
MOTILIUM[®]

DATASHEET

NAME OF MEDICINE

Domperidone base

PRESENTATION

MOTILIUM 10 mg tablets are white, circular, film-coated, biconvex tablets with m/10 imprinted on one side and JANSSEN on the other.

USES

Pharmacodynamics

Mechanism of Actions

Domperidone is a dopamine antagonist with antiemetic properties. Domperidone does not readily cross the blood-brain barrier. It seldom causes extrapyramidal side effects, but does cause a rise in prolactin levels. Its antiemetic effect may be due to a combination of peripheral (gastrokinetic) effects and antagonism of central dopamine receptors in the chemoreceptor trigger zone which lies in the area postrema and is regarded as being outside the blood-brain barrier.

It also antagonises the behavioural effects of dopamine much more effectively when administered intracerebrally than when given systemically. These findings, together with the low concentrations found in the brain, indicate a predominantly peripheral effect of domperidone on dopamine receptors.

Studies in humans have shown intravenous and oral domperidone to increase lower oesophageal pressure, improve antroduodenal motility and accelerate gastric emptying. Domperidone has 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 therapeutic doses (10 or 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 was 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 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 concentrations of domperidone after 80 and 160 mg daily had no clinically significant effect on QTc in healthy subjects.

Pharmacokinetics

Absorption: in fasting subjects, domperidone is rapidly absorbed following oral administration with peak plasma concentrations occurring at approximately 30 to 60 minutes.

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

Distribution: Oral domperidone does not appear to accumulate or induce its own metabolism; a peak plasma level after 90 minutes of 21 ng/mL after two weeks oral administration of 30 mg per day was almost the same as that of 18 ng/mL after the first dose. Domperidone is 91 to 93% bound to plasma proteins. Distribution studies with radiolabelled drug in animals have shown wide tissue distribution, but low brain concentration. Small amount 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 (see **INTERACTIONS**).

Elimination: Urinary and faecal excretion amounts to 31 and 66%, respectively, of the oral dose. The proportion of the medicine 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 studies 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 **WARNINGS AND PRECAUTIONS**).

Paediatric Patients: based on the limited pharmacokinetic data, domperidone plasma concentration in preterm neonates were consistent with those reported in adults.

Indications - Adults and children weighing \geq 35kg

Symptomatic treatment of the dyspeptic symptom complex that may be associated with delayed gastric emptying such as epigastric sense of fullness, abdominal distension or swelling, or epigastric pain or discomfort.

Treatment of acute symptoms of nausea and vomiting.

There is insufficient evidence to support the use of domperidone in childhood gastro-oesophageal reflux disease. Domperidone may not be suitable for chemotherapy- or radiotherapy-induced nausea and vomiting or post-operative nausea and vomiting.

DOSAGE AND ADMINISTRATION

General

MOTILIUM should be taken 15-30 minutes before meals and, if necessary, before retiring. If taken after meals, absorption is somewhat delayed.

Adults and children weighing \geq 35 kg

1 tablet three to four times daily. The dose of MOTILIUM should be the lowest effective dose for the individual situation (typically 30 mg/day). The dose may be increased, if necessary, to a maximum daily oral dose of 40 mg (1 tablet four times daily).

Usually, the maximum treatment duration should not exceed one week for the treatment of acute nausea and vomiting. 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 re-assessed.

For children, the total daily dose has been determined as 0.25 mg/kg three to four times per day with a maximum **daily** dose of 1.0 mg/kg. However, the MOTILIUM tablet formulation is unsuitable for treatment in children weighing less than 35 kg. Use in children under 2 years of age is contraindicated (see **CONTRAINDICATIONS**). Since metabolic functions and the blood-brain barrier are not fully developed in the first months of life, the risk of neurological side effects is higher in young children (see **ADVERSE EFFECTS**). Overdosing may cause nervous system disorders in children (see **OVERDOSAGE**).

Use in renal impairment

It is unlikely that the dose needs to be adjusted for single administration in patients with renal insufficiency. However, since the elimination half-life of domperidone is prolonged in severe renal impairment, on repeated administration the dosing frequency of MOTILIUM should be reduced to

once or twice daily depending on the severity of the impairment (see **WARNINGS AND PRECAUTIONS**). Generally, patients on prolonged therapy should be reviewed regularly.

CONTRAINDICATIONS

MOTILIUM is contraindicated in the following situations:

- Known hypersensitivity to domperidone or any of the excipients
- Prolactin-releasing pituitary tumour (prolactinoma)
- Use in children under 2 years of age.
- Co-administration with potent CYP3A4 inhibitors has been shown to increase domperidone concentrations to the point where QT interval prolongation may occur. Examples of potent CYP3A4 inhibitors include some azole antifungals (eg, itraconazole, voriconazole, posaconazole), some macrolide antibiotics (eg, clarithromycin, telithromycin), and some protease inhibitors (ritonavir, saquinavir, telaprevir).
- Co-administration with medicines that prolong the QTc interval.
- MOTILIUM should not be used whenever stimulation of gastrointestinal motility might be dangerous such as in the presence of gastrointestinal haemorrhage, mechanical obstruction, or perforation. In patients with moderate or severe hepatic impairment (see **PHARMACOKINETICS**).

WARNINGS AND PRECAUTIONS

Cardiovascular effects

MOTILIUM should be used with caution in older patients or those with current or history of cardiac disease. An increase in the risk of serious ventricular arrhythmias and sudden cardiac death has been reported in epidemiology studies (see **Postmarketing ADVERSE EFFECTS**). Those studies suggest this increased risk may be higher in patients older than 60 years or at total daily doses of more than 30mg. MOTILIUM should be used at the lowest effective dose in adults and children. Treatment with domperidone should be stopped if signs or symptoms occur that may be associated with cardiac arrhythmia, and the patient should consult their physician.

Use of MOTILIUM and other drugs which prolong QTc intervals requires that caution be exercised in patients who have existing prolongation of cardiac conduction intervals, particularly QTc, patients with significant electrolyte disturbances or underlying cardiac diseases such as congestive heart failure. Other risk factors for sudden cardiac arrest include a family history of coronary artery disease, high blood pressure, high blood cholesterol, obesity, diabetes, smoking and excessive alcohol consumption. It is desirable to optimise electrolyte levels prior to starting domperidone.

Drug interaction potential

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. Co-administration of domperidone with potent CYP3A4 inhibitors which have been shown to cause QT interval prolongation is contraindicated (see **CONTRAINDICATIONS**).

Caution should be exercised when domperidone is co-administered with potent CYP3A4 inhibitors which have not been shown to cause QT interval prolongation such as indinavir and patients should be monitored closely for signs or symptoms of adverse reactions (see **ADVERSE EFFECTS**).

Caution should be exercised when domperidone is co-administered with drugs which have been shown to cause QT interval prolongation and patients should be monitored closely for signs or symptoms of cardiovascular adverse reactions (see **ADVERSE EFFECTS**). Examples include:

- anti arrhythmics class IA (e.g., disopyramide, quinidine)
- anti arrhythmics 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)
- certain antifungal agents (e.g., pentamidine)
- certain antimalarial agents (e.g., halofantrine)
- certain azole antifungals, (e.g., itraconazole, ketoconazole, voriconazole)
- certain calcium antagonists, (e.g., diltiazem, verapamil)
- certain gastro intestinal drugs (e.g., dolasetron)
- certain HIV protease inhibitors (e.g., amprenavir, atazanavir, fosamprenavir, indinavir, nelfinavir, ritonavir, saquinavir)
- certain drugs used in cancer (e.g., toremifene, vandetanib)
- certain macrolide antibiotics (e.g., clarithromycin, erythromycin)
- certain other drugs (e.g., aprepitant, bepridil, methadone, nefazodone, telithromycin)

Antacids or antisecretory agents should not be taken simultaneously with MOTILIUM, as they lower the oral bioavailability of domperidone (see **INTERACTIONS**). When used concomitantly, MOTILIUM should be taken before meals and antacids or antisecretory agents after meals.

Intolerance to lactose

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

Prolactin levels

MOTILIUM produces an increase in plasma prolactin. The raised level persists with chronic administration but falls to normal on discontinuing the medicine. During chronic oral administration of 30 mg daily for two weeks the plasma prolactin level measured 90 minutes after medicine intake remained fairly constant at 25 ng/mL in males (normal value was 5 ng/mL) whilst in females the level

of 117 ng/mL after the first dose decreased to 56 ng/mL after 14 doses (pretreatment normal value was 9 ng/mL).

Tissue culture experiments indicate that approximately one-third of human breast cancers are prolactin-dependent *in vitro*, a factor of potential importance if the administration of domperidone is contemplated in a patient with a past history of breast cancer. Although disturbances such as galactorrhoea, amenorrhoea, gynaecomastia and impotence have been reported with other prolactin-elevating medicines, the clinical significance of elevated serum prolactin levels is unknown. An increase in mammary neoplasms has been found in rodents after chronic administration of domperidone and other prolactin-stimulating medicines.

Neither clinical studies nor epidemiological studies conducted to date have shown an association between chronic administration of these medicines and mammary tumorigenesis. Domperidone does not affect plasma growth hormone or aldosterone levels.

Carcinogenicity, Mutagenicity, Teratogenicity

MOTILIUM was administered to mice for 18 months and rats for 24 months in carcinogenicity studies. No dose-related effects were observed except for an increased incidence of malignant mammary tumours at 25 times the maximum human dose in female mice and rats and an increased incidence of pituitary tumours at 25 times the human dose in male rats.

No evidence for mutagenic potential was seen in dominant lethal studies in male and female mice, micronucleus tests in female mice and female rats, a study of chromosomal aberrations in human lymphocytes, a sex-linked recessive lethal test on *Drosophila melanogaster*, and in the Ames metabolic activation test with *Salmonella typhimurium*. Minor teratogenic effects were seen in one study where MOTILIUM was administered to rats orally at approximately 125 times the maximum human dose level. These findings were not confirmed by another study where the medicine was administered orally to rats at dosage levels as high as 400 times than that given to man.

Embryotoxicity without maternal toxicity was encountered when MOTILIUM was administered intravenously to rats (> 6 times the maximum human dose level) and orally to mice (44 times the maximum human dose level). Concurrent embryotoxicity and maternal toxicity were inconsistently found at oral dose levels approximately 6 times the maximum human level in rabbits and in rats and approximately 24 times the maximum human dose level.

Renal impairment

Since the elimination half-life of domperidone is prolonged in severe renal impairment, the dosing frequency of MOTILIUM should to be reduced to once or twice daily depending on the severity of the impairment. The dose may also need to be reduced. Such patients with severe renal impairment should be reviewed regularly (see **PHARMACOKINETICS and DOSAGE AND ADMINISTRATION**).

Hepatic Impairment

MOTILIUM is contraindicated for patients with moderate or severe hepatic impairment (see **CONTRAINDICATIONS**). Dose adjustment is not required for patients with mild hepatic impairment (see **PHARMACOKINETICS**).

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.

Lactation

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.

Infants

MOTILIUM tablets are unsuitable for use in children weighing less than 35 kg. Since metabolic functions and the blood-brain barrier are not fully developed in the first months of life the risk of neurological side effects is higher in young children (see **ADVERSE EFFECTS**). Therefore it is recommended that the dose be determined accurately and followed strictly in toddlers and small children. Overdosing may cause nervous system disorders in children, but other causes should be taken into consideration.

Effects on Ability to Drive and Use Machines

Dizziness and somnolence have been observed following use of domperidone (see **ADVERSE 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.

ADVERSE EFFECTS

Clinical Trial Data

The safety of MOTILIUM was evaluated in 1221 patients with gastroparesis, dyspepsia, gastro-oesophageal 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).

Table 1. Adverse - Reactions Reported by $\geq 1\%$ of MOTILIUM-Treated Patients in 45 Clinical Trials

System/Organ Class Adverse Reaction	MOTILIUM (n=1221) %
Psychiatric Disorders	
Depression	2.5
Anxiety	1.6
Libido Decreased/Loss of Libido	1.5

System/Organ Class	MOTILIUM (n=1221)
Adverse Reaction	%
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

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

Table 2. Adverse Drug Reactions Reported by <1% of MOTILIUM -Treated Patients in 45 Clinical Trials

System/Organ Class	MOTILIUM (n=1221)
Adverse Reaction	%
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 effects reported during clinical studies and listed above, the following adverse drug reactions have been reported (Tables 3 and 4). In each 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, ADRs are presented by frequency category based on spontaneous reporting rates, when known.

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

Immune System Disorders	
<i>Very rare</i>	Anaphylactic Reaction (including Anaphylactic Shock)
Psychiatric Disorders	
<i>Very rare</i>	Agitation, Nervousness
Nervous System Disorders	
<i>Very rare</i>	Dizziness, Extrapyramidal Disorder, Convulsion
Cardiac Disorders	
<i>Very rare</i>	Sudden Cardiac Death*, Serious Ventricular Arrhythmias*
Skin and Subcutaneous Tissue Disorders	
<i>Very rare</i>	Angioedema, Urticaria
Renal and Urinary Disorders	
<i>Very rare</i>	Urinary Retention
Reproductive System and Breast Disorders	
<i>Rare</i>	Gynaecomastia, Amenorrhoea
Investigations	
<i>Very rare</i>	Liver Function Test Abnormal, Blood Prolactin Increased

* Based on epidemiology data (see below)

Very rare case reports of QTc prolongation, ventricular arrhythmia, and sudden death have occurred with domperidone use. Although most reported cases have occurred in patients receiving the

intravenous form of domperidone, or in patients with other risk factors, an association with oral domperidone cannot be completely ruled out. Therefore, domperidone should be used with caution in patients with other risk factors for QTc prolongation including hypokalaemia, severe hypomagnesaemia, structural heart disease, the concomitant administration of QTc prolonging medicines, or an underlying genetic predisposition.

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.

An increase in the risk of serious ventricular arrhythmias and sudden cardiac death has been reported in some epidemiology studies. The risk may be higher in patients older than 60 years or at total daily doses of more than 30mg. Domperidone should be used at the lowest effective dose in adults and children. Due to the limitations of these data, the exact frequency of these adverse reactions could not be defined.

Paediatric population

In postmarketing experience, there were no differences in the safety profile of adults and children, with the exception of extrapyramidal disorder which occurred primarily in neonates and infants (up to one year of age), and other central nervous system-related effects of convulsion and agitation which were reported primarily in infants and children.

INTERACTIONS WITH OTHER MEDICINES

Concomitant administration of anticholinergic drugs may antagonise the anti-dyspeptic effect of MOTILIUM.

If administered prior to atropine, domperidone reduces the relaxant effect of atropine upon the lower oesophageal sphincter, but has no reversing effect if atropine is administered first. The main metabolic pathway of domperidone is through the cytochrome P450 isoenzyme 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.

When domperidone 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 domperidone with certain drugs is contraindicated (see **CONTRAINDICATIONS**).

Caution should be exercised when domperidone is co-administered with potent CYP3A4 inhibitors which have not been shown to cause QT interval prolongation or drugs which have been shown to cause QT interval prolongation (see **WARNINGS AND PRECAUTIONS**).

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 stabilised on digoxin or paracetamol, concomitant administration of domperidone did not influence the blood levels of these drugs.

Domperidone has been used with:

- neuroleptics, without potentiation of their activity,
- dopaminergic agonists (bromocriptine, L-dopa) for suppression of unwanted peripheral effects such as digestive disorders, nausea and vomiting, without affecting their central activity.

OVERDOSAGE

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, but in the event of a large overdose, gastric lavage within one hour of ingestion as well as the administration of activated charcoal may be useful. Anticholinergics, anti-Parkinsonian agents may be helpful in controlling the extrapyramidal reactions. Close observation and supportive therapy is recommended.

PHARMACEUTICAL PRECAUTIONS

Shelf Life

3 years when stored at or below 30°C

Special Precautions for Storage

Protect from light. Store at room temperature.

MEDICINE CLASSIFICATION

Prescription Medicine.

PACKAGE QUANTITIES

Blisters of 100 tablets.

FURTHER INFORMATION

MOTILIUM 10 mg tablets also contain lactose, maize starch, microcrystalline cellulose, pregelatinized potato starch, povidone, magnesium stearate, hydrogenated cottonseed oil, sodium lauryl sulfate and hypromellose.

NAME AND ADDRESS

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