Professional Information for Medicines for Human Use

SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

VOMIDON TABLETS

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains domperidone 10 mg.

Contains sugar: 70,00 mg lactose monohydrate per tablet

Preservatives: Sodium benzoate 0,19 % *m/m*

For full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Tablet.

Light blue coloured, round, flat, bevelled edged, uncoated tablets, with a breakline on one side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

VOMIDON TABLETS are indicated in adults and adolescents over 12 years of age and weighing over 35 kg for:

- Short-term management (not exceeding 7 days) of delayed gastric emptying of function origin with gastro-oesophageal reflux and/or dyspepsia.
- Short-term management (not exceeding 7 days) for control of nausea and vomiting of central or local origin.
- As an anti-emetic in patients receiving cytostatic and radiation therapy for up to 4 weeks.

- Facilitation of radiological examination of the upper gastro-intestinal tract administered at the time before the examination as directed by the radiologist.

4.2 Posology and method of administration

Posology

Adults and adolescents ≥ 12 years of age and > 35 kg

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

The dose of **VOMIDON TABLETS** film coated tablets should be lowest effective dose for the individual situation (typically 30 mg/day) with a maximum daily oral dose of 30 mg.

If the conditions mentioned under indications are not resolved within the time frames indicated, patients should be re-evaluated and the need for continued treatment be assessed.

Formulation (domperidone per unit)	**Dosage**	**Maximum dose per day**
Tablet (10 mg/tablet)	1 tablet three to four times a day	30 mg (3 x 10 mg tablet

Paediatrics

The efficacy of domperidone was not demonstrated in children less than or equal to 12 years of age (see section 5.1).

The safety of VOMIDON TABLET in adolescents weighing ≤ 35 kg has not been established.

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 **VOMIDON TABLETS** should be reduced to once or twice daily, depending on the severity of the impairment. Patients with severe renal impairment should be reviewed regularly.

Hepatic impairment

VOMIDON TABLETS is contraindicated for patients with moderate (Child-Pugh 7 to 9) or severe (Child-Pugh > 9) hepatic impairment (see CONTRA-INDICATIONS). Dose adjustment is not required for patients with mild (Child-Pugh 5 to 6) hepatic impairment (see **Section 5.2**)

Method of administration

For oral use.

4.3 Contraindications

VOMIDON TABLETS are contra-indicated in the following situations:

- Known hypersensitivity to domperidone or to any of the excipients of **VOMIDON TABLETS** listed in **Section 6.1**.
- Prolactin-releasing pituitary tumour (prolactinoma).
- Co-administration with other potent CYP3A4 inhibitors which have been shown to cause QT interval prolongation such as fluconazole, itraconazole, ketoconazole, voriconazole, posaconazole, clarithromycin, erythromycin, azithromycin, roxithromycin, amiodarone, telithromycin, amprenavir, atazanavir, fosamprenavir, indinavir, nelfinavir, ritonavir, saquinavir and quinolones (see **Sections 4.4** and **4.5**).

- Co-administration with medicines known to induce Torsades de Pointes and/or prolong the QT interval e.g. cisapride, class 1A antidysrhythmics.
- Hypokalaemia, hypomagnesaemia.
- Bradycardia or heart block.
- Pre-existing cardiac disease.
- Known congenital long QT interval or family history thereof.
- In certain heart conditions (including heart failure, previous heart attack, angina and heart dysrhythmia disorders).
- Whenever stimulation of gastric motility might be dangerous, e.g. in the presence of gastric-intestinal haemorrhage, mechanical obstruction or perforation.
- In patients with moderate (child pugh score 7 – 9) or severe (child pugh score > 9) hepatic impairment (see **Section 5.2**).

4.4 Special warnings and precautions for use

VOMIDON TABLETS are unsuitable for use in children weighing less than 35 kg.

Cardiac effects

Epidemiological studies have shown that **VOMIDON TABLETS** 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 or in patients taking oral doses greater than 30 mg per day.

Therefore, **VOMIDON TABLETS** should be used with caution in older patients.

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 **VOMIDON TABLETS** with potent CYP3A4 inhibitors which have been shown to cause QT interval prolongation is contraindicated (see **Section 4.3**).

Caution should be exercised when **VOMIDON TABLETS** is co-administered with potent CYP3A4 inhibitors which have been shown to cause QT interval prolongation and patients should be monitored closely for signs and symptoms of adverse reactions (see **Section 4.8**).

Caution should be exercised when **VOMIDON TABLETS** is co- administered with medicines which have shown to cause QT interval prolongation and patients should be monitored closely for signs or symptoms of cardiovascular adverse reactions (see **Section 4.8**). Examples include:

- Anti-arrhythmias class IA (e.g. disopyramide, quinidine).
- Anti- arrhythmias 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. levofloxacin, moxifloxacin and quinolones).
- Certain antifungal medicines (e.g. pentamidine).
- Certain antimalarial medicines (e.g. halofantrine).
- Certain gastro-intestinal medicines (e.g. dolasetron).
- Certain medicines in cancer (e.g. toremifene, vandetanib).
- Certain other medicines (e.g. bepridil, methadone).

The above list is representative and not exhaustive.

Domperidone base

Antacids and anti-secretory medicines should not be taken simultaneously with oral formulations of **VOMIDON TABLETS** as they lower the oral bioavailability of **VOMIDON**

TABLETS. When used concomitantly, **VOMIDON TABLETS** should be taken before meals and antacids or anti-secretory medicines after meals.

Excipients

VOMIDON TABLETS contain lactose.

Patients with rare hereditary conditions of galactose intolerance e.g. galactosaemia, Lapp lactase deficiency, glucose-glucose malabsorption or fructose intolerance should not take **VOMIDON TABLETS**.

VOMIDON TABLETS contain lactose, which may have an effect on the glycaemic control of patients with diabetes mellitus.

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 the concomitant use of medicines that significantly inhibit this enzyme may result in increased plasma levels of domperidone.

When **VOMIDON TABLETS** was co-administered with potent CYP3A4 inhibitors which have been shown to cause QT interval prolongation, clinically relevant changes in QT intervals were observed. Therefore, co-administration of **VOMIDON TABLETS** with certain medicines is contraindicated (see **Section 4.3**).

Caution should be exercised when **VOMIDON TABLETS** is co-administered with potent CYP3A4 inhibitors which have not been shown to cause QT interval prolongation or medicines which have been shown to cause QT interval prolongation (see **Section 4.4**).

Concomitant administration of anti-cholinergic medicines (e.g. dextromethorphan, diphenhydramine) may antagonise the antidyspeptic effect of **VOMIDON TABLETS**.

Since **VOMIDON TABLETS** 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 **VOMIDON TABLETS** did not influence the blood levels of these medicines.

VOMIDON TABLETS 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 are suppressed without counteracting their central properties.

Reduced gastric acidity impairs the absorption of **VOMIDON TABLETS**. Oral bioavailability is decreased by prior Concomitant administration of cimetidine or sodium bicarbonate.

As **VOMIDON TABLETS** interferes with serum prolactin levels, it may interfere with other hypoprolactinaemic agents and with some diagnostic tests.

4.6 Fertility, pregnancy and lactation

The safety of use during pregnancy and lactation has not been established.

Domperidone is excreted in human breast milk therefore breast feeding is not recommended for mothers who are taking **VOMIDON TABLETS**.

4.7 Effects on ability to drive and use machines

Dizziness and somnolence have been observed following use of **VOMIDON TABLETS** (see **Section 4.8**). Therefore, patients should be advised not to drive or use machinery or engage in

other activities requiring mental alertness and coordination until they have established how **VOMIDON TABLETS** affects them.

4.8 Undesirable effects

System Organ Class	Frequent	Less frequent	Frequency Unknown
Psychiatric disorders	Depression, anxiety, decreased libido/loss of libido		Agitation, nervousness
Nervous system disorders	Headache, somnolence, akathisia		Dizziness, extrapyramidal disorder, convulsion
Gastrointestinal disorders	Diarrhoea		
Immune system disorders		Hypersensitivity	Anaphylactic reaction (including anaphylactic shock)
Skin and subcutaneous tissue disorders	Rash, pruritus	Urticaria	Angioedema
Reproductive system and breast disorders	Breast enlargement/gynaecomastia, breast tenderness, galactorrhoea, amenorrhoea, breast pain, irregular menstruation, lactation disorder	Breast discharge, breast swelling	
General disorders and administration site conditions	Asthenia		Dry mouth has also been reported
Cardiac disorders			Sudden cardiac death, serious ventricular dysrhythmias (see **Section 4.4**).

Renal and Urinary Disorders			Urinary retention
Investigations			Abnormal liver function test, blood prolactin increased

Paediatric population

Although not approved for paediatric use, inappropriate/inadvertent ingestion in children resulted in extrapyramidal disorders and central nervous system related effects of convulsions, agitation and somnolence (see **Section 4.9**).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continuing monitoring of the benefit/risk balance of the medicine. Health care providers 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

4.9 Overdose

Signs and Symptoms

Overdose has been reported primarily in infants and children. Symptoms of overdosage may include agitation, altered consciousness, convulsions, disorientation, somnolence and extrapyramidal reactions.

Treatment

There is no specific antidote to domperidone. Symptomatic and supportive therapy is indicated. Close medical supervision and supportive therapy is recommended. Anticholinergic or anti-Parkinson medicines may be helpful in controlling the extrapyramidal reactions.

It is advisable to contact a poison control centre without delay to obtain the latest recommendations for the management of an overdose.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacological classification: A 5.7.2 Anti-emetics & antivertigo preparations

Pharmacotherapeutic group: Propulsives, ATC code: A03F A 03

Domperidone is a dopamine-receptor blocking agent. 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 the duration of antral and duodenal contractions to increase gastric emptying. Domperidone does not alter gastric secretions and has no effect on intracranial pressure or on the cardiovascular system.

Effect on QT/QTc interval and cardiac electrophysiology

In accordance with ICH-E14 guidelines, a thorough QT study was performed in healthy subjects. This study included a placebo, active comparator and positive control and was conducted using recommended and supra-therapeutic doses (10 and 20 mg administered 4 times a day). This study included a placebo, active comparator and positive control and was conducted using recommended and supra-therapeutic doses (10 and 20 mg administered 4 times a day). 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, and the 2-sided 90 % CI (1,0 5,9 msec) did not exceed 10 msec. 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. ECGs were recorded prior to the study, on Day 5 at 1 hour (approximately at t_{max}) after the morning dose, and 3 days later. In both studies, no difference between QTc after active treatment and placebo was observed. It was therefore conducted that domperidone administration of 80 and 160 mg daily doses had no clinically significant effect on QTc in healthy subjects.

5.2 Pharmacokinetic properties

Absorption

Domperidone is rapidly absorbed with peak plasma concentrations at approximately 1 hour after oral administration.

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

Distribution

Domperidone is 91-93 % bound to plasma proteins. 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.

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 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), in 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 (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 are lower than in subjects with normal renal function.

Very little unchanged medicine (approximately 1 %) is excreted via the kidneys (see **Section 4.2**).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

- Colour brilliant blue lake Cl No.: 42090
- Gelatine

- Lactose
- Maize starch
- Magnesium stearate
- Purified water
- Sodium benzoate

6.2 Incompatibilities

Not applicable

6.3 Shelf life

24 months

6.4 Special precautions for storage

Store at or below 25 °C. Protect from light.

6.5 Nature and contents of container

10 tablets in aluminium strip pack and 1 of these in one carton (i.e. 10 tablets per pack) or 10 of these strips in one carton (i.e. 100 tablets per pack). And 100 tablets in a securitainer.

6.6 Special precautions for disposal and other handling

Not applicable.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Ranbaxy Pharmaceuticals (Pty) Ltd

14 Lautre Road

Stormill Ext. 1

Roodepoort

1724

South Africa

8. REGISTRATION NUMBER(S)

31/5.7.2/0330

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

18 August 2000

10. DATE OF REVISON OF THE TEXT

31 October 2022