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-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
It is recommended to take oral Motilium-V 15-30 minutes before meals. If taken after meals, absorption of the drug is somewhat delayed.
Adults and adolescents ≥ 12 years of age and weighing ≥ 35 kg, and children <12 years of age and weighing ≥ 35 kg
The dose of Motilium-V should be the lowest effective dose for the individual situation (typically 30 mg/day) and can be increased if necessary to a maximum daily oral dose of 40 mg. Usually, the maximum treatment duration should not exceed one week for the treatment of acute nausea and vomiting. If nausea and vomiting persists for longer than one week, patients should consult their physician. For other indications, the initial duration of treatment is up to four weeks. If treatment exceeds four weeks, patients should be reevaluated and the need for continued treatment reassessed.

Formulation (domperidone per unit)	Dosage	Maximum dose per day
Film-coated tablets (10 mg/tablet)	1 tablet three to four times per day	40 mg (4×10 mg tablet)

Adults and adolescents (≥ 12 years of age) weighing < 35 kg
The dose of Motilium-V should be the lowest effective dose. The total daily dose is dependent on body weight.
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 up to four weeks. If treatment exceeds four weeks, patients should be reevaluated and the need for continued treatment reassessed. Film-coated tablets are unsuitable for use in adults and adolescents weighing less than 35 kg.
Infants and children < 12 years of age and weighing < 35 kg
The efficacy of Motilium-V has not been established in infants and children < 12 years of age and weighing < 35 kg.
Adults (>60 years of age)
Patients older than 60 years of age should consult their physician before taking Motilium-V.
Infants and children <12 years old
Motilium-V should not be administered to children <12 years old and weighing ≥ 35 kg unless prescribed for use. The efficacy of Motilium-V has not been established in infants and children < 12 years of age and weighing < 35 kg .

Renal impairment
Since the elimination half-life of domperidone is prolonged in severe renal impairment (serum creatinine > 6 mg/100 mL, i.e. > 0.6 mmol/L), 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. Patients with severe renal impairment should be reviewed regularly.

Hepatic impairment
Domperidone is contraindicated for patients with moderate (Child-Pugh 7 to 9) or severe (Child-Pugh >9) hepatic impairment (see Contraindications). Dose adjustment is not required for patients with mild (Child-Pugh 5 to 6) hepatic impairment.

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 ketoconazole, 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 proarrythmic 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). The above list is representative and not exhaustive. Please refer to relevant lists appropriately.
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. (see Adverse Reactions). 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
Throughout this section, adverse reactions are presented. Adverse reactions are adverse events that were considered to be reasonably associated with the use of domperidone based on the comprehensive assessment of the available adverse event information. A causal relationship with domperidone cannot be reliably established in individual cases. Further, because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

Clinical Trial Data I
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:

Table 1: Adverse Reactions Reported by ≥ 1% of Domperidone -Treated Patients in 45 Clinical Trials (n=1221):
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%)

Table 2: ARs that occurred in < 1% of Domperidone-treated patients in the 45 Clinical Trials (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
In addition to the ARs reported during clinical studies and listed above, the following ARs have been reported during postmarketing experience (Tables 3 and 4). In each table, the frequencies are provided according to the following convention:

Very common	≥ 1/10
Common	≥ 1/100 and < 1/10
Uncommon	≥ 1/1000 and < 1/100
Rare	≥ 1/10000 and < 1/1000
Very rare	< 1/10000, including isolated reports.

In Table 3, ARs are presented by frequency category based on spontaneous reporting rates, while in Table 4, the same ARs are presented by frequency category based on incidence in clinical trials or epidemiology studies, when known.

Table 3: Adverse Reactions Identified During Postmarketing Experience with Domperidone by Frequency Category Estimated from Spontaneous Reporting Rates

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

* Based on epidemiology data

Table 4. Adverse Reactions Identified During Postmarketing Experience with Domperidone by Frequency Category Estimated from Clinical Trial Incidence

Immune System Disorders	
Not known	Anaphylactic Reaction (including Anaphylactic Shock)
Psychiatric Disorders	
Uncommon	Agitation, Nervousness
Nervous System Disorders	
Common	Dizziness
Rare	Convulsion
Not known	Extrapyramidal Disorder
Cardiac Disorders	
Not known	Sudden Cardiac Death*, Serious Ventricular Arrhythmias*
Skin and Subcutaneous Tissue Disorders	
Not known	Angioedema
Renal and Urinary Disorders	
Uncommon	Urinary Retention
Investigations	
Uncommon	Liver Function Test Abnormal
Rare	Blood Prolactin Increased

*Based on epidemiology data

Pediatric population
In post-marketing experience, there were no differences in the safety profile of adults and children.

Clinical Trial Data II
The safety of MOTILIUM was evaluated in 1275 patients with dyspepsia, gastro-esophageal 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 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.

Table 1. Adverse Reactions Reported by ≥ 1% of Domperidone-Treated Patients in 31 Clinical Trials

System Organ Class:	(N=1275)
Adverse Reaction	(%)
Gastrointestinal disorders:	
Dry Mouth	(1.7)

Table 2. Adverse Reactions Reported by < 1% of Domperidone-Treated Patients in 31 Clinical Trials

System Organ Class Domperidone	(N=1275)
Adverse Reaction	*%*
Psychiatric Disorders:	
Loss of libido	(0.2)
Anxiety	(0.1)
Nervous System Disorders:	
Somnolence	(0.8)
Headache	(0.6)
Gastrointestinal Disorders:	
Diarrhea	(0.4)
Skin and Sub-cutaneous Disorders:	
Rash	(0.2)
Pruritis	(0.1)
Reproductive System & Breast Disorders:	
Galactorrhoea	(0.5)
Breast pain	(0.2)
Breast tenderness	(0.2)
General Disorders and Administration Site Conditions:	
Asthenia	(0.1)

In 45 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 in Tables 1 and 2, akathisia, breast discharge, breast enlargement, breast swelling, depression, hypersensitivity, lactation disorder and irregular menstruation, were also noted.

Postmarketing
In addition to the ARs reported during clinical studies and listed above, the following ARs have been reported in postmarketing experience (Tables 3 and 4). In each table, the frequencies are provided according to the following convention:

Very common	≥ 1/10
Common	≥ 1/100 and < 1/10
Uncommon	≥ 1/1000 and < 1/100
Rare	≥ 1/10000 and < 1/1000
Very rare	< 1/10000, including isolated reports.

In Table 3, ARs are presented by frequency category based on spontaneous reporting rates, while in Table 4, the same ARs are presented by frequency category based on incidence in clinical trials or epidemiology studies, when known.

Table 3. Adverse Reactions Identified During Postmarketing Experience with Domperidone by Frequency Category Estimated from Spontaneous Reporting Rates

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	
Not known	Sudden Cardiac Death*, Serious Ventricular Arrhythmias*
Skin and Subcutaneous Tissue Disorders	
Very rare	Angioedema, Urticaria
Renal and Urinary Disorders	
Very rare	Urinary Retention
Reproductive System and Breast Disorders	
Rare	Gynaecomastia, Amenorrhea
Investigations	
Very rare	Liver Function Test Abnormal, Blood Prolactin Increased

* Based on epidemiology data

Table 4. Adverse Reactions Identified During Postmarketing Experience with Domperidone by Frequency Category Estimated from Clinical Trial Incidence

Immune System Disorders	
Not known	Anaphylactic Reaction (including Anaphylactic Shock)
Psychiatric Disorders	
Uncommon	Agitation, Nervousness
Nervous System Disorders	
Uncommon	Dizziness, Extrapyramidal Disorder
Not known	Convulsion
Cardiac Disorders	
Not known	Sudden Cardiac Death*, Serious Ventricular Arrhythmias*
Skin and Subcutaneous Tissue Disorders	
Uncommon	Urticaria
Not known	Angioedema

Renal and Urinary Disorders

Not known	Urinary Retention

Reproductive System and Breast Disorders

Not known	Gynaecomastia, Amenorrhea

Investigations

Not known	Liver Function Test Abnormal, Blood Prolactin Increased

* Based on epidemiology data

Pediatric population
In postmarketing experience, there were no differences in the safety profile of adults and children.

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
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 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.
This lack of clinical relevance is corroborated by pharmacokinetics and QTc interval data from two older studies which involved a 5-day treatment of 20 mg and 40 mg domperidone administered 4 times a day. ECGs were recorded prior to the study, on Day 5 at 1 hour (approximately at tmax) after the morning dose, and 3 days later. In both studies, no difference between QTc after active treatment and placebo was observed. It was therefore concluded that domperidone administration of 80 and 160 mg daily doses had no clinically significant effect on QTc in healthy subjects.

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.

PHARMACEUTICAL INFORMATION
Shelf Life
Observe expiry date on the outer pack.

Special Precautions for Storage
As prescribed by the physician.
Do not store above 30°C.
Protect from light and moisture.
Keep out of reach of children.

ہدایات :
ڈاکٹر کی ہدایت کے مطابق استعمال کریں۔
۳۰ ڈگری سینٹی گریڈ سے زیادہ درجہ حرارت پر نہ رکھیں۔
دوا کو روشنی اور نمی سے بچائیں۔
بچوں کی پہنچ سے دور رکھیں۔

Nature and Contents of Container
Motilium-V (domperidone maleate) 12.72mg (equivalent to 10mg domperidone) tablets are available in a blister pack of 100's (5x20's).

Manufactured by:
Aspin Pharma (Pvt) Ltd.,
Plot No. 10 & 25, Sector No. 20, Korangi Industrial Area,
Karachi-74900, Pakistan. www.aspin.com.pk

ASPIN
An OBS Group Company

REVISION DATE
February 2024

Code: CCDS-V007-01/2018-MO-LF-C-02-01