Rx DOMPERIDONE

APULDON

10 mg Film-Coated Tablet

Gastrokinetics (Propulsives)

FORMULATION:
Each film-coated tablet contains:
Domperidone (as Maleate) BP. ..... 10 mg

PRODUCT DESCRIPTION:
Domperidone (Apuldon) 10 mg Film-Coated Tablet is available as a white, pentagonal and biconvex film-coated tablet, having a breakline on one side and none on the other side.

PHARMACOLOGY:
Pharmacodynamics:
Pharmacotherapeutic group: Propulsives, ATC code: A03F A03
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 disorders 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.
Pharmacokinetics:
Although absorption is rapid, the systemic bioavailability of domperidone is only about 15% 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. The bioavailability of rectal domperidone is similar to that after oral doses, although peak plasma concentrations are only about one-third that of an oral dose and are achieved after about an hour, compared with 30 minutes after an oral dose.
Domperidone is more than 90% bound to plasma proteins, and has a terminal elimination half-life of about 7.5 hours. 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. About 30% of an oral dose is excreted in urine and feces over several days, about 10% as unchanged drug. It does not readily cross the blood-brain barrier.
Small amounts of domperidone are distributed into breastmilk; concentrations are 10 to 50% of those in maternal serum.

INDICATION:
It is used as an antiemetic for the short-term treatment of nausea and vomiting of various etiologies. It is also used for its prokinetic actions in dyspepsia and has been tried in diabetic gastroparesis.

DOSAGE AND ADMINISTRATION:
Adults and adolescents (12 years of age and older and weighing 35 kg or more): One 10mg tablet up to three times per day with a maximum dose of 30 mg per day. **Neonates, infants, children (less than 12 years of age) and adolescents weighing less than 35 kg:** Due to the need for accurate dosing, tablets are unsuitable for use in children and adolescents weighing less than 35 kg. Or as prescribed by the physician.
Domperidone should be used at the lowest effective dose for the shortest duration necessary to control nausea and vomiting. It is recommended to take Domperidone tablet before meals. If taken after meals, absorption of the drug is somewhat delayed.
Patients should try to take each dose at the 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.
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 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.

PREGNANCY AND LACTATION:
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, Apuldon 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 woman. Caution should be exercised in case of QTc-prolongation risk factors in breast-fed infants.

OVERDOSAGE & TREATMENT:
Symptoms of overdosage may include agitation, altered consciousness, convulsions, disorientation, somnolence and extrapyramidal reactions.
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.

CONTRAINDICATIONS:
Domperidone is contraindicated in the following situations:
- Known hypersensitivity to domperidone or any of the excipients;
- Prolactin-releasing pituitary tumor (prolactinoma);
- When stimulation of the gastric motility could be harmful e.g. in patients with gastro-intestinal hemorrhage, mechanical obstruction or perforation;
- 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;
- Co-administration with potent CYP3A4 inhibitors (regardless of their QT prolonging effects).

WARNINGS & PRECAUTIONS:
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.
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 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.

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.
Use in infants
Although neurological side effects are rare, the risk of neurological side effects is higher in young children since metabolic functions and the blood-brain barrier are not fully developed in the first months of life. 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.

ADVERSE EFFECTS:
Plasma prolactin concentrations may be increased, which may lead to galactorrhoea or gynecomastia. There have been reports of reduced libido, and rashes and other allergic reactions. Domperidone does not readily cross the blood-brain barrier and the incidence of central effects such as extrapyramidal reactions or drowsiness may be lower than with metoclopramide, however, there have been reports of dystonic reactions. Domperidone by injection has been associated with convulsions, arrhythmias, and cardiac arrest. Fatalities have restricted use by this route.

REPORTING OF SUSPECTED ADVERSE REACTIONS:
To allow continued monitoring of the benefit/risk balance of the medicinal product, reporting of suspected adverse reaction is necessary. Healthcare professionals are encouraged to report any suspected adverse reaction directly to the importer/distributor and/or to FDA: www.fda.gov.ph.

Patients are advised to seek immediate medical attention at the first sign/s of adverse reactions.

DRUG INTERACTIONS:
The main metabolic pathway of domperidone is through CYP3A4. 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 pharmacodynamic and/or pharmacokinetic interactions.
Concomitant use of the following substances is contraindicated
QTc prolonging medicinal products
- Anti-arrhythmics class IA (e.g., disopyramide, hydroquinidine, and quinidine)
- Anti-arrhythmics class III (e.g., amiodarone, dofetilide, dronedarone, ibutilide, sotalol)
- certain anti-psychotics (e.g., haloperidol, pimozide, sertindole)
- certain anti-depressants (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 antihistaminics (e.g., mequitazine, mizolastine)
- certain medicines used in cancer (e.g., toremifene, vandetanib, vincamine)
- certain other medicines (e.g., bepridil, diphemanil, methadone) Potent CYP3A4 inhibitors (regardless of their QT prolonging effects), i.e.:
- Protease inhibitors
- Systemic azole antifungals
- some macrolides (erythromycin, clarithromycin, telithromycin)

Concomitant use of the following substances is not recommended
Moderate CYP3A4 inhibitors i.e. diltiazem, verapamil and some macrolides.

As with other dopamine antagonists, there is a theoretical potential that domperidone may antagonize the hypoprolactinemic effect of drugs such as bromocriptine. In addition, the prokinetic effects of domperidone may alter the absorption of some drugs. Opioid analgesics and antimuscarinic may antagonize the prokinetic effects of domperidone.
Domperidone is metabolized via the cytochrome P450 isoenzyme CYP3A4; use with ketoconazole has been reported to produce a threefold increase in plasma concentrations of domperidone, and an associated slight prolongation in QT interval. Similar increases in domperidone concentrations might theoretically be seen with other potent inhibitors of CYP3A4 such as erythromycin or ritonavir, and such combinations may best avoided.

CAUTION:
Foods, Drugs, Devices and Cosmetics Act prohibits dispensing without prescription.

STORAGE:
Store at temperatures not exceeding 30°C.

AVAILABILITY:
Alu-Clear PVC Blister Pack x 10's (Box of 100's)

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Manufactured by:
ARISTOPHARMA LTD.
Plot # 14-22, Road # 11 & 12, Shampur-Kadamtali I/A.
Dhaka-1204, Bangladesh.

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SAHAR INTERNATIONAL TRADING INC.
354 Aguirre Ave, Phase III, BF Homes
Parañaque City.