Applicant : Eurolab (Pty) Ltd
Proprietary name : Zothena 4 mg & 8 mg
Dosage form and strength : Orodispersable tablet 4 mg & 8 mg
Date of submission : 09 September 2022
Approval date : 07 December 2022

Approved Professional Information

SCHEDULING STATUS S4

1 NAME OF THE MEDICINE

ZOTHENA 4 mg, 4 mg orodispersible tablets

ZOTHENA 8 mg, 8 mg orodispersible tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

ZOTHENA 4 mg: Each orodispersible tablet contains 4 mg ondansetron.

ZOTHENA 8 mg: Each orodispersible tablet contains 8 mg ondansetron.

Contains sugar:

ZOTHENA 4 mg: Each orodispersible tablet contains 167,14 mg mannitol.

ZOTHENA 8 mg: Each orodispersible tablet contains 334,28 mg mannitol.

Contains artificial sweetener:

ZOTHENA 4 mg: Each orodispersible tablet contains 3 mg aspartame.

ZOTHENA 8 mg: Each orodispersible tablet contains 6 mg aspartame.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Orodispersible tablets.

Round, white to off-white, flat, bevelled edged, tablets plain on both the surfaces, having strawberry odour, packed in Aluminium-Aluminium blister.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

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

ZOTHENA 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 the medicine 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

Posology

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.

Adults

Emetogenic Chemotherapy and Radiotherapy

For most patients receiving emetogenic chemotherapy or radiotherapy, **ZOTHENA** 8 mg orally should be administered 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, **ZOTHENA** may be continued orally, 8 mg twice daily for up to five days after a course of treatment.

Highly Emetogenic Chemotherapy

Ondansetron IV or IM maybe administered determined by the severity of the emetogenic challenge.

To protect against delayed or prolonged emesis after the first 24 hours, **ZOTHENA** may be continued orally, 8 mg twice daily for up to 5 days after a course of treatment.

Special populations

Elderly patients

Efficacy and tolerance in patients aged over 65 years is similar to that seen in younger adults indicating no need to alter dosage or route of administration in the elderly.

Paediatric Population

Ondansetron IV may be administered, followed by oral therapy at doses of **ZOTHENA** 4 mg every 12 hours for up to 5 days.

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 patients

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

Patients with renal impairment

No alteration of daily dosage or frequency of dosing, or route of administration are required. There is limited information available on severe renal impairment.

Patients with hepatic impairment

Clearance of ondansetron is significantly reduced and serum half-life significantly prolonged in patients with moderate or severe impairment of hepatic function. In such patients a total daily dose of 8 mg should not be exceeded.

Paediatric Population

No studies have been conducted on the use of orally administered ondansetron in the prevention or treatment of post-operative nausea and vomiting in children. Slow IV injection is recommended for this purpose. Repeat dosing for paediatric patients who continue to experience nausea and/or vomiting has not been studied and should thus not be given.

Method of administration

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

4.3 Contraindications

ZOTHENA is contraindicated in

- patients known to have hypersensitivity to ondansetron or to any components of **ZOTHENA** (see section 6.1)
- concomitant use with apomorphine is contraindicated (see section 4.4 and 4.5).
- 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.
- post-operative nausea and vomiting in pregnancy (see section 4.6).
- patients with 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 clinicians should pay particular attention to them as precursors of hypersensitivity reactions.

Ondansetron prolongs the QT interval in a dose-dependent manner. In addition, cases of Torsade de Pointes have been reported in patients using ondansetron. Avoid ondansetron in patients with congenital long QT syndrome (see section 4.3). Ondansetron 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 medicinal products that lead to QT prolongation or electrolyte abnormalities.

Cases of myocardial ischemia have been reported in patients treated with ondansetron. In some patients, especially in the case of intravenous administration, symptoms appeared immediately after administration of ondansetron. Patients should be alerted to the signs and symptoms of myocardial ischaemia.

Hypokalaemia and hypomagnesaemia should be corrected prior to ondansetron administration.

There have been 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.

Ondansetron orodispersible tablets formulation contains aspartame and therefore should be taken with caution in patients with phenylketonuria.

Hepatic impairment

Clearance of **ZOTHENA** is significantly reduced and serum half-life significantly prolonged in patients with moderate or severe impairment of hepatic function. In such patients, a total daily dose of 8 mg should not be exceeded.

Paediatric Population

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

4.5 Interaction with other medicinal products 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 arrhythmias. (See section 4.4).

Serotonergic medicines (e.g. SSRIs and SNRIs): There have been 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: Ondansetron may reduce the analgesic effect of tramadol.

Paediatric population

The similarity of interactions to adults has not been established.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential / Contraception in males and females

Women of childbearing potential should use contraception and for 2 days after stopping treatment, as **ZOTHENA** is contraindicated in the first 12 weeks of pregnancy, irrespective of the cause of nausea and vomiting (see section 4.3).

Pregnancy

ZOTHENA is contraindicated for post-operative nausea and vomiting during pregnancy, as well as during the first 12 weeks of pregnancy, irrespective of the indication (see section 4.3). During the first 12 weeks of pregnancy **ZOTHENA** can be associated with an increased risk of developing oral cleft palate and/ or lip to the foetus.

Breastfeeding

Tests have shown that ondansetron passes into the milk of lactating animals. It is therefore recommended that mothers receiving **ZOTHENA** should not breastfeed 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

ZOTHENA may affect the ability of patients to drive or operate machines and caution is advised until the effects of **ZOTHENA** in patients on treatment are known (see section 4.8).

4.8 Undesirable effects

Tabulated summary of adverse reactions

Adverse events are listed below by system organ class and frequency. Frequencies are defined as: *Frequent*, *Less Frequent* and *Frequency unknown*. The frequencies are estimated at the standard recommended doses of ondansetron.

SOC category	Frequency	Side effect
Immune system disorders	Less frequent	Immediate hypersensitivity reactions sometimes severe, including anaphylaxis, bronchospasm, shortness of breath, hypotension, shock, angioedema, urticaria.
Nervous system disorders	Frequent	Headache
	Less frequent	Seizures, movement disorders (including extrapyramidal reactions such as dystonic reactions, oculogyric crisis and dyskinesia).(1)

SOC category	Frequency	Side effect
Cardiac disorders	Less frequent	Dysrhythmias, chest pain with or without ST segment depression, bradycardia. QTc prolongation (including Torsade de Pointes).
	Frequency unknown	Myocardial ischemia.
Vascular disorders	Frequent	Sensation of warmth or flushing.
	Less frequent	Hypotension.
Respiratory, thoracic and mediastinal disorders	Less frequent	Hiccups.
Gastrointestinal disorders	Frequent	Constipation.
Hepatobiliary disorders	Less frequent	Asymptomatic increases in liver function tests.(2)

1. Observed without definitive evidence of persistent clinical sequelae.

2. These events were observed frequently in patients receiving chemotherapy with cisplatin.

Paediatric population

The adverse event profiles in children and adolescents were comparable to that seen in adults.

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. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the "**6.04 Adverse**

Drug Reactions Reporting Form", found online under SAHPRA's publications:

https://www.sahpra.org.za/Publications/Index/8.

4.9 Overdose

Symptoms and Signs

There is limited experience of ondansetron overdose. 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.

Paediatric population

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

Treatment

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

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

A 5.10 Medicines affecting autonomic functions. Serotonin antagonists

Pharmacotherapeutic group: Serotonin ($5HT_3$) antagonist, 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 medicines 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.

5.2 Pharmacokinetic properties

Absorption

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.

Distribution

The absolute oral bioavailability of the medicine 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 %.

Biotransformation and Elimination

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

Elderly

Studies in healthy elderly volunteers have shown a slightly increased oral bioavailability (65 %) and prolonged elimination half-life (5 hours) for ondansetron. 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 pre-systemic metabolism.

Paediatric population

In a study of 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

Basic Butylated Methacrylate Copolymer

Crospovidone

Magnesium stearate

Mannitol

Mannitol granular

Silica colloidal anhydrous

Flavour - Strawberry (Nature identical flavourings, Natural flavours, Corn maltodextrin, E 1520 Propylene glycol)

6.2 Incompatibilities

Not reported.

6.3 Shelf life

36 months.

6.4 Special precautions for storage

Store at or below 25 °C.

6.5 Nature and contents of container

Alu-Alu blisters packed in plain cartons of 7, 10, 14, 15, 20, 28, 30, 56, 60, 84, 90, 100, 112 and 120 tablets. Not all pack sizes may be marketed.

6.6 Special precaution for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 HOLDER OF CERTIFICATE OF REGISTRATION

Eurolab (Pty) Ltd.

Woodmead Office Park,

3 Stirrup Lane, Van Reenens Avenue,

Woodmead,

2144

8 REGISTATRATION NUMBER

Zothena 4 mg: 52/5.10/1010

Zothena 8 mg: 52/5.10/1011

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

21 June 2022

10 DATE OF REVISION OF THE TEXT

07 December 2022

11 DOSIMETRY

Not applicable

12 INSTRUCTIONS FOR PREPARATION OF RADIOPHARMACEUTICALS

Not applicable