1. Name of the medicinal Product

DOMI 10 (Domperidone Tablets 10 mg)

2. Qualitative and Quantitative Composition

Qualitative declaration

Each tablet contains Domperidone BP 10 mg

Quantitative declaration

For full list of Excipients, see section 6.1.

3. Pharmaceutical Form

Oral Tablet

Distribution category POM

White coloured, round shaped, biconvex, sugar coated tablet plain on both sides.

4. Clinical Particulars

1. Therapeutic Indications

It is indicated for the relief of the symptoms of nausea (feeling sick) and vomiting (being sick).

2. **Posology and Method of Administration**

Method of administration:

It is recommended to take oral tablets 15 to 30 minutes before a meal. If taken after meals, absorption of the drug is somewhat delayed. To take dose as prescribe and advised by physician. Symptoms usually resolve within 3-4 days of taking this drug, if it not resolve consult physician. Usually the maximum treatment duration should not exceed one week. The lowest, effective dose for short duration should be used to cure and control nausea and vomiting. Patients should try to take each dose at the scheduled time. If a scheduled dose is missed, it should be omitted and the usual dosing schedule resumed. The dose should not be doubled to make up for a missed dose.

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

Hepatic Impairment: It 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 supervised regularly

Paediatric: The efficacy in less than 12 years of age has not been established.

The breakline is only to facilitate breaking for ease of swallowing and not to divide into equal doses.

3. Contraindications

It is contra-indicated in patients with allergic (hypersensitive) to domperidone or any of the other ingredients product. It is contraindicated in the following situations: Prolactin-releasing pituitary tumor (prolactinoma). When stimulation of the gastric motility could be harmful, e.g. in patients with gastro-intestinal haemorrhage, 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 potent CYP3A4 inhibitors, QT-prolonging drugs, at the exception of Apo morphine.

4. Special warnings and precautions for use

Cardiovascular effects: It has been contraindicated and associated in patients with known existing prolongation of cardiac conduction intervals, particularly QTC, in patients with significant electrolyte disturbances, or bradycardia, or in patients with underlying cardiac diseases such as congestive heart failure due to increased risk of ventricular arrhythmia. Epidemiological studies showed that domperidone was associated with an increased risk of serious ventricular arrhythmias or sudden cardiac arrest. A higher risk was observed in patients older than 60 years, taking daily doses>30 mg, and patients concomitant use of the moderate CYP3A4 inhibitors (i.e. diltiazem, verapamil, macrolides) is not recommended. It should be used at the lowest effective dose in adults and adolescents 12 years of age and older. 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 with apomorphine: It is contra-indicated with QT prolonging drugs; apomorphine, unless the benefit of the co-administration with apomorphine outweighs the risks, and only if the recommended precautions for co-administration apomorphine.

Renal and Hepatic 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 and prolonged therapy should be reviewed regularly depending on the severity of the impairment. It is contraindicated in moderate or severe hepatic impairment.

Pregnancy: There are limited data on the use of domperidone in pregnant women. Therefore, it should not be used during pregnancy.it should only be used during pregnancy when justified by the anticipated therapeutic benefit.

Lactation: Small amounts of domperidone detected in breast milk. Therefore, should not be used during breast-feeding. It may cause unwanted side effects affecting the heart in a breast-fed baby.

5. Interaction with other medicinal products and other forms of interaction

QTc prolonging medicinal products: Disopyramide, hydroquinidine, quinidine, amiodarone, dofetilide, dronedarone, ibutilide, sotalol, haloperidol, pimozide, sertindole, citalopram, escitalopram, erythromycin, levofloxacin, moxifloxacin, spiramycin, pentamidine, halofantrine, lumefantrine, cisapride, dolasetron, prucalopride, mequitazine, mizolastine, toremifene, vandetanib, vincamine, 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): protease inhibitors, systemic azole antifungals some macrolides (erythromycin, clarithromycin, telithromycin).
Concomitant use of moderate CYP3A4 inhibitors is not recommended: diltiazem, verapamil and some macrolides.

Concomitant use of the following substances requires caution in use: Bradycardia and hypokalaemia-inducing drugs, as well as with the macrolides involved in QT-interval prolongation: azithromycin and roxithromycin, clarithromycin (as potent CYP3A4 inhibitor). Oral ketoconazole (QTc prolongation of 9.8 msec) or erythromycin (QTc prolonged by 9.9 msec) inhibition of domperidone‘s CYP3A4 mediated first pass metabolism by these drugs.

6. Pregnancy and Lactation

Pregnancy: There are limited data on the use of domperidone in pregnant women. Therefore, it should not be used during pregnancy.it should only be used during pregnancy when justified by the anticipated therapeutic benefit.

Lactation: Small amounts of domperidone detected in breast milk. Therefore, should not be used during breast-feeding. It may cause unwanted side effects affecting the heart in a breast-fed baby.

7. **Effects on ability to Drive and use Machines**
Effects on ability to drive and use machine is not known

8. Undesirable effect

The following terms and frequencies are applied: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000), Where frequency cannot be estimated from literature data, it is recorded as "Not known". The safety was evaluated base on literature in patients of dyspepsia, gastro-oesophageal reflux disorder, Irritable Bowel Syndrome, nausea and vomiting or other related conditions. Immune system disorders: Not known: anaphylactic reaction (shock). Psychiatric disorders: Uncommon; Loss of libido, anxiety. Not known: agitation, nervousness. Nervous system disorders: Uncommon; somnolence headache, not known; convulsion, extrapyramidal disorder. Eye disorders: Not known; Oculogyric crisis. Cardiac disorders; Not known; Ventricular arrhythmias, QTc prolongation, torsade de pointes. Gastrointestinal disorders: Common: dry mouth, uncommon: diarrhoea, regurgitation; appetite disorder; nausea; heartburn; constipation Skin and subcutaneous tissue disorder: Rash, pruritus, urticaria. Renal and urinary disorders: Urinary retention, pollakiuria; dysuria. Reproductive system: amenorrhoea, breast pain, menstruation irregular, lactation disorder, galactorrhoea and gynaecomastia. Musculoskeletal disorders: Muscle spasms; asthenia. Other: asthenia, conjunctivitis; stomatitis; drug intolerance. Investigations: Liver function test abnormal, Blood prolactin increased. It was used at higher dosages, for longer duration and for additional indications including diabetic gastroparesis, apart from dry mouth was considerably higher. This was particularly evident for pharmacologically predictable events related to increased prolactin. Akathisia, breast discharge, enlargement and swelling, depression, hypersensitivity, lactation disorder, and irregular menstruation also noted. Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the ADR reporting tool.

9. Overdose

Symptoms: The 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.

5. Pharmacological Properties

5.1 Pharmacodynamics Properties

Pharmacotherapeutic Group: Propulsives
ATC Code: A03F A 03

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-pyramidal side effects, but does cause a rise in prolactin levels. Its antiemetic effect may be due to a combination of peripheral (gastrokinetic) 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.

5.2 Pharmacokinetic Properties

Absorption: It is rapidly absorbed with peak plasma concentrations approx. 1 hour after oral dose. The plasma concentration and area under curve values increased proportionally with dose range 10 to 20 mg. A 2 to 3-fold accumulation of AUC was observed with repeated four times daily (every 5 hr) dosing for 4 days. The low absolute bioavailability (approx. 15%) is due to an extensive first-pass metabolism in the gut wall and liver. Although bioavailability is enhanced in normal subjects when taken after a meal, patients with gastro-intestinal complaints should take 15-30 minutes before a meal. Reduced gastric acidity impairs the absorption of domperidone.

Distribution: It is 91-93% bound to plasma proteins. A peak plasma level after 90 minutes of 21 ng/ml after two weeks' oral dose of 30 mg per day was almost the same as that of 18 ng/ml after the first dose. Based data radiolabelled drug in non-clinical have shown wide tissue delivery, but low brain concentration and small extents of drug cross the placenta.

Metabolism: Domperidone undergoes rapid and extensive hepatic metabolism by hydroxylation and N-dealkylation. In vitro data with diagnostic inhibitors revealed that CYP3A4 is a major form of cytochrome P450 involved in the N-dealkylation of domperidone, whereas CYP3A4, CYP1A2 and CYP2E1 are involved in domperidone aromatic hydroxylation.

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

Hepatic impairment: In subjects with moderate hepatic impairment (Pugh score 7 to 9, Child-Pugh rating B), the AUC and Cmax is 2.9 and 1.5-fold higher, respectively, than in healthy subjects. The unbound fraction is increased by 25%, and the terminal elimination half-life is prolonged from 15 to 23 hours. It is contraindicated in patients with moderate or severe hepatic impairment.

Renal impairment: In subjects with severe renal insufficiency (creatinine clearance <30ml/ min/1.73m2) the elimination half-life is increased from 7.4 to 20.8 hours, but plasma drug levels are lower than in healthy human. Since very little unchanged drug (approx. 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 dose, the dosing rate should be reduced to once or twice daily depending on the severity of the impairment, and the dose may need to be reduced.

Paediatric: No pharmacokinetic data are available

5.3 Preclinical Safety Data

Electrophysiological in vitro and in vivo studies indicate an overall moderate risk of domperidone to prolong the QT interval in humans. In in vitro experiments on isolated cells transfected with hERG and on isolated guinea pig myocytes, exposure ratios ranged between 26- 47-fold, based on IC50 values inhibiting currents through IKr ion channels in comparison to the free plasma concentrations in humans after administration of the maximum daily dose of 10 mg administered 3 times a day. Safety margins for prolongation of action potential duration in in vitro experiments on isolated cardiac tissues exceeded the free plasma concentrations in humans at maximum daily dose (10 mg administered 3 times a day) by 45-fold. Safety margins in in vitro pro-arrhythmic models (isolated Langendorff perfused heart) exceeded the free plasma concentrations in humans at maximum daily dose (10 mg administered 3 times a day) by 9- up to 45- fold. In in vivo models the no effect levels for QTc prolongation in dogs and induction of arrhythmias in a rabbit model sensitized for torsade de pointes exceeded the free plasma concentrations in humans at maximum daily dose (10 mg administered 3 times a day) by more than 22-fold and 435-fold, respectively. In the anesthetized guinea pig model. following slow intravenous infusions, there were no effects on QTc at total plasma concentrations of 45.4 ng/mL, which are 3-fold higher than the total plasma levels in humans at maximum daily dose (10 mg administered

3 times a day). The relevance of the latter study for humans following exposure to orally administered domperidone is uncertain.

In the presence of inhibition of the metabolism via CYP3A4 free plasma concentrations of domperidone can rise up to 3- fold.

At a high, maternally toxic dose (more than 40 times the recommended human dose), teratogenic effects were seen in the rat. No teratogenicity was observed in mice and rabbits.

6. Pharmaceutical Particulars

6.1 List of Excipients

Microcrystalline Cellulose (PH 102) BP
Sodium starch glycolate (Type-A) BP
Colloidal Anhydrous Silica (Aerosil) BP
Purified Talc BP
Magnesium Stearate BP

6.2 Incompatibilities

Not applicable

6.3 Shelf Life

36 Months

6.4 Special Precautions for Storage

Do not store above 30°C. Protect from light.

6.5 Nature and contents of container

10 tablets are packed in Alu-PVC blister pack. Such 10 blister packs are packed in a printed carton with packing insert.

6.6 Special precautions for disposal and other handling

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. Marketing Authorization Holder and Manufacturing Site Addresses

7.1 Name and Address of Marketing Authorization Holder

Lincoln Pharmaceuticals Limited
Trimul Estate, Khatraj, Taluka: Kalol,
District: Gandhinagar Gujarat, India.
Telephone no.: +91-79-41078096
Fax: +91-79-41078062
Email: hiren@lincolnpharma.com
Website: www.lincolnpharma.com

7.2 Name and Address of Manufacturing Site(s)

Lincoln Pharmaceuticals Limited
Trimul Estate, Khatraj, Taluka: Kalol,
District: Gandhinagar Gujarat, India.
Telephone no.: +91-79-41078096
Fax: +91-79-41078062
Email: hiren@lincolnpharma.com
Website: www.lincolnpharma.com

8 Marketing Authorization Number

TAN 22 HM 0387

9 Date of First <Registration> / Renewal of The <Registration>

21/09/2022

10 Date of Revision of the Text

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