Motilium®

(domperidone)

Film-coated Tablet / Suspension

NAME OF THE MEDICINAL PRODUCT
MOTILIUM® (Domperidone)

QUALITATIVE AND QUANTITATIVE COMPOSITION
Motilium Tablet:
Each film-coated tablet contains 10 mg domperidone
Motilium Suspension:
Each ml of oral suspension contains 1 mg domperidone

CLINICAL INFORMATION
Indications
1. The dyspeptic symptom complex that is often associated with delayed gastric emptying, gastro-esophageal 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.

Oral suspension
10 ml (of 1 mg/ml oral suspension) up to three times per day with a maximum dose of 30 ml per day.

Hepatic impairment
Motilium 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 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 in children less than 12 years of age has not been established.
The efficacy of MOTILIUM in adolescents 12 years of age and older and weighing less than 35 kg has not been established

Contraindications
MOTILIUM is contraindicated in the following situations:

- In patients with moderate to severe hepatic impairment
- In patients who have known existing prolongation of cardiac conduction intervals (particularly QTc) and in patients with significant electrolyte disturbances or underlying cardiac diseases such as congestive heart failure
- During co-administration with QT-prolonging drugs
- During co-administration with potent CYP3A4 inhibitors (regardless of their QT-prolonging effects)

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 should be used with caution in older patients. Patients older than 60 years of age should consult their physician before taking Motilium.

Due to increased risk of ventricular arrhythmia, MOTILIUM 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 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
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 as they lower the oral bioavailability of domperidone. When used concomitantly, MOTILIUM 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.

Theoretically, since MOTILIUM 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 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 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.

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 affects them.

Adverse Reactions
Clinical Trial Data
The safety of MOTILIUM 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 ≥1% of patients treated with domperidone in these 45 clinical trials are shown in below Tables:

Adverse Reactions Reported by ≥ 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 (1.0%)

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%)
Galactorrhoea (3.3%)
Amenorrhea (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, Urticaria
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 has been 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 approximately 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 outer pack

خوراک: ڈاکٹر کی ہدایت کے مطابق استعمال کریں۔

Special precautions for storage
Do not store above 30°C
Keep all medicines out of reach of children
Protect from light and moisture

۳۰ ڈگری سینٹی گریڈ سے زیادہ درجہ حرارت پر نہ رکھیں۔
بچوں کی پہنچ سے دور رکھیں۔ دوا کو روشنی اور نمی سے بچائیں۔

Nature and contents of container
Motilium 10 mg (domperidone) is supplied in a blister pack of 5x10 tablets.
Motilium 1mg/ml (domperidone) oral suspension is supplied in bottle of 120 mL with a measuring cup of 5 ml.

Instructions for use and handling
Motilium suspension: Shake well before use

Manufactured by:
Aspin Pharma (Pvt.) Ltd.
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Motilium, TM of JANSSEN PHARMACEUTICA, Breese, Belgium.

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