FDA CIRCULAR
No. 2024-001

15 MAR 2024

SUBJECT : **Recall and Withdrawal of the Classification and Registration of Domperidone as Over-the-Counter Drug**

I. BACKGROUND

It is the policy of the State to promote and protect the right to health of the people and instill health consciousness among them. In the implementation of the foregoing policy, the Food and Drug Administration (FDA), in accordance with the provisions of Republic Act (RA) No. 3720, as amended by Executive Order (EO) No. 175 and further amended by RA No. 9711, is mandated to adopt measures to ensure pure, safe, efficacious and good quality drugs and devices in the country, and the rational use of drugs and devices, such as, but not limited to, banning, recalling or withdrawing from the market drugs and devices which are not registered, unsafe, inefficacious or of doubtful therapeutic value.

Domperidone is a dopamine antagonist with pro-kinetic, and antiemetic properties. This drug product may be dispensed either by its classification, prescription or Over-the-Counter (OTC) drug. OTC drug products are accessible to the general public as these drugs are sold without physician's prescription.

The FDA conducted a literature review to assess the safety of Domperidone considering regulatory actions made by other countries in response to an epidemiological study showing that this drug is associated with an increased risk of serious ventricular arrhythmias or sudden cardiac death. A higher risk was observed in patients older than 60 years, patients taking daily doses greater than 30 mg, and patients concurrently taking QT-prolonging drugs *(e.g. disopyramide, quinidine, amiodarone, dofetilide, dronedarone, ibutilide, sotalol, haloperidol, pimozide, sertindole, citalopram, escitalopram)* or CYP3A4 inhibitors *(e.g. clarithromycin, erythromycin, itraconazole, oral ketoconazole, posaconazole, ritonavir, saquinavir, telithromycin, telaprevir and voriconazole)*.

Section 4 of Administrative Order (AO) No. 23-C s. 2000 entitled "Policies and Guidelines on Over-the-Counter (OTC) Drug Products" states that the Secretary of Health, through the Director General of the FDA, shall retain the authority to recall and

withdraw the approval of the classification as OTC of a drug product in the event of any documented and verified adverse reactions endangering public health and safety.

The FDA, in its commitment to guarantee the safety, quality, purity, and efficacy of registered health products to the general public, hereby issues this Circular recalling and withdrawing the classification and registration of existing Domperidone as OTC drug for the guidance of the Marketing Authorization Holders (MAHs).

II. OBJECTIVE

This Circular aims to recall and withdraw the classification and registration of existing registered Domperidone products as OTC drug.

Specifically, this Circular shall provide guidelines in the submission of labeling materials and additional requirements for Domperidone products under initial and renewal applications as Prescription drug.

III. SCOPE

This shall apply to all MAHs, licensed drug manufacturers, traders, distributors, retail drugstores, healthcare professionals, and advertisers of Domperidone.

IV. DEFINITION OF TERMS

A. **Processed Application** refers to an application that has been evaluated and a decision or outcome has been determined.
B. **On-going Application** refers to an application that is currently in active phase of evaluation.

V. GENERAL GUIDELINES

A. All Domperidone products shall be classified as Prescription drug considering the associated risks identified on the use of this drug.
B. All currently registered Domperidone as OTC drug shall be reclassified as Prescription drug.
    1. The MAH shall recall the existing inventory of their products.
    2. The MAH shall update the labeling materials and package inserts to reflect the information on the increased risk of cardiovascular effects. The information shall be reflected under Contraindications and Special Warnings and Precautions.

3. MAHs that have not yet revised the package inserts in relation to the above safety concern shall submit a variation application and the following statement shall be printed on the package insert:

Contraindications:

- *Domperidone is contraindicated in the following situations:*
- *Known hypersensitivity to domperidone or any of the excipients*
- *Prolactin-releasing pituitary tumor (prolactinoma)*
- *Co-administration with QT-prolonging drugs, at the exception of apomorphine*
- *Co-administration with potent CYP3A4 inhibitors (regardless of their QT prolonging effects)*
- *In patients who have known existing prolongation of cardiac conduction intervals, particularly QTc, patients with significant electrolyte disturbances or underlying cardiac diseases such as congestive heart failure*
- *When stimulation of the gastric motility could be harmful e.g., in patients with gastro-intestinal hemorrhage, mechanical obstruction, or perforation.*
- *In patients with moderate or severe hepatic impairment*

Special warnings and precautions for use:

Cardiovascular effects:

Domperidone has been associated with prolongation of the QT interval on the electrocardiogram. During post-marketing surveillance, there have been very rare cases of QT prolongation and torsades de pointes in patients taking domperidone. These reports included patients with confounding risk factors, electrolyte abnormalities and concomitant treatment which may have been contributing factors.

Epidemiological studies showed that domperidone may be associated with an increased risk of serious ventricular arrhythmias or sudden cardiac death. A higher risk was observed in patients older than 60 years, patients taking daily doses greater than 30 mg, and patients concurrently taking QT-prolonging drugs or CYP3A4 inhibitors.

Domperidone should be used at the lowest effective dose in adults and adolescents 12 years of age and older.

Domperidone is contraindicated in patients with known existing prolongation of cardiac conduction intervals, particularly QTc, in patients with significant electrolyte disturbances (hypokalemia, hyperkalemia, hypomagnesaemia), or bradycardia, or in patients with underlying cardiac diseases such as congestive

heart failure due to increased risk of ventricular arrhythmia. Electrolyte disturbances (hypokalemia, hyperkalemia, hypomagnesaemia) or bradycardia are known to be conditions increasing the proarrhythmic risk.
Treatment with domperidone should be stopped if signs or symptoms occur that may be associated with cardiac arrhythmia, and the patients should consult their physician.

Patients should be advised to promptly report any cardiac symptoms.

***

4. A new Certificate of Product Registration (CPR) shall be issued to reflect the changes in classification from OTC to Prescription drug.
5. Distribution of Dear Healthcare Professional (DHCP) Letter is subject to the MAH's initiative on disseminating safety information.

C. Receiving of any application for registration and other related actions for Domperidone products shall be based according to existing regulations on Prescription drug.

D. All Post-Marketing Surveillance (PMS) activities shall be implemented accordingly.

VI. SPECIFIC GUIDELINES

A. Domperidone with existing CPR as OTC Drug

1. Recall notification shall be submitted by the MAH.
    a. All MAHs of existing Domperidone products shall submit the recall notification through email at fdac.letters.cdrr@fda.gov.ph with the Subject: Recall (Reclassification of Domperidone from OTC to Rx)
    b. Notification shall indicate existing stock inventory and distribution record list.
    c. Facsimile of Rx stick-on label for primary and secondary labels shall be submitted.
    d. Relabeling for existing inventory and recalled products shall be allowed for stickering of the Rx symbol.
    e. An exhaustion period for one (1) year until retail level shall be allowed for relabeled products.
    f. Any excess printed OTC label shall undergo inventory and appropriate destruction.
2. The MAHs of Domperidone shall apply for variation (MaV-2) for labeling changes and surrender their CPR to reflect the Prescription classification.
3. Any advertisement and/or sales promo of Domperidone shall be discontinued, accordingly.

B. Domperidone under Initial Application as OTC

1. Processed Application
   a. The Center for Drug Regulation and Research (CDRR) shall issue an electronic-Notice of Deficiencies (e-NOD) to the MAH requiring to submit facsimile of labeling materials as prescription drug within 20 working days.
   b. The CDRR will issue the CPR once revised labeling materials are submitted and a Post-Approval Commitment (PAC) letter requiring the MAH to submit additional requirements as prescription drug within one (1) year.
2. On-going Application
   The CDRR shall issue an e-NOD requiring the MAH to submit revised labeling materials as prescription drug within 20 working days and a PAC letter for additional requirements as prescription drug within one (1) year.

C. Domperidone under Renewal Application as OTC

The CDRR shall issue an e-NOD requiring the MAH to submit revised labeling materials as prescription drug within 20 working days and a PAC letter for the additional requirements as prescription drug within one (1) year.

As part of the PAC letter, the MAH shall submit the Bioavailability (BA)/Bioequivalence (BE) studies for Domperidone within three (3) years after the effectivity of this Circular.

All applications for Domperidone affected by this Circular shall be facilitated.

VII. SEPARABILITY CLAUSE

If any part, term, of provision of this Circular shall be declared invalid or unenforceable, the validity or enforceability of the remaining portions or provisions shall not be affected and this Circular shall be construed as if it did not contain the particular invalid or unenforceable or unconstitutional part, term, or provision.

VIII. PENALTY

Those found in violation of the provisions of this Circular shall be penalized under RA No. 9711, and other applicable laws.

IX. EFFECTIVITY DATE

This Circular shall take effect immediately due to imminent danger to public health, safety, and welfare, and to be published in a newspaper of general circulation and filed with the University of the Philippines – Office of the National Administrative Register (UP-ONAR).

DR. SAMUEL A. ZACATE
Director General