MHRA PUBLIC ASSESSMENT REPORT

Oral liquid cough medicines containing codeine: should not be used in children and young people under 18 years

October 2010

PLAIN-LANGUAGE SUMMARY

Background

The Medicines and Healthcare products Regulatory Agency (MHRA) is the government agency responsible for regulating medicines and medical devices in the UK. We continually review the safety of all medicines in the UK, and inform healthcare professionals and the public of the latest updates. In our public assessment reports we discuss safety issues associated with a particular medicine or group of medicines. The following report discusses our review of the risks and benefits of over-the-counter (OTC) oral liquid cough medicines containing codeine, in children younger than 18 years.

Codeine has been used for many years for cough suppression and pain relief. Medicines that contain codeine for the relief of dry, non-productive cough are available OTC in pharmacies in the UK[a]. All products containing codeine indicated for cough are sold or supplied under the supervision of a pharmacist (P legal status).
As with any medicine, the use of cough medicines may be associated with risks or adverse drug reactions[b] in some individuals. Adverse reactions that are known to potentially occur in association with a medicine are listed in its product information[c].
Following initial concerns raised in the US about the safety of OTC cough and cold medicines in young children, the risks and benefits of OTC cough and cold medicines for children were reviewed in the UK over 2008–2009 by the MHRA and Commission on Human Medicines[d] (CHM). A package of measures to ensure safer use of these medicines in children was subsequently announced in 2009 (see MHRA webpage [February 2009] and an article in Drug Safety Update, April 2009). As a result of the review, the CHM concluded that OTC cough and cold medicines should not be used in children younger than age 6 years. For children age 6–12 years, these medicines would continue to be available from pharmacies, with clearer advice on the packaging on their use in this age group.

OTC oral medicines containing codeine for the treatment of cough in children were reviewed later and an assessment of the data on the benefits and risks of these products has now been completed as part of the overall review of OTC cough and cold medicines in children. The outcome of the review on codeine-containing cough medicines for children is discussed in this report.

Outcome of review

The CHM and the Paediatric Medicines Expert Advisory Group (one of its expert advisory groups) considered all available data on the safety and efficacy[e] of codeine for the treatment of cough in children, from sources including literature, therapeutic reviews, drug monographs and clinical guidelines. They considered data on all of the safety risks

[a] Brand names of cough medicines containing codeine available in the UK: Bepro Syrup; Care Codeine; Codeine Phosphate Linctus; Evacode Paediatric Linctus; Galcodine Linctus; Galcodine Linctus Paediatric; Pulmo Bailly; Terpin & Codeine Linctus
[b] A response to a drug that is unintended, and harmful or unpleasant. You can report a suspected adverse reaction to any drug or vaccine to the MHRA via the Yellow Card Scheme (www.yellowcard.mhra.gov.uk)
[c] See the Electronic Medicines Compendium (product information) website
[d] An independent body that gives advice to UK government Ministers on the safety, quality and efficacy of medicines
[e] A measurement of the effectiveness of a medicine to produce a desired effect; in this instance, the effectiveness of codeine in relieving cough

associated with codeine, including the risk of possible abuse and dependence in adolescents.

The CHM found that there was a lack of robust evidence supporting the efficacy of codeine in treating cough in children.
The CHM also concluded that the risks associated with OTC oral liquid medicines containing codeine for the treatment of cough outweighed the benefits in children and young people under 18 years, and advised that:

- OTC oral liquid medicines containing codeine should no longer be used to treat cough in children and young people under 18 years

- All OTC oral liquid codeine medicines should be supplied in child-resistant containers to minimise the risk of accidental ingestion by children.

The packaging and leaflets for OTC liquid cough medicines that contain codeine are being updated with the new advice that they are not for use in children and young people under 18 years. The new information will begin to appear in 2011; in the meantime, existing medicines will continue to be sold as before.

Although coughs and colds occur frequently in children, they are self-limiting conditions and will usually get better by themselves. Please refer to our webpages for information on children's OTC cough and cold medicines, and general information on medicines for children.

1. INTRODUCTION

(See glossary on pg 17 for explanation of terms used in this report)

The Medicines and Healthcare products Regulatory Agency (MHRA) is the government agency responsible for regulating medicines and medical devices in the UK. We continually review the safety of all medicines in the UK, and inform healthcare professionals and the public of the latest updates. In our public assessment reports we discuss safety issues associated with a particular drug or drug class. The following report discusses our review of the risks and benefits of over-the-counter (OTC) oral cough medicines containing codeine, in children younger than age 18 years.

Codeine, or methylmorphine, is a natural alkaloid opiate found in opium poppy and was first isolated in 1832 in France. It is currently the most widely used opiate as an analgesic and is also used as an antitussive in syrups and oral solutions, manufactured under several different brand names and generic labels. In the UK, medicines containing codeine or codeine phosphate are currently licensed for the management of dry, non-productive cough commonly associated with upper respiratory tract infections (URTIs), and are only available in pharmacies[a].

As with any medicine, the use of cough medicines may be associated with risks or adverse drug reactions in some individuals. Following initial concerns raised in the US about the safety of OTC cough and cold medicines in young children, the risks and benefits of OTC cough and cold medicines for children were reviewed in the UK over 2008–2009 by the MHRA and the Commission on Human Medicines[b] (CHM). A package of measures to ensure safer use of these medicines in children was subsequently announced in 2009 (see MHRA webpage [February 2009] and an article in Drug Safety Update, April 2009). As a result of the review, the CHM concluded that OTC cough and cold medicines should not be used in children younger than age 6 years. For children age 6–12 years, these medicines would continue to be available from pharmacies, with clearer advice on the packaging on their use in this age group.

OTC oral medicines containing codeine for the treatment of cough in children were reviewed later and an assessment of the data on the benefits and risks of these products has now been completed by the MHRA and the CHM as part of the overall review of OTC cough and cold medicines in children. The results of the review of codeine-containing cough liquid medicines for children are discussed in this report.

[a] Brand names of cough medicines containing codeine available in the UK: Bepro Syrup; Care Codeine; Codeine Phosphate Linctus; Evacode Paediatric Linctus; Galcodine Linctus; Galcodine Linctus Paediatric; Pulmo Bailly; Terpin & Codeine Linctus

[b] An independent body that gives advice to UK government Ministers on the safety, quality and efficacy of medicines

2. EFFICACY DATA ON CODEINE AS AN ANTITUSSIVE IN CHILDREN

Cough serves as a physiological function to clear airways of obstructive or irritating material or to warn of noxious substances in inspired air. The causes or origins and prognosis of cough in children is significantly different to adults. Data on the effect of sleep on cough is also different in children compared to adults. It is thought that cough does not occur in the Rapid eye Movement (REM) stage of sleep in adults, however a study in children has objectively recorded cough in the active or REM sleep phase[1]. Three of the main causes of chronic cough in adults (asthma, gastro-oesophageal reflux and post-nasal drip) are less common in children. Furthermore the reasons for seeking medical attention for cough in children differ from adults. The common concerns expressed by parents seeking medical attention for their child's cough are: lack of sleep; concerns about the child having asthma; fear of their child choking; and fear that cough can cause permanent chest damage.

Although the use of codeine as a cough medication has been widespread, evidence of its efficacy is lacking in both adults and children. A 2008 Cochrane review[2] reported that the effect of codeine in adults was tested in two trials and appeared no more effective than placebo in reducing cough symptoms[3,4]. One of these studies tested codeine in a two-phase study (laboratory and home) at a dose of 30 mg four times daily for four days (n=81)[3]. Codeine was no more effective than placebo either as a single dose or as a total daily dose of 120 mg ($p > 0.2$). In the second study, only the effect of a single 50 mg dose of codeine was tested against placebo (n=82)[4]. The mean subjective score on a five-point rating scale was non-significantly reduced from 2.0 to 1.0 ninety minutes after treatment ($p = 0.8$) in both treatment groups. Neither study provided any data on side effects.

There are four studies identified in the literature in children up to age 18 years, which have investigated the efficacy of cough and cold medicines containing codeine in the management of acute cough. Overall, although codeine has been widely used for many years, there is no robust evidence to prove it beneficial in the paediatric population. Matthys H et al (1982)[5] conducted a double-blind, crossover trial using both an objective and subjective assessment of efficacy in sixteen patients with chronic, stable cough comparing dextromethorphan (another opiate compound which suppresses cough) to codeine in children age 0–18 years. Both medications (dextromethorphan 20mg, codeine 20mg) were similarly effective in reducing cough frequency. Dextromethorphan significantly reduced cough intensity by a greater degree than codeine ($p < 0.0008$) and was considered the better antitussive by the majority of patients ($p < 0.001$).

Another study compared the effect of codeine and dextromethorphan compared to placebo in the paediatric population[6]. The study looked at 57 children (mean age 4.7 years, range 18 months to 12 years) with night cough due to URTI. The children were randomly allocated to dextromethorphan 15 mg/5 mL in conjunction with guaifenesin (an expectorant used for management of coughs) or codeine 10 mg/5 mg in conjunction with guaifenesin 100 mg, or placebo as a single dose at bed time for three nights. The effect of the treatment was measured using parental questionnaires which evaluated cough scores from 0 to 4, where a score of 4 indicated cough at its worst. Mean cough and composite scores decreased in each of the three treatment groups on each day of the study, including the placebo group and neither codeine with guaifenesin, nor dextromethorphan with guaifenesin, was superior to placebo in alleviating the symptoms of acute night cough in children. The two medications and placebo were virtually identical

in efficacy regardless of the outcome measure employed, and after three days, cough was significantly reduced regardless of specific therapy.

A report in 1963[7] described the results of two paediatric studies investigating the antitussive effects of pholcodine (another opioid-based antitussive medicine). One of the studies, a pilot study, looked at 25 children with acute cough. Complete cough suppression was observed in 19 children, and marked improvement in cough was observed in the remaining six. A full sized comparative study was subsequently undertaken in children age between 8 months to 17 years. In this study 26 children with productive and unproductive cough received codeine, 27 received pholcodine, and eight received both treatments on a crossover basis. The children were allocated to groups on a matching basis, and parents were asked to keep records of efficacy and side effects. Both dosing regimes produced an antitussive effect in 90% of patients, but the duration of effect was greater in the pholcodine group than in the codeine group (4 hours versus 3 hours). Both productive and non-productive symptoms were improved, with the efficacy rating incorporating cough suppression, sleep, and disturbance of rest.

Finally, a randomised, single-blind comparative trial looked at 217 children aged between 6 –12 years and compared the efficacy and palatability of two combination products given for 3 days[8]. Patients had acute cough but no severe infection, with median symptom duration of 3 days. Each patient received either a product containing (per 5 mL) paracetamol 150 mg, pholcodine 5 mg and phenylpropanolamine 12·5 mg 5 mL four times daily, or a product containing (per 5 mL) triprolidine hydrochloride, pseudoephedrine hydrochloride and codeine phosphate 10 mg 7·5 mL three times daily. No placebo groups were included, and the characteristics of each treatment group were similar. Efficacy was measured using scores for productive cough, dry cough, sore throat and other cold symptoms. Both products showed highly significant improvements for productive cough and sore throat. The group using the codeine-containing product showed a significant improvement in dry cough whereas the non-codeine group showed significant improvement in other symptoms, based primarily on headache, earache and catarrh.

Summary comments:

Codeine has been considered to be the most effective antitussive for acute cough and has been regarded as the reference drug to which the effects of other antitussive agents should be compared. Based on the above literature review however, it is clear that there is little evidence to support the use of codeine to relieve cough caused by the common cold in children.

3. SAFETY DATA ON CODEINE IN CHILDREN

3.1 Pharmacogenetics of codeine metabolism

Laboratory studies in both animals and adult humans have shown that there is significant variability in both the pharmacokinetics and pharmacodynamics of codeine. These studies also suggest that the therapeutic effects of codeine (as an analgesic) as well as the opioid-related side effects are either wholly or mostly dependent on its metabolism to morphine. Generally, up to 3% of codeine is metabolised in the liver to morphine[9]; other metabolites include norcodeine, normorphine and hydrocodone. Quiding et al (1992)[10] have reported findings in infants and young children (6 months to 4 years) after rectal administration, concluding that children were capable of demethylating codeine to morphine at the age of 6 months although glucuronidation of morphine appeared to be impaired when compared with older children.

Metabolism to morphine is through demethylation mediated by the cytochrome P450 isoenzyme CYP2D6, which shows genetic polymorphism. Over 50 different genetic variants are known to exist for CYP2D6, which leads to a wide spectrum of metabolic capabilities within populations. Individuals are normally classified as either 'poor metabolisers' (PM) or 'extensive metabolisers' (EM), depending on the activity of the enzyme, although this is thought to be an oversimplification. PMs will produce little or no morphine from codeine, whereas EMs will produce morphine, although the actual amount may show wide variation between individuals. Approximately 6–10% of Europeans, 2% of Asians, and 1% of Arabs are PMs[11]; however even these patients will still experience many of the adverse effects due to the presence of the metabolite morphine[a].

The implications of paediatric codeine use with regard to its metabolism to morphine have been investigated in a number of articles[11,12,13]. In these studies, the researchers concluded that "reduced ability for codeine metabolism may be more common than previously reported"[11]. The frequency of CYP2D6 ultra-rapid metaboliser genotypes ranges from 1% in Finland and Denmark, to 10% in Greece and Portugal, and 29% in Ethiopia[14]. The clinical importance of CYP2D6 genetic polymorphism is undisputed as it leads to uncertainty and variability in the efficacy and safety of drugs such as codeine in the paediatric population, as well as in adults. All available pharmacokinetic data for the recommended doses of codeine in children have been extrapolated from adults, as there are no specific data in the paediatric subsets.

3.2 Potential interactions with other medicines

Codeine may delay the absorption of a number of drugs and may antagonise the effects of metoclopramide on gastrointestinal motility. The effects of other CNS depressants, eg, hypnotics, sedatives or alcohol may be potentiated by codeine.

CYP2D6 inhibitors and can reduce or even completely block the conversion of codeine to morphine. The most well-known of these medications are two selective serotonin reuptake inhibitors (antidepressant medicines) paroxetine and fluoxetine, as well as the

[a] Common adverse effects of morphine include: respiratory depression; nausea; vomiting; constipation; dizziness; drowsiness; dependence and withdrawal (see the Summary of Product Characteristics on the electronic Medicines Compendium for more information)

antihistamine diphenhydramine and the antidepressant buproprion. Other drugs, such as rifampicin and dexamethasone, induce CYP450 isozymes and thus increase the conversion rate.

3.3 Toxicity and overdose

The toxicity of codeine is associated with its opioid effects; however it is important to notice that the effects of overdose will be potentiated by simultaneous ingestion of alcohol and psychotropic drugs. Reduced levels of consciousness and respiratory depression are recognised features of codeine toxicity. The pupils may beome pin-point in size and nausea and vomiting are common. Hypotension and tachycardia are also possible consequences of codeine overdose.

Toxbase (the online database of the National Poisons Information Service) states that because codeine is metabolised to the active metabolite morphine, the course of poisoning due to an overdose of codeine may be prolonged. A fatal dose is likely to vary between individuals depending on tolerance and rates of metabolic conversion to morphine. This is especially the case where poisoning effects may be prolonged, such as in patients with renal impairment, and in the elderly. The renal clearance of codeine and its metabolites is significantly reduced in patients with end-stage renal disease on regular haemodialysis therapy.

The estimated minimum lethal dose is 800 mg, but codeine is much less toxic than morphine and death directly attributable to codeine is rare; in most fatalities involving codeine, other drugs and/or alcohol are also present. Drug addicts may use doses up to 10 times the normal dose before showing toxic effects, whilst children may show toxicity with only 1/20th of the dose[15].

Management of overdose includes the use of naloxone if coma or respiratory depression is present (0.4 mg to 2 mg for an adult and 0.01 mg/kg body weight for children). The use of activated charcoal is not established but a dose of 50 g for adults and 1 g/kg body weight for children is recommended if more than 3 mg/kg has been ingested within 1 hour, provided the airway can be protected.

3.4 Contraindications and special warnings

Codeine causes slight bronchoconstriction (as does morphine) and therefore should be used with caution if a bronchospastic condition already exists. Codeine should not be used in patients with chronic bronchitis and bronchiectasis, and should be used with caution in patients with other respiratory disorders, and in patients with kidney and liver disease.

At recommended antitussive doses and duration of treatment, addiction to codeine is unlikely to occur, however prolonged use of codeine-containing products can lead to a morphine-type of dependence. Due to this safety consideration, the majority of the codeine-containing products include a warning in the Summary of Product Characteristics (SPC) regarding the potential dependence of the drug, recommending ‘do not exceed the stated dose’ and ‘short term use only’.

Codeine is subject to abuse, but produces less euphoria and sedation than morphine. Cough and cold remedies are mentioned by both pharmacists and the public in most

studies as products prone to abuse among adolescents and adults, but no individual data on abuse for codeine and its paediatric use have been produced.

For more information on contraindications and special warnings for codeine, please refer to the SPCs of individual products

3.5 Side effects

3.5.1 Data on known side effects

In therapeutic doses codeine is much less liable than morphine to produce adverse effects, although constipation may be troublesome with long-term use. After large doses of codeine, excitement, euphoria, hallucinations and convulsions may occur. Codeine, like morphine, has a dose-related histamine-releasing effect; however anaphylactic reactions after intravenous use have only been reported rarely. The following side effects have also been seen with codeine: nausea, vomiting, biliary spasm, orthostatic hypotension, oliguria, allergic reactions (pruritis, skin rash, and facial oedema), syncope, dizziness, sedation, visual disturbances, tachycardia, bradycardia and palpitations.

In the previously-mentioned efficacy studies in children (section 2), mild side effects were reported, although the relevant data is mostly unavailable. In most cases the duration of the treatment and the follow up review period within the investigations was very short. As in most of these studies children were treated with either codeine or another centrally acting antitussive with similar safety profile, the assessment of the individual findings per treatment arm is very difficult. The most commonly reported effect was drowsiness, hyperactivity, nausea and constipation (Jaffe and Grimshaw 1983, Kelly 1963, Taylor 1993). These findings do not differ from the side effects reported in the adult efficacy studies.

Breast-fed infants of mothers taking codeine may be at an increased risk of toxicity from its metabolite, morphine, if the mother is an ultrarapid metabolizer of codeine. The US Food and Drug Administration (FDA)[16] issued advice in 2007 that nursing mothers taking codeine should be informed of the potential risk of morphine overdose and the need to monitor breast-fed infants of mothers taking codeine-containing medicines for signs of toxicity such as increased sleepiness, difficulty feeding or breathing, or limpness. Nursing mothers, themselves, may also experience overdose symptoms including extreme sleepiness, confusion, shallow breathing, and severe constipation. Similar advice has also been issued by the MHRA in the UK (see Drug Safety Update November 2007)[17]. Nonetheless, several prescribing lists including the American Academy of Pediatrics[18] and the British National Formulary (BNF)[19] consider that the maternal consumption of codeine is usually compatible with breast feeding as ‘the amount is usually too small to be harmful’; however, the BNF also states that ‘mothers vary considerably in their capacity to metabolise codeine – there may be a risk of morphine overdose in infant (BNF March 2010).

3.5.1 Case reports of suspected side effects

A suspected adverse drug reaction (ADR) to any medicine or vaccine can be reported to the MHRA using the Yellow Card Scheme (www.yellowcard.mhra.gov.uk). All reports of suspected ADRs made to the MHRA are listed in Drug Analysis Prints on our website. Up until 9 March 2010, there were 1284 reports of suspected ADRs associated with codeine. Of these cases, 48 were reported in children age 0–16 years, or in an age group defined as neonate, infant, child or adolescent. Five of the case reports in children were reported

specifically with a liquid formulation of codeine administered for cough or cold. The suspected reactions in these five reports included purpura, encephalitis, and urticaria. One report was of a fatality of a child age 7 months treated for a respiratory infection but there are insufficient data on this case to determine the cause of death, or whether codeine was associated with the fatality.

There were also case reports of ADRs associated with use of codeine for pain relief across the age groups. The most frequently reported reactions were skin reactions, including erythema, pruritus, urticaria and rash (11 cases), GI reactions including abdominal pain and/or vomiting (six cases), respiratory reactions (four cases) including wheezing, dyspnoea and respiratory depression (one case). There was also one case of hallucination and one case of epilepsy (both in adolescents) and four cases of dizziness and loss of consciousness, all of them in children older than age 15 years. The more severe ADRs were associated with parenteral administration of codeine as pain relief. All these reactions are known to be associated with the established safety profile of codeine. Overall there do not appear to be significant differences of reported ADRs between children in the different age groups. However are no comprehensive paediatric usage data for codeine and it is difficult to determine frequency and incidence of adverse events from case reports.

3.5.2 Data on the safety of codeine published in literature

There are a number of documented cases of codeine overdose in children in published literature. Hermanns-Clausen et al (2009)[20] reported two cases of codeine intoxication in twin brothers age 3 years while being treated with a codeine slow-release formulation. The twins had identical CYP2D6 gene polymorphisms corresponding to the EM type, which could have caused ultra-rapid metabolism of codeine to morphine. The genetic polymorphism leading to ultra-rapid metabolism of codeine into morphine has been also defined as the aetiological factor for other incidences of serious codeine intoxications, particularly in very young children. Voronov et al in 2007[21] described a similar serious case in a child age 29 months. A near-fatal case in a child age 3 months was reported in the UK in 1981[22], demonstrating that infants are at special risk for severe adverse events such as respiratory depression, due to immaturity, genetic polymorphism, and dosing errors.

Acute codeine intoxication in 430 children, due to accidental ingestion of antitussive preparations, was reviewed in 1976[23]. The children were nearly all age 1–6 years. Symptoms in decreasing order of frequency included somnolence, rash, miosis, vomiting, itching, ataxia, and swelling of the skin. Respiratory failure occurred in eight children, of whom two died; all eight children who experienced respiratory failure had taken 5 mg/kg of codeine or more.

The risk of adverse effects increases if the child has an underlying medical condition. A boy age 5 years with renal impairment received codeine; after four doses, he was found apnoeic. Accumulation of the active morphine metabolite (M6G) because of renal insufficiency was presumed (M6G serum level 230 ng/ml)[24]. Seizures associated with intravenous administration of codeine have been reported in the literature in a child with sickle cell anaemia[25], although such a risk has not been identified in the oral preparations. However, a case of dystonia in a girl age 3 years as an acute reaction to codeine cough preparation has been reported[26], which was concluded to be due to depression of the CNS sensory area and excitation of subcortical and spinal motor pathways. These cases highlight the rare but serious adverse effects in the nervous system in children treated with centrally acting cough suppressants, including irritability, restlessness, lethargy and hallucinations.

The overall use of OTC cough and cold medicines in children has been under scrutiny in the last couple of years due to efficacy as well as major safety concerns. A report from the USA in 2008 reviewed adverse events associated with cough and cold medicines in children. The report estimated that, nationally, 7091 patients age younger than 12 years attended emergency departments as a result of ingesting inappropriate doses of cough and cold medicines, and that of these 64% were in the age group 2–5 years. Neither the medicines nor their ingredients were specifically named. Most children (93%) did not require admission or extended observation[27].

3.6 Data from UK National Poisons Centres

23 case reports of poisoning associated with accidental consumption or therapeutic error with liquid preparations of codeine, were reported to UK National Poisons Centres between 1 Jan 2008 – 31 Dec 2009. 20 of the 23 cases were in children age younger than 5 years. Despite limitations in the data, and the overall very small number of cases, it is clear that codeine liquid formulations could be associated with a risk for incorrect dosing or accidental use particularly in the cases of very young children.

Summary comments:

The safety data available on codeine-containing products suggests there are serious concerns which need to be taken into account when assessing the risk:benefit balance of these products The information relevant to use in the treatment of cough is even harder to assess as codeine is widely used in adults and in children for moderate to severe pain.

4. DISCUSSION

Codeine has been used extensively over many years as an antitussive in patients across all age groups, including children. It is generally accepted as a standard or reference antitussive against which newer antitussive medications can be compared, although its efficacy has been questioned by some authors.

Drug actions:

As codeine is not considered to act differently in children compared with adults, PD and PK data have been widely extrapolated from adults. In addition, metabolism of codeine to morphine is catalysed by the cytochrome P450 enzyme CYP2D6, which is subject to genetic polymorphism. The clinical importance of this genetic polymorphism is undisputed as it leads to variable outcomes regarding codeine's efficacy and safety profile in the paediatric population as well as in adults.

Efficacy:

Efficacy across the age groups, particularly in paediatric patients, is not based on robust data. Most of the paediatric studies identified in the literature are very old and fail to prove claims of efficacy across the investigated outcomes. In all of them, there are important issues regarding the overall quality of the trial design and the measurement of endpoints such as: definition and timing of treatment outcomes, adequacy of dose, dosing frequency, and duration of therapy. No well-controlled scientific studies were found to support the efficacy and the antitussive effect of codeine in children.

Safety: Codeine has a central mode of action and its toxicity is associated with its opioid effects. Based on the overall review, there are serious concerns of its safety profile as codeine is metabolized to morphine in an unpredictable rate. Additionally there is a risk of misuse and abuse of codeine preparations, mainly associated with the risk of addiction to over-the-counter painkillers. The risk of addiction with codeine has not been investigated extensively in association with treatment for cough, although such cases have been reported globally and in the UK.

Summary:

From the ADRs reported to the MHRA it is clear that there is no cut-off age group in children that is safe for codeine-based antitussives to be used. Based on the overall 2009 review of the centrally acting opioid antitussives dextromethorphan and pholcodine, the evidence suggested that they should not be used in children younger than age 6 years due to safety concerns and lack of robust efficacy data. However codeine has a less favourable safety profile than these products due to its variable metabolism and the possible abuse and dependence in young adults and adolescents. These characteristics differentiate codeine from the other related antitussive agents which had already been considered in the previous review of OTC cough and cold remedies. Therefore, liquid codeine medicines should no longer be indicated as antitussives for children and young people from age 0–18 years.

5. CONCLUSIONS AND RECOMMENDATIONS

After consideration of all available data the CHM found that there was a lack of robust evidence supporting the efficacy of codeine in cough suppression in children. They also considered data on all of the safety risks associated with codeine, including the risk of possible abuse and dependence in adolescents.

The CHM concluded that the risks associated with OTC oral liquid codeine medicines for cough suppression outweighed the benefits in children and young people under 18 years, and advised that:

- OTC oral liquid medicines containing codeine should no longer be used for cough suppression in children and young people under 18 years

- All OTC oral liquid codeine medicines should be supplied in child-resistant containers to minimise the risk of accidental ingestion by children.

The packaging and leaflets for OTC liquid cough medicines that contain codeine are being updated with the new advice that they are not for use in children and young people under 18 years. The new information will begin to appear in 2011; in the meantime, existing medicines will continue to be sold as before.

Recommended wording in SPCs for codeine-containing antitussive products

Indication (4.1)

Codeine is indicated in adults….

Posology (4.2)
Paediatric population:
Codeine should not be used for the treatment of cough in children under the age of 18 years.

Recommended wording in SPCs for all codeine-containing products

Section 4.4 special warnings and precautions:

Codeine is partially metabolised by CYP2D6. If a patient has a deficiency or is completely lacking this enzyme they will not obtain adequate analgesic effects. Estimates indicate that up to 7% of the caucasian population may have this deficiency. However, if the patient is an ultra-rapid metaboliser there is an increased risk of developing side effects of opioid toxicity even at low doses. General symptoms of opioid toxicity include nausea, vomiting, constipation, lack of appetite and somnolence. In severe cases this may include symptoms of circulatory and respiratory depression. Estimates indicate that up to 1 to 2% of the caucasian population may be ultra-rapid metabolisers.

The leaflet will state in the "Pregnancy and breast-feeding" subsection of section 2 "Before taking your medicine":

Usually it is safe to take “brand name” while breast feeding as the levels of codeine in breast milk are too low to cause your baby any problems. However, some women who are at increased risk of developing side effects at any dose may have higher levels of codeine in their breast milk. If any of the following side effects develop in you or your baby stop taking this medicine and seek immediate medical advice; feeling sick, vomiting, constipation, decreased or lack of appetite, feeling tired or sleeping for longer than normal, and shallow or slow breathing.

Section 4.6 Pregnancy and lactation

At normal therapeutic doses codeine may be present in breast milk at very low doses and is unlikely to adversely affect the breast fed infant.

However, if the patient is an ultra-rapid metaboliser of CYP2D6, higher levels of codeine may be present in breast milk and on very rare occasions may result in symptoms of opioid toxicity in the infant.

If symptoms of opioid toxicity develop in either the mother or the infant, then all codeine containing medicines should be stopped and alternative non-opioid analgesics prescribed. In severe cases consideration should be given to prescribing naloxone to reverse these effects.

6. REFERENCES

1. Fuller P, Picciotto A, Davies M, McKenzie SA. Cough and sleep in inner-city children. *Eur Respir J* 1998; **12**: 426–431.

2. Smith SM, Schroeder K, Fahey T. Over-the-counter medications for acute cough in children and adults in ambulatory settings. *Cochrane Database Syst Rev* 2008 Jan; **23**(1): CD001831.

3. Eccles R, Morris S, Jawad M. Lack of effect of codeine in the treatment of cough associated with acute upper respiratory tract infection. *J Clin Pharm Ther* 1992 **17**: 175–180.

4. Freestone C, Eccles R. Assessment of the antitussive efficacy of codeine in cough associated with common cold. *J Pharm Pharmacol* 1997; **49**: 1045–1049.

5. Matthys H, Bleicher B, Bleicher U. Dextromethorphan and codeine: objective assessment of antitussive activity in patients with chronic cough. *J Int Med Res* 1983; **11**(2): 92–100.

6. Taylor JA, Novack AH, Almquist JR, Rogers JE. Efficacy of cough suppressants in children. *J Pediatr* 1993; **122**(5 Pt 1): 799–802.

7. Kelly DA. Comparative clinical test of pholcodine with codeine as control. *Northwest Med* 1963; **62**: 871–874.

8. Jaffe G, Grimshaw JJ. Randomized single-blind trial in general practice comparing the efficacy and palatability of two cough linctus preparations, ‘Pholcolix’ and ‘Actifed’ Compound in children with acute cough. *Curr Med Res Opin* 1983; **8**(8): 594–599.

9. Armstrong SC, Cozza KL. Phramcokinetic drug interactions of morphine, codeine and their derivatives: theory and clinical reality, Part II. *Psychosomatics* 2003; **44**: 515–520

10. Quiding H, Olsson GL, Boreus LO, Bondesson U. Infants and young children metabolise codeine to morphine. A study after single and repeated rectal administration. *Br J Clin Pharmacol* 1992; **33**: 45–49

11. Williams DG, Patel A, Howard RF. Pharmacogenetics of codeine metabolism in an urban population of children and its implications for analgesic reliability. *Br J Anaesth* 2002; **89**(6): 839–845.

12. Madadi P, Koren G. Pharmacogenetic insights into codeine analgesia: implications to pediatric codeine use. *Pharmacogenomics* 2008; **9**(9): 1267–1284.

13. Koren G, Cairns J, Chitayat D, Gaedigk A, Leeder SJ. Pharmacogenetics of morphine poisoning in a breastfed neonate of a codeine-prescribed mother. *Lancet* 2006; **368**: 704

14. Cascarbi I. Pharmacogenetics of cytochrome P4502D6: genetic background and clinical implication. *Eur J Clin Invest* 2003 **33**: (suppl 2): 17–22.

15. Clarke's Analysis of Drugs and Poisons http://www.medicinescomplete.com/mc/clarke/current/ [last accessed in September 2010].

16. FDA, http://www.fda.gov/ [last accessed in September2010].

17. MHRA. Codeine: very rare risk of side-effects in breastfed babies. *Drug Safety Update* 2007; **1**(4): 3.

18. American Academy of Pediatrics Committee on Drugs. Use of codeine- and dextromethorphan-containing cough remedies in children. *Pediatrics* 1997; **99:** 918–920

19. British National Formulary, http://bnf.org/bnf/index.htm [last accessed in September 2010]

20. Hermanns-Clausen M, Weinmann W, Auwärter V, Ferreirós N, Trittler R, Müller C, Pahl A, Superti-Furga A, Hentschel R. Drug dosing error with drops: severe clinical course of codeine intoxication in twins. *Eur J Pediatr* 2009; **168**(7): 819–824.

21. Voronov P, Przybylo HJ, Jagannathan N. Apnea in a child after oral codeine: a genetic variant—an ultra-rapid metabolizer. *Paediatr Anaesth* 2007; **17**: 684–687

22. Wilkes TC, Davies DP, Dar MF () Apnoea in a 3-month-old baby prescribed compound linctus containing codeine. *Lancet* 1981; **23**:1(8230):1166–1167.

23. von Muhlendahl KE, Scherf-Rahne B, Krienke EG, Baukloh G. Codeine intoxication in childhood. *Lancet* 1976; **7**:2(7980): 303–305.

24. Talbott GA, Lynn AM, Levy FH, Zelikovic I. Respiratory arrest precipitated by codeine in a child with chronic renal failure. *Clin Pediatr (Phila)* 1997; **36**: 171–173

25. Zolezzi M, Al Mohaimeed SA. Seizures with intravenous codeine phosphate. *Ann Pharmacother* 2001; **35**(10):1211–1213.

26. Polizzi A, Incorpora G, Ruggieri M. Dystonia as acute adverse reaction to cough suppressant in a 3-year-old girl. *Eur J Paediatr Neurol* 2001; **5**(4): 167–168.

27. Schaefer MK, Shehab N, Cohen AL, Budnitz DS. Adverse events from cough and cold medications in children. *Pediatrics* 2008 Apr; **121**(4): 783–787.

7. GLOSSARY

Activated charcoal
Porous charcoal that is used to treat poisonings and overdoses

Aetiology
The causes or origins of a disease

Alkaloid
A family of chemical compounds found in plants, many of which are **pharmacologically** active

Analgesic
Medicine used to relieve pain

Anaphylactic reactions
A sudden, severe allergic reaction in the body. The symptoms include a sharp drop in blood pressure and breathing difficulties.

Antihistamine
A drug used to treat allergic reactions

Antitussive
Medicine used to relieve or suppress cough

Ataxia
Loss of voluntary muscle control, which results in lack of balance and coordination

Biliary spasm
Spasms of the gallbladder or its ducts (within the **gastrointestinal** system)

Bradycardia
Abnormally slow heartbeat

Bronchi
Respiratory airways

Bronchiectasis
Abnormal and chronic dilation (widening) of the **bronchi**

Bronchitis
Inflammation of the **bronchi**

Bronchoconstriction
Narrowing (constriction) of bronchi due to exposure to irritant chemicals or diseases such as asthma

Bronchospastic
Contraction of bronchial walls in conditions such as asthma, which causes breathing difficulties

Clinical trial

A research study that tests the effectiveness and safety of medicines in humans

Codeine
An **opiate antitussive** or **analgesic** medicine

Cross-over study
A **clinical trial** which tests a medicine in one group of volunteers against another group taking either an inactive treatment or a different medicine for comparison. The groups exchange treatment after an agreed amount of time

CYP2D6
One of the **cytochrome P450 isoenzyme** family

Cytochrome
A substance in cells in the body consisting of a protein linked to haem (another substance containing iron)

Cytochrome P450 isoenzymes
A family of proteins which break down many substances in the body

Demethylation
Removal of a chemical called a methyl group from a substance, which occurs during its **metabolism**

Dependency
A compulsion to keep taking a drug or substance

Dexamethasone
A drug used to treat inflammation

Dextromethorphan
A drug used to treat cough (an **antitussive**)

Double-blind trial
A clinical trial in which the identity of the test medicine is hidden from both the volunteers and the study investigators (to remove any possible bias from the results)

Dyspnoea
Difficulty in breathing

Dystonia
Abnormal muscle contractions

Efficacy
The effectiveness of a drug measured under laboratory conditions or in clinical trials

Encephalitis
Inflammation of the brain, usually caused by a viral infection

Epilepsy
A brain condition characterised by fits or **seizures**

Erythema

Abnormal redness of the skin resulting from the widening of blood vessels called capillaries. It is usually caused by inflammation or sunburn

Euphoria
A feeling of exaggerated well-being experienced by users of certain drugs, such as **opiates**

Extrapolate
To make an extended or general estimate, based on specific cases

Gastrointestinal
Related to the stomach and intestines

Gastro-oesophageal reflux
The return of some stomach contents and/or stomach acids back up into the oesophagus (feeding tube) which occurs normally. The acids can produce a burning sensation in the oesophagus, and may cause cough

Genetic polymorphism
Differences in DNA between individuals which can result in different forms, eg, blood group types, or metabolisers of certain drugs such as opiates

Glucuronic acid
A substance in the body that combines with certain drugs such as codeine during its **metabolism**

Guaifenesin
A drug that helps expel the excess mucus from the respiratory tract that may occur in upper respiratory tract infections or colds. As excess mucus may worsen cough, guaifenesin is often found in OTC cough and cold remedies

Haemodialysis
The process of filtering waste products from the blood. This is performed by a specialised machine and is usually needed by patients whose kidneys (which perform this function naturally) do not work properly

Half-life
The time required for the concentration or amount of drug in the body to be reduced by half

Hallucinations
Perception of visions or sounds that are not actually real. They can be caused by a number of factors, including consumption of certain drugs such as **opiates**

Hypnotics
A drug used to induce sleep

Ibuprofen
Type of pain-relief medicine

Medulla oblongata
The lowest part of the brainstem which controls breathing, heart rate and blood pressure

Metabolism

The chemical processes or changes that occur in the body in order to maintain life. This involves either breaking down substances or making new ones

Metoclopramide
A drug used to treat nausea and vomiting

Miosis
Constriction (narrowing) of the pupil of the eye, as a normal response to light or resulting from the use of certain drugs such as **opiates**

Morphine
An **opiate analgesic** medicine

Naloxone
A drug that blocks the actions of **opiates**, and is used to counteract the effects of opiate overdose

Neonate
Newborn infant

Noxious
May cause harm or injury to mental or physical health

Oedema
Accumulation of fluid in body tissues from injury, inflammation or disease, resulting in swelling

Oliguria
The production of an abnormally small amount of urine, which may be caused by kidney disease

Opiate
A drug derived from opium (a substance found in the plant opium poppies) which is used in medicine as an **analgesic** or **antitussive**. Opiates also cause euphoria and are therefore sometimes misused, leading to addiction and **dependence**, and sometimes overdose

Opioid
A drug that acts by binding to opioid receptors in the body. These include **opiates** derived from the opium poppy such as **codeine** and **morphine**, synthetically-produced opioid drugs such as **pholcodeine** and naturally-occurring opioids produced by the body

Orthostatic hypotension
Sudden low blood pressure that occurs in some people when they stand up suddenly

Paediatric
Related to, or occurring in, children

Paracetamol
Type of pain-relief medicine

Pharmacodynamics
The biochemical and physiological effects of drugs in the body, and the mechanisms of their actions

Pharmacogenetics
A subsection of genetics which examines genetically-determined variations in responses to drugs

Pharmacokinetics
The process by which a drug is absorbed, distributed, metabolised and eliminated by the body

Phenylpropanolamine
A drug used to relieve allergic reactions or respiratory infections

Pholcodine
An **opioid** cough suppressant (antitussive)

Placebo
Inactive dummy treatment given in a **clinical trial** to a particular patient group so their responses can be compared with the group receiving the test medicine

Post-nasal drip
Where excessive mucus is produced, due to allergies or infection, and accumulates in the back of the nose the throat

Potentiate
Increase the effect of a drug

Prognosis
A prediction of the probable course and outcome of a disease

Pruritis
Severe itching of skin

Pseudoephedrine hydrochloride
A drug that narrows blood vessels, used mainly to clear a blocked nose (a nasal decongestant)

Psychotropic drugs
Drugs that act primarily upon the central nervous system causing alterations in brain function, which can result in changes in mood and behaviour

Purpura
A skin rash resulting from bleeding into the skin from small blood vessels called capillaries

Randomised controlled trial
A **clinical trial** in which the study participants are randomly assigned to receive a test medicine, or a **placebo** or comparator medicine

Rapid Eye Movement (REM) sleep
A period during the normal sleep cycle during which dreams occur, which is characterised by the eyes moving rapidly behind the eyelids

Renal clearance
A measurement used to test kidney function

Renal impairment
Partial or complete loss of normal kidney function

Respiratory depression
A decrease in breathing rate, which can be caused by an overdose of **opiate** medication. It can become potentially life-threatening

Rifampicin
An antibacterial and antifungal drug

Sedation
A state of reduced excitement or activity that is induced by drugs called sedatives

Seizure
Uncontrolled electrical activity in the brain that produces fits or convulsions of the body

Somnolence
Sleepiness

Spinal motor pathways
A nerve pathway that conducts nerve impulses from the brain down through the spinal cord

Subcortical pathways
Nerve pathways located in a part of the brain called the subcortex

Syncope
Faint, or temporary loss of consciousness

Tachycardia
An abnormal increase in heart rate

Tolerance
Where a drug user has become physically accustomed to a particular dose of the drug which causes an effect and therefore requires increasing doses to obtain the same effect

Triprolidine hydrochloride
A drug used to treat allergic symptoms which is sometimes combined with cold medicines

Upper respiratory tract infections
An illness caused by infection in the nose, sinuses or throat, such as the common cold, characterised by symptoms such as cough, sneezing and a sore throat

Urticaria
An itchy skin eruption which is usually a sign of an allergic response