
AUSTRALIAN PRODUCT INFORMATION

MOTILIUM[®] (Domperidone)

Tablets

1. NAME OF THE MEDICINE

Domperidone

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 10 mg domperidone.

Excipient(s) with known effect:

Contains sugars as lactose. Each tablet contain 54.2 mg of lactose monohydrate. (see **section 4.4 Special warnings and precautions for use**)

For a full list of excipients, see **section 6.1 List of excipients**.

3. PHARMACEUTICAL FORM

Film-coated tablets

MOTILIUM 10 mg tablets are white to faintly cream-coloured, circular, biconvex film coated tablets with the inscription "JANSSEN" on one side and "M 10" on the other side.

4. CLINICAL PARTICULARS

4.1 THERAPEUTIC 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.

4.2 DOSE AND METHOD ADMINISTRATION

Long-term use and use with medicines that prolong the QT interval or medicines that inhibit CYP3A should be avoided. The lowest dose needed to alleviate symptoms should be taken for the shortest period of time (see **section 4.4 Special warnings and precautions for use - Cardiac effects**).

MOTILIUM should be taken 15-30 minutes before meals and, if necessary, before retiring. Patients should try to take each dose at the scheduled time. If a scheduled dose is missed, the missed dose should be omitted and the usual dosing schedule resumed. The dose should not be doubled to make up for a missed dose.

Adults (weighing \geq 35 kg)

10 mg three times daily. Domperidone should be initiated at the lowest effective dose for the individual situation, which may be adjusted upward with caution to achieve the desired effect. The expected benefit of an increased dose should outweigh the potential risks. 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 limited to 4 weeks. Patients should undergo a benefit/risk re-analysis if treatment beyond 4 weeks is contemplated.

The maximum daily dose is 30 mg.

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

MOTILIUM tablets are unsuitable for use in adults weighing less than 35 kg. MOTILIUM should not be used in children.

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. Patients with severe renal impairment on prolonged therapy should be reviewed regularly (see **section 5.2 Pharmacokinetic properties**).

Hepatic impairment – MOTILIUM is contraindicated for patients with moderate or severe hepatic impairment (see **section 4.3 Contraindications**).

Food - It is recommended that MOTILIUM be taken 15-30 minutes before meals. If taken after meals absorption of the drug is somewhat delayed. Patients should try to take each dose at the scheduled time. If a scheduled dose is missed, the missed dose should be omitted and the usual dosing schedule resumed. The dose should not be doubled to make up for a missed dose.

4.3 CONTRAINDICATIONS

MOTILIUM is contraindicated in the following situations:

- In patients who have known existing prolongation of cardiac conduction intervals, particularly QTc, patients with significant electrolyte disturbances underlying cardiac diseases such as congestive heart failure
- Co-administration with medicines that prolong the QTc interval (see **section 4.4 Special warnings and precautions for use** and **section 4.5 Interactions with other medicines and other forms of interactions**)
- Co-administration with potent CYP3A4 inhibitors (see **section 4.4 Special warnings and precautions for use** and **section 4.5 Interactions with other medicines and other forms of interactions**)
- Known hypersensitivity to domperidone or any of the excipients
- Prolactin-releasing pituitary tumour (prolactinoma).
- 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 **section 5.2 Pharmacokinetic properties**).

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

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

Antacids or antisecretory drugs should not be taken simultaneously with MOTILIUM since they reduce its oral bioavailability of domperidone (see **section 4.5 Interactions with other**

medicines and other forms of interactions). When used concomitantly, MOTILIUM should be taken before meals and antacids or antisecretory agents after meals.

Cardiac effects

MOTILIUM is associated with an increased risk of sudden cardiac death of approximately 4 per 1000 years compared with no use of medication. This risk is increased in patients aged over 60 years or who have cardiac disease or diabetes. The risk is also increased with MOTILIUM doses > 30 mg daily and when taken in combination with medicines that prolong the QT interval and medicines that inhibit CYP3A4.

Concurrent use of MOTILIUM with medicines that prolong the QTc interval is contraindicated. Concurrent use of MOTILIUM with medicines that are potent inhibitors of CYP3A4 is contraindicated (see **section 4.3 Contraindications** and **section 4.5 Interactions with other medicines and other forms of interactions**).

Concurrent use of MOTILIUM with medicines that are moderate inhibitors of CYP3A4 should be avoided. Long term use of MOTILIUM should be avoided. The lowest dose needed to alleviate symptoms should be taken for the shortest period of time.

MOTILIUM should be used with caution in older patients or those with current or a history of cardiac disease.

In a case-control study by van Noord et al (2010), the odds of sudden cardiac death with current domperidone use (10 cases) were two-fold higher than the odds of sudden cardiac death in matched controls from the general population (adjusted odds ratio, 1.99 [95% CI, 0.80 - 4.96]). The adjusted odds ratio for sudden cardiac death in current users of a dose higher than 30 mg daily, relative to matched controls from the general population, was 11.4 (95% CI, 1.99 - 65.2) based on 4 identified cases. In a larger case-control study by Johannes et al (2010), the adjusted odds ratio for the composite of sudden cardiac death and serious ventricular arrhythmias was 1.44 (95% CI, 1.12 - 1.86) for current domperidone users relative to current proton-pump inhibitor users.

A population based, case-control study nested in a cohort of 681,104 patients with at least one recorded prescription for domperidone, any proton pump inhibitor medication, or metoclopramide found 90 cases of out-of-hospital Sudden Cardiac Death (SCD) with current domperidone use.

The incidence rate of SCD per 1,000 person -years with current usage of domperidone was 4.47 (95% CI, 43.59 – 5.49). This was higher than that for during person-time with no use of any of the study medications (0.87; 95% CI, 0.82 – 0.92).

After adjusting for demographic characteristics, medical conditions, medications, and other potentially confounding factors, the point estimate for current use of domperidone compared with non-use of study medications was OR, 1.71 (95% CI, 0.92 – 3.18).

In all of the medication group strata, the incidence increased with age, was higher in men than women, and was higher in those with diabetes than without.

With exposure to domperidone, the highest OR for SCD was with current exposure to only domperidone for 8-14 days (adjusted OR, 7.77; 95% CI, 1.70 – 35.53). The adjusted OR was 1.69 (95% CI, 0.38 - 7.57) for exposure of ≤ 7 days and 1.12 (95% CI, 0.50 – 2.53) for durations of ≥ 15 days. The risk of SCD compared with no exposure was highest for those prescribed > 30 mg/day (adjusted OR, 3.20; 95% CI, 0.59 – 17.34).

When domperidone was taken concomitantly with any QTc prolongating agent associated with torsade de pointes the risk of SCD increased from an adjusted OR of 1.64 (95% CI, 0.73 – 3.72) to 4.95 (95% CI, 0.84 – 29.07).

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.

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 **section 4.8 Adverse effects (Undesirable effects)**). 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.

Renal Impairment

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 **section 5.2 Pharmacokinetic properties** and **section 4.2 Dose and method administration**).

Use in the elderly

See **section 4.4 Special warnings and precautions for use - Cardiac effects**.

Paediatric Use

MOTILIUM should not be used in children.

Effects on laboratory tests

No data available.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Medicines that prolong the QTc interval

Co-administration with medicines that prolong the QTc interval is contraindicated due to an increased risk of sudden cardiac death shown in post-market studies (see **section 4.3 Contraindications** and **section 4.4 Special warnings and precautions for use**).

Examples of QTc-prolonging medicines include:

- anti arrhythmics class IA (e.g. disopyramide)
- anti arrhythmics class III (e.g. amiodarone*, dronedarone, sotalol)
- some antipsychotics (e.g. haloperidol)
- some antidepressants (e.g. citalopram, escitalopram)
- some antibiotics (e.g. erythromycin*, clarithromycin*, levofloxacin, moxifloxacin)
- some antifungal agents (e.g. pentamidine)
- some antimalarial agents (e.g. lumefantrine)
- some azole antifungals, (e.g. itraconazole*, ketoconazole*, voriconazole*, fluconazole*)
- some calcium antagonists, (e.g. diltiazem*, verapamil*)
- some gastrointestinal agents (e.g. prucalopride, granisetron, ondansetron)
- certain HIV protease inhibitors (e.g. atazanavir*, fosamprenavir*, indinavir*, ritonavir*, saquinavir*)
- some antineoplastic agents (e.g. toremifene, vandetanib)
- others (e.g. aprepitant* and methadone)

*also potent CYP3A4 inhibitors (see **section 4.3 Contraindications**)

Potent CYP3A4 inhibitors

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.

Concurrent use of MOTILIUM with medicines that are potent inhibitors of CYP3A4 is contraindicated due to an increased risk of sudden cardiac death shown in postmarket studies (see **section 4.3 Contraindications** and **section 4.4 Special warnings and precautions for use**).

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 **section 4.3 Contraindications**)

Separate pharmacokinetic/pharmacodynamic interaction studies with oral ketoconazole or oral erythromycin in healthy subjects confirmed domperidone C_{max} increases <3 fold under maximal CYP3A4 inhibition by these drugs.

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 4.9 msec, respectively, over the observation period. 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 **section 4.3 Contraindications**).

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

Moderate CYP3A4 inhibitors

Concurrent use of MOTILIUM with medicines that are moderate inhibitors of CYP3A4 should be avoided due to an increased risk of sudden cardiac death shown in postmarket studies (see **section 4.4 Special warnings and precautions for use**).

Miscellaneous 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) (see **section 4.4 Special warnings and precautions for use**). 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.

MOTILIUM has been used with:

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

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

No relevant data are available.

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. The potential risk for humans is unknown. 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 amount of domperidone that could be ingested by an infant through breast milk is extremely 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.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Dizziness and somnolence have been observed following use of domperidone (see **section 4.8 Adverse effects (Undesirable 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.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Clinical Trial Data

The safety of MOTILIUM was evaluated in 1221 patients with gastroparesis, or symptoms of it 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 (ARs) - reported by $\geq 1\%$ of patients treated with domperidone in these 45 clinical trials are shown in **Table 1**.

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

| System/Organ Class | Domperidone (n=1221) |
|---|-----------------------------|
| Adverse Reaction | % |
| 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 |

| System/Organ Class Adverse Reaction | Domperidone (n=1221) % |
|---|---------------------------|
| General Disorders and Administration Site Conditions | |
| Asthenia | 1.9 |

ARs 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 |

Postmarketing Data

The adverse 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: >1/10000, <1/1000
- Very rare: <1/10000 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* (see **section 4.4 Special warnings and precautions for use**)

Musculoskeletal disorders

Uncommon: Muscle spasms; asthenia

Other

Uncommon: Conjunctivitis; stomatitis; drug intolerance

Investigations:

Uncommon: liver function test abnormal; cholesterol

*Based on epidemiology data

During long-term studies with MOTILIUM there have been reports of adverse effects possibly related to increases in serum prolactin (see **section 4.4 Special warnings and precautions for use**). 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 **section 4.4 Special warnings and precautions for use**).

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

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

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. Anticholinergic antiparkinson drugs may be useful in controlling extrapyramidal reactions.

The patient should be observed closely and supportive measures employed.

For information on the management of overdose, contact the Poison Information Centre on 131126 (Australia).

5. PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of Action

MOTILIUM is a dopamine antagonist with antiemetic properties similar to those of metoclopramide and certain neuroleptic drugs. Unlike these drugs, however, domperidone 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 domperidone 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 domperidone 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.

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.

Clinical trials

No data available.

5.2 PHARMACOKINETIC PROPERTIES

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 **section 4.5 Interactions with other medicines and other forms of interactions**).

Excretion

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 **section 4.3 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 (see **section 4.3 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 **section 4.4 Special warnings and precautions for use** and **section 4.2 Dose and method administration**).

Paediatric Patients

No pharmacokinetics data are available in this population.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

No relevant data are available.

Carcinogenicity

See Prolactin levels.

6. PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Lactose, maize starch, microcrystalline cellulose, pregelatinised potato starch, povidone, magnesium stearate, hydrogenated cottonseed oil, sodium lauryl sulfate, and hypromellose.

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 30°C.

6.5 NATURE AND CONTENTS OF CONTAINER

MOTILIUM domperidone 10 mg film coated tablets are supplied in PVC/Aluminium blister packs of 25 or 100 tablets.

Not all pack sizes are marketed.

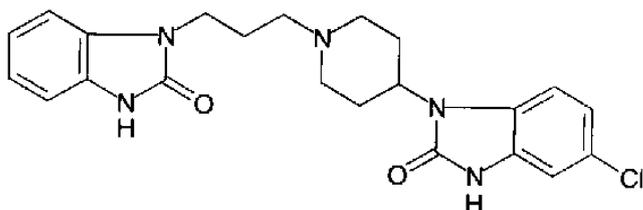
6.6 SPECIFIC PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical structure

Domperidone has the following chemical structure.



$C_{22}H_{24}ClN_5O_2$

MW: 425.9

The chemical name for domperidone is 5-Chloro-1-[1-[3-(2-oxo-2,3-dihydro-1H-benzimidazol-1-yl)propyl]piperidin-4-yl]-1,3-dihydro-2H-benzimidazol-2-one.

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.

CAS number

57808-66-9

7. MEDICINE SCHEDULE (POISON STANDARD)

S4 – Prescription Only Medicine

8. SPONSOR

JANSSEN-CILAG Pty Ltd

1-5 Khartoum Road

Macquarie Park NSW 2113 Australia

Telephone: 1800 226 334

NZ Office: Auckland New Zealand

Telephone: 0800 800 806

9. DATE OF FIRST APPROVAL

13 May 1992

10. DATE OF REVISION

30 July 2021

Summary table of changes

| Section changed | Summary of new information |
|-----------------|---|
| 2 | Editorial update to excipients with known effect. |