MOTIDONE TABLET 10MG

DESCRIPTION:
An oblong shaped tablet, pink in colour with marking "DUO".

COMPOSITION:
Each tablet contains Domperidone 10 mg.

PHARMACODYNAMICS:
Pharmacologically, domperidone is a dopamine antagonist with antiemetic properties similar to those of metoclopramide and certain neuroleptic drugs. Unlike these drugs, however, domperidone does not readily cross the blood brain barrier. It seldom causes extra-pyrimidal side effects, but does cause a rise in prolactin levels. Its antiemetic effect may be due to a combination of peripheral (gastro-kinetic) effects and antagonism of central dopamine receptors in the chemo-receptor trigger zone which lies in the area postrema and is regarded as being outside the blood brain barrier. Animal studies have shown that domperidone has no effect on plasma concentrations of homovanillic acid, a metabolite of dopamine. It also antagonises the behavioural effects of dopamine much more effectively when administered intracerebrally than when given systemically. These findings, together with the low concentrations found in the brain, indicate a predominantly peripheral effect of domperidone on dopamine receptors.
Studies in humans have shown intravenous and oral domperidone to increase the duration of antral and duodenal contractions, to increase the gastric emptying of liquids and semi solids in healthy subjects and in patients in whom, it was delayed, and to increase lower oesophageal sphincter pressure in healthy subjects. Domperidone has no effect on gastric secretion.

PHARMACOKINETICS:
Domperidone is rapidly absorbed following intramuscular and oral administration with peak plasma concentrations occurring at approximately 10 and 30 minutes respectively. Systemic bioavailability of oral domperidone is 13 to 17%. The low oral bioavailability is probably due to "first-pass" gut wall and hepatic metabolism. Oral bioavailability is decreased by prior administration of cimetidine or sodium bicarbonate. The time of peak absorption is slightly delayed and the AUC somewhat increased when the oral drug is taken after a meal.
Oral domperidone does not appear to accumulate or induce its own metabolism; a peak plasma level after 90 minutes of 21 ng/ml after two weeks oral administration of 30 mg per day was almost the same as that of 18 ng/ml after the first dose. Domperidone is 91-93% bound to plasma proteins.
Distribution studies with radiolabelled drug in animals have shown wide tissue distribution with low brain concentration. Small amounts of drug cross the placenta in rats and the drug is excreted in the breast milk of this species.
Domperidone undergoes rapid and extensive hepatic metabolism by hydroxylation and N-dealkylation. Urinary and faecal excretion amounts to 31 and 66% respectively of the oral dose. The proportion of the drug excreted unchanged is small (10% of faecal 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.

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.

RECOMMENDED DOSAGE:
It is recommended to take Motidone 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 & children <12 years of age and weighing ≥ 35 kg
The dose of Motidone 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
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
Due to the need for accurate dosing, 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 Motidone 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 Motidone 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
Motidone is contraindicated for patients with moderate (Child-Pugh 7 to 9) or severe (Child-Pugh >9) hepatic impairment. Dose adjustment is not required for patients with mild (Child-Pugh 5 to 6) hepatic impairment.

ROUTE OF ADMINISTRATION: Oral

CONTRAINDICATIONS:
Motidone 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 (see Warnings and Precautions).
- Co-administration with QT-prolonging drugs
- Co-administration with potent CYP3A4 inhibitors regardless of their QT-prolonging effects (See Section Interactions).
- Whenever stimulation of gastric motility might be dangerous, e.g., in the presence of gastro-intestinal haemorrhage, mechanical obstruction or perforation.
- In patients with moderate or severe hepatic impairment).

WARNINGS & PRECAUTIONS:
Prolactin levels
There are limited safety data in long term use (ie. beyond six months) of domperidone. However, it has been shown to produce an increase in plasma prolactin. The raised level persists with chronic administration but falls to normal on discontinuing the drug.
It has been shown in vitro that about 1/3 of breast cancers are prolactin dependent and hence this point must be considered when prescribing for a patient with a past history of breast cancer.
Endocrine disturbances such as galactorrhoea, amenorrhoea, gynaecomastia and impotence have been reported with drugs which stimulate prolactin release.

Use with impaired hepatic function
Since domperidone is extensively metabolised in the liver, it should be used with caution in patients with hepatic impairment.

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 Adverse Reactions).

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Epidemiological studies showed that domperidone was associated with an increased risk of serious ventricular arrhythmias or sudden cardiac death (see Adverse Reactions). 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 Contraindications).
Electrolyte disturbances (hypokalaemia, hyperkalaemia, hypomagnesaemia) or bradycardia are known to be conditions increasing the proarrythmic 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.

INTERACTION WITH OTHER MEDICAMENTS:

Concomitant administration of anticholinergic drugs may antagonise the anti-dyspeptic effect of domperidone. If administered prior to atropine, domperidone reduces the relaxant effect of atropine upon the lower oesophageal sphincter, but has no reversing effect if atropine is administered first. Since domperidone has gastro-kinetic effects it could influence the absorption of concomitantly orally administered drugs, particularly those of sustained release or enteric coated formulations. However, in patients already stabilized on digoxin, paracetamol or haloperidol concomitant administration of domperidone did not influence the blood levels of these drugs.
Concomitant use with antacids and antisecretory drugs with domperidone will reduce its oral bioavailability. Dosing with these 2 agents should be separated from dosing of domperidone by at least 2 hours.
In patients stabilised on digoxin, paracetamol or haloperidol administration of domperidone did not influence the blood levels of these drugs. Domperidone has been used with neuroleptics without potentiation of their activity. Dopaminergic: Antagonism of hypoprolactin effect of bromocriptine.
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 (See Section Contraindications).

USE IN PREGNANCY & LACTATION:

Use in Pregnancy: There are no adequate and well controlled studies in pregnant women and hence this drug should be used during pregnancy only if clearly needed.
Use in Lactation: The drug is excreted in breast milk of lactating rats and probably also in humans. It is therefore not recommended for nursing mothers unless the expected benefits outweigh any potential risk.

SIDE EFFECTS:

Mild and transient abdominal cramps and dry mouth have been reported rarely. There have been no extrapyramidal side effects reported during controlled therapeutic trials although a few anecdotal reports of such effects have been published.

- May induce an increase in the plasma prolactin level which may be associated with galactorrhoea and less frequently with gynaecomastia.
- Rashes and other allergic reactions.
- Acute dystonic reactions

Central Nervous System: Dry mouth, headache, insomnia, dizziness, thirst, lethargy, irritability, extrapyramidal reactions (rare).
Gastrointestinal: Abdominal cramps, diarrhoea, regurgitation, changes in appetite, nausea, heartburn, constipation.
Dermatologic: Rash, pruritus, urticaria.
Urinary: Urinary frequency, dysuria
Cardiovascular: Oedema, palpitations.
Musculoskeletal: Leg cramps, asthenia.
Other: Conjunctivitis, stomatitis, drug intolerance.
There have been reports of adverse effects possibly related to increases in serum prolactin. These effects include: Gynecomastia, breast tenderness, swelling of the breasts, irregular menses, amenorrhoea, a decrease or loss of libido, breast secretion and lactation. These effects occurred in patients who received up to 120 mg per day in four divided doses.
Postmarketing:
Cardiac Disorders
Frequency: Very rare
Ventricular arrhythmias, QTc prolongation, Torsade de Pointes, Sudden cardiac death (see Warnings and Precautions)

SYMPTOMS AND TREATMENT OF OVERDOSE:

Overdosage: Symptoms of overdosage may, include drowsiness, disorientation and extrapyramidal reactions, particularly in children. Acute toxicity studies in animals resulted in primarily central nervous system symptoms.
Treatment:

- Gastric lavage
- Activated charcoal and close observation of the patient are recommended.
- Anticholinergic, anti-Parkinson drugs or antihistamines with anticholinergic properties may be helpful in controlling the extrapyramidal reactions.

STORAGE CONDITIONS:

Store below 30˚C. Protect from light.
KEEP OUT OF REACH OF CHILDREN. JAUHI DARIPADA KANAK-KANAK.

SHELF LIFE:

Please refer to outer package.

PACK SIZE:

Pack in Blister pack of 10 x 10's and 50 x 10's. Container of 500's (For Export Only)

PRODUCT REGISTRATION HOLDER & MANUFACTURER:

DUOPHARMA (M) SDN BHD
Lot 2599, Jalan Seruling 59 Kawasan 3,
Taman Klang Jaya, 41200 Klang, Selangor, MALAYSIA.