has been suggested that infants and neonates have a reduced metabolic capacity for codeine as CYP2D6 activity is absent or less than one per cent of adult values in foetal liver microsomes. Some authors consider that CYP2D6 expression rapidly reaches adult levels within the first 6 months after birth (*Stevens JC et al 2008*), while others suggest that enzyme activity may still be less than 25% of the adult values up to 5-years of age (*Tateishi T et al 1997*). The effect of age was examined in a study by *Quiding et al (1992)*. The study investigated whether infants and young children are capable of demethylating codeine to morphine. Thirteen infants and young children participated in the study. Nine were between six and ten months old and four were between three and four years old. The study concluded that at the age of six months, infants are capable of demethylation of codeine to morphine. Codeine administered rectally in infants at 0.5 mg/kg and in older children at 8 mg resulted in similar plasma concentrations of codeine and morphine as 60 mg codeine administered orally to adults. The mean half-life was found to be 2.6 hours, but in infants with the lowest weight, the half-life was over two hours longer than this value.

The PRAC concluded that the influence of childhood development on the efficacy and side-effects of codeine has not been well-investigated. In summary, the limited data available appear to suggest that the PK of codeine and its active metabolite morphine may be similar in older children and adults; however the data is largely inconclusive. The evidence suggests that children are capable of demethylating codeine to morphine at the age of six months. However, glucuronidation in younger children may be impaired, resulting in an additional influence on the unpredictable metabolism of

codeine. As a result, caution should be applied when interpreting the effect of age and consideration should be given not only to genetic polymorphism but also the increasing enzymatic activity with age. Moreover, the rate at which most drugs are absorbed is generally slower in younger children, particularly if unwell or under sedation so the time to achieve maximum plasma concentrations may be prolonged. *Bhat R et al (1996)* studied morphine metabolism in acutely ill preterm newborn infants and concluded that nearly two thirds of acutely ill preterm infants born at less than 32 weeks of gestational age conjugate morphine. However, irrespective of their ability to produce morphine conjugates, preterm infants excrete large amounts of morphine unmetabolised, as late as 24 hours after a single dose and morphine handling patterns are highly variable among premature infants. The authors proposed that variability in morphine handling in general and the production of the highly potent morphine-6-glucuronide in particular could explain the variance in morphine pharmacokinetic measures and in the clinical responses to morphine during the newborn period. Therefore, the PRAC raised concerns that when codeine is used in very young children, the lack of a clinical response to the medication as a result of slower absorption could lead to unnecessary and potentially harmful dosing adjustments. For products with age restrictions, it was noted that a cut-off age of 12 years was stated in the majority of the SmPCs, based on a lack of established safety and efficacy of codeine. The PRAC regarded this age restriction as adequate, taking into account the reviewed data suggesting that the enzymatic system responsible for the metabolism of codeine can be considered fully matured by the age of 12.

### **2.2.3. Efficacy data**

The PRAC reviewed the available data on the efficacy of codeine, including in combination products. Studies conducted in children compared codeine alone or in combination with ibuprofen, paracetamol and morphine for indications such as musculoskeletal injuries, fracture, neurosurgery, and post-operative pain-relief. Most of these trials suggested comparable efficacy of codeine with other active treatments, although for musculoskeletal pain/extremity injuries, NSAIDs were shown to have equal or better efficacy compared to codeine/paracetamol (*Drendel AL et al, 2006; Friday JH et al 2009; Drendel AL et al 2009; Clark E et al 2007, Charney RL et al 2008, Swanson CE et al 2012*).

The PRAC also reviewed studies on the use of codeine for post-surgical pain relief in children, mostly after tonsillectomy or other ear, nose and throat (ENT) operations, after neurosurgery and also for dental extraction. Overall, these studies showed that paracetamol with codeine provides effective analgesia in children. Studies in neurosurgery by *Ou et al (2008), McEwan et al (2000), (Warren et al, 2010)* and *Teo JH et al (2001)* and concluded that there is no strong evidence suggesting that the use of codeine plus paracetamol is a safer or more efficacious choice compared to morphine in paediatric patients undergoing neurosurgical procedures. Studies in ENT by *Tremlett et al (2010), Khetani JD et al (2012), Subraamanyam R et al (2012), Rawlinson E et al 2011 and Harley et al (1998)* showed a reluctance of clinicians to prescribe NSAIDs following tonsillectomy due to the risk of bleeding, although this risk was inconsistent with other similar paediatric studies by *Charles et al (1997), Shaikh et al (2011), Tobias J et al (1995), St Charles CS et al 1997), Semple D et al (1999), Moir MS et al (2000), Ewah BN et al (2006) and Pappas AL et al (2003)*.

The PRAC considered that the available studies are small and offer limited information regarding the efficacy of codeine in post-operative analgesia as there are no studies identified using codeine as a single analgesic compared against placebo. In the presented studies, the clinical efficacy of codeine was mostly assessed in combination with paracetamol and compared to other medications (ibuprofen, paracetamol alone, morphine etc.) in various clinical settings. In the studies in children with skeletal trauma, it was concluded that ibuprofen has efficacy comparable to codeine in combination with paracetamol when used for acute paediatric arm fracture pain, acute traumatic extremity pain and outpatient fracture pain. However, for acute paediatric arm fracture pain, the side effects were fewer with ibuprofen use compared to the use of codeine with paracetamol. In paediatric tonsillectomies and/or adenoidectomy, no significant differences between treatments were demonstrated. Pain appeared to worsen after operation within the first five days post operatively. However one study showed that codeine plus paracetamol had a better analgesic effect compared to ibuprofen in the first two to three post-operative days but that there was no difference between treatments at day five (*Harley et al 1998*). The type of operation (coblation or electrocautery tonsillectomy) has to be taken

into consideration both in term of analgesia required and the risk of post-operatively bleeding. *Parker and Walner* (2011) found that the average number of post-operative days with severe pain was 4.2 for coblation and 5.9 for electrocautery ( $P = 0.006$ ), days rating pain  $\geq 5$  were 3.6 for coblation and 4.8 for electrocautery ( $P = 0.037$ ), days of codeine use were 2.5 for coblation and 2.9 for electrocautery ( $P = 0.324$ ), and days until resumption of a regular diet were 5.2 for coblation and 6.2 for electrocautery (0.329). The use of ibuprofen is associated with good pain control after tonsillectomies, however it has been linked to an increased risk of bleeding, albeit not clearly established. Interestingly, a study found that parents indicated that they would accept a higher bleeding risk (3%) for their children in exchange for better pain control (*Low TH et al* 2009). Furthermore, a study by *Khetani et al* (2012) explored the respiratory risks for patients undergoing adenotonsillectomies for obstructive sleep apnoea (OSAS). The authors stated that the lack of improvements in rates of saturation observed the day after surgery may be due to residual effect of the anaesthetics, presence of blood or oedema in the area of surgery as well as increased airway compliance and decreased airway neuromuscular function in children with OSAS. However the fact that in certain cases the rates of apnoea rose dramatically during the night following surgery suggest that the prescribed opioids may have exerted respiratory depression in some children. The PRAC was concerned by these findings in paediatric patients undergoing tonsillectomy and/or adenoidectomy for obstructive sleep apnoea syndrome.

With regards to dose, limited data is available from studies in children, and the posology is mostly extrapolated from results observed in adults. Doses such as 30 to 60 mg every six hours, with a maximum daily dose of codeine of 240 mg are usually recommended while higher doses cannot be routinely recommended in the absence of additional efficacy and safety data. A British guideline stated that the recommended use of codeine for short-term treatment of moderate pain involves a dosing schedule based on body weight of 0.5-1 mg/kg 4-6 hourly in neonates and paediatric patients. The PRAC noted that in children, this represents doses of 30 to 60 mg every six hours. The duration of use should be limited to three days, after which the need for alternative treatment should be considered.

#### **2.2.4. PRAC conclusions on clinical efficacy**

Based on the available efficacy data the PRAC therefore concluded that there is no strong evidence of a superior analgesic profile of codeine compared to other analgesics such as non-steroidal anti-inflammatory drugs and non-opioid analgesics in the management of post-operative pain in children, although it is recognised that codeine containing medicinal products have demonstrated efficacy in the treatment of acute moderate pain that is not solely relieved by other analgesics such as paracetamol and ibuprofen. The PRAC noted that the analgesic effect of codeine equals approximately 1/10<sup>th</sup> that of morphine, making it suitable for mild to moderate pain but unsuitable for severe or chronic pain, even in larger doses.

The genetic polymorphism of CYP2D6 was considered to be clinically relevant to the efficacy and safety profile of codeine in the paediatric population, as the prevalence of a reduced ability to metabolise codeine may be more common in children than in the general population. The limited data available also suggests that the activity of CYP2D6 increases markedly after birth but remains inferior to the activity of adults, which may result in lower analgesic effect. Clinicians prescribing codeine should consider the potential for a reduced response leading to an inadequate analgesic effect in some children. The enzymatic system responsible for the metabolism of codeine can be considered to be fully matured by the age of 12, with comparable metabolic behaviour to that of adults, in terms of drug absorption, distribution and renal clearance. In addition, enhanced adverse effects may be observed in patients which are ultra-rapid metabolisers (resulting in higher than expected serum morphine levels) and therefore clinicians should be highly alert to the signs and symptoms of opioid toxicity.

Doses are typically extrapolated from adult data and doses such as 30 to 60 mg every six hours, with a maximum daily dose of codeine of 240 mg are usually recommended. Higher doses, however, cannot be routinely recommended in the absence of additional efficacy and safety data. This is particularly important due to the confirmed risk associated with administration of codeine in UMs. The PRAC considered that if no effective pain relief is observed after a period of three days, a revision of the treatment needs to be considered.

### **2.3. PRAC review of clinical safety**

The PRAC noted that the MAHs did not conduct any preclinical, clinical or pharmacoepidemiological studies in the context of this review and all the evidence provided was collected from post-marketing spontaneous reports, including reports published in the literature. No preclinical data to support the use of codeine in the paediatric population was submitted.

#### **2.3.1. Summary of serious and fatal paediatrics reports**

The PRAC reviewed the 6 cases (including three with a fatal outcome) of opioid toxicity in children aged two to five years who were treated with codeine after undergoing tonsillectomy for obstructive sleep apnoea, as identified by *Talbott et al* (1197), *Voronov et al* (2007), *Ciszkowski et al* (2009) and *Kelly et al* (2012). All children received codeine at recommended dose and where known, the children were subsequently found to be either ultra-rapid or extensive metabolisers. Since these children had underlying breathing problems, it has been suggested that they may more sensitive to developed respiratory depression when codeine converts to high levels of morphine.

In addition, 14 fatal cases were identified in EudraVigilance where codeine was used for analgesia in paediatric patients. Most of the cases are scarcely documented. In 3 cases, the cause of death was an underlying disease, in one case an accidental overdose and in another one death was related to paracetamol (hepatic failure). The remaining cases involved patients from 2 to 17 years of age. Half of the cases occurred in children between 2 and 6 years of age. Toxic morphine levels were reported in 4 cases, and in 2 cases children appeared to receive codeine in the range of the recommended dose. Genotype/phenotype was not available. Indications were AT (2 cases), headache (1 case) sporting injury (1 case), aphthous stomatitis (1 case) and unknown in the remaining cases.

Cases associated with codeine exposure through breastfeeding were reviewed to investigate whether breast-fed infants of mothers taking codeine could be at an increased risk of opioid toxicity if the mother was an ultra-rapid metaboliser. In a report by *Koren G et al* (2006), a 13-day-old infant experienced respiratory depression resulting in death after being exposed to morphine in his mother's breast milk; the mother had been taking oral codeine 30mg and paracetamol 500mg twice daily for episiotomy pain for about two weeks. The clinical and laboratory picture was consistent with opioid toxicity leading to neonatal death. Assayed morphine concentrations in the breast milk were found to be 87 ng/mL, compared to the usual range of 1.9 to 20.5 ng/mL after repeated doses of codeine 60mg four times daily. Subsequent investigations found that the mother's genotype for the cytochrome P450 isoenzyme CYP2D6 classified her as an ultra-rapid metaboliser.

A review of 72 mother–child pairs showed that 17 (24%) breastfed infants exhibited central nervous system depression while their mothers used codeine (*Madadi P et al*. 2009). Ultra-rapid metabolisers were identified in 3 (11.8%) cases. One case was asymptomatic, of the other two, one was described previously (*Koren G et al* 2006) and the second was a mother who used 120 mg/day codeine for severe muscle pain after childbirth. Her breastfed infant was described as extremely drowsy and feeding poorly. She began supplementing breast milk with formula after delivery because of personal exhaustion and due to her infant's feeding difficulties. On the seventh day after delivery, the mother had switched completely to formula feeding and a complete reversal of the infant's symptoms was noted in the following days.

A further review by *Madadi et al* (2012) identified 44 cases of neonatal respiratory depression in breastfed infants of mothers who were using codeine.

Although it was acknowledged that opioid toxicity may occur at all ages, the PRAC concluded that the current evidence suggests that children are at special risk of life-threatening or fatal respiratory depression in association with the treatment of pain with codeine, particularly the specific subpopulation of patients who might already have a compromised airway and require post-operative pain relief.

In addition, the PRAC noted an abstract citing four near-term breastfed infants who exhibited neonatal apnoea attacks which started 4–6 days following administration of 60 mg codeine (q 4–6 h) to breastfeeding mothers (*Davis JM et al*, 1985) and an abstract reporting that 10 of 12 full-term infants who had unexplained episodes of apnoea, bradycardia, and/or cyanosis occurring in the hospital

between 0.5 and 7 days of age were exposed to opioids through breast milk, with six of the infants specifically exposed to codeine in breast milk (Naumburg EG, 1987).

A study by *Willmann S et al* (2009) which investigated the risk of opioid poisoning to breast-fed neonates using coupled physiologically-based pharmacokinetic models for the mother and child was also considered in the review. The simulations demonstrated that the mother's codeine and morphine clearances and the neonate's morphine clearance are the most critical determinants of morphine accumulation in the neonate and that given the added effect of low neonatal elimination capacity for morphine, potentially toxic morphine plasma concentrations can be reached within four days in the neonate after repeated codeine dosing to the mother. Neonates of mothers with the UM CYP2D6 genotype and neonates of mothers who are EMs had comparable risks of opioid poisoning.

Regarding the risk of trans-placental exposure to codeine, the PRAC noted a study by *Nezvalová-Henriksen K et al* (2011) which analysed the effect of codeine on pregnancy outcome in a large population-based cohort study (2,666 women who used codeine during pregnancy were compared with 65,316 women who used no opioids during pregnancy). It was concluded that no effects of maternal codeine intake during pregnancy were observed on infant survival or congenital malformation rate.

Finally, the PRAC noted a review by *Neisters et al* (2012) of case reports of opioid-induced respiratory depression (OIRD) in children. Opioid treatment is potentially life-threatening, although there are no numbers available on the incidence of OIRD in paediatrics. To get an indication of specific patterns in the development/causes of OIRD, the authors searched PubMed (May 2012) for all available case reports on OIRD in paediatrics, including patients 12 years of age or younger who developed OIRD from an opioid given to them for a medical indication or due to transfer of an opioid from their mother in the perinatal setting, requiring naloxone, tracheal intubation, and/or resuscitation. Twenty seven (27) cases are described in 24 reports, of which seven cases were fatal. In eight cases, OIRD was due to an iatrogenic overdose. Three distinct patterns in the remaining data set specifically related to OIRD include: (i) morphine administration in patients with renal impairment, causing accumulation of the active metabolite of morphine; (ii) codeine use in patients with CYP2D6 gene polymorphism associated with the ultra-rapid metaboliser phenotype, causing enhanced production of morphine; and (iii) opioid use in patients after adenotonsillectomy for recurrent tonsillitis and/or obstructive sleep apnoea, where OIRD may be related to hypoxia-induced enhancement of OIRD.

### **2.3.2. PRAC conclusions on clinical safety**

Having reviewed the available data on the safety of codeine in paediatric patients, including serious and fatal cases, the PRAC considered that the respiratory depressant effects of opioids may influence the occurrence of respiratory complications and that high levels of morphine as a result of codeine-treatment can result in severe respiratory depression, which can be fatal in some cases. Taking codeine after tonsillectomy and/or adenoidectomy may increase the risk of respiratory depression and subsequently death. This appeared to be of particular concern in children who are ultra-rapid metabolisers although it was acknowledged that the CYP2D6 status was not known in the majority of the serious and fatal cases. In conclusion, the PRAC considered that the review of the cases involving codeine alone or in combinations recorded in post marketing pharmacovigilance databases suggests that codeine may be responsible for opioid toxicity with a possible fatal outcome. The ultra-rapid metaboliser phenotype and young age appear to be risk factors as the majority of all the reported events reviewed occurred in children 0 to 12 years of age and the PRAC therefore concluded that this age group is especially susceptible to the toxic effects of codeine. In addition, the PRAC considered that all paediatric patients who undergo tonsillectomy and/or adenoidectomy for obstructive sleep apnoea or are treated for post-operative pain after tonsillectomy and/or adenoidectomy for obstructive sleep apnoea are at particular risk, given the possibility of respiratory depression.

In order to adequately minimise the risk, the PRAC therefore considered that codeine-containing medicinal products indicated in the management of pain in children should only be administered to children above the age of 12 years of age and contraindicated in all paediatric patients below 18 years of age undergoing tonsillectomy and/or adenoidectomy for obstructive sleep apnoea syndrome, regardless of CYP2D6 status. Warnings on the signs and symptoms of opioid toxicity should be reflected in the product information. In addition, restrictions should be placed on the maximum daily dose and the duration of use.

## **2.4. Other information relevant to the assessment**

### **2.4.1. Consultation of the Paediatric Committee**

The Paediatric Committee (PDCO) was consulted regarding the use of codeine as an analgesic in the paediatric population. It was recognised that the use of codeine varies significantly in paediatric clinical practice across the EU. The risk of morphine intoxication due to genetic polymorphism of its metabolic pathway was discussed and it was noted that the reported cases of severe or fatal adverse drug reactions were limited and mainly identified in young children. The PDCO also discussed the lack of robust evidence of a superior therapeutic effect for codeine when compared to other simple analgesics (i.e. paracetamol and ibuprofen) although it was acknowledged that there is a lack of robust studies investigating the use of codeine in the paediatric population. Concerns were expressed regarding the lack of alternative safe and effective analgesics particularly for younger age groups. The PDCO also supported a contraindication of the use of codeine in all paediatric patients (0 to 18 years of age) that undergo tonsillectomy and/or adenoidectomy for Obstructive Sleep Apnoea Syndrome due to an increased risk of respiratory depression. The PDCO recommended that the risk of codeine's genetic polymorphism should be communicated to healthcare professionals across the EU.

### **2.4.2. Clinical Practice Research Datalink (CPRD) review of the use of codeine in tonsillectomies and adenoidectomies**

As the majority of the adverse events and cases with fatal outcomes following the use of codeine as an analgesic were identified in children undergoing tonsillectomies and adenoidectomies particularly associated with sleep apnoea, the PRAC reviewed specific data extracted from the Clinical Practice Research Datalink (CPRD) to estimate how many of these procedures occurred in children in England between 1st January 2009 and 31st December 2011. Data from children aged 18 years or under who had a record of a tonsillectomy, adenoidectomy or dual procedure in the 3-year period were reviewed. The PRAC noted that 5,942 children with a record of a tonsillectomy and/or adenoidectomy were identified during the study period, although the proportion of children with a diagnosis of apnoea was very low. Out of these children, only 77 were prescribed a codeine-containing product in the one month period following the procedure. There were no records of children with a diagnosis of sleep apnoea and who were also prescribed codeine-containing products following their procedure. The PRAC noted that tonsillectomies and/or adenoidectomies occur more commonly in children below the age of 12 years. These patients appeared to be diagnosed with sleep apnoea more frequently than older children but the numbers are overall very low. A survey of paediatric anaesthesiologists in the UK in 1996 (*de Lima J et al*) showed that alongside morphine and fentanyl, codeine is the most widely prescribed opioid analgesic in paediatric anaesthetic practice. However in recent years in the UK, the use of codeine postoperatively has become less common, as indicated by this CPRD review. The PRAC considered that the reason for this decline in use is unclear and commented that one explanation may be that the published reports of fatal cases in these patients have deterred prescribers.

### **2.4.3. Consultation of the Pharmacogenomics Working Party**

The PRAC also consulted the Pharmacogenomics Working Party (PGWP) to obtain input on CYP2D6 phenotype assays and the capacity to predict ultra-rapid metabolisers.

The PGWP noted that besides the therapeutic drug monitoring, CYP2D6 phenotyping allows determination of the actual enzymatic activity by administering a specific probe drug and measuring the concentration of the drug and its metabolite in the urine. This allows the identification of the four previously defined metaboliser groups (UMs, EMs, IMs and PMs). However, it was noted that phenotype prediction according to allele combination is more complex and very different predictive powers are observed depending on the group of metabolisers considered. On the other hand, genotyping allows precise determination of the individual's CYP2D6 DNA sequence and the possibility to predict a phenotype based on the alleles identified. Of note, almost 100% of PMs are identified by genotyping, whereas only 20% of UMs are correlated to an increased number of CYP2D6 gene copies. Reviewing the Rebsamen et al. (2009) publication, the PGWP noted that the AmpliChip CYP450 test is the first genotyping array allowing simultaneous analysis of 33 CYP2D6 alleles, including CYP2D6. The AmpliChip CYP450 test genotyping accuracy for five CYP2D6 alleles was verified (alleles 3,4,5,6, xN;

n=100) and the results confirmed those obtained by real-time PCR. Major improvements using the array are the detection of CYP2D6 intermediate alleles and identification of the duplicated alleles. The CYP2D6 phenotype was determined by assessing urinary elimination of dextromethorphan and its metabolite dextrorphan and compared to the array prediction (n=165). The sensitivity for detecting UM was very low (only 6 %). Therefore, although the genotyping method may predict PM phenotype, the PGWP considered that the method cannot be recommended for UM phenotype prediction. The PGWP considered the publication by *Crews et al* (2012) which recommends using alternative analgesics in patients who are CYP2D6 poor metabolizers or ultra-rapid metabolizers but was of the view that currently, considering the risks of opioid toxicity following the use of codeine in UMs and the lack of practical accurate testing method for the UM status, the risk minimisation measures should include close monitoring of the symptoms and signs of opioid intoxication. The PGWP agreed that the use of codeine in children should be carefully evaluated considering the serious consequences in the reported cases in UMs and that the risk minimization for codeine use should be harmonized in the EU.

#### **2.4.4. EMA analysis of fatal reports in EudraVigilance and case reports in the scientific literature**

The PRAC also considered an analysis of fatal cases included in EudraVigilance carried out by the EMA. This EudraVigilance analysis describes the paediatric adverse drug reaction reports where codeine was a suspect or interacting substance. The analysis was based on fatal and non-fatal case reports in the scientific literature and individual case safety reports (ICSR) in EudraVigilance.

A total of fifteen ICSRs reporting fatal cases where codeine was used for analgesia in paediatric patients were identified and reviewed individually. In three cases, codeine did not seem to be a part of the causal mechanism while in the remaining twelve case reports, codeine was considered at least as a contributory cause. Of note, in three of these cases, codeine was considered the cause either due to an accidental overdose, due to the presence of significant baseline risks, such as renal failure, or as a triggering factor for citrullinaemia. In five of the fifteen case reports, codeine was used to manage pain following a surgical procedure, three of which were adenotonsillectomy. In the remaining ten cases, codeine was used either for managing general pain or for an unknown indication. The blood level of codeine was reported in five case reports, of these four were above the toxic threshold whereas one was within normal therapeutic values. Regarding concomitant medications it was noted that in two case reports, fentanyl and in three case reports valproic acid were co-administered.

In addition, eight text articles (by *Voronov et al* 2007, *Hermanns-Claussen et al* 2008, *Ciszkowski and Madadi*, 2009, *Kelly et al* 2012, *Meyer and Tobias*, 2005, *Magnani and Evans*, 1999, *Talbott et al* 1997 and *Tong and Ng*, 2001) were reviewed, corresponding to 11 individual cases, 6 of which in the indication for analgesia. In the analgesia indication, the age range for the 6 cases of opioid toxicity was from 2 to 5 years-old. The time-to-onset described was under 2 days for all these cases. Most papers provided morphine blood levels and the lowest morphine level in the fatal cases was 17 ng/ml in a 4 year-old which was subsequent to having taken 4 doses of 8 mg. The phenotype was known in all but one case report in the literature, and in all of those the child was a CYP2D6 UM. Additional cases were retrieved from two scientific papers but the full text articles were not available.

In conclusion, opioid toxicity in codeine exposed patients was found to occur either due to toxic levels of morphine in the blood or due to exposure to multiple narcotic analgesics or other drugs that share the same respiratory depression effect. In CYP2D6 UM patients for whom a normal dose of codeine was administered, opioid toxicity may stem uniquely and directly from the fact that these patients metabolise higher proportions of codeine into morphine. Noticeably, in all but one literature papers where the indication was pain management following adenotonsillectomy, the children were found to be CYP2D6 UMs. While this pathological mechanism is well recognised, it even seems unclear whether the kinetics can be predictable, considering the multiple polymorphisms and the influence of ontogeny in these patients. Additionally, other causes for higher blood levels of morphine may be considered, such as the total dose administered, the blocking of other metabolic pathways or the accumulation due to impaired drug elimination routes.

#### **2.4.5. EMA Drug utilisation of codeine in children: analyses of The Health Improvement Network and of the IMS Health German databases**

The PRAC also reviewed a drug utilisation analysis investigating the use of codeine in children and the incidence of death occurring within this population, focusing on the tonsillectomy/adenoidectomy indication. The analyses were performed using The Health Improvement Network (THIN) database (UK general practice) and the IMS database (German general and specialists practice). Prevalence data from these sources were also compared with data from Sweden and Denmark. The objectives of the analyses were to estimate prevalence of codeine exposure in children in the UK, DE, SE and DK, the incidence of death in UK children prescribed codeine by different time windows, the cause of death analysis in UK children prescribed codeine and dying within a short time frame and the UK prevalence of prescription of codeine in tonsillectomy and/or adenoidectomy procedures. For both analyses, the study population was defined as less than 20 years old with a prescription of codeine during the study period, to allow comparing the results with Danish and Swedish national data. The study period was defined as 1<sup>st</sup> January 2001 to 31<sup>st</sup> December 2011.

The THIN database analysis showed that 91,112 children out of 2,515,938 in THIN were prescribed codeine during the study period. A total of 289 deaths were reported in these children, with 10 deaths occurring within 14 days of codeine prescription but none of these had a reported cause of death related to codeine toxicity. More than 80% of children prescribed codeine received only one codeine prescription during a calendar year and more than 70% received only one codeine prescription during the whole study period. 21,171 tonsillectomy procedures, 7,317 adenoidectomy procedures and 8,254 combined tonsillectomy and adenoidectomy procedures were recorded in the database. Codeine was prescribed in 9% of tonsillectomy procedures and 0.5% of adenoidectomies (within +/- 7 days), with a prescription peak in the period 4 to 7 days post-operatively, which was considered relatively low, although it was noted that codeine prescribed at the hospital during the procedure or codeine given at the hospital is not captured by THIN. In addition, no tonsillectomies and/or adenoidectomies were conducted in these patients within plus/minus 365 days of the final prescription before death, although it was noted that the cause of death is often not recorded in the database. While the date of death is considered reliable, the cause of death had to be found indirectly for a majority of the 10 patients dead within 14 days after a codeine prescription.

The IMS database analysis showed that 59,625 children received at least one prescription of codeine during the study period. In 2011, there were 12,259 codeine-prescribed children, this was 0.34% of the total population of children in 2011 (3,547,640). The total of 99,529 codeine prescriptions to 59,625 children gives an average number of prescriptions per children of 1.67, which indicates that use is predominately acute.

The PRAC noted that the populations analysed were mainly from Northern Europe, where the prevalence of CYP2D6 ultra-rapid metabolisers is the lowest, around 1-4% (Ingelman-Sundberg, 2005). It was also noted that prevalence in THIN is higher for females compared to males (double in 2011), while in IMS prevalence was similar between genders. Both in THIN and IMS, prescription seems predominantly for acute use. The PRAC also noted an analysis conducted using BIFAP (Spanish General Practitioners database), which showed that the overall prevalence of use in children is higher in Spain than in northern countries, with 3.7 users per 100 persons, as per 2011.

#### **2.5. Risk management plan**

The PRAC, having considered the data submitted in the application, is of the opinion that the proposed restrictions of use, together with the other changes to be introduced to the product information (PI), will be adequate to address the concerns assessed in this procedure and that no additional risk minimisation activities are required beyond those included in the product information.

#### **2.6. Overall discussion and benefit-risk assessment**

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 breastfed 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.

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.

## **2.7. Communication plan**

The PRAC agreed on the following key elements for national communication, which should be considered by MAHs when agreeing a communication strategy with their national competent agency:

- Codeine is a widely used analgesic, which requires the cytochrome P450 enzyme CYP2D6 for conversion morphine. Morphine is responsible for codeine's pharmacological effect.
- There are genetic differences in the expression of the CYP2D6 enzyme, according to racial or ethnic group. These differences determine the extent to which codeine is metabolised. Some individuals are deficient in this enzyme and will obtain no analgesic effect from codeine. Whilst other individuals have more than two copies of the gene for this enzyme and are known as ultra-rapid metabolisers, these individuals are more likely to have side-effects because they convert codeine to morphine more quickly or in greater quantities.
- PRAC has reviewed the benefit-risk of products containing codeine for the relief of pain in children. The reason for this review was some fatal or life-threatening cases of morphine intoxication in children who were found to be ultra-rapid or extensive metabolisers and were receiving codeine for the management of pain after adenoidectomy/tonsillectomy for obstructive sleep apnoea.
- Considering that no tests are available for routine screening of CYP2D6 polymorphism, and therefore the conversion to codeine to morphine may be unpredictable, PRAC recommends a number of risk minimisation measures to ensure that only children for whom benefits are greater than the risks are given codeine for pain relief:
  - Codeine is indicated in children older than 12 years of age for the treatment of acute moderate pain which is not relieved by other analgesics such as paracetamol or ibuprofen alone
  - Codeine is contraindicated in paediatric patients 0 to 18 years of age that undergo tonsillectomy and/or adenoidectomy for Obstructive Sleep Apnoea Syndrome due to an increased risk of developing serious and life-threatening adverse reactions including loss of consciousness and respiratory arrest.
  - Codeine is contraindicated in patients known to be CYP2D6 ultra-rapid metabolisers as the risk of morphine intoxication is extremely high in these patients.
  - Codeine is not recommended for use in children whose breathing might 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.
- Due to an increased risk for the breastfeeding child when mother is using codeine and she is an ultra-rapid metaboliser, the use of codeine is contraindicated in women when breastfeeding.
- 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 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.
- Clinicians should remain aware that patients may respond differently to codeine. Those caring for patients taking codeine should be advised to seek medical advice if symptoms of toxicity occur.

Symptoms of codeine toxicity include reduced levels of consciousness, lack of appetite, somnolence, constipation, respiratory depression, 'pin-point' pupils, nausea and vomiting.

## **2.8. Changes to the product information**

Regarding Section 4.1, the PRAC considered that codeine-containing products should only be used when other analgesics have failed to relieve the pain. In order to minimise the risk of opioid toxicity, based on the reviewed data and the established knowledge of the maturation of the codeine metabolising enzymes, it was also considered it appropriated to restrict the use of codeine to children older than 12 years, for whom the system is considered to be similar to that of adults. Regarding pain intensity, the PRAC considered that the available data provides strong evidence demonstrating that the analgesic effect of codeine is limited in severe pain, even at high doses. The indication was therefore restricted to acute moderate pain, which is considered sufficiently inclusive to cover the different types of acute pain for which codeine has shown efficacy, but only when not relieved by other analgesics. In conclusion, the PRAC recommended the indication in patients 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.

Regarding Section 4.2, the PRAC reviewed the duration of use of codeine-containing products and decided that it was necessary, based on the available data, to limit the use of codeine to the lowest effective dose for the shortest period of time and that the maximum duration of use should be restricted to 3 days as a risk minimisation measure. This time period was considered a reasonable time to get an effect, bearing in mind that 7% of Caucasians will not respond to treatment due to a deficiency in CYP2D6. A statement was also added advising that a physician should be consulted if no effective pain relief is achieved. The PRAC also reviewed the available pharmacokinetic data to determine the interval for administration. While the data supports an analgesic duration of effect between 4 and 6 hours, the PRAC considered a 6-hours interval to be appropriate since this longer interval among doses may mitigate the life-threatening reactions derived from morphine toxic levels in ultra-rapid metabolisers. With regard to the maximum daily dose, taking into account the proposed paediatric dose range of 30 to 60 mg body weight (based on 0.5 to 1mg/kg), the PRAC considered that the available data supports a maximum daily dose of 240 mg for codeine-only products. However, for combination products, the PRAC acknowledged that this maximum limit needs to be adjusted for each individual dose, due to the lower codeine content.

Regarding Section 4.3, the PRAC was of the view that the fatal cases identified in children with sleep apnoea syndrome after tonsillectomy or adenoidectomy warrant a contraindication in this population, especially since the respiratory depression caused by morphine intoxication may be more severe in these children. Similarly, fatal cases of newborns being breastfed by ultra-rapid metaboliser women have been published. A warning was considered to be insufficient, as women will not normally know if they are ultra-rapid metabolisers and a contraindication in women during breastfeeding was therefore recommended, together with a statement in Section 4.6. Finally, the PRAC also considered it appropriate to contraindicate the use of codeine in patients for whom it is known they are CYP2D6 ultra-rapid metabolisers.

The PRAC was of the view that information on CYP2D6 polymorphisms, including a tabular presentation of prevalence, should be provided to prescribers in Section 4.4, since prevalence according to population varies broadly. Based on the available data, the PRAC also considered it highly relevant to include extensive metabolisers, alongside ultra-rapid metabolisers, as one of the cases of severe codeine intoxication in the published literature that triggered this review was observed in an extensive metaboliser. Furthermore, in the majority of the reported adverse drug reaction cases, the lack of information on CYP2D6 status does not allow any robust conclusions on the risk of harm in EMs. Finally, a statement regarding the analgesic properties of codeine was added in Section 5.1.

The package leaflet was revised accordingly.

### 3. Conclusion and grounds for the 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. The PRAC also considered that it may be relevant to consider the need to extrapolate this recommendation to other codeine indications.

A divergent position is appended to the Recommendation.

# Appendix 1

Divergent positions dated 13 June 2013

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

Procedure No: EMEA/H/A-31/1342

Codeine-containing medicinal products indicated for the treatment of pain in children

### **Divergent statement**

The following member of PRAC did not agree with the PRAC's Recommendation on the Article 31 referral resulting from pharmacovigilance data for codeine-containing medicinal products used for pain in children based on the following reasons:

- I support the PRAC conclusion on the benefit-risk of codeine in the treatment of pain in children and the product information wording as adopted by PRAC, with the exception of the contraindication in breastfeeding. While I agree that there is an unpredictable risk of morphine toxicity for the infant depending on mother's metabolism of codeine, this risk depends on doses in milk and length of treatment. Milk levels of codeine and morphine are low, also oral bioavailability of morphine is quite low, however due to prolonged morphine plasma clearance in very young infants their plasma morphine levels increase gradually during prolonged treatment of the mother. Simultaneously the signs of morphine toxicity can appear and worsen gradually. After short-term treatment no important risk can manifest, therefore I consider that the breastfeeding contraindication should be restricted only to treatment longer than 3 days. This is also in line with expert recommendations (e.g. Madadi et al. in Guidelines for maternal codeine use during breastfeeding – CNS depression in the infant appears to worsen after 4 days). One or few doses of codeine could be sufficient in the treatment of acute pain in some cases and such a short-term treatment does not raise any significant risk for the breastfed infant.

However even with minimal probability of any risk during short-term therapy the product information should describe the possible signs of morphine toxicity (increased sleepiness, limpness, feeding and breathing difficulties) and recommendation to stop immediately the treatment and contact the physician in case any of these signs appear.

### **PRAC member expressing a divergent position:**

Eva Jirsovà (CZ)	13 June 2013	Signature: .....
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