SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Domperidone BP

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains:

Domperidone BP	10 mg
Excipients	q.s.
Colour : Brilliant Blue Lake	

3. PHARMACEUTICAL FORM

Tablet

Light blue coloured, smooth, round, flat, beveled edged, uncoated tablets with break line on side and plain on other.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Adults: The relief of symptoms of nausea and vomiting.

Children (above 12 years of age and weighing more than 35kg or more): The relief of symptoms of nausea and vomiting.

This medicine should not be used in children below 12 years of age or weighing less than 35 kg.

4.2 Posology and method of administration

Posology

Domperidone tablets 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 tablets 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.

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

One 10mg tablet up to three times a day with a maximum dose of 30mg per day.

Neonates, infants, children (less than 12 years of age) and adolescents weighing less than 35 kg

It is unsuitable for use in children and adolescents below 12 years of age and weighing less than 35 kg.

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.

Method of administration

For oral administration.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients.

Prolactin-releasing pituitary tumor (prolactinoma.)

Domperidone should not be used when stimulation of gastric motility could be harmful: 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 disease such as congestive heart failure.

Co-administration with QT-prolonging drugs.

Co-administration with potent CYP3A4 inhibitors (regardless of their QT prolonging effects)

4.4 Special warnings and precautions for use

Pediatric population

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.

This medicine should not be used in children below 12 years of age or weighing less than 35 kg.

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. Such patients on prolonged therapy should be reviewed regularly.

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 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. 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.
Co-administration of levodopa: Although no dosage adjustment of levodopa is deemed necessary, an increase of plasma levodopa concentration (max 30-40%) has been observed when domperidone was taken concomitantly with levodopa.
Excipients
The film-coated tablets contain lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction
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. Separate in vivo pharmacokinetic/pharmacodynamic interaction studies with oral ketoconazole or oral erythromycin in healthy subjects confirmed a marked inhibition of domperidone's CYP3A4 mediated first pass metabolism by these drugs.
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 Cmax and the 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) and erythromycin monotherapy (500mg three times daily) led to increases in QTc of 3.8 and 4.9 msec, respectively, over the observation period.

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, 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 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 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 contra-indicated as it is a potent CYP3A4 inhibitor).

Levodopa: Increase of plasma levels of levodopa (max 30-40%).

The above list of substances is representative and not exhaustive.

Opioids may antagonise the effects of domperidone on gastric emptying.

4.6 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, 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 woman. Caution should be exercised in case of QTc prolongation risk factors in breast-fed infants.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Immune System Disorder: Not known: Allergic reaction, including anaphylaxis, anaphylactic shock, anaphylactic reaction.

Endocrine disorder: Rare: increased prolactin levels

Psychiatric system 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, sudden cardiac death.

Renal and urinary disorders: Not known: urinary retention.

Gastro-intestinal disorders: Common: dry mouth; Uncommon: diarrhoea

Skin and subcutaneous tissue disorders: Uncommon: pruritus, rash; Not known: Urticarial, Angioedema

General disorders and administration site conditions: Uncommon: Asthenia

Reproductive system and breast disorders: Uncommon: breast pain, galactorrhoea**,** breast tenderness; Not known: gynaecomastia, amenorrhoea.

Investigations: Unknown: liver function test abnormal, blood prolactin increased.

Paediatric population

Extrapyramidal disorders occur primarily in neonates and infants.

Other central nervous system-related effects of convulsion, agitation and somnolence are also very rare and primarily reported in infants and children.

Reporting of suspected adverse reactions

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 email ID: Safety.cadila.global@cadilapharma.co.in

4.9 Overdose

Symptoms

Overdose has been reported primarily in infants and children. Symptoms of overdosage may include agitation, altered consciousness, convulsion, 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 pf QT prolongation. Close medical supervision and supportive therapy is recommended. Anticholinergic, Anti-Parkinson drugs may be helpful in controlling extrapyramidal reactions.

5. PHARMACOLOGICAL PROPERTIES

5.1 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 (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.

Studies in man have shown oral domperidone to increase lower oesophageal pressure, improve antroduodenal motility and accelerate gastric emptying. There is no effect on gastric secretion.

In accordance with ICH—E14 guidelines, a thorough QT study was performed. This study included a placebo, an active comparator and a positive control and was conducted in healthy subjects with up to 80 mg per day 10 or 20 mg administered 4 times a day of domperidone. This study found a maximal difference of QTc between domperidone and placebo in LS-means in the change from baseline of 3.4 msec for 20 mg domperidone administered 4 times a day on Day 4. The 2-sided 90 % CI (1.0 to 5.9 msec) did not exceed 10 msec. No clinically relevant QTc effects were observed in this study when domperidone was administered at up to 80 mg/day (i.e., more than twice the maximum recommended dosing).

However, two previous drug-drug interaction studies showed some evidence of QTc prolongation when domperidone was administered as monotherapy (10 mg 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 7.5 msec (95 % CI: 0.6 to 14.4), respectively.

5.2 Pharmacokinetic properties

Absorption

Domperidone is rapidly absorbed after oral administration with peak plasma concentrations at approximately 1 hr after dosing. The Cmax and AUC values of domperidone increased proportionally with dose in the 10 mg to 20 mg 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.

Although domperidone's bioavailability is enhanced in normal subjects when taken after a meal, patients with gastro-intestinal complaints should take domperidone 15-30 minutes before a meal. 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; 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, but low brain concentration. Small amounts of drug cross the placenta in rats.

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 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). 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.

<u>Hepatic impairment</u>

In subjects with moderate hepatic impairment (Pugh score 7 to 9, Child-Pugh rating B), the AUC and Cmax of domperidone 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. Subjects with mild hepatic impairment have a somewhat lower systemic exposure than healthy subjects based on Cmax and AUC, with no change in protein binding or terminal half-life. Subjects with severe hepatic impairment were not studied. Domperidone is contraindicated in patients with moderate or severe hepatic impairment.

<u>Renal impairment</u>

In subjects with severe renal insufficiency (creatinine clearance<30 ml/min/1.73m2) the elimination half-life of domperidone was increased from 7.4 to 20.8 hours, but plasma drug levels were lower than in healthy volunteers.

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 the severity of the impairment, and the dose may need to be reduced.

Paediatric population
No pharmacokinetic data are available in the Pharmacokinetic properties.

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 (10mg administered 3 times a day) by 45-fold. Safety margins in in-vitro proarrhythmic 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

Maize starch , Lactose , Sodium benzoate, Starch for Paste, Purified water, Magnesium stearate, Colour Brilliant blue Lake

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

48 months.

6.4 Special precautions for storage

Store between 15°C-30°C

Protect from light.

6.5 Nature and contents of container

Blister of 50 tablets, such two blisters are packed in a carton.

6.6 Special precautions for disposal and other handling

No special requirements.

7. MARKETING AUTHORISATION HOLDER

CADILA PHARMACEUTICALS LTD.
1389, Trasad Road, Dholka - 382 225,
District: Ahmedabad,
Gujarat, India.

8. MARKETING AUTHORISATION NUMBER(S)

04451/06921/REN/2018

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of Authorization of Renewal : 29/04/2019

10. DATE OF REVISION OF THE TEXT

July 2023