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 drugs that prolong the QT interval and/or cause electrolyte abnormalities.

Apomorphine
Based on reports of profound hypotension and loss of consciousness when ondansetron was administered with apomorphine hydrochloride, concomitant use with apomorphine is contraindicated.

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.

Serotonergic Drugs (e.g., SSRIs and SNRIs)
Serotonin syndrome (including altered mental status, autonomic instability and neuromuscular abnormalities) has been described following the concomitant use of ondansetron and other serotonergic drugs, including selective serotonin reuptake inhibitors (SSRIs) and serotonin noradrenaline reuptake inhibitors (SNRIs).

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

16. OVERDOSE
There is limited experience of ondansetron overdose. In the majority of cases, symptoms were similar to those already reported in patients receiving recommended doses.
Ondansetron prolongs QT interval in a dose-dependent fashion. ECG monitoring is recommended in cases of overdose.

Cases consistent with serotonin syndrome have been reported in young children following oral overdose.

Treatment
There is no specific antidote for ondansetron, therefore in cases of suspected overdose, symptomatic and supportive therapy should be given as appropriate.
The use of ipecacuanha to treat overdose with ondansetron is not recommended as patients are unlikely to respond due to the anti-emetic action of ondansetron itself.

17. Storage Condition
Store below 30°C.
Keep out of reach of children

18. Nature and contents of container
VOMIZ 8 is available in blister packs of 3x10 Tablets.

19. Special precautions for disposal and other handling
Any unused product or waste material should be disposed of in accordance with local requirements.

20. Product Registration Holder:
Mansa Healthcare Sdn. Bhd.,
B-05-3A, 3 Two Square, No 2, Jalan 19/1, 46300 Petaling Jaya, Selangor Malaysia.

21. MANUFACTURER

Zydus Lifesciences Limited,
Kundaim Industrial Estate,
Plot No. 203-213, Kundaim,
Goa - 403 115, INDIA.

22. DATE OF REVISION
18-Apr-2024

XXXXXXX

1. NAME OF THE MEDICINAL PRODUCT

Vomiz 8
(Ondansetron Tablet USP 8mg)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
Each film-coated tablet contains:
Ondansetron hydrochloride USP (as dihydrate)
Equivalent to Ondansetron 8mg
Excipients
Microcrystalline Cellulose
Lactose Anhydrous
Pregelatinised Starch
Magnesium stearate
Colour: Yellow oxide of Iron and Titanium Dioxide

3. PHARMACEUTICAL FORM
Film coated Tablet
Yellow coloured, capsule shaped, biconvex, film coated tablets plain on both the sides. The tablet should be free of all physical defects.

4. Mechanism of Action
Ondansetron is a potent, highly selective 5HT3 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 5HT3 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 probably due to antagonism of 5HT3 receptors on neurons located both in the peripheral and central nervous system.
The mechanisms of action in post-operative nausea and vomiting are not known but there may be common pathways with cytotoxic induced nausea and vomiting.

5. Pharmacodynamics
Ondansetron does not alter plasma prolactin concentrations.

QT Prolongation
The effect of ondansetron on the QTc interval was evaluated in a double blind, randomized, 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.

6. Pharmacokinetics
The pharmacokinetic properties of ondansetron are unchanged on repeat dosing.

Absorption
Following oral administration, ondansetron is passively and completely absorbed from the gastrointestinal tract and undergoes first pass metabolism. Peak plasma concentrations are attained approximately 1.5 hours after dosing. For doses above 8 mg the increase in ondansetron systemic exposure with dose is greater than proportional; this may reflect some reduction in first pass metabolism at higher oral doses.
Mean bioavailability in healthy male subjects, following the administration of a single 8 mg tablet, is approximately 55 to 60%. Bioavailability is slightly enhanced by the presence of food but unaffected by antacids

Distribution
Ondansetron is not highly protein bound (70 to 76%).

The disposition of ondansetron following oral, IM or IV dosing in adults is similar with a steady state volume of distribution of about 140 L.

Metabolism
Ondansetron is cleared from the systemic circulation predominantly by hepatic metabolism through multiple enzymatic pathways. The absence of the enzyme CYP2D6 (the debrisoquine polymorphism) has no effect on ondansetron's pharmacokinetics.

Elimination
Ondansetron is cleared from the systemic circulation predominantly by hepatic metabolism. Less than 5% of the absorbed dose is excreted unchanged in the urine.
The disposition of ondansetron following oral, IM or IV dosing is similar with a terminal elimination half-life of about 3 hours.

Special Patient Populations
Gender
Gender differences were shown in the disposition of ondansetron, with females having a greater rate and extent of absorption following an oral dose and reduced systemic clearance and volume of distribution (adjusted for weight).

Geriatric population (65 years of age or older)
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.

Pediatric population (aged 3 years to 17 years)
The half-life is 2.9 hours for patients 3 to 12 year age range.
Use of weight-based dosing compensates for age-related changes and is effective in normalising systemic exposure in paediatric patients.
Volume of distribution was related to age and was lower in adults than in infants and children. Clearance was related to weight but not to age with the exception of infants aged 1 to 4 months.

Hepatic impairment
In patients with severe hepatic impairment, ondansetron's systemic clearance is markedly reduced with prolonged elimination half-lives (15 to 32 hours) and an oral bioavailability approaching 100% due to reduced pre-systemic metabolism.

7. Indication/ Usage
Adults
Ondansetron oral formulations are indicated for the management of nausea and vomiting induced by cytotoxic chemotherapy and radiotherapy.
Ondansetron is also indicated for the prevention of post-operative nausea and vomiting.

Paediatric Population
Oral formulation:
Ondansetron is indicated for the management of nausea and vomiting induced by cytotoxic chemotherapy.

400 mm
180 mm
Size : 180 x 400 mm (Front Side) Colour : Black Keyline - Do not print
/Volumes/PTC/Pkg. Dev/Commercial/ARTWORKS_COM/EMB COMMERCIAL/Malaysia/Vomiz Tabs/XXXXXXX_PI Vomiz 8 Tablets Malaysia.indd

No studies have been conducted on the use of orally administered ondansetron in the prevention or treatment of post-operative nausea and vomiting.

8. Dosage and Administration Dosage regimen

CHEMOTHERAPY AND RADIOTHERAPY INDUCED NAUSEA AND VOMITING (CINV and RINV)
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.

CINV and RINV in Adults
The recommended oral dose is 8 mg taken 1 to 2 hours before chemotherapy or radiation treatment, followed by 8 mg orally every 12 hours for a maximum of 5 days.

For highly emetogenic chemotherapy a single oral dose of up to 24 mg ondansetron taken together with 12 mg oral dexamethasone sodium phosphate, 1 to 2 hours before chemotherapy, may be used. After the first 24 hours, oral treatment with ondansetron may be continued for up to 5 days after a course of treatment. The recommended oral dose is 8 mg to be taken twice daily.

IV doses greater than 8 mg and up to a maximum of 16 mg must be diluted in 50 mL to 100 mL of 0.9% Sodium Chloride Injection or 5% Dextrose Injection before administration and infused over not less than 15 minutes.

For patient who require Ondansetron 4mg and IV doses, it is recommended to seek for other product/brand alternatives based on patient's need.

CINV in Children and Adolescents (aged 3 years to 17 years)
The dose for CINV can be calculated based on body surface area (BSA) or weight. In paediatric clinical studies, ondansetron was given by IV infusion diluted in 25 to 50 mL of saline or other compatible infusion fluid and infused over not less than 15 minutes.

Dosing by BSA
Ondansetron should be administered immediately before chemotherapy as a single IV dose of 5 mg/m2. The IV dose must not exceed 8 mg. Oral dosing can commence 12 hours later and may be continued for up to 5 days (Table 1). Adult doses must not be exceeded.

Table 1 BSA-based dosing for CINV (aged 3 years to 17 years)

BSA	Day 1	Days 2 - 6
≥ 0.6 m^2 to ≤ 1.2 m^2	5 mg/m^2 IV plus 4 mg tablet after 12 hours	4 mg tablet every 12 hours
> 1.2 m^2	5 mg/m^2 IV or 8 mg IV plus 8 mg tablet after 12 hours	8 mg tablet every 12 hours

Dosing by body weight
Ondansetron should be administered immediately before chemotherapy as a single IV dose of 0.15 mg/kg. The IV dose must not exceed 8 mg. On Day 1, two further IV doses may be given in 4-hourly intervals. Oral dosing can commence 12 hours later and may be continued for up to 5 days (Table 2). Adult doses must not be exceeded.

Table 2 Weight-based dosing for CINV (aged 3 years to 17 years)

Body Weight	Day 1	Days 2 - 6
> 10 kg	Up to 3 doses of 0.15 mg/kg IV every 4 hours	4 mg tablet every 12 hours

There are no dosing recommendations for children with BSA <0.6 m2, body weight ≤10 kg or who are unable to swallow tablets.

CINV and RINV in Elderly
Ondansetron is well tolerated by patients over 65 years of age.

In patients 65 years of age or older, all IV doses should be diluted and infused over 15 minutes and, if repeated, given no less than 4 hours apart.

In patients 65 to 74 years of age, the initial IV dose of ondansetron 8 mg or 16 mg, infused over 15 minutes, may be followed by 2 doses of 8 mg infused over 15 minutes and given no less than 4 hours apart.

In patients 75 years of age or older, the initial IV dose of ondansetron should not exceed 8 mg infused over 15 minutes. The initial dose of 8 mg may be followed by 2 doses of 8 mg, infused over 15 minutes and given no less than 4 hours apart.

POST-OPERATIVE NAUSEA AND VOMITING (PONV)
PONV in Adults
For prevention of post-operative nausea and vomiting, the recommended oral dose is 16 mg given 1 hour prior to anaesthesia.
For treatment of established post-operative nausea and vomiting ondansetron administration by injection is recommended.

PONV in Children and Adolescents (aged 3 years to 17 years)
No studies have been conducted on the use of orally administered ondansetron in the prevention or treatment of post-operative nausea and vomiting; slow IV injection (not less than 30 seconds) is recommended for this purpose.

PONV in Elderly
There is limited experience in the use of ondansetron in the prevention and treatment of post- operative nausea and vomiting in the elderly, however ondansetron is well tolerated in patients over 65 years receiving chemotherapy.

Special populations
Renal impairment
No alteration of daily dosage or frequency of dosing, or route of administration are required.

Hepatic impairment
Clearance of ondansetron 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 IV or oral should not be exceeded.

Patients with Poor Sparteine/Debrisoquine Metabolism
The elimination half-life of ondansetron is not altered in subjects classified as poor metabolisers of sparteine and debrisoquine. Consequently in such patients repeat dosing will give drug exposure levels no different from those of the general population. No alteration of daily dosage or frequency of dosing is required.

9. METHOD OF ADMINISTRATION
For oral use
The tablets should be swallowed whole with liquid.

10. CONTRAINDICATIONS
Based on reports of profound hypotension and loss of consciousness when ondansetron was administered with apomorphine hydrochloride, concomitant use with apomorphine is contraindicated.

Hypersensitivity to any component of the preparation.

11. SPECIAL WARNINGS AND PRECAUTIONS
Hypersensitivity reactions have been reported in patients who have exhibited hypersensitivity to other selective 5HT3 receptor antagonists.

Ondansetron prolongs the QT interval in a dose-dependent manner. In addition, post-marketing cases of Torsade de Pointes have been reported in patients using ondansetron. Avoid ondansetron in patients with congenital long QT syndrome. 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.

Myocardial ischemia has been reported in patients treated with ondansetron. In some cases, predominantly during intravenous administration, the symptoms appeared immediately after administration but recovered with prompt treatment. Therefore, caution should be exercised during and after administration of ondansetron.

Hypokalemia and hypomagnesemia should be corrected prior to ondansetron administration.

Serotonin syndrome has been described following the concomitant use of ondansetron and other serotonergic drugs. If concomitant treatment with ondansetron and other serotonergic drugs 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.

Lactose intolerance: This tablet contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency of glucose-galactose malabsorption should not take this medicine.

12. DRIVING AND USING MACHINES
Ondansetron has no or negligible influence on the ability to drive and use machines.

In psychomotor testing ondansetron does not impair performance nor cause sedation. No detrimental effects on such activities are predicted from the pharmacology of ondansetron.

13. USE IN SPECIFIC POPULATIONS
Pregnancy, Lactation and Fertility

Women of childbearing potential
Women of childbearing potential should consider the use of contraception.

Pregnancy
Based on human experience from epidemiological studies, Ondansetron is suspected to cause orofacila malformations when administered during the first trimester of pregnancy. In one cohort study including 1.8 million pregnancies, first trimester Ondansetron use was associated with an increased risk of oral clefts (3 additional cases per 10, 000 women treated; adjusted relative risk, 1.24, (95% CI 1.03-1.48)). 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.

Breast-feeding
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.

14. ADVERSE REACTIONS
Summary of the safety profile
Adverse events are listed below by system organ class and frequency. Frequencies are defined as: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1000 to <1/100); rare (≥ 1/10,000 to <1/1000); and very rare (<1/10,000), including isolated reports. Very common, common and uncommon events were generally determined from clinical trial data. The incidence in placebo was taken into account. Rare and very rare events were generally determined from post-marketing spontaneous data. The following frequencies are estimated at the standard recommended doses of ondansetron. The adverse event profiles in children and adolescents were comparable to that seen in adults.

Table 3 Adverse Drug Reactions

Immune system disorders	
Rare:	Immediate hypersensitivity reactions sometimes severe, including anaphylaxis.
Nervous system disorders	
Very common:	Headache
Uncommon:	Seizures, movement disorders (including extrapyramidal reactions such as dystonic reactions, oculogyric crisis and dyskinesia) have been observed without definitive evidence of persistent clinical sequelae.
Rare:	Dizziness predominantly during rapid IV administration
Eye disorders	
Rare:	Transient visual disturbances (e.g. blurred vision) predominantly during IV administration.
Very rare:	Transient blindness predominantly during IV administration.
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.	
Cardiac disorders	
Uncommon:	Arrhythmias, chest pain with or without ST segment depression, bradycardia.
Rare:	QTc prolongation (including Torsade de Pointes)
Vascular disorders	
Common:	Sensation of warmth or flushing
Uncommon:	Hypotension
Respiratory, thoracic and mediastinal disorders	
Uncommon:	Hiccups
Gastrointestinal disorders	
Common:	Constipation
Hepatobiliary disorders	
Uncommon:	Asymptomatic increases in liver function tests#
#These events were observed commonly in patients receiving chemotherapy with cisplatin.	
Skin and subcutaneous tissue disorders	
Very rare:	Toxic skin eruption, including toxic epidermal necrolysis

15. DRUG INTERACTIONS
There is no evidence that ondansetron either induces or inhibits the metabolism of other drugs commonly co- administered with it. Specific studies have shown that there are no pharmacokinetic interactions when ondansetron is administered with alcohol, temazepam, furosemide, tramadol or propofol.

Ondansetron is metabolised by multiple hepatic cytochrome P450 enzymes: CYP3A4, CYP2D6 and CYP1A2. Due to the multiplicity of metabolic enzymes