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Pharmacovigilance Risk Assessment Committee (PRAC)

Assessment report

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

Codeine containing medicinal products for the treatment of cough and/or cold in paediatric patients

International non-proprietary name: codeine

Procedure number: EMEA/H/A-31/1394

Note

Assessment report as adopted by the PRAC and considered by the CMDh with all information of a commercially confidential nature deleted.

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1. Background information on the procedure

In 2012 - 2013, the Pharmacovigilance Risk Assessment Committee (PRAC) reviewed the benefit-risk of products containing codeine for the relief of pain in children (Referral procedure EMEA/H/A-31/1342[1]). The reason for this review were 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. A number of the children were subsequently found to be ultra-rapid or extensive codeine-to morphine metabolisers.

In June 2013, PRAC recommended the following risk minimisation measures to ensure that only children for whom benefits are greater than the risks are given codeine for pain relief:

- codeine is only 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 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;
- 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 of any age known to be CYP2D6 ultra-rapid metabolisers as the risk of morphine intoxication is extremely high in these patients.
- Codeine is contraindicated in women during breastfeeding, as if the mother is an ultra-rapid metaboliser of CYP2D6, higher levels of the active metabolite, morphine, may be present in breast milk and on very rare occasions may result in symptoms of opioid toxicity in the infant, which may be fatal.
- 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.

As the above risk minimisation measures could also be applicable to the approved indication of codeine for cough and/or cold, on 02 April 2014, the German National Competent Authority (BfArM) initiated a referral under Article 31 of Directive 2001/83/EC to review the benefit-risk balance of codeine in the treatment of cough and/or cold in paediatric patients (hereafter refer as “children”).

The PRAC was requested to give its opinion on whether the marketing authorisations for codeine-containing medicinal products indicated for cough and/or cold in children, should be maintained, varied, suspended or revoked.

After reviewing all the available data to address the concerns discussed, the PRAC adopted its recommendation on 12 March 2015.

[1] Article 31 pharmacovigilance referral for codeine used for mangement 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

As the request resulted from the evaluation of data from pharmacovigilance activities concerning products only approved nationally (including via the mutual recognition and decentralised procedures), the PRAC recommendation is forwarded to the Co-ordination Group for Mutual Recognition and Decentralised Procedures (CMDh) for a position/agreement to be reached.

2. Scientific discussion

2.1. Introduction

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[2] (Buck ML, 2004). Apart from its use as an analgesic for relief of pain, it is also used for the symptomatic treatment of cough and/or cold.

Cough is one of the most common symptoms in children worldwide[3] (Smith S et al, 2008). In most children, acute cough is due to viral upper respiratory tract infection (URTI), i.e., the common cold[4] (De Blasio F et al, 2012).

Numerous preparations containing codeine are available for the symptomatic treatment of cough and/or cold for children in the European Union. The preparations may contain codeine as a single agent or in combination with other active substances.

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 as an antitussive as current evidence does not find codeine to be more effective than placebo for acute cough in children[5] (Schroeder and Fahey, 2002).

Codeine is converted into morphine in the body by cytochrome P450 2D6 (CYP2D6), an enzyme which shows genetic polymorphism. It has been established that some patients who are 'CYP2D6 ultra-rapid metabolisers' convert codeine to morphine at a faster than normal rate. This results in high levels of morphine in their blood that can lead to toxic effects such as breathing difficulties. There have been a number reports of serious adverse events in children prescribed codeine, some of which were cases of fatal or life-threatening respiratory depression. As mentioned above, the PRAC has issued a recommendation in 2013 for risk minimisation measures for when codeine is used for relief of pain in children.

The present review concerns the use of codeine in paediatric patients for the cough and/or cold indications as triggered by the German National Competent Authority (BfArM) due to the applicability of the above risk measures also to these indications.

All codeine containing medicinal products approved for the treatment of cough and/or cold in the paediatric population, including single and combination products authorised in the European Union were included in this review.

In April 2014, PRAC agreed a list of questions to be addressed by the marketing authorisation holders (MAHs) of codeine-containing medicinal products used for treatment of cough and/or cold in children.

[2] Buck, M.L., 'Therapeutic Uses of Codeine in Pediatric Patients' Pediatric Pharmacotherapy, 2004;10(4).
[3] Smith S., Schroeder K., Fahey T., 'Over-the-counter (OTC) medications for acute cough in children and adults in ambulatory settings (Review)', Cochrane Database Syst, Rev 2008.
[4] De Blasio F., Dicpinigaitis P.V., Rubin B.K., De Danieli G., Lanata L., Zanasi A., 'An observational study on cough in children: epidemiology, impact on quality of sleep and treatment outcome', Cough, 2012;8(1):1.
[5] Schroeder K., Fahey T., 'Should we advise parents to administer over the counter cough medicines for acute cough? Systematic review of randomised controlled trials', Arch Dis Child, 2002 Mar;86(3):170-5.

2.2. Clinical aspects

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.

Acute cough is defined as cough lasting less than 3 weeks whereas chronic cough lasts more than 8 weeks (or more than 4 weeks, depending on the definition). The majority of children with acute cough have a viral respiratory tract infection and for the majority of children acute cough resolves within 14 days and - more rarely - within 3-4 weeks. Rarer causes of acute cough in children include seasonal allergic rhinitis, inhaled foreign body or first presentation of a chronic disease[6,7,8](Brodlie M et al 2012, Irwin RS et al 2006, Shields MD et al 2008).

The aetiology of chronic cough in children usually comprises underlying diagnoses such as asthma, allergic rhinitis, persistent endobronchial infection, recurrent aspiration, interstitial lung disease, tuberculosis or cardiac diseases. Most chronic coughs in childhood are not due to the same conditions as occur in adults; the 'big three' causes of adult chronic cough are noted to be cough variant asthma, postnasal drip and gastro-oesophageal reflux. The use of adult-based cough algorithms is unsuitable for application in children[8] (Shields MD et al 2008). Chronic cough in children should be managed by making an accurate underlying diagnosis and then applying specific treatment for this condition[8,9] (Shields MD et al 2008, ACCP evidence-based clinical practice guidelines 2006).

The frequency of acute upper respiratory tract infections (URTIs) is also age-related and differs between adults and children. Studies from the 1940s to the 1960s have shown that children have 5 to 8 acute respiratory infection episodes per year, while in more recent studies children aged < 5 years have 3.8 to 5 infections per year and adults have only 2[9] (ACCP evidence-based clinical practice guidelines 2006).

In conclusion, acute cough in children is frequent, usually caused by viral infection and self-limiting whereas in the case of chronic cough, treatment should be directed at the underlying disease[10,11] (American Academy of Paediatrics Committee on Drugs 1997, American Academy of Paediatrics, AAP publications retired or reaffirmed 2006).

In its assessment, the PRAC considered the data available from different sources: clinical trials, observational studies, meta-analyses, post-marketing data and further published 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. Moreover the PRAC consulted European healthcare professional organisations and the Paediatric Committee (PDCO).

A summary and discussion of relevant data is presented hereafter.

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[6] Brodlie M., Graham C., McKean M.C., 'Childhood cough', BMJ, 2012;344:e1177.

[7] Irwin R.S., Baumann M.H., Bolser D.C. et al. 'Diagnosis and management of cough executive summary: Accp evidence-based clinical practice guidelines', Chest, 2006;129(1_suppl):1S-23S.

[8] Shields M.D., Bush A., Everard M.L., McKenzie S., Primhak R., 'Recommendations for the assessment and management of cough in children', Thorax, 2008;63(Suppl 3):iii1-iii15.

[9] American College of Chest Physicians evidence-based clinical practice guidelines 2006

[10] American Academy of Pediatrics Committee on Drugs 'Use of codeine- and dextromethorphan-containing cough remedies in children', Pediatrics 1997;99:918-20.

[11] American Academy of Pediatrics. AAP Publications Retired or Reaffirmed, October 2006. Pediatrics 2007;119(2):405.

2.2.1. Pharmacokinetics, Pharmacogenomics and Pharmacodynamics

During the Article 31 referral review on codeine containing medicinal products indicated in the management of pain in children an extensive discussion took place regarding the pharmacokinetics (PK), pharmacogenomics and pharmacodynamics (PD) of codeine metabolism. A brief summary is presented hereafter on aspects relevant to codeine containing medicinal products indicated for cough and/or cold in paediatric population.

O-demethylation of codeine into morphine is mediated by the enzyme CYP2D6[12] (Kirchheiner et al, 2007). It has been established that CYP2D6 is subject to extensive polymorphism resulting from more than 100 different known allelic variants. Individuals are commonly grouped in 4 different phenotypes: poor metaboliser (PM), intermediate metaboliser (IM), extensive metaboliser (EM) and ultra-rapid metaboliser (UM). 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%).

The vast majority of PK and PD data for codeine have been obtained from investigations in adults and the data mainly focus on codeine's analgesic properties. PK, PD data and clinical evidence that explain how CYP2D6 phenotypes relate to variable efficacy in cough control after codeine intake are lacking.

There have been no direct pharmacogenomics studies identified in the published literature related to codeine administration for cough and/or cold in the paediatric population. It is believed that the antitussive action of codeine works via stimulation of μ-opioid receptors[13] (McDonald, 2005). μ-Opioid receptors are found within the cough centres of the brain and therefore, it is thought that opioids exert their antitussive effects via a central action[14] (Gibson et al, 2011).

Bibliographic literature indicates that codeine has a 200-fold weaker affinity for μ-opioid receptors than morphine[15] (Crews et al, 2014). Therefore, codeine antitussive properties (similar to codeine analgesic properties) may be closely related to CYP2D6 and will vary depending on its conversion to morphine.

The phenotypic variability refer above is translated into a wide spectrum of metabolic capacity in terms of the ability to metabolise codeine. Hence, in terms of efficacy, weaker antitussive properties can be expected in poor metabolisers because less codeine would be converted into morphine; whereas extensive and ultra-rapid metabolisers would have the opposite effect which may result in potentially toxic concentration of morphine even when low doses of codeine are given.

The unpredictable and variable metabolism of codeine in children, as governed by CYP2D6 polymorphism may cause some children to exhibit codeine toxicity even within the recommended doses. Therefore, this continues to represent a variable safety risk across all paediatric age groups.

The PRAC recommended that information regarding ultra-metabolisers CYP2D6 need to be reflected in the product information for all codeine containing medicinal products approved for cough and/or cold in children in line with the PRAC recommendation for the medicinal products of codeine indicated for pain relief, in the same population.

[12] Kirchheiner J., Schmidt H., Tzetkov M. et al. 'Pharmacokinetics of codeine and its metabolite morphine in ultra-rapid metabolisers due to CYP2D6 duplication', Pharmacogenomics, J 2007;7:257–265.

[13] McDonald J., Lambert D.G.,'Opioid receptors. Continuing Education in Anaesthesia, Critical Care & Pain', 2005;5(1):22-25.

[14] Gibson P.G. et al. 'Cough pharmacotherapy: current and future status. Expert Opin. Pharmacother', 2011;12(11). (P11-09653).

[15] Crews K.R., Gaedigk A., Dunnenberger H.M., et al. 'Clinical Pharmacogenetics Implementation Consortium (CPIC). Guidelines for Codeine Therapy in the Context of Cytochrome P450 2D6 (CYP2D6) Genotype', Clin Pharmacol Ther, 2012; 91:321-326.

2.2.2. Clinical Efficacy

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 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[16] (Schroeder and Fahey, 2002).

Published studies

In total, only 4 published studies investigating the use of codeine-containing medicines for the treatment of cough and/or cold in children could be identified. There was also a Cochrane review in 2012 which identified two studies on the use of codeine in cough and/or cold in adults and only one in children.

Two older studies, which do not meet today's guidelines, did not include a placebo group. Firstly, Kelly and colleagues[17] (1963) conducted a single blind study in children aged 8 months to 17 years with acute cough due to respiratory infection. 26 children received codeine (8 mg/16 mg four times a day for productive/unproductive cough), 27 received pholcodine (5 mg/10 mg) and 8 received both treatments on a crossover basis. Treatment duration was approximately 5 days. 96 % of patients treated with pholcodine and 93 % of patients of patients treated with codeine had excellent or good results, but the duration of effect was greater in the pholcodine group than in the codeine group (4 hours versus 3 hours). No adverse drug reactions were observed in the pholcodine group while 8 of 26 patients in the codeine group complained of mild constipation.

Secondly, a randomised, single-blind trial included 217 children aged 6 –12 years with acute cough and compared the efficacy and palatability of two combination products given for 3 days. Patients had acute cough due to upper respiratory or chest infection with median symptom duration of 3 days. Each patient received either a product containing paracetamol 150 mg, pholcodine 5 mg and phenylpropanolamine 12.5 mg four times daily, or a product containing triprolidine hydrochloride 1.875 mg, pseudoephedrine hydrochloride 45 mg and codeine phosphate 15 mg three times daily. Both products showed highly significant improvements for productive cough and sore throat. Side effects were significantly less frequent in the pholcodine-containing product, and drowsiness was observed significantly more frequently with the codeine-containing product. Analysis of palatability showed numerical superiority for the pholcodine-containing product[18] (Jaffe G et al, 1983).

The PRAC also noted one observational study evaluating the epidemiology and impact of cough on quality of sleep and children's activities, and the outcome of cough with antitussive treatments in paediatric routine clinical practice. A total of 433 children aged 1 month to 14 years (mean age 6.1 years (SD 3.6 - median 5.2 years)) with acute cough (onset ≤ 3 weeks) associated with URTI were enrolled[4] (De Blasio F et al, 2012).

In a subset of 241 children who were either treated with antitussive medicines (levodropropizine n=101, central antitussives (cloperastine n = 51 or codeine n=9) or received no treatment (n = 80), the outcome of cough after 6 days was analysed in terms of resolution, improvement, no change, or worsening. Both levodropropizine and central drugs reduced cough intensity and frequency. However, percentage of cough resolution was significantly higher with levodropropizine than with central

[16] Schroeder K., Fahey T., 'Should we advise parents to administer over the counter cough medicines for acute cough? Systematic review of randomised controlled trials', Arch Dis Child, 2002 Mar;86(3):170-5.
[17] Kelly D.A., 'Comparative clinical test of pholcodine with codeine as control'. Northwest Med 1963;62:871-874
[18] Jaffe G., Grimshaw J.J., 'Randomized single-blind trial in general practice comparing comparing the efficacy and palatability of two cough linctus preparations, 'Pholcodix' and 'Actifed' compound, in children with acute cough', Curr Med Res Opin, 1983;8:594-599.

antitussives (47% vs. 28% respectively, p = 0.0012). Improvement was observed in 40% of patients receiving levodropropizine *vs.* 53 % for central antitussives and no change/worsening was reported in 3% receiving levodropropizine *vs*. 18% for central antitussives. Of note 20% of patients receiving no therapy reported resolution of cough, while 55% reported improvement of their symptoms and 25% no change/worsened. Multivariate analysis showed a statistically significant difference of cough improvement with levodropropizine *vs.* central antitussives or no therapy. No information on adverse drug reactions was presented in this publication.

There was a double-blind, randomised controlled trial (RCT) that compared the effects of dextromethorphan, codeine and placebo on 57 patients aged between 18 months to 12 years presenting with acute cough of less than 2 weeks duration. Cough and composite symptom scores, based on symptom severity at bedtime, were obtained using parent questionnaires. Mean cough and composite symptom scores were found to decrease significantly in each of the 3 groups ($p<0.0002$). However, regression analysis showed that neither dextromethorphan ($p = 0.41$) nor codeine ($p=0.70$) was significantly better than placebo in relieving night time symptoms[19] (Taylor et al, 1993).

In 2012, a Cochrane review of non-prescription/over-the-counter (OTC) medications for acute cough in children and adults in ambulatory settings[20] (Smith SM et al, 2012) identified two randomised controlled trials where codeine was tested in adults[21,22] (Eccles R et al, 1992; Freestone C 1997). In these two studies, codeine was found to be no more effective than placebo. In the review published by the Cochrane Collaboration (addressing the efficacy and safety of OTC cough and/or cold medications in the ambulatory setting), only one trial[20] (Taylor et al, 1993, discussed above) on codeine was identified in children.

Conclusions on efficacy

Overall, there is limited evidence in the medical literature to support the use of codeine in cough and/or cold and a clear paucity of clinical trials investigating the antitussive efficacy of codeine in children.

In total, only 4 published studies investigating the use of codeine-containing medicines for the treatment of cough in children could be identified along with a systematic review published by the Cochrane Collaboration.

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.

2.2.3. Clinical safety

The use of opioids in children entails a known risk of central respiratory depression. The safety profile of codeine raises greater concerns as codeine is metabolised to morphine at an unpredictable rate.

[19] Taylor J.A., Novack A.H., Almquist J.R., Rogers J.E., 'Efficacy of cough suppressants in children' J Pediatr 1993;122:799-802.
[20] Smith S.M., Schroeder K., Fahey T., 'Over-the-counter (OTC) medications for acute cough in children and adults in ambulatory settings', Cochrane Database Syst Rev, 2012;8:CD001831.
[21] Eccles R., Morris S., Jawad M.S., 'Lack of effect of codeine in the treatment of cough associated with acute upper respiratory tract infection', J Clin Pharm Ther, 1992;17:175-80.
[22] Freestone C., Eccles R., 'Assessment of the antitussive efficacy of codeine in cough associated with common cold', J Pharm Pharmacol, 1997;49(10):1045-9.

The most common adverse reactions to codeine (independently of the indication of its use) include drowsiness, light-headedness, dizziness, sedation, shortness of breath, nausea, vomiting and sweating. Serious adverse reactions include respiratory depression and, to a lesser degree, circulatory depression, respiratory arrest, shock and cardiac arrest.

Post marketing data

A review of spontaneous case reports revealed 9 fatal cases and 41 serious cases associated with codeine use in the paediatric population. In many of these cases, the indication of use for codeine is not clear. Out of the 9 fatal cases, 3 cases were reported in the setting of codeine being used for cough or respiratory infection. Out of the 41 serious cases, there were 5 cases in which the indication of use has been reported as cough or upper respiratory tract infection or peri-tonsillar abscess. These five cases involved 1 case of apnoea, 3 cases of skin reactions and 1 case of paracetamol intoxication/acute liver failure.

The fatal and serious cases reviewed highlight the risk of morphine toxicity in the subpopulation of patients with compromised respiratory function, (e.g. post-operatively after tonsillectomy and/or adenoidectomy) and also indicate a higher reporting of opioid toxicity and respiratory depression in young children (<12 years) regardless of the indication of use of codeine.

Nonetheless, the under-reporting issue of suspected adverse reactions for all non-prescription/over-the-counter (OTC) medicines and particularly for long-established products is recognised. Therefore the evaluation of a safety signal in the paediatric population based on these cases is difficult.

Literature data

An overview of all published cases is presented in table 1. below.

Table 1. Summary tabulation of case reports of codeine intoxication in children related to the treatment of cough and respiratory infection

Author (year)	Age	Codeine dose / concomitant medication	Indication	Adverse reactions	Outcome	Comments
Magnani (1999)	29 d	2 doses of 2 mg codeine + 6 mg pseudoephedrine + 0.4 mg chlorpheniramine + 5 % alcohol within 6 hours (1.26 mg/kg/d of codeine)	Cough, respiratory infection	Apnoea 2 hours after second dose	Fatal	Post mortem heart blood: 0.34µg/ml free codeine, 0.48 µg/ml total codeine
Lee (2004)	3 months	5 mg codeine + 2.5 mg ephedrine + 1 mg dexchlorpheniramine + 50 mg ammonium 3 times daily (2 mg/kg/d) / Ceftibuten 50 mg/d, L-chlorpheniramine 3 x 1mg/d	Persistent cough	Cyanosis, dusky complexion and mottled Skin, with poor response to external stimuli on second day	Full recovery	
Hermans-Clausen (2009), Ferreiros (2009)	3 years (twin 1)	About 12.3 mg to 23.4 mg of codeine per day for 6 days (0.9 – 1,7 mg/kg/d) / Acetaminophen, ibuprofen, ivy leaf extract	Persistent cough, fever, URTI	Apnoea, vomiting	Full recovery	Serum concentration: 174.0 ng/ml codeine, 25.6 ng/ml morphine, CYP2D6 extensive metaboliser genotype. Medication error
Hermans-Clausen (2009), Ferreiros (2009)	3 years (twin 2)	About 12.3 mg to 23.4 mg of codeine per day for 6 daysd (0.9 – 1.7 mg/kg/d) / Acetaminophen, ibuprofen, ivy leaf extract	Persistent cough, fever, URTI	Apnoea, vomiting	Fatal	Serum concentration: 463.3 ng/ml codeine, 138.7 ng/ml morphine, CYP2D6 extensive metaboliser

Author (year)	Age	Codeine dose / concomitant medication	Indication	Adverse reactions	Outcome	Comments
						genotype. Medication error
Tong (2001)	17 days	6mg of codeine three times daily (6.6 mg/kg/d) / Chlorpheniramine 0.5 mg three times daily	Cough	Cyanotic episodes 2, 3 and 6 hours after the third codeine administration	Full recovery	Codeine blood level: 0.24 µg/ml 9 hours after last dose.
Friedrichsdorf (2013)	6 years	3 doses of 10 to 20 mg codeine with guaifensin within 12 hours (0.22-0.44 mg/kg/d) / Azithromycin	Severe cough and respiratory infection	Death during sleep 13 hours after last dose	Fatal	0.08 mg/l free codeine, 0.17 mg/l total codeine, 0.08 mg/l total morphine, obesity (44.9 kg, BMI 26.6). Correct dose despite medication error.
Wilkes (1976)	3 months	2 doses of 10 mg codeine with pseudoephedrine and triprolidine (6.6 mg/kg/d)	URTI	Sleepiness, heavy breathing, miosis, apnea following 2 doses within 24 hours	Full recovery	Medication error
Riedler (1988)	7 weeks	2 doses of 5 mg codeine with dimethylaminophenazone, diallylbarbiturate and phenylcyclohexylacetate within 12 hours	URTI	Coma, hypertension, opistothotonus, miosis and respiratory depression 2 hours after the second dose. Apnea 10 hours after the second dose	Full recovery	Medication error
Rumler et al (1963)	4 months	At least 20 mg of codeine per day for 2 days (3.9 mg/kg/d)	URTI	Gray and pale complexion, restlessness, opisthotonus, miosis, obstipation	Full recovery	Iatrogenic overdose
Rumler et al (1963)	4 weeks	30 mg of codeine within 8 hours (9.7 mg/kg)	URTI	Difficulty breathing, screaming, severe cyanosis, tonic stiffness of arms and legs, opisthotonus, trism, bradycardia, obstipation, miosis	Full recovery	Prescribing error, medication error by parents.
Rumler et al (1963)	9 months	At least 12 mg of codeine per day for 10 days (1.4 mg/kg/d)	Pertussis	Cyanosis , tonic clonic convulsions, subileus, death a few hours after admission	Fatal	Medication error by parents
Rumler et al (1963)	3 months	2 suppositories containing in total 10 mg codeine, 5 mg theobromine and 5 mg atropa belladonna extract within a short period of time (2 mg/kg)	URTI, bronchitis	Facial edema, moderate cyanosis, subileus, tonic convulsions,	Full recovery	Medication error by parents
Rumler et al (1963)	11 weeks	About 20 mg of codeine within 3 days (1.1 mg/kg/d)	URTI,	Gray pale complexion, generalized edema, shallow breathing, miosis, obstipation, limp	Full recovery	Iatrogenic overdose
Rumler et al (1963)	5 months	1 suppository for adults containing 30 mg codeine, 400 mg aminophenazone , 75 mg theobromine and 25 mg atropa belladonna extract (4.1 mg/kg)	URTI,	Generalized hyperaemia, somnolence, tachycardia, tonic convulsions, mydriasis, obstipation	Full recovery	Off-label use/Medication error by parents

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.

The dose of codeine given varied from 0.22 mg/kg/day to 6.6 mg/kg/day. Assuming a recommended maximum daily dose of 1 mg/kg/day[10] (American Academy of Paediatrics Committee on Drugs 1997), one patient was given a dose within the recommended dosing range and 13 of the patients were overdosed. The patient who had received codeine within the recommended antitussive dosing range (0.22-0.44 mg/kg/d) died during their sleep thirteen hours after the last dose[23] (Friedrichsdorf et al, 2013).

The majority (8 out of 13) of the overdoses including the 3 fatal cases however were only in the range of ≤ 2 mg/kg per day or per single dose corresponding to only 2 times the maximum recommended daily dose and a dose generally considered as not life-threatening[24] (von Muhlendahl et al, 1976).

The CYP2D6 genotype was known in two cases. Both children were extensive metabolisers[25] (Hermanns-Clausen et al, 2009).

Combination products containing other centrally acting drugs (antihistamine, barbiturates) were reported in four cases.

EudraVigilance data

Case reports with adverse drug reactions that could be related to opiate toxicity in paediatric patients were selected (cut-off 31 July 2014). In total 50 case reports were identified of which 31 cases were in those < 6 years (including 4 fatal cases), 7 cases were in those ≥ 6 and <12 years (including 1 fatal case) and 12 cases in those ≥ 12 and <18 years (including 1 fatal case).

Overall, the majority (38/50) of the cases were in patients < 12 years of age and 6 were fatal cases. The additional fatal case occurred in a patient aged between ≥ 12 and <18 years.

Of the 7 fatal case reports [ages 4 mths, 2 years, 3 years, 5 years (n=2 but likely duplicates), 6 years, 15 years] one is sufficiently well documented to suggest opiate toxicity despite dosing within the recommended range. In one other case an overdose due to medication error cannot be excluded. The remaining cases (including 1 duplicate) provide insufficient information for a causality assessment or are suggestive of alternative causes of death. Dose and duration of codeine treatment were reported only in the first two cases mentioned.

The System Organ Class for which the highest numbers of cases were reported were general disorders and administration site conditions (15), injury, poisoning and procedural complications (13), nervous system disorders (27) and respiratory, thoracic and mediastinal disorders (19). The most frequently reported reactions (MedDRA preferred term, > 3 case reports) were vomiting (7 reports), accidental overdose (4), medication error (4), toxicity to various agents (4), convulsion (7), lethargy (4), somnolence (5), apnoea (5) and dyspnoea (5).

[23] Friedrichsdorf S.J., Nugent A.P., & Strobl A.Q., 'Codeine-associated pediatric deaths despite using recommended dosing guidelines: three case reports', J Opioid Manag, 2013;9(2):151-155.
[24] von Muehlendahl KE, Scherf-Rahne B, Krienke EG, et al. Codeine intoxication in childhood. *Lancet* 1976;7:303-305.
[25] Hermanns-Clausen M. ,Weinmann W., et al. 'Drug dosing error with drops: severe clinical course of codeine intoxication in twins', Eur J Pediatr, 2009;168(7):819-24.

Codeine misuse and dependence in adolescents

In adolescents, the additional risk of codeine dependence and abuse has been identified. There have been reports both in the published literature and also from spontaneous reporting that codeine containing products are used as substances of abuse either on their own or as substitutes for conventionally abused drugs, especially in adolescents.

Several MAHs searched their safety databases and performed literature searches, with a particular focus on the potential for codeine abuse and dependence in the 12-18 year age group.

Haifeng and colleagues[26] (2011) reported that chronic abuse of codeine containing cough syrups can induce physical and psychological dependence. The results suggested that chronic abuse of those syrups may cause serious damage to the brain. Chronic abuse of codeine containing cough syrups could lead to chronic overdose and opioid toxicity.

Several authors have also reported that codeine-containing products are used as substances of abuse either on their own or as substitutes for conventionally abused drugs such as heroin, amphetamine and cocaine, especially in adolescents[27,28,29](Lao YZ et al 2010, Mattoo SK et al 1997, Yang and Yuan 2008).

Reed and colleagues[30] (2011) have stated that recreational use of over-the-counter codeine-containing products by young people (younger than 16 years), although likely to be spasmodic, often occurs in combination with other drugs or alcohol leading to potentially greater adverse effects.

The misuse of OTC cough and/or cold medications among adolescents was also examined with data from the 2006 National Survey on Drug Use and Health (USA)[31] (Ford JA, 2009). Findings from this research indicate that a small percentage (nearly 4%) of adolescents report lifetime misuse of OTC medications. The analysis indicates that risk for misuse increases with age, as respondents between ages 13 and 17 are more likely to report misuse than adolescents of 12 year old.

Codeine in breastfeeding mothers

Over the recent years there have been reports of infant deaths due to high levels of morphine in breast milk because their mothers were ultra-rapid metabolisers of codeine[32] (Watt et al, 2013). This evidence indicates a significant risk to the infants when breastfeeding mothers are exposed to codeine regardless of the indication.

One case reported in a MAH's database involved a 1-year-old female child who experienced foetal arrhythmia, hepatotoxicity, jaundice, developmental delay and dependence after exposure of codeine phosphate/paracetamol and paracetamol via transplacental route. The female infant was born to a

[26] Haifeng H., et al. 'Decreased striatal dopamine transporters in codeine-containing cough syrup abusers' Drug and Alcohol Dependence, 2011;118:148-151.
[27] Lao Y.Z., Jiang Z.Y., Tong Z.S., Pang Z.T., Xu J.X., 'Clinical features and defense styles in patients with cough medicine abuse', Med J Chinese People's Health, 2010; 22:272–274.
[28] Mattoo S.K., Basu D., Sharma A., Balaji M., Malhotra A., 'Abuse of codeine containing cough syrups: a report from India', Addiction, 1997; 92:1783–1787.
[29] Yang Y., Yuan Q.Y., 'Investigation and analysis on personalities of male—codeine phosphate addicts by MMPI', Chinese J Drug Abuse Prev Treat, 2008;14:143–145.
[30] Reed K., Bond A., Witton J., Cornish R., Hickman M., Strang J., 'The changing use of prescribed benzodiazepines and z-drugs and of over-the-counter codeine-containing products in England: a structured review of published English and international evidence and available data to inform consideration of the extent of dependence and harm', The National Addiction Centre, Kings College London and School of Social and Community Medicine University of Bristol, University of Bristol, 2011.
[31] Ford J.A., 'Misuse of Over-the-Counter Cough or Cold Medications Among Adolescents: Prevalence and Correlates in a National Sample', Journal of Adolescent Health, 2009; 44:505–507.
[32] Watt L.D., Arnstein P. et al. 'Codeine for children: Weighing the risks', Nursing, 2013;63.

mother who had been inadvertently overdosing on codeine phosphate/paracetamol and paracetamol for six months. The infant developed hepatotoxicity. The infant displayed dependence on codeine phosphate/paracetamol and required treatment with morphine. After approximately six weeks in hospital, the infant was discharged.

During the referral review of codeine for pain relief in children the PRAC had previously recommended that, the use of codeine should be contraindicated in breastfeeding mothers. This contraindication is also considered applicable to breastfeeding mothers who use codeine-containing products also management of cough and/or cold as there is a risk of opioid toxicity to the breastfeeding child when the mother is using codeine and this risk is particularly high if the mother is an ultra-rapid metaboliser.

The PRAC recommended therefore, the contraindication of the use of these products in breastfeeding mothers. In addition, the PRAC considered that all codeine containing products, including those approved for adults and regardless of the indication, should have this contraindication in their labelling. Therefore, the PRAC suggests that National Competent Authorities of the EU Members States take the necessary actions to have the labelling of codeine products approved only for adults updated with this contraindication.

Conclusions on safety

The use of opioids in children entails a known risk of central respiratory depression. The safety profile of codeine raises greater concerns as codeine is metabolised to morphine at an unpredictable rate.

As discussed in section 2.2.1 of this assessment report, codeine is metabolised by the liver enzyme CYP2D6 into morphine, its active metabolite.

If a patient has a deficiency or is completely lacking this enzyme an adequate therapeutic effect will not be obtained. Estimates indicate that up to 7% of the Caucasian population may have this deficiency. However, if the patient is an extensive or ultra-rapid metaboliser there is an increased risk of developing side effects of morphine toxicity even at commonly prescribed doses. These patients convert codeine into morphine rapidly resulting in higher than expected serum morphine levels.

Children who are CYP2D6 ultra-rapid metabolisers, even within recommended doses can develop morphine toxicity[33,34,35](Ciszkowski et al, 2009; Friedrichsdorf et al, 2013; Kelly et al, 2012). 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 ultra-rapid metabolisers 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.

[33] Ciszkowski C., Madadi P., Phillips M.S., Lauwers A.E., Koren G., 'Codeine, ultrarapid-metabolism genotype, and postoperative death', N Engl J Med, 2009;361(8):827-8.
[34] Friedrichsdorf S.J., Nugent A.P., Strobl A.Q. 'Codeine-associated pediatric deaths despite using recommended dosing guidelines: three case reports' *J Opioid Manag* 2013;9(2):151-155.
[35] Kelly L.E., Rieder M., van den Anker J., Malkin B., Ross C., Neely M.N., et al. 'More codeine fatalities after tonsillectomy in North American children', Pediatrics, 2012; 129:e1343-7.

General symptoms of opioid toxicity include confusion, somnolence, shallow breathing, small pupils, nausea, vomiting, constipation and lack of appetite. In severe cases this may include symptoms of circulatory and respiratory depression, which may be life-threatening and very rarely fatal.

Codeine adverse drug reactions in paediatrics, as a result of opioid-induced toxicity, are a public health concern[36] (Madadi P, 2008). In addition to the key safety risk of ultra-rapid metabolism in certain patients with resulting life-threatening or fatal opioid toxicity and respiratory depression, codeine may also mask or delay treatment of a more serious underlying condition in children, and available data also highlighted a concern of codeine dependence and abuse in adolescents. There is also the risk of opioid toxicity in infants of breastfeeding mothers taking codeine.

As discussed in the previous referral procedure of codeine for pain in children, the PRAC recommended caution in the specific subpopulation of patients who might already have a compromised respiratory function. It is considered that with underlying breathing problems, the symptoms of morphine toxicity and respiratory depression may be increased. In view of these concerns, the PRAC concluded that codeine is not recommended for use in children whose breathing might be compromised.

The PRAC also considered that the risk of accidental overdose (four cases identified above) 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.

2.3. Other information relevant to the assessment

2.3.1 Consultation of healthcare professional organisations

The PRAC also obtained additional information from European healthcare professionals' organisations (HCPO) on the paediatric population which could benefit from the use of codeine in the symptomatic treatment of cough and/or cold.

Overall, HCPOs were of opinion that there was no specific paediatric age group or condition that could benefit from the use of codeine as an antitussive. However, the use of codeine in cases of persistent irritating cough that is resistant to other antitussives was suggested.

It was also stated that there would be no detrimental impact if codeine was to be restricted in the paediatric population. Clinical experience did not demonstrate any known risks with alternative antitussives but the range of medications used (including unconventional and herbal medications) is very wide and these medications may have associated concerns.

2.3.2 Consultation of the Paediatric Committee (PDCO)

The PDCO was consulted in order to obtain additional information on the use of codeine-containing products in paediatric patients.

The PDCO, supported by majority, had the view that the benefits of codeine as an antitussive in children and adolescents are unclear, and no paediatric population or group could be defined where codeine as an antitussive would be considered as an essential therapeutic option. The PDCO acknowledged that the data demonstrating the efficacy of codeine as an antitussive in children are

[36] Madadi P., Koren G., 'Pharmacogenetic insights into codeine analgesia: implications to pediatric codeine use', Pharmacogenomics, 2008; 9(9),1267-84.

weak and therefore it is considered that there is not enough evidence to support codeine use in any paediatric patient group.

Additionally, it was highlighted 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 lasting for a few days. In such clinical settings, it is not expected that codeine use brings any significant benefit, while the risks identified can be of serious consequences.

The PDCO by majority, considered that there would be no significant detrimental impact for paediatric patient care if the use of codeine in the cough indication was restricted to adults only. The Committee stated that there are fewer risks recognised with the use of alternative antitussives than with codeine used as an antitussive, in the paediatric population.

Codeine has an unpredictable therapeutic profile and may cause opioid intoxication in 'CYP2D6 ultra-rapid metabolisers'. Furthermore, it was pointed out that the variability in CYP2D6 genetic polymorphism and developmental changes during childhood put children at higher risk of opioid toxicity compared with adults. However, it was highlighted that data concerning safety of alternative antitussive medications should be taken in consideration.

The PDCO strongly indicated that codeine has a potential for abuse and dependence (in particular amongst adolescents) which could influence the drug's overall benefit-risk for the paediatric population. The Committee noted that OTC availability of codeine whether for pain or cough increases the risk of potential abuse and dependence, and commented that codeine-containing products should be subject to medical supervision..

2.3.3 EMA study on prescribing of codeine to children and adolescents for cough and/or cold

The EMA has performed a drug utilisation study (DUS) using IMS Health and THIN electronic health records and Nordic registries. The present analyses primarily concern the utilisation of codeine in children and were performed in the THIN database (UK general practice) and IMS database (general and paediatric practice in Germany, general practice in France). In addition, available on-line Nordic prescription registries have been queried. The study also analyses the incidence of death occurring within a short time span of a codeine prescription.

The proportion of prescribing of codeine related to cough varies significantly between countries. In Germany and Denmark the prescribing is predominantly defined as for cough. In France also a large proportion of the use is for cough. In Norway, Sweden and the UK prescribing for cough only accounts for a very small proportion.

The prescribing of codeine increases with age in all countries analysed even if at a different degree. In Germany the increase is lower due to the higher proportion of codeine prescribed against cough.

In the three countries where an analysis over-time was conducted, a small increase in prevalence for both codeine and codeine prescribed for cough is observed in France until 2011, while a decrease is observed in Germany and the UK. The UK showed the sharped decrease, driven by the decline of prescribing of codeine for cough in the younger group (0 – 11 years).

2.4. Risk minimisation activities

The PRAC, having considered the data submitted in the application is of the opinion that the following risk minimisation activities are necessary for the safe and effective use of the medicinal product: changes to the product information and child resistant containers should be recommended for all oral liquid codeine medicines to avoid accidental ingestion.

2.5. Overall benefit/risk assessment

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.

Cough associated with upper respiratory tract infections (URTIs) is the dominating cause of cough in children. The frequency of acute URTIs is also age-related and occurs more frequently in children than in adults. The large majority of childhood respiratory infections with cough are caused by viral infections, which are self-limiting and only lasting for a few days. International guidelines have stated that cough associated with these conditions may be satisfactorily managed with fluids and increased ambient humidity. In the case of chronic cough, treatment should be directed at the underlying disease[24,11] (American Academy of Paediatrics Committee on Drugs 1997, American Academy of Paediatrics, AAP publications retired or reaffirmed 2006).

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 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.

The PRAC reviewed all data available from clinical trials, observational studies, meta-analyses, post-marketing data and further published 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. Moreover the PRAC consulted European healthcare professional organisations and the Paediatric Committee (PDCO).

Overall, only four published studies investigating the use of codeine-containing medicines for the treatment of cough in children could be identified. Two studies[17,18] (Kelly and colleagues, 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 show 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[22,23] (Eccles R 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 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[37,38] (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 have serious consequences.

Based on all the above, the PRAC recommended the restriction 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

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

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[1] 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 Member 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.

2.6. Communication plan

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

- Codeine is an opioid medicine that is widely used for relief of pain and is also authorised for the symptomatic treatment of cough and/or cold. [Insert information on national authorisation and legal status as needed]
- The main therapeutic effects of codeine are due to its conversion into morphine by an enzyme called CYP2D6. Some patients may convert codeine into morphine at a faster than normal (known as ultra-rapid metabolisers), resulting in high levels of morphine in the blood that can cause toxic effects such as breathing difficulties.
- The PRAC, in 2013, had reviewed the benefit-risk of products containing codeine for the relief of pain in children due to some fatal or life-threatening cases of morphine intoxication in children and introduced a number of risk minimisation measures to ensure that only children for whom the benefits are greater than the risks are given codeine for pain relief.
- Given that these risks may also apply to the use of codeine for the symptomatic treatment of cough and/or cold the PRAC subsequently started a review examining the benefits and risks of codeine when used in children for this indication.
- The PRAC has now finalised this review and has recommended that the use of codeine in children for the symptomatic treatment of cough and/or cold should be restricted as follows because of the safety concerns of morphine-like toxicity:
    - Codeine is contraindicated in children under 12 years of age;
    - Codeine is not recommended in paediatric patients aged 12 to 18 years of age with compromised respiratory function.
- In reaching these conclusions the PRAC notes that cough and/or cold is generally a self-limiting condition in children and adolescents and carefully considered the available data relating to safety and efficacy of codeine in the treatment of the cough and/or cold, the advice of the European Paediatric Committee and also clinical guidelines which recommend that persistent chronic cough in children should be treated based on aetiology.

- The PRAC also considered that although morphine-induced side effects may occur at all ages, the current evidence suggests that children below 12 years are at special risk of life-threatening respiratory depression with codeine. There also seems to be a particular risk in those paediatric patients of any age who might already have compromised respiratory function.
- The PRAC also concluded that the following recommendations that arose from the earlier analgesia referral should also apply to the use of codeine in the symptomatic treatment of cough and/or cold:
    - Codeine is contraindicated in patients of any age known to be CYP2D6 ultra-rapid metabolisers as the risk of morphine intoxication is extremely high in these patients.
    - Codeine is contraindicated in women of all ages who are breastfeeding due to an increased risk for the breastfeeding child when the mother is using codeine and she is an ultra-rapid metaboliser.

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, somnolence, respiratory depression, 'pin-point' pupils.

2.7. Changes to the product information

Several sections of the summary of product characteristics (SmPC) have been amended to include the information of this review.

In section 4.2, Posology and method of administration, wording was added on the contraindication in children below the age of 12 years for the symptomatic treatment of acute cough and/or cold. A cross reference to section 4.3 was added.

Also the fact that codeine is not recommended for use in children aged 12 years to 18 years with compromised respiratory function for the symptomatic treatment of cough and/or cold was added to section 4.2. In this regard, in line with the previous referral on codeine for pain relief, a warning was included in the section 4.4., special warning and precautions for use, which list in detail conditions in which the respiratory function might be compromised (i.e. neuromuscular disorders, severe cardiac or respiratory conditions, upper respiratory or lung infections, multiple trauma or extensive surgical procedures).

Regarding Sections 4.3, 4.4 and 4.6 the PRAC was of the view that the previous contraindications, special warning and precautions for use and information introduced in the referral for pain relief in children, should also be applicable to all codeine medicinal products indicated for cough and/or cold in children. These were: the contraindications in women during breastfeeding and also in patients known to be CYP2D6 ultra-rapid metabolisers; warnings on CYP2D6 metabolism including a table listing the estimated prevalence of ultra-rapid metabolisers in different populations; information on breastfeeding women in section 4.6.

Administrative additions to section 4.8, in line with the recent QRD template were introduced.

The package leaflet (PL) was amended 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 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.
- 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.

Therefore, the PRAC recommends 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.

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.

4. Annexes

The list of the names of the medicinal products, marketing authorisation holders, pharmaceutical forms, strengths and route of administration in the Member States are set out Annex I to the opinion.