Peridone® Tablets / Suspension

(Domperidone)

COMPOSITION:

Peridone® Tablets	**Peridone®** Suspension
Each tablet contains:	Each 5ml contains:
Domperidone BP…….10mg	Domperidone BP……5mg

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 (gastro kinetic) effects and antagonism of dopamine receptors in the chemoreceptor trigger zone, which lies outside the blood-brain barrier in the area postrema. Two previous drug-drug interaction studies showed some evidence of QTc prolongation when domperidone was administered as monotherapy (10mg 4 times a day). The largest time-matched mean difference of QTcF between domperidone and placebo was 5.4 msec (95% CI: -1.7 to 12.4) and 7.5msec (95% CI: 0.6 to 14.4), respectively.

PHARMACOKINETIC PROPERTIES:

Absorption: Domperidone is rapidly absorbed after oral administration with peak plasma concentrations occurring at approximately 1 hr. after dosing. The C_{max} and AUC values of domperidone increased proportionally with dose in the 10mg to 20mg dose range. A 2- to 3-fold accumulation of domperidone AUC was observed with repeated four times daily (every 5 hr.) dosing of domperidone for 4 days.
The low absolute bioavailability of oral domperidone (approximately 15%) is due to an extensive first-pass metabolism in the gut wall and liver. Reduced gastric acidity impairs the absorption of domperidone. Oral bioavailability 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: Oral domperidone does not appear to accumulate or induce its own metabolism. Domperidone is 91-93% bound to plasma proteins.

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.

Hepatic Impairment: Domperidone is contraindicated in patients with moderate or severe hepatic impairment.

Renal Impairment: Since very little unchanged drug (approximately 1%) is excreted via the kidneys, it is unlikely that the dose of a single administration needs to be adjusted in patients with renal insufficiency. However, on repeated administration, the dosing frequency should be reduced to once or twice daily depending on severity of the impairment, and the dose may need to be reduced.

Paediatric Population: No pharmacokinetic data are available in the pharmacokinetic properties.

THERAPEUTIC INDICATIONS

Domepridone is indicated for the relief of the symptoms of nausea and vomiting.

DOSAGE AND ADMINISTRATION:

Tablets: Domeperidone should be used at the lowest effective dose for the shortest duration necessary to control nausea and vomiting.
Domperidone 10mg tablets are for oral administration. It is recommended to take oral domperidone tablets before meals. If taken after meals, absorption of the drug is somewhat delayed.
Patients should try to take each dose at scheduled time. If a scheduled dose is missed, the missed dose should be omitted and the usual dosing schedule resumed. The dose should not be doubled to make up for a missed dose.
Usually, the maximum treatment duration should not exceed one week.

Adults and adolescents (12 years of age and older and weighing 35kg or more): One 10mg tablet up to three times per day with maximum dose of 30mg per day.

Neonates, infants, children (less than 12 years of age) and adolescents weighing less than 35kg: Due to the need for accurate dosing, domperidone tablets are unsuitable for use in children and adolescents weighing less than 35kg.

Hepatic Impairment: Domperidone 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 domperidone tablets 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.

Suspension:
Adults and adolescents (12 years of age and older and weighing 35kg or more)
10ml (1mg/ml oral suspension) up to three times per day with a maximum dose of 30ml per day.
Domeperidone should be used at the lowest effective dose for the shortest duration necessary to control nausea and vomiting.
It is recommended to take oral domperidone before meals. If taken after meals, absorption of the drug is somewhat delayed.
Patients should try to take each dose at scheduled time. If a scheduled dose is missed, the missed dose should be omitted and the usual dosing schedule resumed. The dose should not be doubled to make up for a missed dose.
Usually, the maximum treatment duration should not exceed one week.

Paediatric Population: The efficacy of domperidone in adolescents 12 years of age and weighing less than 35kg has not been established.

CONTRAINDICATIONS:

Domperidone is contraindicated in the following situations:
- In patients with moderate or severe hepatic impairment.
- 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, at the exception of apomorphine.
- Co-administration with potent CYP3A4 inhibitors (regardless of their QT prolonging effects).
- Known hypersensitivity to domperidone or any of the excipients.
- Prolactin-releasing pituitary tumour (prolactinoma).
- Renal impairment.

Domperidone should not be used when stimulation of gastric motility could be harmful: gastro-intestinal hemorrhage, mechanical obstruction or perforation.

WARNING & PRECAUTIONS:

Precautions for use: Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

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 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 .
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.
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 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 proarrythmic risk.

Use with apomorphine: Domperidone 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. Treatment with domperidone 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.

INTERACTION WITH OTHER MEDICINAL PRODUCTS & OTHER FORMS OF INTERACTION:

When antacids or antisecretory drugs are used concomitantly, they should not be taken simultaneously with oral formulations of domperidone as they lower the oral bioavailability of domperidone.

The main metabolic pathway of domperidone is through CYP3A4. In vitro data suggest that the concomitant use of drugs that significantly inhibit this enzyme may result in increased plasma levels of domperidone.
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 gastro-intestinal medicines (e.g., cisapride, dolasetron, prucalopride)
- certain antihistamines (e.g., mequitazine, mizolastine)
- certain medicines 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.

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.

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 substances are representative and not exhaustive.
- With the combination of oral domperidone 10mg four times daily and ketoconazole 200mg twice daily, a mean QTc prolongation of 9.8 msec was seen over the observation period, with changes at individual time points ranging from 1.2 to 17.5 msec. With the combination of domperidone 10mg four times daily and oral erythromycin 500mg three times daily, mean QTc over the observation period was prolonged by 9.9 msec, with changes at individual time points ranging from 1.6 to 14.3 msec. Both the C_{max} and AUC of domperidone at steady state were increased approximately three-fold in each of these interaction studies.
- In these studies domperidone monotherapy at 10mg given orally four times daily resulted in increases in mean QTc of 1.6 msec (ketoconazole study) and 2.5 msec (erythromycin study), while ketoconazole monotherapy (200mg twice daily) led to increases in QTc of 3.8 and 4.9 msec, respectively, over the observation period.

UNDESIRABLE EFFECTS:
The safety of domperidone was evaluated in clinical trials and in postmarketing experience. The clinical trials included 1275 patients with dyspepsia, gastro-oesophageal reflux disorder (GORD), 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 (domperidone base). The median total daily dose was 30mg (range 10 to 80mg), 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.

Immune system disorders: Anaphylactic reaction (including anaphylactic shock)

Psychiatric disorders: Loss of libido, Anxiety, Agitation. Nervousness

Nervous system disorders: Somnolence, Headache, Convulsion, Extrapyramidal disorder,

Eye disorders: Oculogyric crisis

Gastrointestinal disorder: Dry mouth, diarrhoea

Cardiac disorders: Ventricular arrhythmias, QTc prolongation, Torsades de Pointes, Sudden cardiac death

Skin and subcutaneous tissue disorder: Rash, Pruritus, Urticaria, Angioedema

Renal and urinary disorders: Urinary retention

Reproductive system and breast disorders: Galactorrhoea, Breast pain, Breast tenderness Gynaecomastia, Amenorrhoea

General disorders and administration site conditions: Asthenia

Investigation: Liver function test abnormal, Blood prolactin increased

FERTILITY, PREGNANCY & LACTATION:
Pregnancy: There are limited post-marketing data on the use of domperidone in pregnant women. The potential risk for humans is unknown. Therefore, domperidone should only be used during pregnancy when justified by the anticipated therapeutic benefit.

Breast-feeding: Domperidone is excreted in human milk and breast-fed infants receive less than 0.1% of the maternal weight-adjusted dose. Occurrence of adverse effects, in particular cardiac effects cannot be excluded after exposure via breast milk. A decision should be made whether to discontinue breast-feeding or to discontinue/abstain from domperidone therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the women. Caution should be exercised in case of QTc prolongation risk factor in breast-fed infants.

Effects on ability to drive and use machines: Domperidone has no or negligible influence on the ability to drive or use machines.

OVER DOSE:
Symptoms: Overdose has been reported primarily in infants and children. Symptoms of over dosage 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.

STABILITY
See expiry on the pack

AVAILABILITY
Peridone® tablets in a pack of 30's
Peridone® suspension in a pack of 120ml

INSTRUCTIONS
Dosage as advised by physician.
To be sold on the prescription of registered medical practitioner only.
Keep out of the reach of children.
Avoid exposure to heat, light, humidity and freezing.
Store between 15 to 30°C.
Improper storage may deteriorate the medicine.

For Tablets: Store in the original package in order to protect from moisture.

Please read the contents carefully before use.
This package insert is regularly reviewed and updated.

Manufactured by:
SAMI Pharmaceuticals (Pvt.) Ltd.
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پیریڈون ٹیبلٹ/سسپینشن
(ڈومپیریڈون)

خوراک: ڈاکٹر کی ہدایت کے مطابق استعمال کریں۔
صرف رجسٹرڈ ڈاکٹر کے نسخے کے مطابق فروخت کریں۔
بچوں کی پہنچ سے دور رکھیں۔
دوا کو دھوپ، گرمی، نمی اور منجمد ہونے سے محفوظ ۱۵ سے ۳۰ ڈگری سینٹی گریڈ کے درمیان میں رکھیں
ورنہ دوا خراب ہو جائیگی۔
برائے ٹیبلٹ: دوا کو نمی سے محفوظ رکھنے کے لیے اسکی اصل پیکنگ میں رکھیں۔