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# MOTILIUM<sup>®</sup> 10 mg Tablets

## PRODUCT INFORMATION

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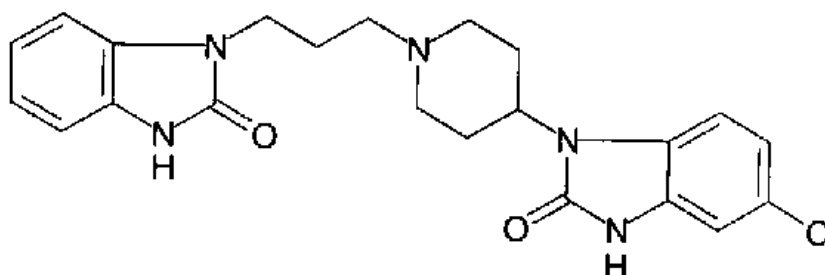
### Name of the Drug

Domperidone

### Description

Domperidone is a white to slightly beige coloured powder; it is freely soluble in 1.0M lactic acid, soluble in 1.0M citric acid, slightly soluble in ethanol and practically insoluble in water.

MOTILIUM 10 mg tablets are white, film coated, circular, normally arched, biconvex tablets, diameter 6.4 mm, one surface debossed with M/10 inscription and the other with JANSSEN. Each tablet contains 10 mg domperidone. Inactive ingredients: lactose, maize starch, microcrystalline cellulose, pregelatinised potato starch, povidone, magnesium stearate, hydrogenated cottonseed oil, sodium lauryl sulfate, hypromellose, and purified water.



### Pharmacology

MOTILIUM is a dopamine antagonist with antiemetic properties similar to those of metoclopramide and certain neuroleptic drugs. Unlike these drugs, however, MOTILIUM does not readily cross the blood-brain barrier. It seldom causes extra-pyramidal 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 chemo-receptor trigger zone, which lies in the area postrema and is regarded as being outside the blood brain barrier. Animal studies have shown that MOTILIUM has no effect on plasma concentrations of homovanillic acid, a metabolite of dopamine. 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 MOTILIUM to: increase the duration of antral and duodenal contractions; increase the gastric emptying of liquids and semi solids in healthy subjects and in patients in whom it was delayed; increase lower oesophageal sphincter pressure in healthy subjects. MOTILIUM has no effect on gastric secretion. Intravenous MOTILIUM 10, 20 and 40 mg had no effect on cardiac output, cardiac electric conduction, heart rate or blood pressure in healthy volunteers up to 1 hour after administration.

## Pharmacokinetics

### **Absorption**

Domperidone is rapidly absorbed following intramuscular and oral administration with peak plasma concentrations occurring at approximately 10 and 30 minutes, respectively.

Systemic bioavailability of intramuscular domperidone is about 83% whereas that of oral domperidone is 13 to 17%. The low oral bioavailability is probably due to 'first-pass' gut wall and hepatic metabolism. Oral bioavailability is decreased by prior administration of cimetidine or 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**

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 91-93% bound to plasma proteins.

Distribution studies with radiolabelled drug in animals have shown wide tissue distribution with low brain concentration. Small amounts of drug cross the placenta in rats and the drug is excreted in the breast milk of this species.

### **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 drug excreted unchanged is small (approximately 1% of urinary excretion and 10% of faecal 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**

MOTILIUM is contraindicated in patients with moderate or severe hepatic impairment (see Contraindications). In subjects with mild hepatic impairment (Pugh score 5 to 6, Child-Pugh rating A), limited data indicate that the pharmacokinetics of domperidone are not significantly altered. In subjects with moderate hepatic impairment (Pugh score 7 to 9, Child-Pugh rating B), the AUC,  $C_{max}$  and terminal elimination half-life of domperidone were substantially increased; the unbound fraction of domperidone was increased by 25%. Subjects with severe hepatic impairment were not studied.

### **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 **Precautions and Dosage and Administration**).

### **Paediatric Patients**

No pharmacokinetics data are available in this population.

## **Indications**

MOTILIUM is indicated for the short-term treatment in adults of:

- Symptoms associated with idiopathic or diabetic gastroparesis (once control of diabetes has been established by diet and/or insulin, an attempt should be made to discontinue MOTILIUM).
- Intractable nausea and vomiting from any cause.

## **Contraindications**

MOTILIUM is contraindicated in patients with a known hypersensitivity to domperidone or any of the excipients and in those with a prolactin-releasing pituitary tumour (prolactinoma).

The co-administration of MOTILIUM with oral ketoconazole, erythromycin, or other potent CYP3A4 inhibitors, which prolong the QTc interval such as fluconazole, voriconazole, clarithromycin, amiodarone, and telithromycin, is contraindicated (see **Interactions**). 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 **Pharmacokinetics**).

## **Precautions**

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

### **Prolactin levels**

There are limited safety data in long-term use (i.e. beyond six months) of MOTILIUM. However, it has been shown to produce an increase in plasma prolactin. The raised level persists with chronic administration but falls to normal on discontinuing the drug (see **Adverse Reactions**). During oral administration of 30 mg daily for two weeks the plasma prolactin level measured 90 minutes after drug 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 prescription of MOTILIUM is contemplated in a patient with a past history of breast cancer.

Endocrine disturbances such as galactorrhoea, amenorrhoea, gynaecomastia and impotence have been reported with drugs which stimulate prolactin release. The clinical significance of elevated serum prolactin levels is unknown for most patients. An increase in mammary neoplasms has been found in rodents after chronic administration of MOTILIUM and other prolactin stimulating drugs. Neither clinical studies nor epidemiologic studies conducted to date have shown an association between chronic administration of these drugs and mammary tumorigenesis.

MOTILIUM does not affect plasma growth hormone or aldosterone.

Despite the lack of penetration of the blood-brain barrier, the possibility that extrapyramidal symptoms may occur in very rare instances after long-term use of domperidone, should be considered.

**Use in renal insufficiency** – 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, and the dose may need to be reduced. Such patients on prolonged therapy should be reviewed regularly (see **Pharmacokinetics and Dosage and Administration**).

**Use in Pregnancy** – Category B2 - Small amounts of MOTILIUM have been found in rat foetal tissues. Reproduction studies were performed in rats with daily doses of MOTILIUM up to 160 mg/kg orally and 40 mg/kg intravenously and in rabbits with daily doses up to 40 mg/kg orally and 1.25 mg/kg intravenously. There was no evidence of drug related dysmorphogenesis. There are however no adequate and well controlled studies in pregnant women. Because animal studies are not always predictive of human response and there are limited post-marketing data on the use of domperidone in pregnant women, this drug should be used during pregnancy only if clearly needed.

**Use in Lactation** – The drug is excreted in breast milk of lactating rats (mostly as metabolites: peak concentration of 40 and 800 ng/mL after oral and IV administration of 2.5 mg/kg respectively). This probably also occurs in women. It is not known whether this is harmful to the newborn. Therefore breast-feeding is not recommended for mothers who are taking MOTILIUM.

### **Interactions**

Antacids or antisecretory drugs should not be taken simultaneously with MOTILIUM since they reduce its oral bioavailability (i.e., they should be taken after meals and not before meals). Dosing with these agents should be separated from dosing with MOTILIUM by at least 2 hours.

Concomitant administration of anticholinergic drugs may antagonise the anti-dyspeptics effects of MOTILIUM. If administered prior to atropine, MOTILIUM reduces the relaxant effect of atropine upon the lower oesophageal sphincter, but has no reversing effect if atropine is administered first.

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

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 potent CYP3A4 inhibitors include:

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

\* also prolong the 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 drugs.

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<sub>max</sub> 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.

## Adverse Effects

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

### Immune system disorder:

*Very rare:* anaphylactic reactions including anaphylactic shock; angioneurotic oedema; allergic reaction

### Endocrine disorder

*Uncommon:* increased prolactin levels

### Psychiatric system disorders

*Uncommon:* nervousness

*Very rare:* agitation

### Nervous system disorders

*Common:* dry mouth; headache

*Uncommon:* insomnia; dizziness; thirst; lethargy; irritability

*Rare:* extrapyramidal side effects

*Very rare:* convulsion; somnolence

### **Gastrointestinal disorders**

*Uncommon:* diarrhoea; regurgitation; appetite disorder; nausea; heartburn; constipation

### **Skin and subcutaneous tissue disorders**

*Uncommon:* urticaria; pruritus; rash

### **Reproductive system and breast disorders**

*Rare:* galactorrhoea; gynaecomastia; amenorrhoea

### **Urinary system disorders**

*Uncommon:* Pollakiuria; dysuria

### **Cardiovascular disorders**

*Uncommon:* Oedema; palpitations

*Very rare:* Sudden Cardiac Death\*, Serious Ventricular Arrhythmias\*

### **Musculoskeletal disorders**

*Uncommon:* Muscle spasms; asthenia

### **Other**

*Uncommon:* Conjunctivitis; stomatitis; drug intolerance

### **Investigations:**

*Uncommon:* liver function test abnormal; cholesterol

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\*Based on epidemiology data (see below)

During long-term studies with MOTILIUM there have been reports of adverse effects possibly related to increases in serum prolactin (see **PRECAUTIONS**). These effects include: Gynaecomastia, breast tenderness, swelling of the breasts, irregular menses, amenorrhoea, a decrease or loss of libido, breast secretion and lactation. These effects occurred in patients who received up to 120 mg per day in four divided doses.

Extrapyramidal disorder occurs very rarely, and when seen occurs primarily in young children.(see **Precautions**).

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.

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.

## Dosage and Administration

MOTILIUM should be taken 15-30 minutes before meals and, if necessary, before retiring.

**Adults** - 10 mg three to four times daily. If necessary this dose can be doubled after two weeks if an adequate therapeutic response is not attained with a maximum daily dose of 80mg.

Safety and efficacy of MOTILIUM (domperidone) use beyond six months has not been established.

**In patients with severe renal insufficiency** - (creatinine serum >0.6 mmol/L) the elimination half life of MOTILIUM was increased from 7.4 to 20.8 hours but plasma drug levels were lower than in healthy volunteers. Since very little unchanged drug is excreted via the kidneys, it is unlikely that the dose needs to be adjusted for single acute 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, and the dose may need to be reduced.

**Food** - It is recommended that MOTILIUM be taken before meals. If taken after meals absorption of the drug is somewhat delayed.

## 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, the administration of activated charcoal may be useful. Anticholinergics, antiparkinson drugs may be useful in controlling extrapyramidal reactions.

The patient should be observed closely and supportive measures employed.

## Presentation

MOTILIUM domperidone 10mg film coated tablets 25s, 100s.

Shelf life: 4 years. Store below 30°C.

## Sponsor

JANSSEN-CILAG Pty Ltd  
1-5 Khartoum Road North Ryde NSW 2113 Australia

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