PRODUCT NAME
MOTILIUM® (domperidone base)

DOSAGE FORMS AND STRENGTHS
One film-coated tablet contains 10 mg domperidone.
The oral suspension contains 1 mg domperidone per mL.

For excipients, see *List of Excipients*.

CLINICAL INFORMATION
Indications
1. The dyspeptic symptom complex that is often associated with delayed gastric emptying, gastro-esophageal reflux and esophagitis:
   - epigastric sense of fullness, early satiety, feeling of abdominal distension, upper abdominal pain;
   - bloating, eructation, flatulence;
   - nausea and vomiting;
   - heartburn with or without regurgitations of gastric contents in the mouth.
2. Nausea and vomiting of functional, organic, infectious or dietary origin.
3. Nausea and vomiting induced by:
   - radiotherapy or drug therapy
   - dopamine agonists (such as L-dopa and bromocriptine) used in the treatment of Parkinson's disease.

Dosage and Administration
It is recommended to take oral MOTILIUM® 15-30 minutes before meals. If taken after meals, absorption of the drug is somewhat delayed.

Adults and adolescents ≥ 12 years of age and weighing ≥ 35 kg
The dose of MOTILIUM® should be the lowest effective dose for the individual situation (typically 30mg/day) and can be increased if necessary to a maximum daily oral dose of 40mg.

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 physician. 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 (4x10mg tablet)
Oral suspension (1 mg/ml)	10 mL three to four times per day	40 mg (40 mL of 1mg/mL oral suspension)

Doses above 30mg/day should be used with caution due to potential risk of arrhythmias associated with the higher doses.

Infants and children < 12 years of age and weighing < 35 kg

The efficacy of MOTILIUM® has not been established in infants and children < 12 years of age and weighing < 35 kg (see *Clinical Studies*).

Use in renal insufficiency

Since the elimination half-life of domperidone is prolonged in severe renal impairment (serum creatinine > 6mg/100mL, i.e. > 0.6mmol/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 (see *Pharmacokinetic Properties*).

Hepatic impairment

MOTILIUM® is contraindicated for patients with moderate (Child-Pugh 7 to 9) or severe (Child-Pugh >9) hepatic impairment (see *Contraindications*). Dose adjustment is not required for patients with mild (Child-Pugh 5 to 6) hepatic impairment (see *Pharmacokinetic Properties*).

Contraindications

MOTILIUM® is contraindicated in the following situations:

- Known hypersensitivity to domperidone or any of the excipients
- Prolactin-releasing pituitary tumour (prolactinoma)
- Co-administration with QT-prolonging drugs (see *Interactions*)
- Co-administration with potent CYP3A4 inhibitors (see *Interactions*)
- In patients who have known existing prolongation of cardiac conduction of intervals, particularly QTc, patients with significant electrolyte disturbances or underlying cardiac diseases such as congestive heart failure (see *Warnings and Precautions*)
- 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 Precautions

Cardiac effects

Epidemiological studies showed that domperidone may be associated with an increased risk of serious ventricular arrhythmias or sudden cardiac death (see *Adverse Reactions*). Those studies suggest this increased risk may be higher in patients older than 60 years or in patients taking oral doses greater than 30 mg per day. Therefore, MOTILIUM® should be used with caution in older patients. Domperidone should be used at the lowest effective dose in adults.

Patients older than 60 years of age should consult their physician before taking MOTILIUM®.

Due to increased risk of ventricular arrhythmia, MOTILIUM® is contraindicated in patients with known existing prolongation of cardiac conduction intervals, particularly QTc, in patients with significant electrolyte disturbances (hypokalaemia, hyperkalaemia, hypomagnesaemia), or bradycardia, or in patients with underlying cardiac diseases such as congestive heart failure. Electrolyte disturbances (hypokalaemia, hyperkalaemia, hypomagnesaemia) and bradycardia are known to be conditions increasing the proarrhythmic risk.

Treatment with MOTILIUM® should be stopped if signs or symptoms occur that may be associated with cardiac arrhythmia, and the patient should promptly consult their physician.

Chronic administration of domperidone is not recommended.

Use with Antacids or antisecretory agents

Antacids or antisecretory agents should not be taken simultaneously with oral formulations of MOTILIUM® as they lower the oral bioavailability of domperidone. When used concomitantly, MOTILIUM® should be taken before meals and antacids or antisecretory agents after meals. Dosing with these agents should be separated from dosing with MOTILIUM® by at least 2 hours.

Excipients

The film-coated tablets contain lactose and may be unsuitable for patients with lactose intolerance, galactosemia or glucose/galactose malabsorption.

The oral suspension contains sorbitol and may be unsuitable for patients with sorbitol intolerance.

Interactions

The main metabolic pathway of domperidone is through CYP3A4. *In vitro* and human data show that the concomitant use of drugs that significantly inhibit this enzyme may result in increased plasma levels 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 medicinal products

- anti-arrhythmics class IA (e.g., disopyramide, hydroquinidine, quinidine)
- anti-arrhythmics class III (e.g., amiodarone, dofetilide, dronedarone, ibutilide, sotalol)
- certain anti-psychotics (e.g., haloperidol, pimozide, sertindole)
- certain anti-depressants (e.g., citalopram, escitalopram)
- certain antibiotics (e.g., erythromycin, levofloxacin, moxifloxacin, spiramycin)
- certain antifungal agents (e.g., pentamidine)
- certain antimalarial agents (in particular halofantrine, lumefantrine)
- certain gastro-intestinal medicines (e.g., cisapride, dolasetron, prucalopride)
- certain antihistaminics (e.g., mequitazine, mizolastine)

- certain medicines used in cancer (e.g., toremifene, vandetanib, vincamine)
- certain other medicines (e.g., bepridil, diphemanil, methadone) (see *Contraindications*)

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

- protease inhibitors
- systemic azole antifungals
- some macrolides (erythromycin, clarithromycin, telithromycin) (see C*ontraindications*)

Concomitant use of the following substances is not recommended

Moderate CYP3A4 inhibitors i.e. diltiazem, verapamil and some macrolides (see *Contraindications*)

Concomitant use of the following substances requires caution in use

Caution with bradycardia and hypokalaemia-inducing drugs, as well as with the following macrolides involved in QT-interval prolongation: azithromycin and roxithromycin (clarithromycin is contraindicated as it is a potent CYP3A4 inhibitor).

The above list of substances is representative and not exhaustive.

Concomitant administration of anticholinergic drugs (e.g., dextromethorphan, diphenhydramine) may antagonize the anti-dyspeptic effect of MOTILIUM®.

Theoretically, since MOTILIUM® has gastro-kinetic effects, it could influence the absorption of concomitantly orally administered drugs, particularly those with sustained release or enteric coated formulations. However, in patients already stabilized on digoxin or paracetamol, concomitant administration of domperidone did not influence the blood levels of these drugs.

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.

Pregnancy and Breast-feeding

Pregnancy

There are limited post-marketing data on the use of domperidone in pregnant women. A study in rats has shown reproductive toxicity at a high, maternally toxic dose. The potential risk for humans is unknown. Therefore, MOTILIUM® should only be used during pregnancy when justified by the anticipated therapeutic benefit.

Breast-feeding

The amount of domperidone that could be ingested by an infant through breast milk is low. The maximal relative infant dose (%) is estimated to be about 0.1% of the maternal weight-adjusted dosage. It is not known whether this is harmful to the newborn. Therefore, breast-feeding is not recommended for women who are taking MOTILIUM®.

Effects on Ability to Drive and Use Machines

Dizziness and somnolence have been observed following use of domperidone (see *Adverse Reactions*). 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.

Adverse Reactions

Throughout this section, adverse reactions are presented. Adverse reactions are adverse events that were considered to be reasonably associated with the use of domperidone based on the comprehensive assessment of the available adverse event information. A causal relationship with domperidone usually cannot be reliably established in individual cases. Further, because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

Clinical Trial Data

The safety of MOTILIUM® was evaluated in 1221 patients with gastroparesis, dyspepsia, gastro-esophageal reflux disorder (GERD), or other related conditions in 45 clinical trials included in the safety database. All patients were ≥15 years old and received at least one dose of oral MOTILIUM® (domperidone base). Slightly fewer than one-half (553/1221) of patients were diabetic. The median total daily dose was 80 mg (range 10 to 160 mg), with 230 patients receiving a dose greater than 80 mg. Median duration of exposure was 56 days (range 1 to 2248 days).

Adverse reactions reported by ≥1% of patients treated with domperidone in these 45 clinical trials are shown in Table 1.

Table 1.	**Adverse Reactions Reported by ≥ 1% of Domperidone-Treated Patients in 45 Clinical Trials**
System/Organ Class Adverse Reaction	**Domperidone (n=1221)** **%**
Psychiatric Disorders	
Depression	2.5
Anxiety	1.6
Libido Decreased/Loss of Libido	1.5
Nervous System Disorders	
Headache	5.6
Somnolence	2.5
Akathisia	1.0
Gastrointestinal Disorders	
Diarrhoea	5.2
Skin and Subcutaneous Tissue Disorders	
Rash	2.8
Pruritus	1.7
Reproductive System and Breast Disorders	
Breast Enlargement/Gynaecomastia	5.3
Breast Tenderness	4.4
Galactorrhoea	3.3
Amenorrhoea	2.9
Breast Pain	2.3
Menstruation Irregular	2.0
Lactation Disorder	1.6
General Disorders and Administration Site Conditions	
Asthenia	1.9

Adverse reactions that occurred in <1% of Domperidone-treated patients in the 45 clinical trials (n=1221) are listed below in Table 2.

Table 2.	**Adverse Reactions Reported by <1% of Domperidone-Treated Patients in 45 Clinical Trials**
System/Organ Class Adverse Reaction	**Domperidone (n=1221)** **%**
Immune System Disorders	
Hypersensitivity	0.2
Skin and Subcutaneous Tissue Disorders	
Urticaria	0.7
Reproductive System and Breast Disorders	
Breast Discharge	0.8
Breast Swelling	0.5

The following adverse reaction has been reported with over-the-counter use: dry mouth.

Postmarketing

In addition to the adverse reactions reported during clinical studies and listed above, the following adverse reactions have been reported during postmarketing experience (Table 3). In the table, the frequencies are provided according to the following convention:

Very common	≥1/10
Common	≥1/100 and < 1/10

Uncommon	≥ 1/ 1,000 and < 1/100
Rare	≥1/10,000 and < 1/1,000
Very rare	<1/10,000, including isolated reports.

In Table 3, adverse reactions are presented by frequency category based on spontaneous reporting rates.

Table 3. Adverse Reactions Identified During Postmarketing Experience with Domperidone by Frequency Category Estimated from Spontaneous Reporting Rates

Immune System Disorders	
Very rare	Anaphylactic Reaction (including Anaphylactic Shock)
Psychiatric Disorders	
Very rare	Agitation, Nervousness
Nervous System Disorders	
Very rare	Dizziness, Extrapyramidal Disorder, Convulsion
Cardiac Disorders	
Very rare	Sudden Cardiac Death*, Serious Ventricular Arrhythmias*(see *Warnings and Precautions*)
Skin and Subcutaneous Tissue Disorders	
Very rare	Angioedema
Renal and Urinary Disorders	
Very rare	Urinary Retention
Investigations	
Very rare	Liver Function Test Abnormal, Blood Prolactin Increased

*Based on epidemiology data

Pediatric population

In postmarketing experience, there were no differences in the safety profile of adults and children.

As the hypophysis is outside the blood brain barrier, domperidone may cause an increase in prolactin levels. In rare cases this hyperprolactinaemia may lead to neuro-endocrinological side effects such as galactorrhoea, gynaecomastia and amenorrhoea.

Overdose

Symptoms and signs

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

Treatment

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

It is advisable to contact a poison control center to obtain the latest recommendations for the management of an overdose.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamic Properties

Pharmacotherapeutic group: Propulsives, ATC code: A03FA03

Domperidone is a dopamine antagonist with anti-emetic properties. Domperidone does not readily cross the blood-brain barrier. In domperidone users, especially in adults, extrapyramidal side effects are very rare, but domperidone promotes the release of prolactin from the pituitary. Its anti-emetic effect may be due to a combination of peripheral (gastrokinetic) effects and antagonism of dopamine receptors in the chemoreceptor trigger zone, which lies outside the blood-brain barrier in the area postrema. Animal studies, together with the low concentrations found in the brain, indicate a predominantly peripheral effect of domperidone on dopamine receptors. Studies in man have shown oral domperidone to increase lower oesophageal pressure, improve antroduodenal motility and accelerate 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 was 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.

Clinical Studies

Infants and children ≤ 12 years of age

A multicenter, double blind, randomized, placebo controlled, parallel group, prospective study was conducted to evaluate the safety and efficacy of domperidone in 292 children with acute gastroenteritis aged 6 months to 12 years (median age 7 years). In addition to oral rehydration treatment (ORT), randomized subjects received domperidone oral suspension at 0.25 mg/kg (up to a maximum of 30 mg domperidone/day), or placebo, 3 times a day, for up to 7 days. This study did not achieve the primary objective, which was to demonstrate that domperidone suspension plus ORT is more effective than placebo plus ORT at reducing the percentage of subjects with no vomiting episodes during the first 48 hours after the first treatment administration.

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 10mg 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 10mg to 20mg 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	**Domperidone 10 mg administered four times a day**	
Mean	**Day 1**	**Day 4**
n	40	40
C_{min}, ng/mL	NA	5.26 (CV: 31.1%)
C_{max}, ng/mL	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/mL	20.4 (CV: 34.4%)	47.8 (CV: 30.5%)

[a] median (range)

Source: Study DOM-DYP-1001

The low absolute bioavailability of oral domperidone (approximately 15%) is due to an extensive first-pass metabolism in the gut wall and liver. Although domperidone's bioavailability is enhanced in normal subjects when taken after a meal, patients with gastro-intestinal complaints should take domperidone 15-30 minutes before a meal. Reduced gastric acidity impairs the absorption of domperidone base. Oral bioavailability of domperidone base is decreased by prior concomitant administration of cimetidine and sodium bicarbonate. The time of peak absorption is slightly delayed and the AUC somewhat increased when the oral drug is taken after a meal.

Distribution

Domperidone is 91-93% bound to plasma proteins. Distribution studies with radiolabelled drug in animals have shown wide tissue distribution, but low brain concentration. Small amounts of drug cross the placenta in rats.

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

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.

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 *Contraindications*).

Renal impairment
In subjects with severe renal insufficiency (serum creatinine > 6 mg/100 mL, i.e. > 0.6 mmol/L) the half-life of domperidone is increased from 7.4 to 20.8 hours, but plasma drug levels are lower than in subjects with normal renal function. Very little unchanged drug (approximately 1%) is excreted via the kidneys (see *Dosage and Administration*).

NON-CLINICAL INFORMATION
At a high, maternally toxic dose of 200mg/kg/day, teratogenic effects (organ abnormalities such as anophthalmia, microphthalmia and displacement of the subclavian artery) were seen in the rat. The clinical significance of these findings is unknown. No teratogenicity was observed in mice and rabbits.

Electrophysiological *in vitro* and *in vivo* studies have shown that domperidone, at high concentrations, may prolong the QTc interval.

In juvenile rats, a no observed adverse effect level of 10mg/kg was observed following 30 days of once daily repeat intraperitoneal dosing. Single intraperitoneal or intravenous doses showed similar LD_{50} values (mean range 53-76mg/kg) in both juvenile and adult rats.

PHARMACEUTICAL INFORMATION
List of Excipients
Film coated tablets
Hydrogenated cottonseed oil, hypromellose, lactose monohydrate, magnesium stearate, maize starch, microcrystalline cellulose, polyvidone, pregelatinized potato starch sodium lauryl sulphate (formulation F42).

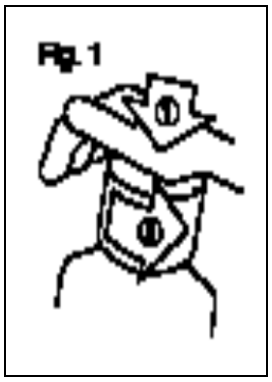
Oral suspension
Methyl-parahydroxybenzoate, microcrystalline cellulose and sodiumcarboxy-methylcellulose, polysorbate, propyl-parahydroxybenzoate, purified water, sodium hydroxide, sodium saccharin, sorbitol liquid non-crystallising(formulation F45).

Incompatibilities
None known.

Shelf Life
Refer to Outer Carton

Storage Conditions
Keep out of reach of children.
Store between 15 and 30°C.

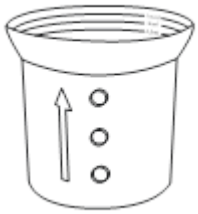
Instructions for Use and Handling
Oral suspension
Mix the contents of the bottle completely using a gentle tilting motion to avoid the formation of foam.



Directions for opening the bottle
Fig. 1: The bottle comes with a childproof cap, and should be opened as follows:

- Push the plastic screw cap down while turning it counter clockwise.
- Remove the unscrewed cap.

Directions for using the measuring cup
A measuring cup is supplied with the MOTILIUM® oral solution. Use the measuring cup just as it sits on the bottle. Make sure that the side with the graduations (the side that holds less) is uppermost; that is the side you have to fill. When the arrow on the side points up, the correct side is uppermost.



BATCH RELEASER

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