PROFESSIONAL INFORMATION

SCHEDULING STATUS S4

1. NAME OF THE MEDICINE

MOTIVOM 10 ODT orodispersible tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each orodispersible tablet contains 10 mg of domperidone.

Excipients with known effect:

Contains sugar alcohol: Each orodispersible tablet contains 187 mg mannitol.

Contains sweetener: Each orodispersible tablet contains 7,5 mg aspartame.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Orodispersible tablets.

White to off-white, round, flat, bevelled edged tablets, plain on both sides, with a peppermint odour.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

MOTIVOM 10 ODT is indicated in adults and children over 35 kg for:

- Short-term management of delayed gastric emptying of functional origin with gastroesophageal reflux and/or dyspepsia.

- Control of nausea and vomiting of central or local origin.
- As an anti-emetic in patients receiving cytostatic and radiation therapy.
- Facilitation of radiological examination of the upper gastrointestinal 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 MOTIVOM 10 ODT 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**
Orodispersible tablet (10 mg per tablet)	1 tablet three to four times per day	40 mg (4 x 10 mg tablet)

Special populations

Renal impairment

Since the elimination hatf-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 MOTIVOM 10 ODT 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

Hepatic impairment

MOTIVOM 10 ODT 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

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

Method of administration

MOTIVOM 10 ODT is for oral administration. The orodispersible tablet dissolves rapidly in the mouth with the help of the saliva, and can be taken with or without water. When taken without water, the MOTIVOM 10 ODT tablet should be placed on the tongue and dissolved in the mouth before swallowing. If convenient, a glass of water can be taken afterwards.
It is recommended to take MOTIVOM 10 ODT, 15 – 30 minutes before meals. If taken after meals, absorption of the medicine is somewhat delayed.

4.3 Contraindications

MOTIVOM 10 ODT is contraindicated in the following situations:

- Known hypersensitivity to domperidone or any of the excipients in MOTIVOM 10 ODT (see section 6.1).
- Prolactin-releasing pituitary tumour (prolactinoma).
- When stimulation of the gastric motility could be harmful e.g., in patients with gastrointestinal haemorrhage, mechanical obstruction or perforation.
- In patients with moderate or severe hepatic impairment (see section 5.2).
- In patients who have known existing prolongation of cardiac conduction intervals, particularly QTc or family history thereof, patients with significant electrolyte

disturbances or underlying cardiac diseases, such as congestive heart failure (see section 4.4).

- Hypokalaemia, hypomagnesaemia, hyperkalaemia.
- Bradycardia or heart block.
- Co-administration with medicines known to induce torsades de pointes and/or with QT-prolonging medicines (see sections 4.4 and 4.5).
- Co-administration with potent CYP3A4 inhibitors (regardless of their QT prolonging effects) (see section 4.5).

4.4 Special warnings and precautions for use

Cardiovascular effects

Domperidone 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, as in MOTIVOM 10 ODT. These reports included patients with confounding risk factors, electrolyte abnormalities and concomitant treatment which may have been contributing factors (see section 4.3 and 4.8).

Epidemiological studies showed that domperidone was associated with an increased risk of serious ventricular dysrhythmias or sudden cardiac death (see section 4.8). A higher risk was observed in patients older than 60 years of age, patients taking daily doses greater than 30 mg, and patients concurrently taking QT-prolonging medicines or CYP3A4 inhibitors. Therefore, MOTIVOM 10 ODT should be used with caution in older patients.

MOTIVOM 10 ODT should be used at the lowest effective dose in adults and adolescents 12 years of age and older (see section 4.2).

MOTIVOM 10 ODT 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 MOTIVOM 10 ODT should be stopped if signs or symptoms occur that may be associated with cardiac dysrhythmia, and the patient should consult their medical practitioner.

Patients should be advised to promptly report any cardiac symptoms.

Use with apomorphine

MOTIVOM 10 ODT 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 MOTIVOM 10 ODT should be reduced to once or twice daily depending on the severity of the impairment. The dose may also need to be reduced.

Children

MOTIVOM 10 ODT is unsuitable for use in children weighing less than 35 kg.

MOTIVOM 10 ODT contains aspartame

(PKU), a rare genetic disorder in which phenylalanine builds up because the body cannot remove it properly.

4.5 Interaction with other medicines and other forms of interaction

The main metabolic pathway of MOTIVOM 10 ODT is through CYP3A4. *In vitro* data suggest that the concomitant use of medicines 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 medicines:

- antidysrhythmics class IA (e.g., disopyramide, hydroquinidine, quinidine)
- antidysrhythmics 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 medicines (e.g., pentamidine)
- certain antimalarial medicines (in particular halofantrine, lumefantrine)
- certain gastrointestinal 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 (see section 4.4).

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 the following substances is not recommended:

Moderate CYP3A4 inhibitors i.e. diltiazem, verapamil and some macrolides (see section 4.3).

Concomitant use of the following substances requires caution in use:

Caution with bradycardia and hypokalaemia-inducing medicines, as well as with the following macrolides involved in QT-interval prolongation: azithromycin and roxithromycin (clarithromycin is contraindicated as it is a potent CYP3A4 inhibitor).

The above list of substances 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 10 mg 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 10 mg 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 (area under the curve) 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 (200 mg twice daily) led to increases in QTc of 3,8 and 4,9 msec, respectively, over the observation period.

Antacids and antisecretory medicines

Antacids and antisecretory medicines should not be taken simultaneously with oral formulations of MOTIVOM 10 ODT as they lower the oral bioavailability of domperidone. When used concomitantly, MOTIVOM 10 ODT should be taken before meals and antacids or anti-secretory medicines after meals.

Reduced gastric acidity impairs the absorption of domperidone. Oral bioavailability is decreased by prior concomitant administration of cimetidine and sodium bicarbonate.

Anticholinergic medicines

Concomitant administration of anticholinergic medicines (e.g., dextromethorphan, diphenhydramine) may antagonise the anti-dyspeptic effects of MOTIVOM 10 ODT.

Prolactin levels

MOTIVOM 10 ODT interferes with serum prolactin levels and may interfere with other hypoprolactinaemic medicines and with some diagnostic tests.

General

Since MOTIVOM 10 ODT has gastrokinetic 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.

MOTIVOM 10 ODT may also be given with:

- Neuroleptics, the action of which it does not potentiate.
- Dopaminergic agonists (e.g. bromocriptine) and L-dopa, whose unwanted peripheral effects, such as digestive disorders, nausea and vomiting, it suppresses without counteracting their central properties.

4.6 Fertility, pregnancy and lactation

Pregnancy

Safety of use during pregnancy has not been established.

Breastfeeding

Domperidone is excreted in human milk and breastfed 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. Breastfeeding is not recommended for mothers who are taking MOTIVOM 10 ODT.

Caution should be exercised in case of QTc prolongation risk factor in breastfed infants.

Fertility

No data is available on fertility.

4.7 Effects on ability to drive and use machines

MOTIVOM 10 ODT may cause dizziness or somnolence (see section 4.8). 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 MOTIVOM 10 ODT affects them.

4.8 Undesirable effects

The safety of domperidone, as in MOTIVOM 10 ODT, was evaluated in clinical trials and in

oesophageal reflux disorder (GORD), irritable bowel syndrome (IBS), nausea and vomiting or other related conditions. Studies in diabetic gastroparesis or symptoms secondary to chemotherapy or parkinsonism were excluded.

Immune system disorders:

Less frequent: hypersensitivity

Psychiatric disorders:

Frequent: depression

Less frequent: loss of libido, anxiety

Nervous system disorders:

Frequent: akathisia, somnolence, headache

Gastrointestinal disorders:

Frequent: dry mouth, diarrhoea

Skin and subcutaneous tissue disorders:

Frequent: rash, pruritus

Less frequent: urticaria

Reproductive system and breast disorders:

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

Less frequent: breast discharge, breast swelling

General disorders and administration site conditions:

Frequent: asthenia

Post-marketing experience:

The following reactions have been reported post-marketing:

Immune system disorders:

Frequency unknown: anaphylactic reaction (including anaphylactic shock), angioedema

Psychiatric disorders:

Frequency unknown: agitation, nervousness

Nervous system disorders:

Frequency unknown: convulsion, extrapyramidal disorder, dizziness

Eye disorders:

Frequency unknown: oculogyric crisis

Cardiac disorders:

Frequency unknown: ventricular dysrhythmias (see section 4.4), sudden cardiac death, QTc prolongation, torsade de pointes

Renal and urinary disorders:

Frequency unknown: urinary retention

Investigations:

Frequency unknown: abnormal liver function tests, increased blood prolactin

Description of selected adverse events

In clincial studies where domperidone, as in MOTIVOM 10 ODT, was used at higher dosages, 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. In addition to the reactions listed above, akathisia, breast discharge, breast enlargement, breast swelling, depression, hypersensitivity, lactation disorder, and irregular menstruation were also noted.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of MOTIVOM 10 ODT is important. It allows continued monitoring of the benefit/risk balance of MOTIVOM 10 ODT. Health care providers are requested to report any suspected adverse reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on the SAHPRA website.

4.9 Overdose

Symptoms

Symptoms of over dosage may include agitation, altered consciousness, convulsions, disorientation, somnolence and extrapyramidal reactions.

Treatment

There is no specific antidote to MOTIVOM 10 ODT, but in the event of overdose, standard symptomatic treatment should be given immediately. Administration of activated charcoal, may be useful. Electrocardiogram (ECG) monitoring should be undertaken, because of the possibility of QT interval prolongation. Close medical supervision and supportive therapy is recommended.

Anticholinergic, anti-parkinson medicines may be helpful in controlling the extrapyramidal reactions.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Propulsives,

ATC code: A03F A 03

Category and class: A 5.7.2 Anti-emetics and anti-vertigo preperations

Mechanism of action

Domperidone is a dopamine antagonist with anti-emetic properties. Domperidone does not readily cross the blood-brain barrier. 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.

Domperidone has been shown to increase lower oesophaegeal pressure, improve antroduodenal motility and accelerate gastric emptying. There is no effect on gastric secretion.

Effect on QT/QTc interval and cardiac electrophysiology

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 medicine 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 occurring at approximately 1 hour after dosing. The C_{max} and area under the curve (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 the bioavailability of domperidone is enhanced in normal subjects when taken after a meal, patients with gastrointestinal 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 medicine 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.

Biotransformation

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 medicine 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.

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 systemic 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. MOTIVOM 10 ODT is contraindicated in patients with moderate or severe hepatic impairment (see section 4.3).

Renal impairment

In subjects with severe renal insufficiency (creatinine clearance < 30mL/min/1,73 m^2) the elimination half-life of domperidone is increased from 7,4 to 20,8 hours, but plasma levels are lower than in healthy volunteers. Since very little unchanged medicine (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 paediatric population.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Aspartame;

Colloidal silicon dioxide;

Crospovidone;

Magnesium stearate;

Mannitol;

Microcrystalline cellulose;

Peppermint flavour.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

- Store at or below 30 °C.
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6.5 Nature and contents of container

Aluminium-Aluminium blister strips containing 10 tablets, packed into an outer carton.

Pack size: 10 or 100 tablets.

6.6 Special precautions for disposal

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Activo Health (Pty) Ltd

Block B, Arena Office Park

272 West Avenue

Centurion, 0157

South Africa

8. REGISTRATION NUMBER(S)

57/5.7.2/0158

9. DATE OF FIRST AUTHORISATION

3 June 2025

10. DATE OF REVISION OF THE TEXT