SCHEDULING STATUS

S4

1 NAME OF THE MEDICINE

BIO DOMPERIDONE 10 Film-coated tablet

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 10 mg domperidone.

Contains sugar (lactose monohydrate 58 mg per tablet.).

For full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablets.

White, round, film-coated, biconvex tablets.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

BIO DOMPERIDONE 10 is indicated in adults and adolescents over 12 years of age and weighing over 35 kg for:

- Short-term management (not exceeding 7 days) of delayed gastric emptying of functional origin with gastro-oesophageal reflux and/or dyspepsia.
- Short term management (not exceeding 7 days) for control of nausea and vomiting of central or local origin.
- As an anti-emetic in patients receiving cytostatic and radiation therapy for up to 4 weeks.
- Facilitation of radiological examination of the upper gastrointestinal tract administered at the time before the examination as directed by the radiologist.

4.2 Posology and method of administration

Posology

Adults and adolescents > 12 years of age and > 35 kg

It is recommended to take oral BIO DOMPERIDONE 10, 15 – 30 minutes before meals. If taken after meals, absorption of the medicine is somewhat delayed.

The dose of BIO DOMPERIDONE 10 film-coated tablets should be the lowest effective dose for the individual situation (typically 30 mg/day) with a maximum daily oral dose of 30 mg.

If the conditions mentioned under indications are not resolved within the time frames indicated, patients should be re-evaluated and the need for continued treatment be assessed.

Formulation **(domperidone per unit)**	**Dosage**	**Maximum dose per day**
Film-coated tablets (10 mg/tablet)	1 tablet three times per day	30 mg (3x10 mg tablet).

Special populations

Renal impairment

Since the elimination half-life of domperidone is prolonged in severe renal impairment (serum creatinine > 6 mg/100 mL, i.e. > 0,6 mmol/L), the dosing frequency should be reduced to once or twice daily, depending on the severity of impairment, and the dose may need to be reduced.

Patients with severe renal impairment should be reviewed regularly (see section 4.4).

Hepatic impairment

BIO DOMPERIDONE 10 is contraindicated for patients with moderate (Child-Pugh 7 to 9) or severe (Child-Pugh > 9) hepatic impairment (see section 4.3). Dose adjustment is not required for patients with mild (Child-

Pugh 5 to 6) hepatic impairment (see section 5.2).

Paediatrics

BIO DOMPERIDONE 10 should not be administered to children under 12 years of age.

The safety of BIO DOMPERIDONE 10 in adolescents weighing ≤ 35 kg has not been established.

Method of administration

For oral use.

4.3 Contraindications

BIO DOMPERIDONE 10 is contraindicated:

- In patients with a known hypersensitivity to domperidone or to any of the excipients of BIO DOMPERIDONE 10 listed in in section 6.1.
- In patients with a prolactin secreting or producing pituitary tumour (prolactinoma)
- Whenever stimulation of gastric motility is to be avoided or could be harmful (e.g., in the presence of gastrointestinal haemorrhage, obstruction or perforation)
- Co-administration with medicines known to induce Torsades de Pointes and/or prolong the QT interval e.g., cisapride, class 1A antidysrythmics
- Hypokalaemia, hypomagnesaemia
- Bradycardia or heart-block.
- Pre-existing cardiac disease.
- Known congenital long QT interval or family history thereof.
- Co-administration with oral ketoconazole, itraconazole, fluconazole, voriconazole, posaconazole and other medicines inhibiting the hepatic cytochrome enzyme CYP3A4 which have been shown to cause QT interval prolongation, such as macrolide antibiotics e.g., erythromycin, azithromycin, roxithromycin, clarithromycin, telithromycin, amiodarone, HIV protease inhibitors e.g., amprenavir, atazanavir, fosamprenavir, indinavir, nelfinavir, ritonavir, saquinavir and quinolones (see sections 4.4 and 4.5).

- In patients with moderate (child pugh score 7 – 9) or severe (child pugh score > 9) hepatic impairment (see section 5.2).

The safe use during pregnancy and lactation has not been established. (See section 4.6).

4.4 Special warnings and precautions for use

BIO DOMPERIDONE 10 should not be administered to children under 12 years of age or weighing less than 35 kg.

Renal impairment

BIO DOMPERIDONE 10 should be used with caution in patients with renal impairment or in those at risk of fluid retention. The elimination half-life of BIO DOMPERIDONE 10 is prolonged in severe renal impairment (creatinine clearance < 30 ml/minute, serum creatinine approximately 530 mmol/L). For repeated administration, the dosing frequency of BIO DOMPERIDONE 10 should be reduced to once or twice daily depending on the severity of the impairment. The dose may also need to be reduced.

Cardiac effects

Epidemiological studies have shown that BIO DOMPERIDONE 10 is associated with an increased risk of serious ventricular dysrhythmias or sudden cardiac death (see section 4.8). These studies suggested that this increased risk may be higher in patients older than 60 years of age or in patients taking oral doses greater than 30 mg per day. Therefore, BIO DOMPERIDONE 10 should be used with caution in older patients.

Medicine interaction potential

The main metabolic pathway of domperidone is through CYP3A4. *In vitro* and human data show that the concomitant use of medicines that significantly inhibit this enzyme may result in increased plasma levels of domperidone. Co-administration of BIO DOMPERIDONE 10 with potent CYP3A4 inhibitors which have been shown to cause QT interval prolongation is contraindicated (see section 4.3 and 4.5).

Caution should be exercised when BIO DOMPERIDONE 10 is co-administered with potent CYP3A4 inhibitors which have not been shown to cause QT interval prolongation and patients should be monitored closely for signs and symptoms of adverse reactions (see section 4.5 and 4.8).

Domperidone base

Antacids and anti-secretory medicines should not be taken simultaneously with oral formulations of BIO DOMPERIDONE 10 as they lower the oral bioavailability of BIO DOMPERIDONE 10. When used concomitantly, BIO DOMPERIDONE 10 should be taken before meals and antacids or anti-secretory medicines after meals (see section 4.5).

BIO DOMPERIDONE 10 should not be given to patients being treated with monoamineoxidase inhibitors (see section 4.5), as dopamine levels can be increased.

BIO DOMPERIDONE 10 contains lactose monohydrate.

Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

This medicine contains less than 1 mmol sodium (23 mg) per tablet, i.e., is essentially 'sodium-free'.

4.5 Interaction with other medicines and other forms of interaction

The main metabolic pathway of BIO DOMPERIDONE 10 is through CYP3A4. As an inhibitor of CYP3A4, macrolide antibiotics can block the metabolism of domperidone, resulting in increased plasma concentrations of domperidone.

Increased risk of occurrence of QT-interval prolongation, due to pharmacodynamic and/or pharmacokinetic interactions.

Concomitant use of the following substances is contraindicated

QTc prolonging medicines

- anti-dysrhythmics class IA (e.g., disopyramide, hydroquinidine, quinidine),
- anti-dysrhythmics class III (e.g., amiodarone, dofetilide, dronedarone, ibutilide, sotalol),
- certain antipsychotics (e.g., haloperidol, pimozide, sertindole),
- certain antidepressants (e.g., citalopram, escitalopram),
- certain antibiotics (e.g., erythromycin, levofloxacin, moxifloxacin, spiramycin)
- certain antifungal medicines (e.g., pentamidine),
- certain antimalarial medicines (e.g., halofantrine, lumefantrine),
- certain gastrointestinal medicines (e.g., cisapride, dolasetron, prucalopride),
- certain antihistaminics (e.g., mequitazine, mizolastine),
- certain medicines in cancer (e.g., toremifene, vandetanib, vincamine),
- certain other medicines (e.g., bepridil, diphemanil, methadone).

Potent CYP3A4 inhibitors (regardless of their QT prolonging effects), i.e.:

- protease inhibitors,
- systemic azole antifungals (e.g., ketoconazole and itraconazole) (see section 4.3),
- some macrolides (erythromycin, clarithromycin, telithromycin) (see section 4.3),

The above list of substances is representative and not exhaustive.

Concomitant use of the following substances is not recommended

Moderate CYP3A4 inhibitors i.e., diltiazem, verapamil and some macrolides (see section 4.3).

Concomitant use of the following substances requires caution in use

Caution with bradycardia and hypokalaemia-inducing medicines.

Use caution when using BIO DOMPERIDONE 10 with MAO inhibitors e.g. selegiline used for the treatment of Parkinson's disease or tranylcypromine and moclobemide used for the treatment of depression, dopamine levels

can be increased (see section 4.4).

The anti-dyspeptic effect of BIO DOMPERIDONE 10 may be antagonised by anti-muscarinic medicines (e.g., dextromethorphan, diphenhydramine) and opioid analgesics.

Due to the gastro-kinetic effects of BIO-DOMPERIDONE 10, the absorption of concomitant oral medication (particularly sustained release or enteric coated formulations) can be influenced. However, in patients already stabilised on digoxin or paracetamol, concomitant administration of BIO DOMPERIDONE 10 did not influence the blood levels of these medicines.

BIO DOMPERIDONE 10 increases with serum prolactin levels, and therefore may interfere with other hypoprolactaemic medicines and with some diagnostic tests.

BIO DOMPERIDONE 10 should not be taken concomitantly with anti-acids, anti-secretory medicines (histamine H_2-receptor antagonists such as cimetidine; proton pump inhibitors; selective antimuscarinics or prostaglandin analogues), or sodium bicarbonate as they lower the oral bioavailability of BIO DOMPERIDONE 10.

Reduced gastric acidity impairs the absorption of BIO DOMPERIDONE 10.

BIO DOMPERIDONE 10 may also be given with:

- Neuroleptics, the action of which it does not potentiate.
- Dopaminergic agonists (bromocriptine, L-dopa), whose unwanted peripheral effects such as digestive disorders, nausea and vomiting it suppresses without counteracting their central properties.

4.6 Fertility, pregnancy and lactation

Pregnancy

BIO DOMPERIDONE 10 should not be administered to pregnant women (see section 4.3).

Administration to pregnant mothers shortly before giving birth, or during labour, may result in the new-born infant being born hypotonic, collapsed and hypoglycaemic.

Breastfeeding

Domperidone is excreted in human breast milk.

BIO DOMPERIDONE 10 should not be administered to lactating women.

4.7 Effects on ability to drive and use machines

Dizziness and somnolence have been observed following use of BIO DOMPERIDONE 10 (see section 4.8). Therefore, patients should be advised not to drive or use machinery or engage in other activities requiring mental alertness and coordination until they have established how BIO DOMPERIDONE 10 affects them.

4.8 Undesirable effects

Tabulated summary of adverse reactions

MedDRA system organ class	*Frequent*	*Less frequent*	*Frequency unknown*
Immune system disorders		Hypersensitivity.	Anaphylactic reaction (incl. anaphylactic shock)*.
Psychiatric disorders	Depression, anxiety, libido decreased/loss of libido.		Agitation*, nervousness.
Nervous system disorders	Headache, somnolence, akathisia.	Irritability, thirst	Dizziness, extrapyramidal disorder, convulsion*.
Eye disorders		Conjunctivitis.	Oculogyric crisis*.
Cardiac disorders		Palpitations.	Sudden cardiac death,

			serious ventricular dysrhythmias (see section 4.4)*, QTc prolongation, Torsade de Pointes.
Vascular disorders			Hypertensive crisis in patients with phaeochromocytoma may occur with administration of BIO DOMPERIDONE 10.
Endocrine disorders		Endocrinological effects (hot flushes).	
Gastrointestinal disorders	Diarrhoea, dry mouth.	Abdominal cramps; change in appetite; constipation; and heartburn.	
Reproductive system and breast disorders	Breast enlargement/ gynaecomastia, breast tenderness, galactorrhoea, amenorrhoea, breast pain (mastalgia), menstruation irregular, lactation disorder.	Breast discharge, breast swelling.	
Skin and subcutaneous tissue disorders	Pruritis, rash	Urticaria and oedema	Angioedema*.
Renal and urinary		Change in urinary	Urinary retention*.

disorders		frequency; dysuria.	
Muscoskeletal and connective tissue disorders		Leg cramps.	
General disorders and administration site conditions	Asthenia	Stomatitis; lethargy.	
Investigations			Abnormal liver function test, increased blood prolactin*.

*Post marketing data

Paediatric population

Although not approved for paediatric use, inappropriate/inadvertent ingestion in children resulted in extrapyramidal disorders and central nervous system related effects of convulsions, agitation and somnolence. See overdose.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the "**6.04 Adverse Drug Reactions Reporting Form**", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8

4.9 Overdose

Symptoms and signs

The following are the clinical effects of an overdose: dysrhythmia (dizziness, fainting, irregular heartbeat); drowsiness; agitation, altered consciousness, convulsion; disorientation; extrapyramidal reactions, especially in children and hypotension.

Treatment

There is no specific antidote or specific medicine for domperidone overdose. In the event of overdosage the administration of activated charcoal may be useful. Symptomatic and supportive measures are recommended. Anticholinergic medicines, anti-parkinson medication or antihistamines with anticholinergic properties may be useful in controlling the extrapyramidal effects associated with domperidone toxicity.

It is advisable to contact a poison control centre without delay to obtain the latest recommendations for the management of an overdose.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Category and class: A.5.7.2 Anti-emetics and anti-vertigo preparations

Pharmacotherapeutic group: Propulsives, ATC code: A03F A 03

Domperidone is a dopamine antagonist. It produces an anti-emetic effect through its action on the dopamine-receptor in the chemo-emetic trigger zone. Domperidone does not cross the blood-brain barrier to any significant degree and therefore exerts a relatively minor effect on cerebral dopaminergic receptors. Domperidone has been shown to increase the duration of antral and duodenal contractions thus improving gastric emptying. Domperidone does not alter gastric secretions and has no effect in intracranial pressure or on the cardiovascular system.

5.2 Pharmacokinetic properties

Absorption

Domperidone is absorbed after oral administration in the fasting state with peak plasma concentrations at approximately 1 hour after administration. Domperidone undergoes rapid and extensive hepatic metabolism by hydroxylation and N-dealkylation. Due to this extensive first-pass hepatic and intestinal metabolism, the absolute bioavailability of oral domperidone is low (approximately 15 %).

Distribution

Domperidone is 90 – 95 % bound to plasma proteins. The plasma half-life after a single oral dose is approximately 7 – 9 hours and is prolonged in patients with severe renal impairment.

Elimination

Urinary and faecal excretion amount to 31 % and 66 % of the oral dose, respectively. The proportion of domperidone excreted unchanged is small (approximately 1 % of urinary and 10 % of faecal excretion).

Special Populations

Hepatic impairment

In subjects with moderate hepatic impairment (Pugh score 7 to 9, Child-Pugh rating B), the AUC and C_{max} of domperidone is 2,9- and 1,5-fold higher, respectively, than in healthy subjects. The unbound fraction is increased by 25 %, and the terminal elimination half-life is prolonged from 15 to 23 hours. Subjects with mild hepatic impairment have a somewhat lower systemic exposure than healthy subjects based on C_{max} and AUC, with no change in protein binding or terminal half-life. Subjects with severe hepatic impairment were not studied (see section 4.3).

Renal impairment

In patients with severe renal insufficiency (serum creatinine more than 6 mg/100 mL, i.e., more than 0,6 mmol/L) the half-life of domperidone was increased from 7,4 to 20,8 hours, but plasma medicine levels are lower than in subjects with normal renal function. Very little unchanged medicine (approximately 1 %) is excreted via the kidneys (see section 4.2).

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Core tablet:

Crospovidone

Lactose monohydrate

Magnesium stearate

Pre-gelatinised starch

Microcrystalline cellulose (PH 102)

Povidone (K 30)

Sodium lauryl sulphate

Coating:

Hypromellose

Macrogol

6.2 Incompatibilities

Not applicable

6.3 Shelf life

48 months

6.4 Special precautions for storage

Store at or below 25 °C. Keep the blister in the outer carton until required for use.

Protect from light.

6.5 Nature and contents of container

BIO DOMPERIDONE tablets are available in transparent PVC-Aluminium blister packs of 10 or 100 tablets.

6.6 Special precautions for disposal and other handling

No special requirements.

7 HOLDER OF CERTIFICATE OF REGISTRATION

BIOTECH LABORATORIES (PTY) LTD

Ground floor, Block K West, Central Park

400 16th Road

Randjespark

Midrand, 1685

8 REGISTRATION NUMBER

42/5.7.2/0836

9 DATE OF FIRST AUTHORISATION/ RENEWAL OF THE AUTHORISATION

Date of registration: 26 November 2010

10 DATE OF REVISION OF THE TEXT

28 September 2023