Changes to the use of Metoclopramide to reduce the risk of neurological side effects

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Information on Metoclopramide

Metoclopramide-containing medicines are used for nausea and vomiting due to various causes (such as after treatment with chemotherapy or radiotherapy, after surgery, or associated with migraine) and for gastrointestinal motility disorders (conditions in which the normal passage of food through the gut is delayed). Metoclopramide 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.

In Malta several preparations are authorised for use;

Active substance	Product Name	Pharmaceutical Form	License Number
Metoclopramide 5mg/ml (as Hydrochloride)	Elitan Injection, 10mg/2ml, Solution for Injection	SOLUTION FOR INJECITON	AA032/05602
Metoclopramide Hydrochloride 10mg	Cloperan 10	TABLET	AA084/06001
Metoclopramide Hydrochloride 10mg	Elitan 10mg	TABLET	MA032/05601
Metoclopramide Hydrochloride 10mg	Metoclopramide 10 mg tablets	TABLET	MA054/06101
Metoclopramide 5mg/ml	Metoclopramide Solution for Injection 5mg/ml	SOLUTION FOR INJECITON	AA244/30901
Metoclopramide Hydrochloride Monohydrate 5.3mg	Metoclopramide Sterile Solution 5mg/1ml	STERILE SOLUTION	AA770/00901
Metoclopramide Hydrochloride 10mg/2ml (as anhydrous)	Metoclopramide 5 mg/ml Injection	SOLUTION FOR INJECTION	AA994/00101
Metoclopramide Hydrochloride 10mg/2ml (as anhydrous)	Metoclopramide Injection BP 10mg/2ml	SOLUTION FOR INJECITON	MA703/00601

Information from European Medicines Agency about the safety concern

The 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. The ANSM asked the European Medicines Agency's Committee on Medicinal Products

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for Human Use (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, and tardive dyskinesia (uncontrollable movements such as grimacing and twitching). The risk of acute 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 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).

For 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 contra-indicated 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.

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- Patients who are currently taking regular metoclopramide should have their treatment reviewed at a routine (non-urgent) medical appointment.

These recommendations are based on a review 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-HT_3 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-HT_3 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-HT_3 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.

Information for 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.

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- 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.

For more information please visit **www.ema.europa.eu**

Reporting Adverse Drug Reactions

Healthcare professionals and patients are encouraged to maintain vigilance on metoclopramide containing medicinal products. Suspected Adverse Drug Reactions (side effects) may be reported using the Medicines Authority ADR form available at **http://www.medicinesauthority.gov.mt/adrportal** or to the marketing authorisation holder or their local representatives.

Dr John J Borg PhD (Bristol)
Post-licensing Director

Healthcare professionals and patients are encouraged to regularly check the Medicines Authority website for product safety updates as these are issued on an ongoing basis.

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