Approved Professional Information for Medicines for Human Use:

ZOFREMET 4 ODT

ZOFREMET 8 ODT

SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

ZOFREMET 4 ODT 4 mg orodispersible tablet

ZOFREMET 8 ODT 8 mg orodispersible tablet

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

ZOFREMET 4 ODT 4 mg orodispersible tablet

Each orodispersible tablet contains 4 mg ondansetron.

ZOFREMET 8 ODT 8 mg orodispersible tablet

Each orodispersible tablet contains 8 mg ondansetron.

Contains sugar: lactose monohydrate

ZOFREMET 4 ODT 4 mg: Each orodispersible tablet contains 55,906 mg lactose monohydrate.

ZOFREMET 8 ODT 8 mg: Each orodispersible tablet contains 111,812 mg lactose monohydrate.

Contains sweetener: aspartame

ZOFREMET 4 ODT 4 mg: Each orodispersible tablet contains 0,994 mg aspartame.

ZOFREMET 8 ODT 8 mg: Each orodispersible tablet contains 1,988 mg aspartame.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Austell Pharmaceuticals (Pty) Ltd, 560081-2, ZOFREMET 4/8 ODT, Orodispersible tablets, 4 mg and 8 mg

ZOFREMET 4 ODT 4 mg orodispersible tablets

White, round flat-faced bevel-edged tablets.

ZOFREMET 8 ODT 8 mg orodispersible tablet

White, round flat-faced bevel-edged tablets.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

ZOFREMET ODT is indicated for the management of nausea and vomiting induced by cytotoxic chemotherapy and radiotherapy.

ZOFREMET ODT is also indicated for the prevention and treatment of post-operative nausea and vomiting. Routine prophylaxis is not recommended for patients in whom there is little expectation that nausea and vomiting will occur. The study population in all trials thus far consisted of mainly women undergoing laparoscopic procedures. While some men were included in some trials with similar results, clearance of ondansetron is more rapid in men and insufficient numbers of men have been clinically studied to be certain that efficacy and safety have been established. Few patients undergoing major abdominal surgery have been studied.

4.2 Posology and method of administration

DO NOT attempt to push ZOFREMET ODT through the lidding foil.

PEEL BACK the lidding foil of one blister and GENTLY remove ZOFREMET ODT.

Place ZOFREMET ODT on the top of the tongue, where it will disperse within seconds, then swallow.

Chemotherapy and Radiotherapy Induced Nausea and Vomiting:

The emetogenic potential of cancer treatment varies according to the doses and combinations of chemotherapy and radiotherapy regimens used. The selection of dose regimen should be determined by the severity of the emetogenic challenge.

Adults:

Emetogenic Chemotherapy and Radiotherapy: For most patients receiving emetogenic chemotherapy or radiotherapy, ZOFREMET 8 ODT 8 mg should be administered orally 1 - 2 hours before treatment, followed by 8 mg orally twelve hourly.
In circumstances where delayed or prolonged emesis is expected after the first 24 hours, ZOFREMET ODT may be continued orally, 8 mg twice daily for up to five days after a course of treatment.

Highly Emetogenic Chemotherapy: To protect against delayed or prolonged emesis after the first 24 hours of parenteral ondansetron, ZOFREMET ODT may be continued orally, 8 mg twice daily for up to 5 days after a course of treatment.

Prevention and Treatment of Post-Operative Nausea and Vomiting:

Adults: For the prevention of post-operative nausea and vomiting, 16 mg may be given orally one hour prior to induction of anaesthesia.
Repeat dosing for patients who continue to experience nausea and/or vomiting post-operatively has not been studied. While recommended as a fixed dose for all, few patients above 80 kg or below 40 kg have been studied.

Special populations

Elderly population

There is limited experience in the use of ZOFREMET ODT in the prevention and treatment of post-operative nausea and vomiting in the elderly.

Based on more recent ondansetron plasma concentrations and exposure-response modelling, a greater effect on QTcF is predicted in patients ≥ 75 years of age compared to young adults.
Specific dosing information for oral dosing of ondansetron is not available for patients over 65 years of

age and over 75 years of age. (See also section 5.1.)

Renal impairment

No alteration of daily dosage or frequency of dosing, or route of administration are required for patients with mild or moderate renal impairment.

There is limited information available on the daily dosage or frequency of dosing, or route of administration for severe renal impairment.

Hepatic impairment

Clearance of ZOFREMET ODT is significantly reduced and serum half-life significantly prolonged in subjects with moderate or severe impairment of hepatic function. In such patients a total daily dose of 8 mg should not be exceeded. (See also section 4.4.)

Paediatric population

Experience is currently limited with ondansetron and children. Ondansetron is administered intravenously, immediately before chemotherapy, followed by oral therapy at doses of ZOFREMET 4 ODT 4 mg every 12 hours for up to 5 days.

4.3 Contraindications

- Hypersensitivity to ondansetron or to any of the excipients listed in section 6.1.
- Concomitant use with apomorphine (see section 4.5).
- The use of ZOFREMET ODT is contraindicated during the first 12 weeks of pregnancy irrespective of the indication, due to an increased risk of developing oral cleft palate and/or lip to the foetus (see section 4.4 and 4.6).
- The use of ZOFREMET ODT for post-operative nausea and vomiting is contra-indicated in pregnancy (see section 4.6).
- Congenital long QT syndrome.

4.4 Special warnings and precautions for use

Hypersensitivity reactions have been reported in patients who have exhibited hypersensitivity to other selective $5HT_3$ receptor antagonists. Respiratory events should be treated symptomatically and medical practitioners should pay particular attention to them as precursors of hypersensitivity reactions.

Ondansetron prolongs the QT interval in a dose-dependent manner (see section 5.1). In addition, post-marketing cases of Torsade de Pointes have been reported in patients using ondansetron. Avoid ZOFREMET ODT in patients with congenital long QT syndrome. ZOFREMET ODT should be administered with caution to patients who have or may develop prolongation of QTc, including patients with electrolyte abnormalities, congestive heart failure, bradyarrhythmias or patients taking other medicines that lead to QT prolongation or electrolyte abnormalities.

Hypokalaemia and hypomagnesaemia should be corrected prior to ZOFREMET ODT administration.

There have been post-marketing reports describing patients with serotonin syndrome (including altered mental status, autonomic instability and neuromuscular abnormalities) following the concomitant use of ondansetron and other serotonergic medicines (including selective serotonin reuptake inhibitors (SSRI) and serotonin noradrenaline reuptake inhibitors (SNRIs)). If concomitant treatment with ondansetron and other serotonergic medicines is clinically warranted, appropriate observation of the patient is advised.

As ondansetron is known to increase large bowel transit time, patients with signs of subacute intestinal obstruction should be monitored following administration.

In patients with adenotonsillar surgery, prevention of nausea and vomiting with ondansetron may mask occult bleeding. Therefore, such patients should be followed carefully after ondansetron.

The use of ZOFREMET ODT during the first 12 weeks of pregnancy increases the risk of developing oral cleft palate and or lip to the foetus (see section 4.3).

Patients with hepatic impairment:

Clearance of ZOFREMET ODT is significantly reduced and serum half-life significantly prolonged in subjects with moderate or severe impairment of hepatic function. In such patients a total daily dose of 8 mg should not be exceeded. The daily dose for children should not exceed 4 mg.

Paediatric population

Paediatric patients receiving Ondansetron with hepatotoxic chemotherapeutic medicines should be monitored closely for impaired hepatic function.

ZOFREMET ODT contain aspartame. Caution is advised in patients with phenylketonuria.

ZOFREMET ODT contains lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose galactose malabsorption should not take this medicine.

4.5 Interaction with other medicines and other forms of interaction

There is no evidence that ondansetron either induces or inhibits the metabolism of other medicines commonly co-administered with it. Specific studies have shown that there are no interactions when ondansetron is administered with alcohol, temazepam, furosemide, alfentanil, tramadol, morphine, lidocaine, thiopental or propofol.

Ondansetron is metabolised by multiple hepatic cytochrome P-450 enzymes: CYP3A4, CYP2D6 and

CYP1A2. Due to the multiplicity of metabolic enzymes capable of metabolising ondansetron, enzyme inhibition or reduced activity of one enzyme (e.g. CYP2D6 genetic deficiency) is normally compensated by other enzymes and should result in little or no significant change in overall ondansetron clearance or dose requirement.

Caution should be exercised when ondansetron is co-administered with medicines that prolong the QT interval and/or cause electrolyte abnormalities (see section 4.4).

Use of ondansetron with QT prolonging medicines may result in additional QT prolongation. Concomitant use of ondansetron with cardiotoxic medicines (e.g. anthracyclines (such as doxorubicin, daunorubicin) or trastuzumab), antibiotics (such as erythromycin), antifungals (such as ketoconazole), antiarrhythmics (such as amiodarone) and beta blockers (such as atenolol or timolol) may increase the risk of dysrhythmias (see section 4.4).

Serotonergic medicines (e.g. SSRIs and SNRIs)

There have been post-marketing reports describing patients with serotonin syndrome (including altered mental status, autonomic instability and neuromuscular abnormalities) following the concomitant use of ondansetron and other serotonergic medicines (including SSRIs and SNRIs) (see section 4.4).

Apomorphine

Based on reports of profound hypotension and loss of consciousness when ondansetron was administered with apomorphine hydrochloride, concomitant use with apomorphine is contraindicated (see section 4.3).

Phenytoin, Carbamazepine and Rifampicin

In patients treated with potent inducers of CYP3A4 (i.e. phenytoin, carbamazepine, and rifampicin), the oral clearance of ondansetron was increased and ondansetron blood concentrations were decreased.

Tramadol

Data from small studies indicate that ondansetron may reduce the analgesic effect of tramadol.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential

Woman of childbearing potential being treated with ZOFREMET ODT should not become pregnant as ZOFREMET ODT is contraindicated in the first 12 weeks of pregnancy, irrespective of the cause of the nausea and vomiting (see section 4.3). Women of childbearing potential to use contraception while taking ZOFREMET ODT and for 2 days after stopping treatment.

Pregnancy

ZOFREMET ODT is contraindicated for post-operative nausea and vomiting during pregnancy, as well as during the first 12 weeks of pregnancy irrespective of the indication due to the risk (see section 4.3).

During the first 12 weeks of pregnancy, ondansetron can be associated with an increased risk of developing oral cleft palate and/or lip to the foetus.

The available epidemiological studies on cardiac malformations show conflicting results.

Animal studies does not indicate direct or indirect harmful effects with respect to reproductive toxicity.

Ondansetron should not be used during the first trimester of pregnancy.

Austell Pharmaceuticals (Pty) Ltd, 560081-2, ZOFREMET 4/8 ODT, Orodispersible tablets, 4 mg and 8 mg

Breastfeeding

Tests have shown that ondansetron passes into the milk of lactating animals. It is therefore recommended that mothers receiving Ondansetron should not breast-feed their babies.

Fertility

There is no information on the effects of ondansetron on human fertility.

4.7 Effects on ability to drive and use machines

ZOFREMET ODT may cause nervous system and eye disorders which may adversely affect the ability of patients to drive or operate machines. Patients taking ZOFREMET ODT should therefore not drive or use machines until the effects of ZOFREMET ODT treatment are known (see section 4.8).

4.8 Undesirable effects

The table below shows all adverse drug reactions (ADRs) observed during clinical trials and postmarket spontaneous reports with ondansetron.

System Organ Class	**Frequency**		
	Frequent	**Less Frequent**	**Not known**
Immune system disorders	-	Immediate hypersensitivity, including cross-sensitivity reactions sometimes severe, including anaphylaxis, bronchospasm, shortness of breath, hypotension, shock, angioedema, urticaria	-
Nervous system disorders	Headache	Seizures, movement disorders (including extrapyramidal reactions such as dystonic reactions, oculogyric crisis and dyskinesia (1) Dizziness predominantly during rapid IV administration	-

Eye disorders	-	Transient visual disturbances (e.g. blurred vision) predominantly during IV administration Transient blindness predominantly during IV administration [(2)]	-
Cardiac disorders	-	Arrhythmias, chest pain with or without ST segment depression, bradycardia. QTc prolongation (including Torsade de Pointes)	-
Vascular disorders	Sensation of warmth or flushing	Hypotension	-
Respiratory [(3)], thoracic and mediastinal disorders	-	Hiccups	-
Gastrointestinal disorders	Constipation, increased bowel transit time	-	-
Hepatobiliary disorders	-	Asymptomatic increases in liver function tests [(4)]	-

[1] Observed without definitive evidence of persistent clinical sequelae.

[2] The majority of the blindness cases reported resolved within 20 minutes. Most patients had received chemotherapeutic agents, which included cisplatin. Some cases of transient blindness were reported as cortical in origin.

[3] Respiratory events should be treated symptomatically and clinicians should pay particular attention to them as precursors of hypersensitivity reactions.

[4] These events were observed commonly in patients receiving chemotherapy with cisplatin.

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

Suspected adverse reactions can also be reported directly to the HCR via medsafety@austell.co.za

Austell Pharmaceuticals (Pty) Ltd, 560081-2, ZOFREMET 4/8 ODT, Orodispersible tablets, 4 mg and 8 mg

4.9 Overdose

Signs and symptoms

In the majority of cases, symptoms were similar to those already reported in patients receiving recommended doses (see section 4.8). Manifestations that have been reported include visual disturbances, severe constipation, hypotension and a vasovagal episode with transient second-degree AV block.

Ondansetron prolongs the QT interval in a dose-dependent fashion. ECG monitoring is recommended in cases of overdose.

Treatment

There is no specific antidote for ondansetron, therefore in all cases of suspected overdose, symptomatic and supportive therapy should be given as appropriate.

Further management should be as clinically indicated or as recommended by the national poisons centre, where available.

Paediatric population

Paediatric cases consistent with serotonin syndrome have been reported after inadvertent oral overdoses of ondansetron (exceeded estimated ingestion of 4mg/kg) in infants and children aged 12 months to 2 years.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacological Classification/ Category and Class: A 5.10 Medicines affecting autonomic functions. Serotonin antagonists.

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Pharmacotherapeutic group: Serotonin (5HT3) antagonists.

ATC Code: A04AA01.

Ondansetron is a potent, highly selective $5HT_3$ receptor-antagonist. Its precise mode of action in the control of nausea and vomiting is not known. Chemotherapeutic agents and radiotherapy may cause release of 5HT in the small intestine initiating a vomiting reflex by activating vagal afferents via $5HT_3$ receptors. Ondansetron blocks the initiation of this reflex. Activation of vagal afferents may also cause a release of 5HT in the area postrema, located on the floor of the fourth ventricle, and this may also promote emesis through a central mechanism.

Thus, the effect of ondansetron in the management of the nausea and vomiting induced by cytotoxic chemotherapy and radiotherapy is due to antagonism of $5HT_3$ receptors on neurons located both in the peripheral and central nervous system.

In psychomotor testing ondansetron does not impair performance nor cause sedation.

Ondansetron does not alter plasma prolactin concentrations.

QT Prolongation: The effect of ondansetron on the QTc interval was evaluated in a double blind, randomised, placebo and positive (moxifloxacin) controlled, crossover study in 58 healthy adult men and women. Ondansetron doses included 8 mg and 32 mg infused intravenously over 15 minutes. At the highest tested dose of 32 mg, the maximum mean (upper limit of 90 % CI) difference in QTcF from placebo after baseline-correction was 19,6 (21,5) msec. At the lower tested dose of 8 mg, the maximum mean (upper limit of 90 % CI) difference in QTcF from placebo after baseline-correction was 5,8 (7,8) msec. In this study, there were no QTcF measurements greater than 480 msec and no QTcF prolongation was greater than 60 msec.

5.2 Pharmacokinetic properties

Following oral administration of ondansetron, absorption is rapid with maximum plasma concentrations of about 30 ng/ml being attained approximately 1,6 hours after an 8 mg dose.

The absolute oral bioavailability of ondansetron is approximately 60 %. The disposition of ondansetron following both oral and intravenous dosing is similar with a terminal elimination half-life of about 3 hours and a steady-state volume of distribution of about 140 L. Plasma protein binding is 70-76 %.

Ondansetron is cleared from the systemic circulation predominantly by metabolism with less than 5 % of a dose excreted unchanged in the urine.

Early studies in healthy elderly volunteers have shown a slightly increased oral bioavailability (65 %) and prolonged elimination half-life (5 hours) for ondansetron. Based on more recent ondansetron plasma concentrations and exposure-response modelling, a greater effect on QTcF is predicted in patients ≥ 75 years of age compared to young adults.

In patients with severe hepatic impairment, systemic clearance is markedly reduced with prolonged elimination half-lives (15 - 32 hours) and an oral bioavailability approaching 100 % because of reduced presystemic metabolism.

In a study of 21 paediatric patients aged between 3 and 12 years undergoing elective surgery with general anaesthesia, the absolute values for both the clearance and volume of distribution of ondansetron following a single intravenous dose of 2 mg (3-7 years old) or 4 mg (8-12 years old) were reduced. The magnitude of the change was age-related, with clearance falling from about 300 mL/min at 12 years of age to 100 mL/min at 3 years. Volume of distribution fell from about 75 L at 12 years to 17 ℓ at 3 years. Use of weight-based dosing (0,1 mg/kg up to 4 mg maximum) compensates for these changes and is effective in normalising systemic exposure in paediatric patients.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Aspartame

Calcium silicate

Colloidal anhydrous silica

Crospovidone

Lactose monohydrate

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Low-substituted hydroxypropylcellulose

Magnesium stearate

Peppermint flavour

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months

6.4 Special precautions for storage

Store at or below 25 °C.

Store in original packaging.

This medicine does not require any special storage conditions.

6.5 Nature and contents of container

ZOFREMET ODT is available in peel-off aluminium/aluminium blisters packed into cardboard cartons in pack sizes of 10’s.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements for disposal.

Austell Pharmaceuticals (Pty) Ltd, 560081-2, ZOFREMET 4/8 ODT, Orodispersible tablets, 4 mg and 8 mg

7. HOLDER OF CERTIFICATE OF REGISTRATION

Austell Pharmaceuticals (Pty) Ltd

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8. REGISTRATION NUMBERS

ZOFREMET 4 ODT 4 mg orodispersible tablets: 56/5.10/0081

ZOFREMET 8 ODT 8 mg orodispersible tablets: 56/5.10/0082

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

11 June 2024

10. DATE OF REVISION OF THE TEXT

To be allocated by the Authority