



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

28 June 2013
EMA/385716/2013

Restrictions on use of codeine for pain relief in children – CMDh endorses PRAC recommendation

The Co-ordination Group for Mutual Recognition and Decentralised Procedures – Human (CMDh) has endorsed by consensus a series of risk minimisation measures to address safety concerns with codeine-containing medicines when used for the management of pain in children. Codeine is an opioid that is authorised as a painkiller in adults and children. The effect of codeine on pain is due to its conversion into morphine in the patient's body.

This follows a review of these medicines by the EMA's Pharmacovigilance Risk Assessment Committee (PRAC), which investigated reports of serious and fatal respiratory depression in children after taking codeine for pain relief. Most of the cases occurred after surgical removal of the tonsils or adenoids for obstructive sleep apnoea (frequent interruption of breathing during sleep).

Some of the children who had suffered severe side effects had evidence of being 'ultra-rapid metabolisers' of codeine. In these patients, codeine is converted into morphine in the body at a faster rate than normal, resulting in high levels of morphine in the blood that can cause toxic effects such as respiratory depression.

The PRAC concluded that a number of risk minimisation measures are necessary to ensure that only children for whom the benefits are greater than the risks are given the medicine for pain relief. The CMDh agreed with the PRAC's conclusions and endorsed the following recommendations:

- Codeine-containing medicines should only be used to treat acute (short lived) moderate pain in children above 12 years of age, and only if it cannot be relieved by other painkillers such as paracetamol or ibuprofen, because of the risk of respiratory depression associated with codeine use.
- Codeine should not be used at all in children (aged below 18 years) who undergo surgery for the removal of the tonsils or adenoids to treat obstructive sleep apnoea, as these patients are more susceptible to respiratory problems.
- The product information of these medicines should carry a warning that children with conditions associated with breathing problems should not use codeine.

The risk of side effects with codeine may also apply to adults. Codeine should therefore not be used in people of any age who are known to be ultra-rapid metabolisers nor in breastfeeding mothers (because



codeine can pass to the baby through breast milk). The product information for codeine should also include general information for healthcare professionals, patients and carers on the risk of morphine side effects with codeine, and how to recognise their symptoms.

As the PRAC recommendation was endorsed by consensus by the CMDh, it will now be implemented directly by all Member States, according to an agreed timetable.

Information to patients

- Because of a risk of breathing problems, the use of codeine medicines for pain relief in children has been restricted: these medicines are now only to be used to treat acute (short lived) moderate pain in children above 12 years of age, and only if it cannot be relieved by other painkillers such as paracetamol or ibuprofen.
- All children (aged below 18 years) who undergo surgery for the removal of the tonsils or adenoids to treat obstructive sleep apnoea (frequent interruption of breathing during sleep) should not be given codeine as they are more at risk of breathing problems.
- Mothers who are breastfeeding should not take codeine because codeine can pass to the baby through breast milk.
- Patients who are known to be 'ultra-rapid metabolisers', which means that they are more at risk of serious side effects with codeine, should not use codeine as pain relief.
- Parents and caregivers who notice any of the following symptoms in a patient given codeine should stop giving the medicine and seek medical attention immediately: slow or shallow breathing, confusion, sleepiness, small pupils, feeling or being sick, constipation and lack of appetite.
- If you or your child are being treated with codeine and have any questions or concerns about your treatment, speak to your doctor or pharmacist.

Information to healthcare professionals

- Codeine is now only indicated in patients older than 12 years of age for the treatment of acute moderate pain that cannot be relieved by other analgesics such as paracetamol or ibuprofen (alone).
- Codeine should be used at the lowest effective dose for the shortest period of time.
- Codeine is now contraindicated: in all paediatric patients (0-18 years of age) who undergo tonsillectomy and/or adenoidectomy for obstructive sleep apnoea syndrome and in patients of any age who are known to be CYP2D6 ultra-rapid metabolisers (up to approximately 10% of Caucasians are CYP2D6 ultra-rapid metabolisers, but prevalence differs according to racial and ethnic group), due to an increased risk of developing serious and life-threatening adverse reactions; and in women who are breastfeeding.
- Codeine is not recommended for use in children in whom respiratory function might be compromised as this may worsen the symptoms of morphine toxicity.

These recommendations follow a review of available safety and efficacy data on codeine when used for pain relief in children, including pharmacokinetic data, clinical studies, post-marketing data in Europe and other published literature:

- 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 who might already have compromised airways and who require pain relief following tonsillectomy and/or adenoidectomy.

- Six cases (including 3 with a fatal outcome) of respiratory depression in children treated with codeine at recommended doses after undergoing tonsillectomy for obstructive sleep apnoea were reviewed. Some of the children were found to be CYP2D6 ultra-rapid metabolisers. In addition, a published case report described a case of respiratory depression resulting in death in a breastfed infant whose codeine-using mother was a CYP2D6 ultra-rapid metaboliser.
- The pharmacokinetic profile of codeine has been studied in adults but limited information is available in children. The available data suggest that there is a reduced ability to metabolise codeine in younger children but that the enzyme system responsible for the metabolism of codeine can be considered to be fully matured by the age of 12.
- The available efficacy data on codeine for pain relief in children suggest that the analgesic effect of codeine on pain is not superior to that of other analgesics, such as non-steroidal anti-inflammatory drugs and non-opioid analgesics. Nevertheless, it is considered that codeine still has a place in the treatment of acute pain in the paediatric population and given the concerns about its risks, it should only be used in line with the updated indication, contraindications, warnings and other changes to the product information described above.

More about the medicine

Codeine is a widely used opioid medicine for pain relief. It is also used in the treatment of coughs, although this use is not covered by the current review. In the European Union (EU), codeine-containing medicines have been approved via national procedures, and are available either on prescription or over the counter in the different Member States. Codeine is marketed as a single-ingredient medicine or in combination with other substances such as aspirin or paracetamol.

The effect of codeine on pain is due to its conversion into morphine. Codeine is converted into morphine in the body by an enzyme called CYP2D6. The children who had suffered severe side effects had evidence of being 'CYP2D6 ultra-rapid metabolisers' of codeine. In these patients, codeine is converted into morphine in the body at a faster rate than normal, resulting in high levels of morphine in the blood that can cause toxic effects such as breathing difficulties.

More about the procedure

The review was initiated on 3 October 2012, at the request of the United Kingdom medicines agency under Article 31 of Directive 2001/83/EC. After discussions, on 31 October 2012 the scope of the review was extended from post-surgery pain relief in children to pain relief in children.

A review of these data was first conducted by the Pharmacovigilance Risk Assessment Committee (PRAC). As codeine-containing medicines are all authorised nationally, the PRAC recommendations were sent to the Co-ordination Group for Mutual Recognition and Decentralised Procedures – Human (CMDh), which adopted a final position. The CMDh, a body representing EU Member States, is responsible for ensuring harmonised safety standards for medicines authorised via national procedures across the EU.

As the CMDh position was adopted by consensus, it will be directly implemented by the Member States.

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