DRUG SAFETY INFORMATION No. 57

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Dear Healthcare Professional

RESTRICTIONS ON THE USE OF METOCLOPRAMIDE-CONTAINING PRODUCTS

The Health Sciences Authority (HSA) would like to update on the new restrictions on the use of metoclopramide-containing products in order to reduce the risk of neurological and other dose-related adverse reactions. This regulatory decision was made, in consultation with HSA's Medicines Advisory Committee (MAC) and local clinical experts, following HSA's benefit-risk assessment of metoclopramide from international and local data.

Background

2 Metoclopramide is a pro-kinetic drug and is licensed in Singapore for the prevention and treatment of nausea and vomiting due to various conditions. Locally, there are 13 registered metoclopramide-containing products (refer to Annex 1).

3 In December 2011, a benefit-risk assessment of metoclopramide use in different age groups in the European Union (EU) was initiated by the European Medicines Agency (EMA) following concerns from the French National Agency for the Safety of Medicine and Health Products (ANSM), regarding the benefit-risk balance of metoclopramide. ANSM expressed that despite its long use for a wide range of indications, there was limited evidence of efficacy for approved indications of metoclopramide, while the risks of neurological and cardiovascular adverse events are known.[1] The review, completed in December 2013, confirmed the relationship between the use of high doses or long-term use of metoclopramide and the increased risks of neurological adverse reactions, such as acute extrapyramidal symptoms and irreversible tardive dyskinesia. In addition, there were also very rare reports of serious cardiovascular reactions, particularly if metoclopramide was administered intravenously. Patients at risk of cardiovascular reactions include the elderly population, patients with cardiac conduction disturbances (including QT prolongation), uncorrected electrolyte balance, bradycardia, and those taking other medicinal products known to prolong the QT interval.

4 In order to minimise the risk of potentially serious neurological adverse reactions, the EMA's Committee on Medicinal Products for Human Use (CHMP) recommended restrictions on the indications, dose and duration of use of metoclopramide-containing medicine in the EU.[1] It was recommended that the use of metoclopramide should be restricted to the short term, i.e. up to 5 days. Indications involving long-term treatment (e.g. gastroparesis, dyspepsia) are no longer supported. In addition, the maximum daily dose in adults and children should not exceed 30 mg and 0.5 mg/kg, respectively, and metoclopramide should be contraindicated in children below one year of age due to increased risks of extrapyramidal disorders and methaemoglobinaemia.

Other international regulatory actions

5 The US Food and Drug Administration (FDA) and Health Canada (HC) have reported the increased risk of irreversible tardive dyskinesia beyond 12 weeks of metoclopramide treatment. Both agencies retained the indications involving long-term treatment but recommended that the maximum treatment duration for metoclopramide should not exceed 12 weeks. The Australia Therapeutic Goods Administration (TGA) adopted the CHMP's recommendations, including restricting the use to short-term indications with a maximum treatment duration of 5 days. In addition, both HC and TGA have recommended that the maximum daily dose of metoclopramide should not exceed 30 mg in adults and 0.5 mg/kg in children, and that the medicine should be contraindicated in children below one year of age.

HSA's benefit-risk assessment and advisory

6 Locally, nearly 1 in 5 neurological adverse reports associated with metoclopramide received by HSA from 1993 to August 2014 were reported in children. Overall, the local incidence rate of neurological side effects in adults and children did not exceed those reported overseas.

7 Taking into consideration the current available scientific evidence, the local incidence of adverse drug reactions, the input from local clinical experts and international regulatory actions, HSA has reviewed the benefits versus the risks of metoclopramide and is recommending the following restrictions on the indications, dose and duration of use of metoclopramide-containing products in Singapore:

- In adults, metoclopramide will be indicated for the following:
    - the prevention of nausea and vomiting associated with chemotherapy and radiotherapy with low and minimal emetogenicity;
    - the prevention of post-operative nausea and vomiting (only via the parenteral route);
    - the symptomatic treatment of acute migraine induced nausea and vomiting;
    - the adjunct treatment of gastroparesis;
    - the management of dyspepsia and gastroesophageal reflux disorder when other treatment options are unsuitable (only via the oral route); and
    - as an adjuvant to surgical and radiological procedures.

  The maximum daily dose is 30 mg by the oral, intravenous or intramuscular route.

- In children (aged one to 18 years old), metoclopramide should be restricted to the treatment of established post-operative nausea and vomiting when other treatment options are unsuitable (only via the intravenous route), and prevention of delayed chemotherapy-induced nausea and vomiting (oral or intravenous routes only). The maximum daily dose is 0.5 mg/kg for oral therapy.

- Metoclopramide is contraindicated in infants less than one year of age.

- Treatment should be kept as short as possible, i.e. up to 5 days. Treatment durations beyond 12 weeks should be avoided unless the therapeutic benefit is judged to outweigh the risk to the patient.

- Intravenous doses should be administered as a slow bolus (over at least three minutes).

8 HSA is working with the companies of metoclopramide-containing products to update their local package inserts with the new restrictions. Healthcare professionals are encouraged to report adverse events suspected to be associated with metoclopramide to the

Vigilance and Compliance Branch at Tel: 6866 3538, Fax: 6478 9069, or report online at http://www.hsa.gov.sg/ae_online. Should you have further queries regarding this matter, please contact Ms Imelda Halim at Tel: 6866 1044 or email: Imelda_HALIM@hsa.gov.sg.

Thank you.

Yours faithfully,

MS JALENE POH
DIRECTOR (THERAPEUTICS PRODUCTS BRANCH)
HEALTH PRODUCTS REGULATION GROUP
HEALTH SCIENCES AUTHORITY

cc Director of Medical Services, Ministry of Health
Chief Executive Officer, Health Sciences Authority

Reference

1. *http://www.ema.europa.eu/docs/en_GB/document_library/Referrals_document/Metoclopramide_31/WC500146610.pdf*

Please scan this QR code for abstracts of Dear Healthcare Professional Letters issued by HSA, Pharmaceutical or Medical Device companies.

ANNEX 1

List of Registered Metoclopramide-Containing Products

Product Name	Active Ingredient/Strength	Licence Holder
Primperan injection 10 mg/2 ml	Metoclopramide 10mg/2ml	sanofi-aventis Singapore Pte Ltd
Primperan tablet 10 mg	Metoclopramide 10mg	sanofi-aventis Singapore Pte Ltd
Apo-metoclop tablet 10mg	Metoclopramide 10mg	Pharmaforte Singapore Pte Ltd
Emeliv tablet 10 mg	Metoclopramide 10mg	Apex Pharma Marketing Pte Ltd
Maril tablet 10 mg	Metoclopramide 10mg	Atlantic Pharmaceutical (S) Pte Ltd
Metoclopramide injection BP 5 mg/ml	Metoclopramide 5mg/ml	Pfizer Private Limited
Metoclopramide syrup 5 mg/5 ml	Metoclopramide 5mg/5ml	Sunward Pharmaceutical Private Limited
Metoclopramide tablet 10 mg	Metoclopramide 10mg	Sunward Pharmaceutical Private Limited
Metoclopramide tablet 10 mg	Metoclopramide 10mg	Drug Houses Of Australia Private Limited
Metoclopramide tablets BP 10 mg	Metoclopramide 10mg	Drug Houses Of Australia Private Limited
Pulin Film-Coated Tablet 10 mg	Metoclopramide 10mg	Yung Shin Pharmaceutical (Singapore) Pte Ltd
Pulin Injection 10 mg/2 ml	Metoclopramide 10mg/2ml	Yung Shin Pharmaceutical (Singapore) Pte Ltd
Syntomide Tablet 10 mg	Metoclopramide 10 mg	Singapore Pharmaceutical Private Limited