



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

25 October 2013
EMA/644345/2013

European Medicines Agency confirms changes to the use of metoclopramide

Changes aim mainly to reduce the risk of neurological side effects

The European Medicines Agency's Committee on Medicinal Products for Human Use (CHMP) has confirmed its previously recommended changes to the use of metoclopramide-containing medicines in the European Union (EU), including restricting the dose and duration of use of these medicines to minimise the known risks of potentially serious neurological (brain and nerve) side effects. This follows a re-examination, at the request of a marketing authorisation holder, of the opinion originally given by the Committee on 26 July 2013.

Metoclopramide-containing medicines have been authorised separately in individual Member States of the EU, with differing licensed indications such as nausea and vomiting of various causes (for example after treatment with anticancer chemotherapy or radiotherapy, after surgery, or associated with migraine) and gastrointestinal motility disorders (conditions in which the normal passage of food through the gut is delayed).

The original review of metoclopramide was carried out at the request of the French medicines regulatory agency (ANSM), following continued safety concerns over side effects and concerns over efficacy. ANSM asked the CHMP to review the benefits and risks of these medicines in all age groups and to recommend consistent indications across the EU. The review confirmed the well-known risks of neurological effects such as short-term extrapyramidal disorders, a group of involuntary movement disorders that may include muscle spasms (often involving the head and neck) and tardive dyskinesia (uncontrollable movements such as grimacing and twitching). The risk of acute (short-term) neurological effects is higher in children, although tardive dyskinesia is reported more often in the elderly, and the risk is increased at high doses or with long-term treatment. The evidence indicated that these risks outweighed the benefits of metoclopramide in conditions requiring long-term treatment. There have also been very rare cases of serious effects on the heart or circulation, particularly after injection.

During the re-examination the Committee confirmed its recommendation that metoclopramide should only be authorised for short-term use (up to 5 days), that it should not be used in children below 1 year of age and that in children over 1 year of age it should only be used as a second-choice treatment (after other treatments have been considered or tried) for the prevention of delayed nausea and vomiting after chemotherapy and for the treatment of post-operative nausea and vomiting. In adults, the Committee recommended use for the prevention and treatment of nausea and vomiting such as



that associated with chemotherapy, radiotherapy, surgery and in the management of migraine. In addition, the maximum recommended doses in adults and children should be restricted, and higher strength formulations, including oral liquids in strengths above 1 mg/ml, removed from the market. Such oral liquids have been associated with overdose in children.

At the request of a manufacturer of higher strength oral solutions, the Committee reconsidered the evidence behind its view that oral solutions above 1 mg/ml should no longer be available, and the arguments and proposals to minimise the risk that were supplied by the company, specifically a restriction on the use of the higher strength solution in children. However, the CHMP concluded that although liquid dose forms had some benefits, such as easier adjustment of doses in patients with reduced kidney or liver function, the 1 mg/ml solution could be used in situations where a liquid dosage form was appropriate, and the Committee was not convinced the proposed restrictions would be sufficient to reduce the risk of error and overdose in children. Although it had been suggested adult doses would be difficult to give accurately as a 1 mg/ml solution because of the large number of drops required, there should be no problem if the Committee's recommendation were followed that liquid dose forms be given by a measuring device such as a graduated oral syringe.

Detailed recommendations for patients and healthcare professionals are available below.

The CHMP recommendation will now be sent to the European Commission for the adoption of a final legally binding decision valid throughout the European Union (EU).

Information to patients

- Metoclopramide is used to prevent or treat nausea and vomiting (feeling or being sick), including nausea and vomiting that may result from anticancer medicines or radiation treatment, surgery, or an attack of migraine. It is given by injection, by mouth, or as suppositories.
- Metoclopramide is known to sometimes cause short-term side effects on the nervous system that result in unintentional movements such as twitches and nervous tics and these are commoner in children and young people, and at high doses. Other nervous system side effects may occur when metoclopramide is used for prolonged periods and may occur more often in the elderly.
- Recommended use in children is therefore now restricted to prevention of nausea and vomiting that occurs in the days after treatment with anticancer medicines, or to treat nausea and vomiting after surgery, and only when other treatments do not work or cannot be used.
- Metoclopramide should no longer be used in children under 1 year old.
- For both adults and children, metoclopramide should only be used for a maximum of 5 days.
- The recommended maximum dose of the medicine has been lowered in adults to a total of 30 mg a day, and some high dose products will be removed from the market as they will no longer be needed.
- In other longer lasting conditions, the benefits of this medicine do not outweigh the risks of side effects. Therefore, it should no longer be used to treat conditions such as indigestion, heartburn and acid reflux, or chronic (long-term) disorders due to slow emptying of the stomach.
- If you are taking metoclopramide (especially for long-term conditions) you will have your treatment reviewed by your doctor at your next scheduled appointment, and in some cases you may be recommended a different treatment. Patients who have any questions should discuss them with their doctor or pharmacist.

Information to healthcare professionals

- In order to minimise the risks of neurological and other adverse reactions, metoclopramide is now only licensed for short-term use (up to 5 days). It should no longer be used in chronic conditions such as gastroparesis, dyspepsia and gastro-oesophageal reflux disease, nor as an adjunct in surgical and radiological procedures.
- In adults, metoclopramide remains indicated for prevention of post-operative nausea and vomiting (PONV), radiotherapy-induced nausea and vomiting and delayed (but not acute) chemotherapy-induced nausea and vomiting, and for symptomatic treatment of nausea and vomiting including that associated with acute migraine (where it may also be used to improve absorption of oral analgesics).
- In children, metoclopramide is only licensed as a second-line option for prevention of delayed chemotherapy-induced nausea and vomiting and treatment of established PONV. Use is contraindicated in children under 1 year of age.
- For adults and children the maximum dose in 24 hours is 0.5 mg per kg body weight; in adults, the usual dose of conventional formulations (all routes) is 10 mg up to 3 times daily. In children the recommended dose is 0.1 to 0.15 mg per kg body weight, repeated up to three times daily. A dosing table for use in children will be included in the product information.
- Oral liquid formulations have been particularly associated with overdose in children. Oral liquids containing more than 1 mg/ml will be withdrawn from the market, and oral doses of remaining formulations should be administered using an appropriately designed graduated oral syringe to ensure accuracy.
- Intravenous formulations with concentrations above 5 mg/ml and suppositories containing 20 mg will also be withdrawn.
- Intravenous doses should be administered as a slow bolus over at least 3 minutes to reduce the risk of adverse effects.
- Given very rare reports of serious cardiovascular reactions associated with metoclopramide, particularly via the intravenous route, special care should be taken in populations likely to be at increased risk, including the elderly, patients with cardiac conduction disturbances, uncorrected electrolyte imbalance or bradycardia, and those taking other drugs known to prolong QT interval.
- Patients who are currently taking regular metoclopramide should have their treatment reviewed at a routine (non-urgent) medical appointment.

The Agency's recommendations are based on a review of the benefit-risk of metoclopramide-containing products in all indications and populations. This included published studies and meta-analyses on the efficacy of metoclopramide and analyses of reports of suspected adverse reactions.

- Data on the use of metoclopramide in acute chemotherapy-induced nausea and vomiting (CINV) were limited and suggested that metoclopramide was inferior to 5-HT₃ antagonists and required high doses which are associated with a greatly increased risk of adverse effects. There was more consistent evidence of comparability with 5-HT₃ antagonists when used for delayed CINV. There was also some evidence suggestive of a role in radiotherapy-induced nausea and vomiting, although again it seemed to be less effective than the 5-HT₃ antagonists. The evidence for intravenous metoclopramide in post-operative nausea and vomiting suggests it is as effective as other licensed treatments.

- The evidence also indicated efficacy in nausea and vomiting associated with acute migraine, but seemed to indicate that doses above 10 mg do not result in increased efficacy. The effects of metoclopramide on gut motility may be of benefit when given orally with analgesics in this acute setting.
- There was no evidence of consistent benefit in gastroparesis, gastro-oesophageal reflux disease and dyspepsia, all of which are chronic conditions requiring prolonged treatment which puts patients at risk of chronic neurological side effects. Evidence to support a role as an adjunct in surgical and radiological procedures was also lacking.
- Extrapyramidal disorders constituted nearly half of all spontaneously reported adverse effects in a manufacturer database (1749 cases out of 4005, up to December 2011). The reporting rate for these disorders was calculated to be 6 times higher in children than in adults, although it was not possible to accurately account for usage patterns in different age-groups. Extrapyramidal disorders were more likely to occur after several doses, although usually early in treatment, and were less likely at slower infusion rates when metoclopramide was given intravenously. Elderly patients seemed to be more at risk of potentially irreversible tardive dyskinesia after longer term treatment. There were also a significant number of reports of overdose in children, particularly with oral liquid formulations.
- Cardiovascular reaction reports associated with metoclopramide appeared to be very rare, and mainly associated with intravenous formulations given to patients with underlying risks for cardiac disease; they included hypotension, shock, syncope, bradycardia or atrioventricular block, and cardiac arrest.

Given the known risk of neurological and other adverse effects, particularly in children and young people, the Committee concluded that the indications for metoclopramide should be restricted to those involving short-term use, at a maximum dose of 0.5 mg per kg body weight daily, and where there is sufficient evidence of efficacy. The product information will be amended appropriately, and prescribers will receive further communication at a national level.

More about the medicine

Metoclopramide is a medicine that acts as an antiemetic (a medicine used to relieve nausea and vomiting) by acting on the part of the brain that triggers the sensation of sickness. It also stimulates the movement of the stomach and upper part of the bowel, speeding passage through the gut. It is authorised for a variety of indications, which differ between EU Member States and is available in different formulations including as an injection (to be given into a vein or muscle), as tablets and oral liquids to be taken by mouth and as suppositories. Metoclopramide-containing medicines have been authorised by national procedures in all the Member States of the EU and have been available for many years under different trade names.

More about the procedure

The review of metoclopramide-containing medicines was initiated in December 2011 at the request of France, under Article 31 of Directive 2001/83/EC. This followed a review by the EU Member States of metoclopramide-containing medicines in children, under Article 45 of the Paediatric Regulation 1901/2006, which in 2010 identified the risk of neurological side effects and recommended a number of risk minimisation measures. In 2011, a review carried out in children at the national level by the

French medicines regulatory agency highlighted that despite various risk minimisation measures implemented over the years, side effects had continued to be reported. The French medicines agency therefore asked the CHMP to carry out an assessment of the benefit-risk balance in all populations, especially in children and the elderly. Following this assessment and the issuing of the CHMP's original opinion, one of the companies producing metoclopramide-containing medicines exercised its legal right to ask for a re-examination of the opinion, which has now been carried out.

The CHMP recommendation will now be sent to the European Commission, which will take an EU-wide legally binding decision.

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