PROFESSIONAL INFORMATION (PI)

SCHEDULING STATUS

Schedule 4

1 NAME OF THE MEDICINE

MOTILIUM® tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 10 mg domperidone.

Contains sugar (lactose monohydrate).

Each tablet contains 54,20 mg lactose monohydrate.

3 PHARMACEUTICAL FORM

Film coated tablets.

White circular, biconvex, film coated tablet 6,5 mm diameter engraved "M" on one side and 10

"JANSSEN" on the other side.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

MOTILIUM tablets are 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 gastro-intestinal 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 MOTILUM 15 – 30 minutes before meals. If taken after meals, absorption of the medicine is somewhat delayed.

The dose of MOTILIUM 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).

Paediatrics

The efficacy of domperidone was not demonstrated in children less than or equal to 12 years of age (see section 5.1).

The safety of MOTILIUM in adolescents weighing ≤ 35 kg has not been established.

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 of MOTILIUM should be reduced to once or twice daily, depending on the severity of the impairment, and the dose may need to be reduced. Patients with severe renal impairment should be reviewed regularly.

Hepatic impairment

MOTILIUM 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, Pharmacokinetic properties).

4.3 Contraindications

MOTILIUM is contraindicated in the following situations:

- Known hypersensitivity to domperidone or any of its excipients.
- Prolactin-releasing pituitary tumour (prolactinoma).
- Co-administration with other potent CYP3A4 inhibitors which have been shown to cause QT interval prolongation such as fluconazole, itraconazole, ketoconazole, voriconazole, posaconazole, clarithromycin, erythromycin, azithromycin, roxithromycin, amiodarone, telithromycin, amprenavir, atazanavir, fosamprenavir, indinavir, nelfinavir, ritonavir, saquinavir and quinolones (see sections 4.4 and 4.5).
- 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.
- Whenever stimulation of gastric motility might be dangerous, e.g. in the presence of gastro-intestinal haemorrhage, mechanical obstruction or perforation.
- In patients with moderate (child pugh score 7 – 9) or severe (child pugh score > 9) hepatic impairment (see section 5.2).

4.4 Special warnings and precautions for use

MOTILIUM film coated tablets are unsuitable for use in children weighing less than 35 kg.

Cardiac effects

Epidemiological studies have shown that MOTILIUM 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, MOTILIUM 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 MOTILIUM with potent CYP3A4 inhibitors which have been shown to cause QT interval prolongation is contraindicated (see section 4.3).

Caution should be exercised when MOTILIUM 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 4.8).

Caution should be exercised when MOTILIUM is co-administered with medicines which have been shown to cause QT interval prolongation and patients should be monitored

closely for signs or symptoms of cardiovascular adverse reactions (see section 4.8).

Examples include:

- Anti-dysrhythmias class IA (e.g. disopyramide, quinidine)
- Anti-dysrhythmias 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. levofloxacin, moxifloxacin and quinolones)
- Certain antifungal medicines (e.g. pentamidine)
- Certain antimalarial medicines (e.g. halofantrine)
- Certain gastro-intestinal medicines (e.g. dolasetron)
- Certain medicines in cancer (e.g. toremifene, vandetanib)
- Certain other medicines (e.g. bepridil, methadone)

The above list is representative and not exhaustive.

Domperidone base

Antacids and anti-secretory medicines should not be taken simultaneously with oral formulations of MOTILIUM as they lower the oral bioavailability of MOTILIUM. When used concomitantly, MOTILIUM should be taken before meals and antacids or anti-secretory medicines after meals.

Excipients

MOTILIUM film coated tablets contain lactose.

Patients with rare hereditary conditions of galactose intolerance e.g. galactosaemia, Lapp lactase deficiency, glucose-galactose malabsorption or fructose intolerance should not take MOTILIUM.

MOTILIUM film coated tablets contains lactose, which may have an effect on the glycaemic control of patients with diabetes mellitus.

4.5 Interaction with other medicines and other forms of interaction

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.

When MOTILIUM was co-administered with potent CYP3A4 inhibitors which have been shown to cause QT interval prolongation, clinically relevant changes in QT intervals were observed. Therefore, co-administration of MOTILIUM with certain medicines is contraindicated (see section 4.3).

Caution should be exercised when MOTILIUM is co-administered with potent CYP3A4 inhibitors which have not been shown to cause QT interval prolongation or medicines which have been shown to cause QT interval prolongation (see section 4.4).

Concomitant administration of anti-cholinergic medicines (e.g. dextromethorphan, diphenhydramine) may antagonise the anti-dyspeptic effects of MOTILIUM.

Since MOTILIUM has gastro-kinetic effects, it could influence the absorption of concomitant orally administered medicines, particularly those with sustained release or enteric coated formulations. However, in patients already stabilised on digoxin or paracetamol, concomitant administration of MOTILIUM did not influence the blood levels of these medicines.

MOTILIUM 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.

Reduced gastric acidity impairs the absorption of MOTILIUM. Oral bioavailability is decreased by prior concomitant administration of cimetidine and sodium bicarbonate.

As MOTILIUM interferes with serum prolactin levels, it may interfere with other hypoprolactinaemic agents and with some diagnostic tests.

4.6 Fertility, pregnancy and lactation

The safety of use during pregnancy and lactation has not been established.

Domperidone is excreted in human breast milk therefore women on treatment with MOTILIUM should not breastfeed their babies.

4.7 Effects on ability to drive and use machines

Dizziness and somnolence have been observed following use of MOTILIUM (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 MOTILIUM affects them.

4.8 Undesirable effects

Clinical Trial Data

The adverse drug reactions are ranked by frequency, using the following convention: Very common (≥1/10); common (≥1/100, <1/10); uncommon (≥1/1 000, < 1/100); rare (≥1/10 000, < 1/1 000); very rare (< 1/10 000), including isolated reports.

Psychiatric disorders

Common:

Depression, anxiety, libido decreased/loss of libido.

Nervous system disorders

Common:

Headache, somnolence, akathisia.

Gastro-intestinal disorders

Common:

Diarrhoea.

Immune system disorders

Uncommon:

Hypersensitivity.

Skin and subcutaneous tissue disorders

Common:

Rash, pruritus.

Uncommon:

Urticaria.

Reproductive system and breast disorders

Common:

Breast enlargement/ gynaecomastia, breast tenderness, galactorrhoea, amenorrhoea, breast pain, menstruation irregular, lactation disorder.

Uncommon:

Breast discharge, breast swelling.

General disorders and Administration site conditions

Common:

Asthenia.

Dry mouth has also been reported.

Postmarketing data

In addition to the adverse effects reported during clinical studies and listed above, the following adverse drug reactions have been reported postmarketing:

Immune System Disorders

Anaphylactic reaction (including anaphylactic shock).

Psychiatric Disorders

Agitation, nervousness.

Nervous System Disorders

Dizziness, extrapyramidal disorder, convulsion.

Cardiac Disorders

Sudden cardiac death, serious ventricular dysrhythmias (see section 4.4).

Skin and Subcutaneous Tissue Disorders

Angioedema.

Renal and Urinary Disorders

Urinary retention.

Investigations

Abnormal liver function test, increased blood prolactin.

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 medicinal product 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

Overdose has been reported primarily in infants and children. Symptoms of overdosage may include agitation, altered consciousness, convulsion, disorientation, somnolence and extrapyramidal reactions.

Treatment

There is no specific antidote to domperidone. Symptomatic and supportive therapy is indicated. Close medical supervision and supportive therapy is recommended. Anticholinergic or anti-Parkinson medicines may be helpful in controlling the extrapyramidal reactions.

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

Domperidone is a dopamine-receptor blocking agent. Its action on the dopamine-receptors in the chemo-emetic trigger zone produces an anti-emetic effect.

Domperidone does not cross the blood-brain barrier to any appreciable degree and so exerts relatively little effect on cerebral dopaminergic receptors.

Domperidone has been shown to increase antroduodenal motility and gastric emptying**.** There is no effect on gastric secretion.

Effect on QT/QTc interval and cardiac electrophysiology

In accordance with ICH-E14 guidelines, a thorough QT study was performed in healthy subjects. This study included a placebo, active comparator and positive control and was conducted using recommended and supra-therapeutic doses (10 and 20 mg administered 4 times a day). This study found a maximal difference of QTc between domperidone and placebo in LS-means in the change from baseline of 3,4 msec for 20 mg domperidone administered 4 times a day on Day 4, and the 2-sided 90% CI (1,0 5,9 msec) did not exceed 10 msec. The QT prolongation observed in this study when domperidone was administered according to the recommended dosing regimen is not clinically relevant.

This lack of clinical relevance is corroborated by pharmacokinetics and QTc interval data from two older studies which involved a 5-day treatment of 20 mg and 40 mg domperidone administered 4 times a day. ECGs were recorded prior to the study, on Day 5 at 1 hour (approximately at t_{max}) after the morning dose, and 3 days later. In both studies, no difference between QTc after active treatment and placebo was observed. It was therefore concluded that domperidone administration of 80 and 160 mg daily doses had no clinically significant effect on QTc in healthy subjects.

5.2 Pharmacokinetic properties

Absorption

In fasting subjects, domperidone is [~~rapidly~~] absorbed after oral administration, with peak plasma concentrations occurring at approximately 60 minutes after dosing.

The absolute bio-availability of oral domperidone is low (approximately 15 %) due to first-pass hepatic and intestinal metabolism.

Distribution

Domperidone is 91 - 93 % bound to plasma proteins. The plasma half-life after a single oral dose is 7 - 9 hours in healthy subjects but is prolonged in patients with severe renal insufficiency.

Metabolism

Domperidone undergoes rapid and extensive hepatic metabolism by hydroxylation and N-dealkylation. *In vitro* metabolism experiments with diagnostic inhibitors revealed that CYP3A4 is a major form of cytochrome P-450 involved in the N-dealkylation of domperidone, whereas CYP3A4, CYP1A2 and CYP2E1 are involved in domperidone aromatic hydroxylation.

Excretion

Urinary and faecal excretion amount to 31 % and 66 % of the oral dose, respectively. The proportion of medicine 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

Lactose monohydrate, maize starch, microcrystalline cellulose, pregelatinised potato starch, polyvidone, magnesium stearate, hydrogenated cottonseed oil, sodium lauryl sulphate and hypromellose.

6.2 Incompatibilities

Not applicable.

6.3 Shelf-life

3 years.

6.4 Special precautions for storage

Store at or below 30 °C. Protect from light.

KEEP OUT OF REACH OF CHILDREN.

6.5 Nature and contents of the container

Cartons containing one or more blister packs of 10.

6.6 Special precautions for disposal and other handling

Not applicable.

7 HOLDER OF CERTIFICATE OF REGISTRATION

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8 REGISTRATION NUMBER

K/5.7.2/261

9 DATE OF FIRST AUTHORISATION

Date of registration of MOTILIUM 10 mg tablets: 18 May 1978

10 DATE OF REVISION OF THE TEXT

12 May 2022

Namibia	Reg No.: 90/5.7.2/00628	NS 2
Botswana	Reg No.: B9315425	S2