

Motilium™ - V (domperidone maleate)

Film-coated Tablet

NAME OF THE MEDICINAL PRODUCT
MOTILIUM-V (domperidone maleate)

QUALITATIVE AND QUANTITATIVE COMPOSITION

One film-coated tablet contains 12.72mg domperidone maleate, equivalent to 10mg domperidone.

PHARMACEUTICAL FORM
Film-coated tablets

CLINICAL INFORMATION

Indications

1. The dyspeptic symptom complex that is often associated with delayed gastric emptying, gastro-oesophageal reflux and esophagitis:
 - Epigastric sense of fullness, early satiety, feeling of abdominal distension, upper abdominal pain;
 - Bloating, eructation, flatulence;
 - Nausea and vomiting;
 - Heartburn with or without regurgitations of gastric contents in the mouth
2. Nausea and vomiting of functional, organic, infectious or dietary origin.
3. Nausea and vomiting induced by:
 - Radiotherapy or drug therapy
 - Dopamine agonists (such as L-dopa and bromocriptine) used in the treatment of Parkinson's disease.

Dosage and Administration

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

Tablets

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

Hepatic impairment

Motilium-V is contraindicated in moderate or severe hepatic impairment. Dose modification in mild hepatic impairment is however not needed.

Renal impairment

Since the elimination half-life of domperidone is prolonged in severe renal impairment, on repeated administration, the dosing frequency of Motilium-V 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

The efficacy of Motilium-V in children less than 12 years of age has not been established.

The efficacy of Motilium-V in adolescents 12 years of age and older and weighing less than 35 kg has not been established.

Contraindications

MOTILIUM-V is contraindicated in the following situations:

- Known hypersensitivity to domperidone or any of the excipients
- Prolactin releasing pituitary tumor (prolactinoma)
- Co-administration with potent CYP3A4 inhibitors which have been shown to cause QT interval prolongation such as, clarithromycin, erythromycin, itraconazole, oral ketconazole, posaconazole, ritonavir, saquinavir, telithromycin, telaprevir and voriconazole
- Whenever stimulation of gastric motility might be dangerous, e.g. in the presence of gastro intestinal hemorrhage, mechanical obstruction or perforation
- In patients with moderate or severe hepatic impairment

Warnings and Precautions

Cardiac effects:

Epidemiological studies have shown domperidone may be associated with an increased risk of serious ventricular arrhythmias or sudden cardiac death. Those studies suggest this increased risk may be higher in patients older than 60 years of age or in patients taking oral doses greater than 30 mg per day. Therefore, MOTILIUM-V should be used with caution in older patients. Patients older than 60 years of age should consult their physician before taking MOTILIUM-V.

Due to increased risk of ventricular arrhythmia, MOTILIUM-V is not recommended 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. Electrolyte disturbances (hypokalaemia, hyperkalaemia, hypomagnesaemia) and

bradycardia are known to be conditions increasing the proarrhythmic risk.

Treatment with MOTILIUM-V should be stopped if signs or symptoms occur that may be associated with cardiac arrhythmia, and the patient should promptly consult their physician.

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.

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.

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.

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 gastro intestinal drugs (e.g., dolasetron), certain drugs used in cancer (e.g., toremifene, vandetanib), certain other drugs (e.g., bepridil, methadone).

Antacids or antisecretory agents should not be taken simultaneously with oral formulations of MOTILIUM-V as they lower the oral bioavailability of domperidone. When used concomitantly, MOTILIUM-V should be taken before meals and antacids or antisecretory agents after meals.

Interactions

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.

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*).

Concomitant administration of anticholinergic drugs (e.g., dextromethorphan, diphenhydramine) may antagonize the anti-dyspeptic effect of MOTILIUM-V. Theoretically, since MOTILIUM-V 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 stabilized on digoxin or paracetamol, concomitant administration of domperidone did not influence the blood levels of these drugs.

MOTILIUM-V may also be given with:

- neuroleptics, the action of which it does not potentiate,
- dopaminergic agonists (bromocriptine, L dopa), whose unwanted peripheral effects such as digestive disorders, nausea and vomiting it suppresses without counteracting their central properties.

Pregnancy and Breast feeding

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-V should only be used during pregnancy when justified by the anticipated therapeutic benefit.

Breast feeding

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-V.

Effects on Ability to Drive and Use Machines:

Dizziness and somnolence have been observed following use of domperidone. 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-V affects

them.

Adverse Reactions

Clinical Trial Data:

The safety of MOTILUM-V was evaluated in 1221 patients with gastroparesis, dyspepsia, gastro esophageal 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 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).

ARs reported by $\geq 1\%$ of patients treated with domperidone in these 45 clinical trials are shown in below Tables:

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

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%)

Gastrointestinal Disorders

Diarrhea (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%),
Galactorrhea (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%)

ARs that occurred in $< 1\%$ of Domperidone treated patients in the 45 clinical trials:

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 Experience:

Immune System Disorders

Very rare Anaphylactic Reaction (including Anaphylactic Shock)

Psychiatric Disorders

Very rare Agitation, Nervousness

Nervous System Disorders

Very rare Dizziness, Extrapyramidal Disorder, Convulsion

Cardiac Disorders

Very rare Sudden Cardiac Death, Serious Ventricular Arrhythmias

Skin and Subcutaneous Tissue Disorders

Very rare Angioedema

Renal and Urinary Disorders

Very rare Urinary Retention

Investigations

Very rare Liver Function Test Abnormal, Blood Prolactin Increased

Overdose

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. It is advisable to contact a poison control center to obtain the latest recommendations for the management of an overdose. Close medical supervision and supportive therapy is recommended. Anticholinergic or anti-Parkinson drugs may be helpful in controlling the extrapyramidal reactions.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamic Properties

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 side effects 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 esophageal pressure, improve antroduodenal motility and accelerate gastric emptying. There is 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 and supra-therapeutic doses (10 and 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 of 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 regimen is not clinically relevant.

Pharmacokinetic Properties

Absorption

In fasting subjects, domperidone is rapidly absorbed after oral administration, with peak plasma concentrations occurring at ~60 minutes after dosing.

The low absolute bioavailability of oral domperidone (approximately 15%) is due to an extensive first pass metabolism in the gut wall and liver. 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 base. Oral bioavailability of domperidone base is decreased by prior concomitant administration of cimetidine and 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

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.

Special Populations

Hepatic impairment

In subjects with moderate hepatic impairment (Pugh score 7 to 9, Child-Pugh rating B), the AUC and Cmax 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 Cmax and AUC, with no change in protein binding or terminal half life. 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.

PHARMACEUTICAL PARTICULARS

Shelf Life

See expiry date on the outer pack.

Special Precautions for Storage

Store between 15 to 30 °C.
Keep all medicines out of reach of children.
Protect from light and moisture.

Nature and Contents of Container

Motilium-V domperidone malleate 12.72mg (equivalent to 10mg domperidone) is supplied in blister pack of 5x10 tablets.

Manufactured by:

Aspin Pharma (Pvt) Ltd.,
Plot No. 10 & 25, Sector No. 20, Korangi Industrial Area,
Karachi-74900, Pakistan.

Motilium-V, TM of JANSSEN PHARMACEUTICA, Beerse, Belgium.



خبردار: ڈاکٹر کی ہدایت کے مطابق استعمال کریں۔
15 سے 30 ڈگری سینٹی گریڈ تک سرد رکھیں۔
بچوں کی پہنچ سے دور رکھیں۔
دوا کو روشنی اور نمی سے بچائیں۔