DRUG SAFETY INFORMATION No.62

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Health Products Regulation Group
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Dear Healthcare Professional

NEW RECOMMENDATIONS ON THE USE OF PRODUCTS CONTAINING DOMPERIDONE

The Health Sciences Authority (HSA), in consultation with the Medicines Advisory Committee (MAC), would like to inform healthcare professionals about the new recommendations on the use of domperidone due to the potential risk of serious cardiovascular (CV) events associated with its use. The recommendations took into consideration the long-established use of domperidone for the treatment of nausea, vomiting and dyspepsia, isolated CV events that were reported locally as well as the lack of suitable therapeutic alternatives.

Background

2 Domperidone is a pro-kinetic and anti-emetic drug licensed in Singapore for the treatment of dyspepsia, as well as nausea and vomiting due to various conditions. Locally, there are 11 registered products that contain domperidone (refer to Annex 1) and they are available as tablets and suppositories.

3 HSA has recently completed a benefit-risk assessment to determine if additional measures are necessary to further mitigate the risk of CV associated with the use of domperidone. This follows an earlier assessment in 2012, which resulted in the strengthening of the package inserts (PI) of domperidone to include warnings of increased risk of ventricular arrhythmia (VA) and sudden cardiac death (SCD), especially in patients older than 60 years old or those taking oral doses of more than 30 mg daily.

4 Globally, other drug regulatory agencies have also carried out assessments on domperidone and have issued regulatory recommendations on its use. The European Medicines Agency (EMA)[1] removed the indication for dyspepsia due to insufficient long-term efficacy data supporting this indication, and restricted the maximum oral daily dose to 30 mg for its use to treat nausea and vomiting. EMA reviewed epidemiology studies and post market data which indicated that higher doses were associated with an increased risk of CV events. Health Canada has similarly recommended 30 mg as the maximum oral daily dose and strengthened the safety warnings in the PI to highlight the risk of CV events.[2]

HSA's Benefit-risk Re-assessment

5 HSA's benefit-risk assessment took into consideration findings of epidemiology studies, the availability of alternative treatments, local safety data, expert opinion from local clinicians and international regulatory actions.

6 The review of several epidemiology studies has shown an increased risk of VA and SCD with domperidone.[3-4] The increased risk of VA/SCD was significant in patients taking oral domperidone at >30 mg daily (Odds Ratio (OR) 11.4, 95% CI: 1.99, 64.9),[3] those older than 60 years (OR: 1.64, 95% CI: 1.31–2.05)[3] and among domperidone users compared with non-users (OR: 1.59, 95%CI: 1.28-1.98).[4] The identified cardiotoxicity risk factors included advanced age (>60 years old), underlying CV conditions, high domperidone dose (>30 mg/day) and concomitant use with QT prolongation drugs and CYP3A4 inhibitors. Local reports of cardiotoxicity associated with domperidone use were found to be isolated. From 2006 to 2016, HSA received two cases of QT prolongation associated with domperidone

7 The efficacy of domperidone as a pro-kinetic and an anti-emetic drug is long-established and its clinical use for treatment of nausea, vomiting and dyspepsia is widely practised locally. As such, there remains a place for the clinical use of domperidone for dyspepsia, nausea and vomiting in the local context.

8 Based on currently available information, HSA, in consultation with its MAC, concluded that the benefit-risk profile of domperidone for treatment of dyspepsia, nausea and vomiting remains favourable if additional measures are taken to mitigate the risk of cardiotoxicity. These additional measures include restricting the use in high risk patients and strengthening the CV warnings in the PI.

HSA's Advisory to Prescribers

9 Healthcare professionals are advised of the following, when considering the use of products containing domperidone:

- Domperidone products are contraindicated in patients with known existing prolongation of cardiac conduction intervals, particularly QTc, patients with significant electrolyte disturbances or underlying cardiac disease and when co-administrated with QT-prolonging medicines or potent CYP3A4 inhibitors.
- An increased risk of cardiotoxicity was observed in patients older than 60 years.
- Domperidone should be used at the lowest effective dose for the shortest possible duration.
- In adults and children aged ≥ 12 years old weighing ≥ 35 kg, the recommended maximum oral daily dose is 30 mg, given in doses of 10 mg up to three times daily. Taking into account the pharmacokinetic studies and bioavailability of rectal suppositories, the recommended rectal suppository dose is 30 mg twice daily.
- In children aged < 12 years old and those aged ≥ 12 years old weighing < 35 kg, the recommended dose is 0.25 mg/kg orally up to three times daily. For rectal administration, these patients may also be given 0.75 mg/kg twice daily as suppositories.

10 HSA is working with the product licence holders to update the local PIs of products containing domperidone with the new recommendations on the dosing regimen, treatment duration as well as the relevant safety information including contraindications.

11 Healthcare professionals are encouraged to report any suspected serious adverse reactions related to use of products containing domperidone 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 Dr Poonepalli Anuradha at Tel: 6866 3596 or email: Poonepalli_ANURADHA@hsa.gov.sg.

Thank you.

Yours faithfully

MS AGNES CHAN
DIRECTOR (CLINICAL), THERAPEUTIC PRODUCTS BRANCH
HEALTH PRODUCTS REGULATION GROUP
HEALTH SCIENCES AUTHORITY

cc Director of Medical Services, Ministry of Health

ANNEX 1

List of Registered Domperidone-containing Products

Product Name	Product Licence Holder
Motilium tablet 10mg	Johnson & Johnson Pte. Ltd.
Motilium suspension 1mg/ml	Johnson & Johnson Pte. Ltd.
Domper suppository 10mg	Yung Shin Pharmaceutical (Singapore) Pte Ltd
Dompel tablet 10 mg	Pharmaforte Singapore Pte Ltd
Dompenyl tablet 10 mg	Ziwell Medical (s) Pte Ltd
Domper Tablet 10mg	Yung Shin Pharmaceutical (Singapore) Pte Ltd
Doridone tablet 10mg	Drug Houses of Australia Private Limited
Gastrium tablet 10mg	Naina Mohamed & Sons Private Limited
Moridone tablet 10mg	Singapore Pharmaceutical Private Limited
Peptomet tablet 10mg	Goldplus Universal Pte Ltd
Sam Chun Dang Domperidone Tablet 10mg	Zyfas Medical Co

References

1. http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/referrals/Domperidone-containing_medicines/human_referral_prac_000021.jsp&mid=WC0b01ac05805c516f
2. http://www.hc-sc.gc.ca/dhp-mps/medeff/reviews-examens/domperidone-eng.php
3. Drug Saf. 2010; 33: 1003-1014.
4. Pharmacoepidemiology and Drug Safety 2010; 19:881-888.

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