PROFESSIONAL INFORMATION

SCHEDULING STATUS

Schedule 4

PROPRIETARY NAME AND DOSAGE FORM

MOTILIUM® tablets

COMPOSITION

Each tablet contains 10 mg domperidone.

List of excipients:

MOTILIUM tablets also contain the following inactive ingredients: lactose monohydrate, maize starch, microcrystalline cellulose, pregelatinised potato starch, polyvidone, magnesium stearate, hydrogenated cottonseed oil, sodium lauryl sulphate and hypromellose.

PHARMACOLOGICAL CLASSIFICATION

A 5.7.2 Anti-emetics and anti-vertigo preparations

PHARMACOLOGICAL ACTION

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.

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 key pharmacokinetic parameters after a single or multiple doses (administered 4 times a day) of 10 mg domperidone base tablets to healthy subjects are presented in the table below. The

C_{max} and AUC values of domperidone increased proportionally with dose in the 10 mg to 20 mg dose range.

Key domperidone pharmacokinetic parameters after a single or multiple doses (administered 4 times a day) of 10 mg domperidone base tablets to healthy subjects		
PK parameter **Mean**	**Domperidone 10 mg administered four times a day** **Day 1**	**Day 4**
n	40	40
C_{min}, ng/m*l*	NA	5,26 (CV: 31,1 %)
C_{max}, ng/m*l*	11,6 (CV: 50,8 %)	17,3 (CV: 35,4 %)
t_{max}, h[a]	1,02 (range: 0,52 – 5,02)	1,02 (range: 0,50 – 4,03)
AUC_{5h}, ng.h/m*l*	20,4 (CV: 34,4 %)	47,8 (CV: 30,5 %)

[a] median (range)

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 CONTRA-INDICATIONS).

Renal impairment

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

Paediatric patients

Based on limited pharmacokinetic data, domperidone plasma concentrations in preterm neonates were consistent with those reported in adults.

INDICATIONS

MOTILIUM tablets are indicated in adults and children over 35 kg for:

- Short-term management of delayed gastric emptying of functional origin with gastro-oesophageal reflux and/or dyspepsia.
- Control of nausea and vomiting of central or local origin.
- As an anti-emetic in patients receiving cytostatic and radiation therapy.
- Facilitation of radiological examination of the upper gastro-intestinal tract.

CONTRA-INDICATIONS

MOTILIUM is contra-indicated 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 WARNINGS AND SPECIAL PRECAUTIONS and INTERACTIONS).
- 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 or severe hepatic impairment (see Pharmacokinetic properties).

WARNINGS AND SPECIAL PRECAUTIONS

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 SIDE-EFFECTS). 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 CONTRA-INDICATIONS).

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 SIDE-EFFECTS).

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 SIDE-EFFECTS). Examples include:

- Anti-arrhythmias class IA (e.g. disopyramide, quinidine).
- Anti-arrhythmias 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 and may be unsuitable for patients with lactose intolerance, galactosaemia or glucose/galactose malabsorption.

Effects on ability to drive and use machines

Dizziness and somnolence have been observed following use of MOTILIUM (see SIDE-EFFECTS). 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.

INTERACTIONS

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 CONTRA-INDICATIONS).

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 WARNINGS AND SPECIAL PRECAUTIONS).

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.

PREGNANCY AND LACTATION

The safety of use during pregnancy and lactation has not been established.
Domperidone is excreted in human breast milk therefore breast feeding is not recommended for mothers who are taking MOTILIUM tablets.

DOSAGE AND DIRECTIONS FOR USE

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

Adults and adolescents ≥ 12 years of age and weighing ≥ 35 kg, and children weighing ≥ 35 kg

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 40 mg.

Usually, the maximum treatment duration should not exceed one week for the treatment of acute nausea and vomiting. If nausea and vomiting persists for longer than one week, patients should consult their medical practitioners. For other indications, the initial duration of treatment is up to four weeks. If treatment exceeds four weeks, patients should be re-evaluated and the need for continued treatment reassessed.

Formulation (domperidone per unit)	**Dosage**	**Maximum dose per day**
Film-coated tablets (10 mg/tablet)	1 tablet three to four times per day	40 mg (4 x10 mg tablet).

Tablets are unsuitable for use in children weighing less than 35 kg. For this group of patients the suspension is available.

Renal impairment

Since the elimination half-life of domperidone is prolonged in severe renal impairment (serum creatinine > 6 mg/100 m/, 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 CONTRA-INDICATIONS). Dose adjustment is not required for patients with mild (Child-Pugh 5 to 6) hepatic impairment (see Pharmacokinetic properties).

SIDE 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 disorder

Common:

Headache, somnolence, akathisia.

Gastro-intestinal disorders

Common:

Diarrhoea.

Immune system disorder

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 WARNINGS AND SPECIAL PRECAUTIONS).

Skin and Subcutaneous Tissue Disorders

Angioedema.

Renal and Urinary Disorders

Urinary retention.

Investigations

Liver function test abnormal, blood prolactin increased.

Paediatric population

Extrapyramidal disorder occurs primarily in neonates and infants.

Other central nervous system-related effects of convulsion and agitation also are reported primarily in infants and children.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT

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, but in the event of overdosage, gastric lavage as well as the administration of activated charcoal may be useful. Symptomatic and supportive measures are recommended. Anticholinergic or anti-Parkinson medicines may be helpful in controlling the extrapyramidal reactions.

IDENTIFICATION

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

10

and "JANSSEN" on the other side.

PRESENTATION

Cartons containing one or more blisters of 10 or 100 tablets.

STORAGE INSTRUCTIONS

Store at or below 25 °C. Protect from light.

KEEP OUT OF REACH OF CHILDREN.

REGISTRATION NUMBER

K/5.7.2/261

Namibia Reg. No.: 90/5.7.2/..628
NS 2
Botswana Reg. No.: BOT2203863/A
S3
Zimbabwe Reg. No.: 78/16.4/1180
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