

PACKAGE INSERT TEMPLATE FOR DOMPERIDONE TABLET & ORAL SUSPENSION

Brand or Product Name

[Product name] Tablet 10mg

[Product name] Oral Suspension 1mg/ml

Name and Strength of Active Substance(s)

Domperidone ...mg

Domperidone maleate....mg equivalent to domperidone...mg

Product Description

[Visual description of the appearance of the product (eg colour, markings etc)

eg White, circular flat beveled edge tablets marked '10' on one side

Red syrupy liquid with an odour of raspberry and cherry

Pharmacodynamics

Domperidone is a dopamine antagonist (blocking both D1 & D2 receptors) which is structurally related to the benzimidazole. Domperidone is a potent gastrokinetic agent. Domperidone facilitates gastrointestinal smooth muscle activity by inhibiting dopamine at the D1 receptors and inhibiting the release of neural acetylcholine by blocking D2 receptors.

Domperidone binds with high affinity to the dopamine receptor. It does not cross the blood - brain barrier or the placental barrier but exerts its effects at peripheral sites: the chemoreceptor trigger zone (in the brainstem) and the gastrointestinal tract. Domperidone inhibits dopamine-induced gastric relaxation and the inhibitory effects of secretin, whose actions may be mediated by dopamine release. Finally, it stimulates phasic activity in the gastro-duodenal area and improves gastro-duodenal coordination.

Pharmacokinetics

Absorption

Although absorption is rapid, the systemic bioavailability of domperidone is only about 13% to 17% in fasting subjects given an oral dose; this is increased when domperidone is given after food. The low bioavailability is thought to be due to first-pass hepatic and intestinal metabolism. Peak plasma concentrations are achieved 30 minutes after an oral dose.

Distribution

Domperidone is 91 - 93% bound to plasma proteins. Domperidone does not readily cross the blood-brain barrier. In humans, the apparent volume of distribution is 440 L. Small amounts of

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domperidone are distributed into breast milk; concentrations are 10 to 50% of those in maternal serum

Metabolism

It undergoes rapid and extensive hepatic metabolism. The main metabolic pathways are N-dealkylation by cytochrome P450 isoenzyme CYP3A4, and aromatic hydroxylation by CYP3A4, CYP1A2, and CYP2E1.

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). Domperidone has an elimination half-life of about 7 to 9 hours, but is prolonged in patients with severe renal insufficiency.

Indication

1. The dyspeptic symptom complex that is often associated with delayed gastric emptying, gastro-oesophageal reflux and oesophagitis:

- epigastric sense of fullness, early satiety, feeling of abdominal distension, upper abdominal pain.
- bloating, eructation, flatulence
- nausea and vomiting
- heartburn with or without regurgitation of gastric contents in the mouth

2. Nausea and vomiting of functional, organic, infectious or dietetic origin or induced by radiotherapy or drug therapy. A specific indication is nausea and vomiting induced by dopamine agonists, as used in Parkinson's disease (such as L-dopa and bromocriptine).

Recommended Dosage

It is recommended to take oral Domperidone before meals. If taken after meals, absorption of the drug is somewhat delayed.

1. Adults and adolescents (over 12 years and weighing 35 kg or more)

10 mg to 20mg three to four times per day, with a maximum daily dose of 80 mg

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2. Infants and children

0.25 - 0.5 mg/kg three to four times per day with a maximum daily dose of 2.4 mg/kg (but do not exceed 80 mg per day).

Tablets are unsuitable for use in children weighing less than 35 kg.

It is recommended to take oral Domperidone before meals. If taken after meals, absorption of the drug is somewhat delayed.

Use in Infants

Film-coated tablets are unsuitable for use in children weighing less than 35 kg.

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. Therefore, it is recommended that the dose be determined accurately and strictly followed in neonates, toddlers and small children. Overdosing may cause nervous system disorders in children, but other causes should be taken into consideration.

Use in Renal Insufficiency

Since the elimination half-life of domperidone is prolonged in severe renal impairment, on repeated administration the dosing frequency of Domperidone should be reduced to once or twice daily, depending on the severity of the impairment, and the dose may need to be reduced. Such patients on prolonged therapy should be reviewed regularly.

Mode of Administration

Oral

Contraindications

- Known hypersensitivity to domperidone or any of the excipients.
- Prolactin-releasing pituitary tumour (prolactinoma).
- Co-administration with oral ketoconazole, erythromycin, or other potent CYP3A4 inhibitors which prolong the QTc interval such as fluconazole, voriconazole, clarithromycin, amiodarone, and telithromycin
- 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.

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Warnings and Precautions

When antacids or antisecretory agents are used concomitantly, they should not be taken simultaneously with oral formulations of Domperidone; i.e., they should be taken after meals and not before meals.

Domperidone is not recommended for chronic use or for the routine prophylaxis of postoperative nausea and vomiting.

The film-coated tablets contain lactose and may be unsuitable for patients with lactose intolerance, galactosemia or glucose/galactose malabsorption (if applicable).

The oral suspension contains sorbitol and may be unsuitable for patients with sorbitol intolerance (if applicable).

Effects on Ability to Drive and Use Machines

Domperidone has no or negligible influence on the ability to drive or use machinery.

Interactions with Other Medicaments

Antacids and antisecretory drugs should not be given simultaneously with oral formulations of Domperidone as they lower its oral bioavailability.

Concomitant administration of anticholinergic drugs may antagonise the anti-dyspeptic effect of Domperidone.

Domperidone is metabolised via the cytochrome P450 isoenzyme CYP3A4. Concomitant use of drugs that significantly inhibit this enzyme may result in increased plasma levels of domperidone and such combinations may be best avoided.

In patients already stabilized on digoxin or paracetamol, concomitant administration of domperidone did not influence the blood levels of these drugs.

Opioid analgesics and antimuscarinics may antagonise the prokinetic effects of domperidone.

Dosage adjustment may be necessary in patients who are receiving domperidone concomitantly with cimetidine.

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Interaction Effect: weakness, dyskinesias, increased extrapyramidal symptoms, encephalopathy, and brain damage

Domperidone may also be associated 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.

Statement on Usage During Pregnancy and Lactation

Pregnancy

Currently, there is a lack of data on the use of domperidone in pregnant women. Until more human data becomes available, domperidone should only be used if the benefit outweighs the potential risk to the fetus.

Lactation

Domperidone is excreted in small amounts into human breast milk. Breast milk concentrations are approximately 25% of those in maternal serum. The long-term potential for adverse effects in the nursing infant have not been determined. Therefore, breast-feeding is not recommended for mothers who are taking Domperidone.

Adverse Effects / Undesirable Effects

- *Immune System Disorders:* anaphylactic reaction (including anaphylactic shock)
- *Psychiatric Disorders:* agitation, nervousness
- *Nervous System Disorders:* extrapyramidal disorder, convulsion
- *Cardiac Disorders :* sudden cardiac death, serious ventricular arrhythmias
- *Skin and Subcutaneous Tissue Disorders:* angioedema, urticaria, rash, pruritus
- *Renal and Urinary Disorders:* urinary retention
- *Reproductive System and Breast Disorders:* gynaecomastia, amenorrhoea
- *Investigations:* Liver function test abnormal, blood prolactin increased
- *Others:* dry mouth, diarrhoea, transient intestinal cramps, loss of libido, asthenia, headache and oculogyric crisis

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Overdose and Treatment

Symptoms

Symptoms of overdose may include agitation, altered consciousness, convulsion, disorientation, somnolence and extrapyramidal reactions.

Treatment

There is no specific antidote. Gastric lavage and administration of activated charcoal may be useful. Close medical supervision and supportive therapy is recommended. Anticholinergic or anti-Parkinson drugs may be helpful in controlling the extrapyramidal reactions.

Storage Conditions

[eg Store below.... °C]

Dosage Forms and Packaging Available

[Packaging type & pack size]

Name and Address of Manufacturer

[Name & full address of manufacturer]

Name and Address of Marketing Authorization Holder

[Name & full address of marketing authorization holder]

Date of Revision of Package Insert

[day/month/year]

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