

MOTIDOM TABLET

DESCRIPTION

Motidom Tablet is a white round biconvex tablet with bisec-line engraving on one side.

CONTENT

One tablet contains 10 mg domperidone.

INDICATIONS

Domperidone is indicated for the relief of the symptoms of nausea and vomiting. This includes:

- Nausea and vomiting of functional, organic, infectious or dietary origin.
- 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

It is recommended to take oral **Motidom Tablet** 15 to 30 minutes before meals. If taken after meals, absorption of the drug is somewhat delayed.

Adults and adolescents who are 12 years of age and older and weighing 35 kg and more; and children younger than 12 years old and weighing 35 kg and more

The dose of **Motidom Tablet** 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 tablet (10mg/tablet)	1 tablet three to four times per day	40mg (4 x 10mg tablet)
Oral suspension (1mg/ml)	10mL three to four times per day	40mg (40 ml of 1mg/ml oral suspension)

Adults and adolescents who are 12 years of age and older and weighing less than 35 kg

The dose of **Motidom Tablet** should be the lowest effective dose. The total daily dose is dependent on weight (see table below).

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.

Formulation (domperidone per unit)	Dosage	Maximum dose per day
Oral suspension (1mg/ml)	0.25mg/kg three to four times per day	35mg (1mg/kg but no more than 35ml)

Infants and children younger than 12 years of age and weighing less than 35 kg

The efficacy of **Motidom Tablet** has not been established in infants and children younger than 12 years of age and weighing less than 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 **Motidom Tablet** 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 received regularly.

Hepatic impairment

Motidom Tablet is contraindicated in 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.

CONTRAINDICATIONS

Motidom Tablet is contraindicated in the following situations:

- Known hypersensitivity to domperidone or any of the excipients.
- Prolactin-releasing pituitary tumour (prolactinoma).
- 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.
- Co-administration with QT-prolonging drugs.
- Co-administration with potent CYP3A4 inhibitors regardless of their QT prolonging effects (see Section *Drug Interactions*).
- Whenever stimulation of gastric motility might be dangerous, e.g., in the presence of gastrointestinal haemorrhage, mechanical obstruction or perforation.
- In patients with moderate or severe hepatic impairment.

SPECIAL WARNING AND PRECAUTIONS

Precautions for use: **Motidom Tablets** contain lactose and may be unsuitable for patients with lactose intolerance, galactosaemia or glucose/galactose malabsorption.

Use in infants

Neurological side effects are rare. Since metabolic functions and the blood brain barrier are not fully developed in the first months of life the risk of neurological side effects is higher in young children.

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

Renal impairment

The elimination half-life of domperidone is prolonged in severe renal impairment. For repeated administration, the dosing frequency of domperidone should be reduced to once or twice daily depending on the severity of the impairment. The dose may also 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 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 *Side Effects*).

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

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

Motidom Tablet 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 patient with underlying cardiac diseases such as congestive heart failure due to increased risk of ventricular arrhythmia. Electrolyte disturbances (hypokalaemia, hyperkalaemia, hypomagnesaemia) or bradycardia are known to be conditions increasing the proarrhythmic risk.

Motidom Tablet is contraindicated with QT prolonging drugs including apomorphine, unless the benefit of the co-administration with apomorphine outweighs the risks, and only if the recommended precautions for co-administration mentioned in the apomorphine SmPC are strictly fulfilled. (Kindly refer to apomorphine SmPC)

Treatment with **Motidom Tablet** should be stopped if signs or symptoms occur that may be associated with cardiac arrhythmia, and the patient should consult their physician.

Patient should be advised to promptly report any cardiac symptoms.

DRUG 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.

Co-administration of domperidone with potent CYP3A4 inhibitors which have been shown to cause QT prolongation is contraindicated (see *Contraindications*).

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

Concomitant use of the following substances is contraindicated

QTc-prolonging medicinal products:

- 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., pentamidine).
- Certain antimalarial agents (in particular halofantrine, lumefantrine).
- Certain gastrointestinal medicines (e.g., cisapride, dolasetron, prucalopride).
- Certain antihistaminics (e.g., mequitazine, mizolastine).
- Certain medicine used in cancer (e.g., toremifene, vandetanib, vincamine).
- Certain other medicines (e.g., bepridil, diphemanil, methadone).
- Apomorphine, unless the benefit of the co-administration outweighs the risks, and only if the recommended precautions for co-administration are strictly fulfilled (*please refer to the apomorphine SmPC*).

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

- Protease inhibitors.
- Systemic azole antifungals.
- Some macrolides (erythromycin, clarithromycin and telithromycin).

Concomitant use of the following substances is not recommended

Moderate CYP3A4 inhibitors i.e. diltiazem, verapamil and some macrolides (see *Contraindications*).

Concomitant use of the following substances requires caution in 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 representatives and not exhaustive.

PREGNANCY AND LACTATION

Pregnancy: The potential risk for humans is unknown. Therefore, **Motidom Tablet** should only be used during pregnancy when justified by the anticipated therapeutic benefit.

Breastfeeding: **Motidom Tablet** is excreted in human milk. Occurrence of adverse effects, in particular cardiac effect cannot be excluded after exposure via breast milk. A decision should be made whether to discontinue breastfeeding or to discontinue/abstain from domperidone therapy considering the benefit of breastfeeding for the child and the benefit of therapy for the women. Caution should be exercised in case of QTc prolongation risk factor in breastfed infants.

SIDE EFFECTS

System organ class	Adverse drug reaction
Psychiatric disorders	Loss of libido, anxiety, depression
Nervous system disorders	Somnolence, headache, akathisia
Gastrointestinal disorders	Dry mouth, diarrhoea
Skin and subcutaneous tissue disorders	Rash, pruritus
Reproductive system and breast disorders	Galactorrhoea, breast pain, breast tenderness, gynaecomastia, amenorrhoea, menstruation irregular, lactation disorder
General disorder and administration site conditions	Asthenia
<u>Post-marketing experience</u>	
The following adverse drug reactions have been reported.	
Immune system disorders	Anaphylactic reactions including anaphylactic shock, angioedema, allergic reaction
Psychiatric system disorders (very rare)	Agitation, nervousness
Nervous system disorders (very rare)	Extrapyramidal disorder, convulsions, dizziness
Eye disorders	Oculogyric crisis
Skin and subcutaneous tissue disorders	Urticaria, angioedema (very rare)
Reproductive system and breast disorders	Gynaecomastia, amenorrhoea
Cardiac disorders (very rare)	Ventricular arrhythmias, QTc prolongation, Torsade de pointes, sudden cardiac death (See <i>Special Warning and Precautions</i>)
Renal and urinary disorders (very rare)	Urinary retention
Investigations (very rare)	Liver function test abnormal, blood prolactin increased

As the hypophysis is outside the blood-brain barrier, domperidone may cause an increase in prolactin levels. In rare cases this hyperprolactinaemia may lead to neuro-endocrinological side effects such as galactorrhoea, gynaecomastia and amenorrhoea.

Extrapyramidal side effects are very rare in neonates and infants, and exceptional in adults. These side effects reverse spontaneously and completely as soon as the treatment is stopped.

Other central nervous system-related effects of convulsions, agitation and somnolence also are very rare and primarily reported in infants and children.

SYMPTOMS AND TREATMENT OF OVERDOSE

Symptoms: Overdose has been reported primarily in infants and children. Symptoms of overdosage may include agitation, altered consciousness, convulsions, disorientation, somnolence and extrapyramidal reactions.

Treatment: There is no specific antidote to domperidone, but in the event of overdose, standard symptomatic treatment should be given immediately. Gastric lavage as well as the administration of activated charcoal, may be useful. ECG monitoring should be undertaken, because of the possibility of QT interval prolongation. Close medical supervision and supportive therapy is recommended.

Anticholinergic, anti-Parkinson drugs may be helpful in controlling the extrapyramidal reactions.

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 **Motidom Tablet** affects them.

PHARMACODYNAMICS

Domperidone is a dopamine antagonist with antiemetic 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. The low concentrations found in the brain, indicate predominantly peripheral effect of domperidone on dopamine receptors.

PHARMACOKINETICS

Absorption: Domperidone is rapidly absorbed after oral administration, with peak plasma concentrations occurring at approximately 60 minutes after dosing. The C_{max} and AUC values of domperidone increased proportionally with dose in the 10 mg to 20 mg dose range. 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 gastrointestinal 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 oral drug is taken after a meal.

Distribution: Domperidone is 91 - 93 % bound to plasma proteins.

Metabolism: Domperidone undergoes rapid and extensive hepatic metabolism by hydroxylation and N-dealkylation.

Excretion: Urinary and faecal excretions amount to 31 and 66 % of the oral dose respectively. The proportion of the drug excreted unchanged is small (10 % of faecal excretion and approximately 1 % of urinary excretion). The plasma half-life is 7 – 9 hours is prolonged in patients with severe renal insufficiency.

Special populations

Hepatic impairment: 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. The unbound fraction is increased by 25 %, and the terminal elimination half-life is prolonged from 15 to 23 hours.

Renal impairment: 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 hours to 20.8 hours. Very little unchanged drug (approximately 1 %) is excreted via the kidneys.

EXCIPIENTS

Povidone, sodium starch glycolate, lactose monohydrate, talc, glycerine, magnesium stearate, purified water.

PACKING / PACK SIZES

Alu-PVC blister strip of 10 tablets per strip. Box of 50 x 10's.

Other dosage form in the market:

Motidom Oral Suspension: packed in polyethylene bottle of 30ml with a plastic medical spoon. Box of 12 bottles of 30 ml.

STORAGE CONDITIONS

Store below 30°C Protect from light.

Keep out of reach of children.

Jauhi daripada kanak-kanak.

Shelf life: please refer to the outer box label.

MANUFACTURED BY:

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