PROPOSED CLEAN PROFESSIONAL INFORMATION

DOMPERIDONE CIPLA

SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

DOMPERIDONE CIPLA 10 mg orally disintegrating tablets.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 10 mg domperidone.

Contains sugar: Mannitol 187 mg per tablet.

Contains sweetener: Aspartame 7,5 mg per tablet.

For the full list of excipients, **see Section 6.1**.

3. PHARMACEUTICAL FORM

DOMPERIDONE CIPLA are orally disintegrating tablets.

DOMPERIDONE CIPLA are white to off-white, round, flat, bevelled edged tablets, plain on both sides, having peppermint odour.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

DOMPERIDONE CIPLA is indicated in adults and children over 35 kg for:

- Short-term management of delayed gastric emptying of functional origin with gastro-oesophageal reflux and /or dyspepsia.
- Control of nausea and vomiting of central or local origin.
- As an anti-emetic on patients receiving cytostatic and radiation therapy.

- Facilitation of radiological examination of the upper gastro-intestinal tract.

4.2 Posology and method of administration

Posology

Adults and adolescents ≥ 12 years of age and weighing ≥ 35 kg, and children weighing ≥ 35 kg

The dose of DOMPERIDONE CIPLA should be the lowest effective dose for the individual situation (typically 30 mg/day) with a maximum daily oral dose of 40 mg.

Usually, the maximum treatment duration should not exceed one week for the treatment of acute nausea and vomiting. If nausea and vomiting persist for longer than one week, patients should consult their doctors. For other indications, the initial duration of treatment is up to four weeks. If treatment exceeds four weeks, patients should be re-evaluated and the need for continued treatment reassessed.

Formulation (Domperidone per unit)	Dosage	Maximum dose per day
10 mg/tablet	1 tablet 3 to 4 times per day	40 mg (4 x 10 mg tablet)

Special populations

Renal impairment

Since the elimination half-life of domperidone is prolonged in severe renal impairment (serum creatinine > 6 mg/100 mL, i.e., > 0,6 mmol/L), the dosing frequency of DOMPERIDONE CIPLA should be reduced to once or twice daily, depending on the severity of the impairment, and the dose may need to be reduced. Patients with severe renal impairment should be reviewed regularly.

Hepatic impairment

DOMPERIDONE CIPLA is contraindicated for patients with moderate (Child-Pugh 7 to 9) or severe (Child-Pugh > 9) hepatic impairment (see **section 4.3**). Dose adjustment is not required for patients with mild (Child-Pugh 5 to 6) hepatic impairment (see **section 5.2**).

Paediatric population

DOMPERIDONE CIPLA tablets are unsuitable for use in children weighing less than 35 kg**.**

Method of administration

Domperidone 10 mg tablets are for oral administration.

It is recommended to take oral DOMPERIDONE CIPLA 15 – 30 minutes before meals. If taken after meals, absorption of the medicine is somewhat delayed.

4.3 Contraindications

DOMPERIDONE CIPLA is contra-indicated in the following situations:

- Known hypersensitivity to domperidone or any of the excipients of DOMPERIDONE CIPLA (see **section 6.1**).
- Prolactin-releasing pituitary tumour (prolactinoma).
- When stimulation of the gastric motility could be harmful e.g., in patients with gastro-intestinal haemorrhage, mechanical obstruction or perforation.
- Co-administration with other potent CYP3A4 (regardless of their QT prolonging effects) (see **section 4.5**).
- Co-administration with medicines known to induce Torsades de Pointes and /or prolong the QT interval e.g., cisapride, class 1A antidysrythmics.
- Hypokalaemia, hypomagnesaemia.
- Bradycardia or heart block.
- Pre-existing cardiac disease.
- Known congenital long QT interval or family history thereof.

- In patients with moderate or severe hepatic impairment (see **section 5.2**).

4.4 Special warnings and precautions for use

Cardiac effects

Domperidone, as in DOMPERIDONE CIPLA, has been associated with prolongation of the QT interval on the electrocardiogram. During post marketing surveillance, there have been 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 (see **section 4.8**).

Epidemiological studies have shown that domperidone, as in DOMPERIDONE CIPLA, is associated with an increased risk of serious ventricular dysrhythmias or sudden cardiac death (see **section 4.8**). These studies suggested that this increased risk may be higher in patients older than 60 years of age, patients taking oral doses greater than 30 mg per day, and patients concurrently taking QT-prolonging medicines or CYP3A4 inhibitors. Therefore, DOMPERIDONE CIPLA should be used with caution in older patients.

DOMPERIDONE CIPLA should be used at the lowest effective dose in adults and adolescents aged 12 years and older.

DOMPERIDONE CIPLA 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 dysrhythmia (see **section 4.3**). Electrolyte disturbances (hypokalaemia, hyperkalaemia, hypomagnesaemia) or bradycardia are known to be conditions increasing the prodysrhythmic risk.

Treatment with DOMPERIDONE CIPLA should be stopped if signs or symptoms occur that may be associated with cardiac dysrhythmia, and the patients should consult their doctors. Patients should be advised to promptly report any cardiac symptoms.

Medicine interaction potential

The main metabolic pathway of domperidone is through CYP3A4. In vitro and human data show that the concomitant use of medicines that significantly inhibit this enzyme may result in increased plasma levels of domperidone. Co-administration of DOMPERIDONE CIPLA with potent CYP3A4 inhibitors regardless of their potential to cause QT interval prolongation is contraindicated (see **section 4.3 and section 4.5**).

Domperidone base

Antacids and anti-secretory medicines should not be taken simultaneously with DOMPERIDONE CIPLA as they lower the oral bioavailability of domperidone. When used concomitantly, DOMPERIDONE CIPLA should be taken before meals and antacids or anti-secretory medicines after meals.

Use with apomorphine

Domperidone is contraindicated with QT prolonging medicines including apomorphine.

Renal impairment

The elimination half-life of domperidone is prolonged in severe renal impairment. For repeated administration, the dosing frequency of DOMPERIDONE CIPLA should be reduced to once or twice daily depending on the severity of the impairment. The dose may also need to be reduced.

Excipients

DOMPERIDONE CIPLA contains mannitol and may have laxative effect.

DOMPERIDONE CIPLA contains aspartame. Aspartame is a source of phenylalanine. It may be harmful if you have phenylketonuria (PKU), a rare genetic disorder in which phenylalanine builds us because the body cannot remove it properly.

4.5 interaction with other medicines and other forms of interaction

The main metabolic pathway of Domperidone is through CYP3A4. *In vitro* and human data show that concomitant use of medicines that significantly inhibit this enzyme may result in increased plasma levels of domperidone. Co-administration of DOMPERIDONE CIPLA with potent CYP3A4 inhibitors, whether or not they have been shown to cause QT interval prolongation is contraindicated (see **section 4.3**).

Concomitant use of DOMPERIDONE CIPLA with the following medicines is contraindicated:

QTc prolonging medicines:

- anti-dysrhythmics class IA (e.g., disopyramide, hydroquinidine, quinidine)
- anti-dysrhythmics 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 medicines (e.g., pentamidine)
- certain antimalarial medicines (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) (see **section 4.3**).
- apomorphine.

Potent CYP3A4 inhibitors (regardless of their QT prolonging effects), i.e.:

- protease inhibitors
- systemic azole antifungals
- some macrolides (erythromycin, clarithromycin, telithromycin) (see **section 4.3**).

Concomitant use of DOMPERIDONE CIPLA with the following medicines is not recommended:

Moderate CYP3A4 inhibitors i.e.:

- diltiazem, verapamil and some macrolides. (see **section 4.3**)

Concomitant use of DOMPERIDONE CIPLA with the following medicines is not requires caution in use:

Bradycardia and hypokalaemia-inducing medicines, as well as with the following macrolides involved in QTinterval prolongation:

- azithromycin and roxithromycin (clarithromycin is contra-indicated as it is a potent CYP3A4 inhibitor).

The above list of medicines is representative and not exhaustive.

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 medicines.

With the combination of oral domperidone 10mg four times daily and ketoconazole 200 mg 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 500 mg 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 10 mg 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.

Concomitant administration of anti-cholinergic medicines (e.g., dextromethorphan, diphenhydramine) may antagonise the anti-dyspeptic effects of DOMPERIDONE CIPLA.
Since DOMPERIDONE CIPLA has gastro-kinetic effects, it could influence the absorption of concomitant orally administered medicines, particularly those with sustained release or enteric coated formulations. However, in patients already stabilised on digoxin or paracetamol, concomitant administration of domperidone did not influence the blood levels of these medicines.

DOMPERIDONE CIPLA may also be given 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 supresses without counteracting their central properties.

Reduced gastric acidity impairs the absorption of DOMPERIDONE CIPLA. Oral bioavailability is decreased by prior concomitant administration of cimetidine and sodium bicarbonate.
As DOMPERIDONE CIPLA interferes with serum prolactin levels, it may interfere with other hypoprolactinaemic medicines and with some diagnostic tests.

4.6 Fertility, pregnancy and lactation

Pregnancy

The safety of use during pregnancy has not been established.
A study in rats has shown reproductive toxicity at a high, maternally toxic dose. The potential risk for humans is unknown.

Breastfeeding

The safety of use during lactation has not been established.

Domperidone is excreted in human breast milk. 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, therefore DOMPERIDONE CIPLA is not recommended in breastfeeding. Caution should be exercised in case of QTc prolongation risk factor in breastfed infants.

4.7 Effects on ability to drive and use machines

Dizziness and somnolence have been observed following use of DOMPERIDONE CIPLA (see **section 4.8**). Therefore, patients should be advised not to drive or use machines or engage in other activities requiring mental alertness and coordination until they have established how DOMPERIDONE CIPLA affects them.

4.8 Undesirable effects

The following adverse effects have been classified as either being frequent, less frequent, or frequency unknown.

Immune system disorders

Less frequent:	Hypersensitivity.
Frequency unknown:	Anaphylactic reaction (Including anaphylactic shock).

Psychiatric disorders

Frequent:	Depression.
Less frequent:	Libido decreased, loss of libido, anxiety.
Frequency unknown:	Agitation, nervousness.

Nervous system disorders

Frequent: Headache, somnolence, akathisia.

Frequency unknown: Convulsion, extrapyramidal disorder, dizziness.

Eye disorders

Frequency unknown: Oculogyric crisis.

Cardiac disorders

Frequency unknown: Serious ventricular dysrhythmias, sudden cardiac death, QTc prolongation, Torsade de Pointes.

Gastrointestinal disorders

Frequent: Dry mouth, diarrhoea.

Skin and subcutaneous tissue disorders

Frequent: Rash, pruritus.

Less frequent: Urticaria.

Frequency unknown: Angioedema.

Renal and urinary disorders

Frequency unknown: Urinary retention.

Reproductive system and breast disorders

Frequent: Breast enlargement/ gynaecomastia, amenorrhoea, irregular menstruation, breast tenderness, lactation disorder, galactorrhoea, breast pain.

Less frequent: Breast discharge, breast swelling.

General disorders and administration site conditions

Frequent: Asthenia.

Investigations

Frequency unknown: Liver function test abnormal, blood prolactin increased.

In studies where domperidone was used at higher doses, for longer duration and for additional indications including diabetic gastroparesis, the frequency of adverse events (apart from dry mouth) was considerably higher. This was particularly evident for pharmacologically predictable events related to increased prolactin.

Paediatric population

Extrapyramidal disorder occurs primarily in neonates and infants, and exceptional in adults. Other central nervous system-related effects of convulsion and agitation and somnolence are also reported primarily in infants and children.

Reporting of suspected adverse reactions:

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions to SAHPRA via the "**6.04 Adverse Drug Reaction Reporting Form**", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8 and to Cipla Medpro (Pty) Ltd. via email: drugsafetysa@cipla.com

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.

Management of overdose:

There is no specific antidote to domperidone, but in the event of overdose, standard symptomatic treatment should be given immediately. 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 and anti-parkinson medicines may be helpful in controlling the extrapyramidal reactions.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacological classification

A 5.7.2 Anti-emetics and anti-vertigo preparations.

Mechanism of action

Domperidone is a dopamine-receptor blocking medicine. Its action on the dopamine-receptors in the chemo-emetic trigger zone produces an anti-emetic effect. Domperidone does not cross the blood-brain barrier to any appreciable degree and so exerts relatively little effect on cerebral dopaminergic receptors.

Domperidone has been shown to increase antroduodenal motility and gastric emptying. There is no effect on gastric secretion.

Effect on QT/QTc interval and cardiac electrophysiology

A QT study was performed in healthy subjects using recommended and supra-therapeutic doses (10 and 20 mg administered four times a day). The QT prolongation observed in this study when domperidone was administered according to the recommended dosing regimen is not clinically relevant.

This lack of clinical relevance is corroborated by pharmacokinetics and QTc interval data from two older studies which involved a 5-day treatment of 20 mg and 40 mg domperidone administered 4 times a day. In both studies, no difference between QTc was observed. It was therefore concluded that domperidone administration of 80 and 160 mg daily doses had no clinically significant effect on QTc in healthy subjects.

5.2 Pharmacokinetics properties

Absorption

In the fasted state domperidone is rapidly absorbed after oral administration, with peak plasma concentration occurring at approximately 60 minutes after dosing.

The absolute bioavailability of oral domperidone (approximately 15 %) is low due to first-pass hepatic and intestinal metabolism.

Distribution

Domperidone is 91 to 93 % bound to plasma proteins. The plasma half-life after a single oral dose is 7 to 9 hours in healthy subjects but is prolonged in patients with severe renal insufficiency.

Biotransformation

Domperidone undergoes a 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.

Elimination

Urinary and faecal excretion amount to 31 % and 66 % of the oral dose, respectively. The proportion of medicine excreted unchanged is small (approximately 1 % of urinary and 10 % of faecal excretion).

Special populations

Hepatic impairment

In subjects with moderate hepatic impairment (Pugh score 7 to 9, child-Pugh rating B), the AUC and C_{max} 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 systematic exposure than healthy subjects based on C_{max} and AUC, with no change in protein binding or terminal half-life. Subjects with severe hepatic impairment were not studied (see **section 4.3**).

Renal impairment

In patients with severe renal insufficiency (serum creatinine more than 6 mg/100 mL, i.e., more than 0,6 mmol/L) the half-life of domperidone was increased from 7,4 to 20,8 hours, but plasma drug levels were lower than in subjects with normal renal function. Very little unchanged medicine (approximately 1 %) is excreted via the kidneys. (see **section 4.2**).

Paediatric population

Based on limited pharmacokinetic data, domperidone plasma concentrations in preterm neonates were consistent with those reported in adults.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

- Aspartame

- Colloidal silicone dioxide
- Crospovidone
- Magnesium stearate
- Mannitol
- Microcrystalline cellulose
- Peppermint flavour.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months.

6.4 Special precautions for storage

This medicine does not require any special storage conditions.

Store in the original packaging.

6.5 Nature and contents of container

DOMPERIDONE CIPLA 10 mg orally disintegrating tablets are packed in an Alu-Alu blister pack of 10 tablets each. Such 10 blister strips are packed into one carton together with one leaflet.

6.6 Special precautions for disposal and other handling

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

CIPLA MEDPRO (PTY) LTD.

Building 9, Parc du cap

Mispel street

Belville

7350

Customer care: 080 222 6662

8. REGISTRATION NUMBER

DOMPERIDONE CIPLA: 52/5.7.2/0563

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

07 July 2022

10. DATE OF REVISION OF THE TEXT

Not Applicable.