

DATA SHEET

NAME OF MEDICINE

MOTILIUM®

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

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.

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.

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: no pharmacokinetic data are available in this population.

INDICATIONS

- Symptomatic treatment of the dyspeptic symptom complex which is often associated with delayed gastric emptying or gastro-oesophageal reflux and oesophagitis: epigastric sense of fullness, feeling of abdominal distension, upper abdominal pain, eructation, flatulence, heartburn.
- Treatment of nausea and vomiting of various origins including functional, organic, infectious, dietetic origin, or induced by radiotherapy, medicine therapy.

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

1 to 2 tablets three to four times daily. If necessary this dose may be doubled after two weeks if an adequate therapeutic response is not attained with a maximum daily dose of 80 mg.

Children aged 2 and above

The recommended dose of domperidone for children is 0.25-0.5 mg/kg three to four times per day with a maximum **daily** dose of 2.4 mg/kg (but do not exceed a total dose of 80 mg per day). Please note however MOTILIUM tablet dosage form is not suitable for use in children weighing less than 35 kg.

Use in renal impairment

It is unlikely that the dose needs to be adjusted for single administration in patients with renal insufficiency. However, on repeated administration the dosing frequency will need to be reduced to once or twice daily depending on the severity of the impairment (see **WARNINGS AND PRECAUTIONS**). The dose may also need to be reduced. Generally, patients on prolonged therapy should be reviewed regularly.

CONTRAINDICATIONS

- Known hypersensitivity to domperidone or any of the excipients
- Prolactin-releasing pituitary tumour (prolactinoma)
- Co-administration with oral ketoconazole, erythromycin, or other potent CYP3A4 inhibitors which prolong the QTc interval such as fluconazole, voriconazole, clarithromycin, amiodarone, and telithromycin (see **Interactions**)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

Intolerance to lactose

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

When antacids or antisecretory agents are used concomitantly, they should not be taken simultaneously with MOTILIUM, i.e., they should be taken after meals and not before meals.

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.

Use in renal impairment

Since the elimination half-life of domperidone is prolonged in severe renal impairment, on repeated administration 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 on prolonged therapy should be reviewed regularly (see **Pharmacokinetics**).

Use in 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 for humans is unknown. Therefore, MOTILIUM should only be used during pregnancy when justified by the anticipated therapeutic benefit.

Use in Lactation

Domperidone is excreted in breast milk of lactating rats (mostly as metabolites: peak concentration of 40 and 800 ng/mL after oral and i.v. administration of 2.5 mg/kg respectively). Domperidone concentrations in breast milk of lactating women are 10 to 50% of the corresponding plasma concentrations and expected not to exceed 10 ng/mL. The total amount of domperidone excreted in human breast milk is expected to be less than 7 µg per day at the highest recommended dosing regimen. It is not known whether this is harmful to the newborn. Therefore breast-feeding is not recommended for mothers who are taking MOTILIUM.

Use in 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

MOTILIUM has no or negligible influence on the ability to drive and use machines.

ADVERSE EFFECTS

Clinical Trial Data

The safety of MOTILIUM was evaluated in 1275 patients with dyspepsia, gastro-oesophageal reflux disorder (GERD), Irritable Bowel Syndrome (IBS), nausea and vomiting or other related conditions in 31 double-blind, placebo-controlled studies. All patients were at least 15 years old and received at least one dose of MOTILIUM (domperidone base). The median total daily dose was 30 mg (range 10 to 80 mg), and median duration of exposure was 28 days (range 1 to 28 days). Studies in diabetic gastroparesis or symptoms secondary to chemotherapy or parkinsonism were excluded.

Table 1. Adverse Drug Reactions Reported by \geq 1% of MOTILIUM-Treated Patients in 31 Clinical Trials of Oral Domperidone Base

System Organ Class	TRADENAME
Adverse Reaction	(N = 1275)
	%
Gastrointestinal Disorders	
Dry Mouth	1.7

Table 2. Adverse Drug Reactions Reported by < 1% of MOTILIUM-Treated Patients in 31 Clinical Trials of Oral Domperidone Base

System Organ Class	TRADENAME
Adverse Reaction	(N = 1275) %
Psychiatric Disorders	
Loss of Libido	0.2
Anxiety	0.1
Nervous System Disorders	
Somnolence	0.8
Headache	0.6
Gastrointestinal Disorders	
Diarrhoea	0.4
Skin and Subcutaneous Tissue Disorder	
Rash	0.2
Pruritus	0.1
Reproductive System and Breast Disorders	
Galactorrhoea	0.5
Breast Pain	0.2
Breast Tenderness	0.2
General Disorders and Administration Site Conditions	
Asthenia	0.1

In 45 studies where domperidone was used at higher dosages, for longer duration and for additional indications including diabetic gastroparesis, the frequency of adverse events (apart from dry mouth) was considerably higher. This was particularly evident for pharmacologically predictable events related to increased prolactin. In addition to the reactions listed in Tables 1 and 2, akathisia, breast discharge, breast enlargement, breast swelling, depression, hypersensitivity, lactation disorder and irregular menstruation, were also noted.

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	$\geq 1/10$
Common	$\geq 1/100$ and $< 1/10$
Uncommon	$\geq 1/1,000$ and $< 1/100$
Rare	$\geq 1/10,000$ 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>	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 or 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. Due to the limitations of these data, risk factors and the exact frequency of these adverse reactions could not be defined.

INTERACTIONS

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. Since MOTILIUM has gastro-kinetic effects it could influence the absorption of concomitantly orally administered medicines, particularly those of sustained release or enteric-coated formulations.

However, in patients already stabilised on digoxin, paracetamol or haloperidol, concomitant administration of domperidone did not influence the blood levels of these medicines.

Antacids or antisecretory agents should not be given simultaneously with MOTILIUM because they lower its bioavailability.

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. Examples of CYP3A4 inhibitors include:

- Azole antifungals, such as fluconazole*, itracpnazole, ketoconazole* and voriconazole*;
- Macrolide antibiotics, such as clarithromycin* and erythromycin*;
- HIV protease inhibitors, such as amprenavir, atazanavir, fosamprenavir. Indinavir, ritonavir, and saquinavir;
- Calcium antagonists, such as diltiazem and verapamil;
- Amiodarone*
- Aprepitant;
- Nefazodone;
- Telithromycin*

(* Also prolong QTc interval; see **CONTRAINDICATIONS**)

Separate pharmacokinetic/pharmacodynamic interaction studies with oral ketoconazole or oral erythromycin in healthy subjects confirmed a marked inhibition of domperidone's CYP3A4 mediated first pass metabolism by these medicines.

With the combination of domperidone 10 mg four times daily and ketoconazole 200 mg twice daily, a mean QTc prolongation of 9.8 msec was seen over the observation period, with changes at individual time points ranging from 1.2 to 17.5 msec. With the combination of domperidone 10 mg four times daily and erythromycin 500 mg three times daily, mean QTc over the observation period was prolonged by 9.9 msec, with changes at individual time points ranging from 1.6 to 14.3 msec. Both the C_{max} and AUC of domperidone at steady state were increased approximately three-fold in each of these interaction studies (see **CONTRAINDICATIONS**).

The contribution of increased plasma concentrations of domperidone to the observed effect on QTc is not known.

In these studies domperidone monotherapy at 10 mg four times daily resulted in increases in mean QTc of 1.6 msec (ketoconazole study) and 2.5 msec (erythromycin study), while ketoconazole monotherapy (200 mg twice daily) and erythromycin monotherapy (500 mg three times daily) led to increases in mean QTc of 3.8 and 4.8 msec, respectively, over the observation period.

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

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

Treatment

There is no specific antidote to domperidone, but in the event of overdose, gastric lavage 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

4 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.

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