

פורמט עלון זה נקבע ע"י משרד הבריאות ותוכנו נבדק ואושר

1. NAME OF THE MEDICINAL PRODUCT

MOTILIUM

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One tablet contains 10 mg domperidone base.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

White to faintly cream coloured, circular, biconvex tablet.

4. CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Motilium is indicated for the relief of the symptoms of nausea and vomiting.

4.2 POSOLOGY AND METHOD OF ADMINISTRATION

Motilium should be used at the lowest effective dose for the shortest duration necessary to control nausea and vomiting.

It is recommended to take oral MOTILIUM 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.

Usually, the maximum treatment duration should not exceed one week.

Adults, and adolescents (12 years of age and older and weighing 35 kg or more

One 10 mg tablet up to three times per day, with a maximum dose of 30 mg per day.

Neonates, infants, children (less than 12 years of age) and adolescents weighing less than 35 kg

Due to the need for accurate dosing, Film-coated tablets, are unsuitable for use in children and adolescents weighing less than 35 kg.

Hepatic impairment

Motilium is contraindicated in moderate or severe hepatic impairment (see section 4.3). Dose modification in mild hepatic impairment is however not needed (see section 5.2).

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.

4.3 CONTRAINDICATIONS

MOTILIUM is contraindicated in the following situations:

- Known hypersensitivity to domperidone or any of the excipients.
- Prolactin-releasing pituitary tumor (prolactinoma).
- when stimulation of gastric motility could be harmful, e.g. in the presence of gastro-intestinal hemorrhage, mechanical obstruction or perforation.
- In patients with moderate or severe hepatic impairment (see section 5.2).
- in patients who have known existing prolongation of cardiac conduction intervals, particularly QTc, patients with significant electrolyte disturbances or underlying cardiac diseases such as congestive heart failure (see section 4.4)
- co-administration with QT-prolonging drugs (see section 4.5)
- co-administration with potent CYP3A4 inhibitors (regardless of their QT-prolonging effects) (see section 4.5)

4.4 Special warnings and precautions for use

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.

Cardiovascular effects

Domperidone has been associated with prolongation of the QT interval on the electrocardiogram. During post-marketing surveillance, there have been very rare cases of QT-prolongation and *torsades de pointes* in patients taking domperidone. These reports included patients with confounding risk factors, electrolyte abnormalities and concomitant treatment which may have been contributing factors (see section 4.8).

Epidemiological studies showed that domperidone was associated with an increased risk of serious ventricular arrhythmias or sudden cardiac death (see section 4.8). A higher risk was observed in patients older than 60 years, patients taking daily doses greater than 30 mg, and patients concurrently taking QT-prolonging drugs or CYP3A4 inhibitors.

Domperidone should be used at the lowest effective dose in adults and children.

Domperidone is contraindicated in patients with known existing prolongation of cardiac conduction intervals, particularly QTc, in patients with significant electrolyte disturbances (hypokalaemia, hyperkalaemia, hypomagnesaemia), or bradycardia, or in patients with underlying cardiac diseases such as congestive heart failure due to increased risk of ventricular arrhythmia (see section 4.3). Electrolyte disturbances (hypokalaemia, hyperkalaemia, hypomagnesaemia) or bradycardia are known to be conditions increasing the proarrhythmic risk.

Treatment with domperidone should be stopped if signs or symptoms occur that may be associated with cardiac arrhythmia, and the patients should consult their physician.

Patients should be advised to promptly report any cardiac symptoms.

Paediatric population

Although neurological side effects are rare (see section 4.8), the risk of neurological side effects is higher in young children since metabolic functions and the blood-brain barrier are not fully developed in the first months of life. Therefore, it is recommended that the dose be determined accurately and strictly followed in neonates, infants and children (see section 4.2).

Overdosing may cause extrapyramidal disorders in children, but other causes should be taken into consideration.

Precautions for use

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

4.5 Interaction with other medicinal products and other forms of interaction

When antacids or antisecretory drugs are used concomitantly, they should not be taken simultaneously with oral formulations of Motilium (domperidone base), i.e., they should be taken after meals and not before meals.

Co-administration with levodopa

Although no dosage adjustment of levodopa is deemed necessary, an increase (maximum of 30% - 40%) of plasma concentration has been observed when domperidone was taken concomitantly with levodopa.

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

Increased risk of occurrence of QT interval prolongation, due to pharmacodynamic and/or pharmacokinetic interactions.

Concomitant use of the the following substances is contraindicated

QTc-prolonging medicinal products (risk of torsade de points)

- anti-arrhythmics class IA (e.g., disopyramide, hydroquinidine, 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., erythromycin, levofloxacin, moxifloxacin, spiramycin)
- certain antifungal agents (e.g., fluconazole, pentamidine)
- certain antimalarial agents (in particular halofantrine, lumefantrine)
- certain gastro-intestinal medicines (e.g., cisapride, dolasetron, prucalopride)
- certain antihistaminics (e.g., mequitazine, mizolastine)
- certain medicines used in cancer (e.g., toremifene, vandetanib, vincamine)
- certain other medicines (e.g., bepridil, diphemanil, methadone)

(see section 4.3).

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

- protease inhibitors (e.g., ritonavir, saquinavir, telaprevir)
- systemic azole antifungals (e.g., itraconazole, ketoconazole, posaconazole, voriconazole)
- certain macrolides antibiotics (clarithromycin, telithromycin)

(see section 4.3).

Concomitant use of the following substances is not recommended

- Moderate CYP3A4 inhibitors i.e., diltiazem, verapamil and some macrolides.

Concomitant use of the following substances requires caution with use

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

The above list of substances is representative and not exhaustive.

4.6 Pregnancy and lactation

Pregnancy

There are limited post-marketing data on the use of domperidone in pregnant women. A study in rats has shown reproductive toxicity at a high, maternally toxic dose. The potential risk for humans is unknown.

Therefore, MOTILIUM should only be used during pregnancy when justified by the anticipated therapeutic benefit.

Breast-feeding

Domperidone is excreted in human milk and breast-fed infants receive less than 0.1% of the maternal weight-adjusted dose. Occurrence of adverse effects, in particular cardiac effects cannot be excluded after exposure *via* breast milk. A decision should be made whether to discontinue breast-feeding or to discontinue/abstain from domperidone therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman. Caution should be exercised in case of QTc-prolongation risk factors in breast-fed infants.

4.7 Effects on ability to drive and use machines

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

The safety of domperidone was evaluated in clinical trials and post marketing experience. The clinical trials included 1,275 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.

The following terms and frequencies are applied: very common ($\geq 1/10$), common ($\geq 1/100$ to $< 1/10$), uncommon ($\geq 1/1000$ to $< 1/100$), rare ($\geq 1/10,000$ to $< 1/1000$), and very rare ($< 1/10,000$). Where frequency can not be estimated from clinical trials data, it is recorded as "Not known".

System Organ Class	Adverse Drug Reaction Frequency		
	Common	Uncommon	Not known
Immune system disorders			Anaphylactic reaction (including anaphylactic shock)
Psychiatric disorders		Loss of libido Anxiety Agitation Nervousness	
Nervous system disorders		Dizziness Somnolence Headache Extrapyramidal disorder	Convulsion Restless legs syndrome*

Eye disorders			Oculogyric crisis
Cardiac disorders			Ventricular arrhythmias, QTc-prolongation, Torsade de Pointes, Sudden cardiac death, (see section 4.4)
Gastrointestinal disorders	Dry mouth	Diarrhoea	
Skin and subcutaneous tissue disorders		Rash Pruritus Urticaria	Angioedema
Renal and urinary disorders			Urinary retention
Reproductive system and breast disorders		Galactorrhoea Breast pain Breast tenderness	Gynaecomastia, Amenorrhoea
General disorders and administration site conditions		Asthenia	
Investigations			Liver function test abnormal, Blood prolactin increased

*exacerbation of restless legs syndrome in patients with Parkinson's disease

In 45 clinical 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 above, akathisia, breast discharge, breast enlargement, breast swelling, depression, hypersensitivity, lactation disorder, and irregular menstruation were also noted.

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

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.

Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form
<http://forms.gov.il/globaldata/getsequence/getsequence.aspx?formType=AdversEffectMedic@moh.health.gov.il>

Overdose

Symptoms

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. In the event of overdose, standard symptomatic treatment should be given immediately. ECG monitoring should be undertaken, because of the possibility of QTc interval prolongation. Gastric lavage as well as the administration of activated

charcoal may be useful. Close medical supervision and supportive therapy is recommended. Anticholinergic or anti-Parkinson drugs may be helpful in controlling the extrapyramidal disorder .

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Propulsives, ATC code: A03FA03

Domperidone is a dopamine antagonist with anti-emetic properties. Domperidone does not readily cross the blood-brain barrier. In domperidone users, especially in adults, extrapyramidal disorders are very rare, but domperidone promotes the release of prolactin from the pituitary. Its anti-emetic effect may be due to a combination of peripheral (gastrokinetic) effects and antagonism of dopamine receptors in the chemoreceptor trigger zone, which lies outside the blood-brain barrier in the area postrema. Animal studies, together with the low concentrations found in the brain, indicate a predominantly peripheral effect of domperidone on dopamine receptors. Studies in man have shown oral domperidone to increase lower oesophageal pressure, improve antroduodenal motility and accelerate gastric emptying. There is no effect on gastric secretion.

In accordance with ICH-E14 guidelines, a thorough QT study was performed. This study included a placebo, an active comparator and a positive control and was conducted in healthy subjects with up to 80 mg per day (10 or 20 mg administered four times a day) of domperidone. This study found a maximal difference of QTc between domperidone and placebo in LS-means in the change from baseline of 3.4 msec for 20 mg domperidone administered four times a day on Day 4. The 2-sided 90% CI (1.0 to 5.9 msec) did not exceed 10 msec. No clinically relevant QTc effects were observed in this study when domperidone was administered at up to 80 mg/day (i.e., more than twice the maximum recommended dosing).

However, two previous drug-drug interaction studies showed some evidence of QTc-prolongation when domperidone was given as monotherapy (10 mg administered four times a day). The largest time-matched mean difference of QTcF between domperidone and placebo was 5.4 msec (95% CI: -1.7 to 12.4) and 7.5 msec (95% CI: 0.6 to 14.4), respectively.

5.2 Pharmacokinetic properties

Absorption

Domperidone is rapidly absorbed after oral administration, with peak plasma concentrations occurring at approximately 1 hr after dosing. The C_{max} and AUC values of domperidone increased proportionally with dose in the 10 mg to 20 mg dose range. A 2- to 3-fold accumulation of domperidone AUC was observed with repeated four times daily (every 5 hr) dosing of domperidone for 4 days.

Although domperidone's bioavailability is enhanced in normal subjects when taken after a meal, patients with gastro-intestinal complaints should take domperidone 15-30 minutes before a meal. Reduced gastric acidity impairs the absorption of domperidone. Oral bioavailability of domperidone is decreased by prior concomitant administration of cimetidine and sodium bicarbonate.

Based on the C_{max} resulting from administering multiple twice daily doses of 60 mg suppository, a 30 mg suppository given twice daily is expected to provide peak plasma levels similar to those of a 10 mg oral dose administered four times a day.

Distribution

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

Metabolism

Domperidone undergoes rapid and extensive hepatic metabolism by hydroxylation and N-dealkylation. *In vitro* metabolism experiments with diagnostic inhibitors revealed that CYP3A4 is a major form of cytochrome P-450 involved in the N-dealkylation of domperidone, whereas CYP3A4, CYP1A2 and CYP2E1 are involved in domperidone aromatic hydroxylation.

Excretion

Urinary and fecal excretions amount to 31 and 66% of the oral dose respectively. The proportion of the drug excreted unchanged is small (10% of fecal 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.

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. Motilium is contraindicated in patients with moderate or severe hepatic impairment (see section 4.3).

Renal impairment

In subjects with severe renal insufficiency (creatinine clearance < 30 ml/min/1.73 m²) the elimination half-life of domperidone was increased from 7.4 to 20.8 hours, but plasma drug levels were lower than in healthy volunteers. Since very little unchanged drug (approximately 1%) is excreted via the kidneys, it is unlikely that the dose of a single administration needs to be adjusted in patients with renal impairment. However, on repeated administration, the dosing frequency should be reduced to once or twice daily depending on the severity of the impairment, and the dose may need to be reduced.

Paediatric population

No pharmacokinetic data are available in the paediatric population.

5.3 Preclinical safety data

Electrophysiological *in vitro* and *in vivo* studies indicate an overall moderate risk of domperidone to prolong the QTc interval in humans. In *in vitro* experiments on isolated cells transfected with hERG and on isolated guinea pig myocytes, exposure ratios ranged between 26- to 47-fold, based on IC₅₀

values inhibiting currents through IKr ion channels in comparison to the free plasma concentrations in humans after administration of the maximum daily dose of 10 mg administered three times a day. Safety margins for prolongation of action potential duration in *in vitro* experiments on isolated cardiac tissues exceeded the free plasma concentrations in humans at maximum daily dose (10 mg administered three times a day) by 45-fold. Safety margins in *in vitro* pro-arrhythmic models (isolated Langendorff perfused heart) exceeded the free plasma concentrations in humans at maximum daily dose (10 mg administered three times a day) by 9- up to 45-fold. In *in vivo* models, the no effect levels for QTc-prolongation in dogs and induction of arrhythmias in a rabbit model sensitised for *torsade de points* exceeded the free plasma concentrations in humans at maximum daily dose (10 mg administered three times a day) by more than 22-fold and 435-fold, respectively. In the anaesthetised guinea pig model following slow intravenous infusions, there were no effects on QTc at total plasma concentrations of 45.4 ng/ml, which are 3-fold higher than the total plasma levels in humans at maximum daily dose (10 mg administered three times a day). The relevance of the latter study for humans following exposure to orally administered domperidone is uncertain.

In the presence of inhibition of the metabolism *via* CYP3A4, free plasma concentrations of domperidone can rise up to 3-fold.

At a high, maternally toxic dose (more than 40 times the recommended human dose), teratogenic effects were seen in the rat. No teratogenicity was observed in mice and rabbits.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate, maize starch, microcrystalline cellulose, pregelatinized potato starch, polyvidone K90, magnesium stearate, hydrogenated cottonseed oil, sodium lauryl sulphate, hypromellose -

6.2 Incompatibilities

None known.

6.3 Storage conditions

Store between 15 and 30°C.

Keep out of reach of children.

6.4 Nature and contents of container

Pack of thirty, 10 mg, tablets.

Manufacturer: JANSSEN CILAG SA – Val de Reuil, France

Registration Holder: J-C Health Care, Kibbutz Shefayim 6099000, Israel.