Clean Professional Information for ZOFER® range

SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

ZOFER® 4 mg TABLETS film-coated tablets

ZOFER® 8 mg TABLETS film-coated tablets

ZOFER® RAPITAB 4 dispersible tablets

ZOFER® RAPITAB 8 dispersible tablets

ZOFER® 4 mg INJECTION solution for injection

ZOFER® 8 mg INJECTION solution for injection.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

ZOFER 4 mg TABLETS: Each film-coated tablet contains ondansetron hydrochloride equivalent to 4 mg ondansetron.

ZOFER 8 mg TABLETS: Each film-coated tablet contains ondansetron hydrochloride equivalent to 8 mg ondansetron.

ZOFER RAPITAB 4: Each dispersible tablet contains ondansetron hydrochloride equivalent to 4 mg ondansetron.

ZOFER RAPITAB 8: Each dispersible tablet contains ondansetron hydrochloride equivalent to 8 mg ondansetron.

ZOFER 4 mg INJECTION: Each ampoule contains 4 mg ondansetron (as hydrochloride) in 2 mL aqueous solution for intramuscular or intravenous administration.

ZOFER 8 mg INJECTION: Each ampoule contains 8 mg ondansetron (as hydrochloride) in 4 mL aqueous solution for intramuscular or intravenous administration.

Excipients with known effect:

ZOFER 4 mg TABLETS contains sugar (99,35 mg lactose per film-coated tablet).

Sign:

ZOFER 8 mg TABLETS contains sugar (198,70 mg lactose per film-coated tablet).

ZOFER RAPITAB 4 contains sugar alcohol (104,40 mg mannitol) and sweetener (3,90 mg aspartame) per dispersible tablet.

ZOFER RAPITAB 8 contains sugar alcohol (208,80 mg mannitol) and sweetener (7,80 mg aspartame).

ZOFER 4 mg and 8 mg INJECTION: Sugar free.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablets

ZOFER 4 mg TABLETS: White, oval shaped, film-coated tablets debossed with "130" on one side and plain on the other side.

ZOFER 8 mg TABLETS: Yellow, oval shaped, film-coated tablets debossed with "131" on one side and plain on the other.

Dispersible tablets

ZOFER RAPITAB 4: White to off-white, oval shaped, uncoated tablets debossed with "240" on one side and plain on the other side.

ZOFER RAPITAB 8: White to off-white, oval shaped, uncoated tablets debossed with "241" on one side and plain on the other side.

Solution for injection

ZOFER 4 mg and 8 mg INJECTION: Colourless solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

Sign:

ZOFER 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.

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.

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, ZOFER 8 mg should be administered as a slow IV (not less than 2 to 3 minutes) or IM injection in not less than 30 seconds, immediately before treatment, or orally (film-coated tablets/dispersible tablets) 1 to 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, ZOFER may be continued orally, 8 mg twice daily for up to five days after a course of treatment.

Highly emetogenic chemotherapy:

A single dose of ZOFER 8 mg by slow IV (not less than 2 to 3 minutes) or IM injection in not less than 30 seconds, immediately before chemotherapy has been shown to be effective in many patients.

Higher doses may be required in some patients, particularly those on high dose cisplatin, and the doses should be adjusted according to the severity of the emetogenic challenge.

In these patients the following dose schedules have been shown to be effective:

A dose of 8 mg by slow IV or IM injection immediately before chemotherapy, followed by two further IV or IM doses of 8 mg four hours apart, or by a constant infusion of 1 mg/hour for up to 24 hours.

OR ALTERNATIVELY

A maximum single IV dose of 16 mg diluted in 50 to 100 mL of saline or other compatible infusion fluid, infused over not less than 15 minutes immediately before chemotherapy.

A single dose greater than 16 mg must not be given due to dose dependent increase of QT-prolongation risk (see section 4.4).

The efficacy of ZOFER in highly emetogenic chemotherapy may be enhanced by the addition of a single intravenous dose of 20 mg dexamethasone phosphate administered 30 to 45 minutes prior to the first ZOFER dose prior to chemotherapy.

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

Children:

Experience is currently limited, but ondansetron was effective and well tolerated in children over the age of 4 years, when given intravenously at a dose of 5 mg/m^2 over 15 minutes, immediately before chemotherapy, followed by oral therapy of doses of ZOFER 4 mg every 12 hours for up to 5 days.

Elderly patients:

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 intravenous dosing is provided for patients over 65 years of age and over 75 years of age.

Patients aged 75 years and older receiving ZOFER injection:

A single intravenous dose of ZOFER must not exceed 8 mg (infused over at least 15 minutes).

Patients aged less than 75 years (65 – 74 years):

A single dose of intravenous ZOFER given for the prevention of chemotherapy and radiotherapy induced nausea and vomiting in adults (aged less than 75 years) must not exceed 16 mg (infused over at least 15 minutes).

Patients aged 65 years and older receiving ZOFER injection:

The dose schedule for adults can be followed. All intravenous doses should be diluted in

50 – 100 mL of saline or other compatible infusion fluid (see section 6.6) and infused over at least 15 minutes.

Repeat intravenous doses of ZOFER should be given no less than 4 hours apart.

Patients with renal impairment:

No alteration of daily dosage or frequency of dosing, or route of administration is required.

Patients with hepatic impairment:

Clearance of ZOFER 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 and therefore parenteral or oral administration is recommended.

Prevention and treatment of post-operative nausea and vomiting

Adults:

Immediately before induction of anaesthesia, or post-operatively if the patient experiences nausea and/or vomiting occurring shortly after surgery, administer 4 mg undiluted intramuscularly or intravenously. If given intravenously, it must be administered in not less than 30 seconds, preferable over 2 to 5 minutes. Alternatively, for the prevention of post-operative nausea and vomiting, 16 mg may be given orally (film-coated tablets/dispersible tablets) 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.

Children:

For prevention of post-operative nausea and vomiting in paediatric patients two years and older having surgery performed under general anaesthesia, ZOFER may be administered by slow intravenous infusion over 2 to 5 minutes or longer at a dose of 0,1 mg/kg up to a maximum of 4 mg either prior to, at or after induction of anaesthesia.

For the treatment of established post-operative nausea and vomiting in paediatric patients two years and older, ZOFER may be administered by slow intravenous infusion at a dose of 0,1 mg/kg up to a

maximum of 4 mg over not less than 2 to 5 minutes or preferably longer either prior to, at or after induction of anaesthesia.

Repeat dosing for paediatric patients who continue to experience nausea and/or vomiting has not been studied, and should thus not been given.

Elderly patients:

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 intravenous dosing is provided for patients over 65 years of age and over 75 years of age.

A slight age-related decrease in clearance, and an increase in the half-life of ondansetron is predicted, presenting as slight, clinically insignificant age-related increases in both oral bioavailability (65 %) and a prolonged elimination half-life (5 hours) of ondansetron

Patients with renal impairment:

No alteration of daily dosage or frequency of dosing, or route of administration is required for mild or moderate renal impairment. There is limited information available for daily dosage or frequency of dosing, or route of administration for severely impaired renal impairment.

Patients with hepatic impairment:

Clearance of ZOFER 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.

Method of administration:

ZOFER TABLETS and RAPITABS is for oral administration only (see section 6.6).

ZOFER TABLETS should be swallowed whole with liquid.

ZOFER RAPITAB should be placed on the top of the tongue, where it will disperse within seconds, thereafter it should be swallowed.

ZOFER INJECTION is for intramuscular or intravenous administration only (see section 6.6.).

4.3 Contraindications

- Hypersensitivity to the active ingredient namely ondansetron or any of the excipients listed in section 6.1.
- The use of ZOFER 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).
- The use of ZOFER for post-operative nausea and vomiting is contraindicated in pregnancy (see section 4.6).
- Concomitant use with apomorphine is contraindicated (see section 4.5).
- Congenital long QT syndrome.

4.4 Special warnings and precautions for use

Cross-hypersensitivity reactions have been reported in patients who have exhibited hypersensitivity to other selective 5-HT_3 receptor antagonists.

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

Ondansetron in ZOFER 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 ZOFER in patients with congenital long QT syndrome (see section 4.3). ZOFER should be administered with caution to patients who have or may develop prolongation of QTc, including patients with electrolyte abnormalities, congestive heart failure, bradydysrhythmias or patients taking other medicines that lead to QT prolongation or electrolyte abnormalities (see section 4.5).

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.

Hypokalaemia and hypomagnesaemia should be corrected prior to ZOFER administration.

Sign:

Post-marketing reports describe patients with serotonin syndrome (including altered mental status, autonomic instability and neuromuscular abnormalities) following the concomitant use of ZOFER and other serotonergic medicines (including selective serotonin reuptake inhibitors [SSRIs] and serotonin noradrenaline reuptake inhibitors [SNRIs]). If concomitant treatment with ZOFER and other serotonergic medicines is clinically warranted, appropriate and close observation of the patient is advised.

Patients with hepatic impairment: In adult patients with moderate or severe impairment of hepatic function, clearance of ZOFER is significantly reduced and serum half-life significantly prolonged. 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 patients receiving ondansetron with hepatotoxic chemotherapeutic medicines should be closely monitored for impaired hepatic function.

Patients with signs of intestinal obstructions should be monitored following administration, as ZOFER is known to increase large bowel transit time.

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

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

ZOFER TABLETS contains lactose

Patients with rare hereditary problems of galactose intolerance, total lactose deficiency or glucose-galactose malabsorption should not take ZOFER TABLETS.

ZOFER RAPITAB contains aspartame

Aspartame is a source of phenylalanine. It may be harmful if you have phenylketonuria (PKU), a rare genetic disorder in which phenylalanine builds up because the body cannot remove it properly.

ZOFER INJECTION contains sodium

ZOFER INJECTION contains less than 1 mmol sodium (23 mg) per dosage unit, that is to say essentially sodium free.

Sign:

4.5 Interaction with other medicines and other forms of interaction

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

Ondansetron is metabolised by multiple hepatic cytochrome P450 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 for by other enzymes and should result in little or no significant change in overall ZOFER clearance or dose requirement.

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

Use of ZOFER with QT prolonging medicines may result in additional QT prolongation. Concomitant use of ZOFER with cardiotoxic medicines (e.g. anthracyclines [such as doxorubicin, daunorubicin] or trastuzumab), antibiotics (such as erythromycin), antifungals (such as ketoconazole), antidysrhythmics (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 ZOFER and other serotonergic medicines (including SSRIs and SNRIs) (see section 4.4).

Apomorphine: Cases of profound hypotension and loss of consciousness when ZOFER was administered concomitantly with apomorphine hydrochloride have been reported. Concomitant use of ZOFER and apomorphine is contraindicated and may intensify QT prolongation (see section 4.3).

Phenytoin, carbamazepine and rifampicin: In patients treated with potent inducers of CYP3A4 (i.e. phenytoin, carbamazepine and rifampicin), the clearance of oral ZOFER was increased and

blood concentrations of ondansetron were decreased causing a reduced antiemetic efficacy.

Tramadol: ZOFER may reduce the analgesic effect of tramadol.

4.6 Fertility, pregnancy and lactation

Pregnancy:

Safety in pregnancy has not been established (see section 4.3 and 4.4).

ZOFER 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).

An increased risk of developing oral cleft palate and/or lip to the foetus is associated during the first 12 weeks of pregnancy.

Women of childbearing potential should not become pregnant and should consider the use of contraception while taking ZOFER, as well as for two days after stopping treatment with ZOFER.

Breastfeeding:

Tests have shown that ondansetron passes into the milk of lactating animals. It is therefore recommended that mothers receiving ZOFER 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

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

4.8 Undesirable effects

Immune system disorders

Less frequent: Immediate hypersensitivity reactions, including cross-sensitivity reactions which are sometimes severe (e.g. anaphylaxis, bronchospasm, shortness of breath, hypotension, shock, angioedema, urticaria) have been reported.

Sign:

Nervous system disorders

Frequent: Headache.

Less frequent: Seizures, movement disorders (including extrapyramidal reactions such as oculogyric crisis, involuntary movement disorders such as dystonic reactions and dyskinesia have been observed without definitive evidence of persistent clinical sequelae), dizziness has been observed after rapid intravenous administration.

Eye disorders

Frequent: Transient visual disturbances (e.g. blurred vision) have been reported predominantly during intravenous administration.

Less frequent: Transient blindness predominantly during intravenous administration.

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

Cardiac disorders

Less frequent: Dysrhythmias, bradycardia and chest pains with or without ST segment depression, QTc prolongation (including torsade de pointes), myocardial ischaemia.

Vascular disorders

Frequent: *S*ensation of warmth or flushing.

Less frequent: Hypotension.

Respiratory, thoracic and mediastinal disorders

Less frequent: Hiccups.

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

Gastrointestinal disorders

Frequent: Increase in large bowel transit time is known to be caused by ZOFER which cause constipation in some patients.

Sign:

Hepato-biliary disorders

Less frequent: Transient, asymptomatic increases in liver function tests.

These events were commonly observed in patients receiving cancer chemotherapy with cisplatin.

General disorders and administration site conditions

Less frequent: Pain, redness and burning at site of injection**.**

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 requested to report any suspected adverse drug reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website.

4.9 Overdose

Symptoms:

See section 4.8. Manifestations that have been reported include severe constipation, visual disturbances, hypotension and vasovagal episode with transient second-degree AV block. Ondansetron prolongs the QT interval in a dose-dependent manner. 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, treatment is symptomatic and supportive as appropriate.

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Category and class: A 5.10 Medicines affecting autonomic functions. Serotonin antagonists.

Pharmacotherapeutic group: Serotonin ($5\text{-}HT_3$) antagonist.

ATC code: A04AA01.

Ondansetron is a potent, highly selective $5\text{-}HT_3$ receptor antagonist. Chemotherapeutic medicines and radiotherapy may cause release of 5-HT in the small intestine initiating a vomiting reflex by activating vagal afferents via $5\text{-}HT_3$ receptors. The initiation of this reflex is blocked by ondansetron. Activation of vagal afferents may also cause a release of 5-HT 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 chemotherapy and radiotherapy may be due to the antagonism of $5\text{-}HT_3$ receptors on neurons located both in the peripheral and central nervous system.

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

The mechanisms of action in post-operative nausea and vomiting are not known but there may be common pathways with cytotoxically-induced nausea and vomiting.

Ondansetron does not alter plasma prolactin concentrations.

The role of ondansetron in opiate-induced emesis is not yet established.

5.2 Pharmacokinetic properties

Absorption:

Plasma prolactin concentrations are not altered by ondansetron. Ondansetron is rapidly absorbed following oral administration, with maximum plasma concentrations of about 30 ng/mL being attained approximately 1,6 hours after an 8 mg dose. 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.

The absolute oral bioavailability of the drug is approximately 60 %. The disposition of ondansetron

following both intravenous and oral dosing is similar with a terminal elimination half-life of about 3 hours and a steady-state volume of distribution of about 140 L.

Bioavailability, following oral administration, is slightly enhanced by the presence of food but unaffected by antacids.

The disposition of ondansetron following oral, intramuscular (IM) and intravenous (IV) dosing is similar with a terminal half-life of about 3 hours and steady state volume of distribution of about 140 L. Equivalent systemic exposure is achieved after IM and IV administration of ondansetron.

A 4 mg intravenous infusion of ondansetron given over 5 minutes results in peak plasma concentrations of about 65 ng/mL. Following intramuscular administration of ondansetron, peak plasma concentrations of about 25 ng/mL are attained within 10 minutes of injection.

Distribution:

Plasma protein binding is 70 to 76 %.

Biotransformation:

Ondansetron is cleared from the systemic circulation predominantly by hepatic metabolism through multiple enzymatic pathways.

Elimination:

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

The absence of the enzyme CYP2D6 (the debrisoquine polymorphism) has no effect on ondansetron's pharmacokinetics. The pharmacokinetic properties of ondansetron are unchanged on repeat dosing.

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

As a result of reduced pre-systemic metabolism in patients with severe hepatic impairment, the systemic clearance of ondansetron is markedly reduced with prolonged elimination half-lives (15 to 32 hours) and an oral bioavailability approaching 100 %.

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).

Children and adolescents:

The differences in pharmacokinetic parameters in the patient population of 1 to 4 months old, can be explained in part by the higher percentage of total body water in neonates and infants and a higher volume of distribution for water soluble medicines like ondansetron.

Elderly:

Specific dosing information is provided for intravenous dosing patients over 65 years of age and over 75 years of age.

Renal impairment:

In patients with renal impairment (creatinine clearance 15 – 60 mL/min), systemic clearance and volume of distribution are reduced, resulting in a slight, but clinically insignificant increase in elimination half-life (5,4 hours). A study in patients with severe renal impairment who required regular haemodialysis (studied between dialyses) showed ondansetron's pharmacokinetics to be essentially unchanged.

Hepatic impairment:

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

ZOFER 4 mg and 8 mg TABLETS:

Lactose

Magnesium stearate

Microcrystalline cellulose

Polyethylene glycol 400

Pregelatinised starch.

ZOFER 4 mg TABLETS only:

Opadry White, containing hypromellose, polyethylene glycol 400 and titanium dioxide (C.I.77892).

ZOFER 8 mg TABLETS only:

Opadry Yellow, containing hypromellose, iron oxide yellow (Cl 77492), polyethylene glycol 400, polysorbate 80 and titanium dioxide (C.I.77891).

ZOFER RAPITAB 4 and 8:

Aspartame

Colloidal silicon dioxide

Croscarmellose sodium

Glyceryl distearate

Magnesium stearate

Mannitol

Strawberry flavoured powder (052312 AP 0551)

Purified talc.

ZOFER 4 mg and 8 mg INJECTION:

Citric acid (monohydrate)

Sodium chloride

Sodium citrate (dihydrate)

Water for injection.

6.2 Incompatibilities

ZOFER INJECTION should not be administered in the same syringe or infusion as any other medication. ZOFER INJECTION should only be mixed with those infusion solutions that are recommended (see section 6.6).

Sign:

6.3 Shelf life

36 months.

6.4 Special precautions for storage

ZOFER TABLETS:

Store at or below 25 °C.

Protect from light and moisture.

Keep blister strip in outer carton until required for use.

ZOFER RAPITAB:

Store at or below 25 °C.

Protect from light and moisture.

Keep blister strip in outer carton until required for use.

ZOFER INJECTION:

Store at or below 25 °C.

Protect from light.

Do not refrigerate.

6.5 Nature and contents of container

ZOFER 4 mg and 8 mg TABLETS: PVDC/PVC and aluminium blister strip.

Pack size: 1 blister strip contains 10 tablets, packed in an outer carton.

ZOFER RAPITAB 4 and 8: White PVDC/PVC and aluminium blister strip.

Pack size:1 blister strip contains 10 dispersible tablets, packed in an outer carton.

ZOFER 4 mg INJECTION: 2 mL clear glass ampoules with a violet dot.

ZOFER 8 mg INJECTION: 5 mL clear glass ampoules with a grey dot.

Pack size: Five ampoules are packed in a plastic tray, in an outer carton.

Not all pack sizes may be marketed.

Sign:

6.6 Special precautions for disposal and other handling

ZOFER INJECTION ampoules should not be autoclaved.

Compatibility with intravenous fluids:

In accordance with Good Clinical Practice, intravenous solutions should be prepared just before infusion.

When diluted with compatible infusion solutions, ondansetron is stable for up to seven days at room temperature or under refrigeration in polypropylene-neoprene syringes with syringe caps. Preparation must be under the appropriate aseptic conditions if extended storage periods are required.

ZOFER INJECTION is compatible with the following intravenous infusion fluids:

- Sodium chloride intravenous infusion 0,9 % *m/v*.
- Glucose intravenous infusion 5 %.
- Ringer's intravenous infusion.
- Potassium chloride 0,3 % *m/v* and sodium chloride 0,9 % *m/v* intravenous infusion.
- Potassium chloride 0,3 % *m/v* and glucose 5 % *m/v* intravenous infusion.

Intravenous infusions of ondansetron retain their potency for 48 hours at room temperature under normal lighting after dilution with 5 % dextrose injection, dextrose and sodium chloride injections, 0,9 % sodium chloride injection, and 3 % sodium chloride injection.

Compatibility with other medicines:

ZOFER INJECTION may be administered by intravenous infusion at 1 mg/hour, e.g. from an infusion bag or syringe pump. The following medicines may be administered via a Y-site:

Cisplatin: Concentrations up to 0,48 mg/mL (e.g. 240 mg in 500 mL) administered over one to eight hours.

Dexamethasone: 20 mg dexamethasone sodium phosphate may be administered as a slow intravenous injection over 2 to 5 minutes via the Y-site of an infusion set delivering 8 mg of ZOFER diluted in 50 to 100 mL of compatible infusion fluid over approximately 15 minutes. Compatibility

between dexamethasone sodium phosphate and ZOFER has been demonstrated supporting administration of these medicines through the same giving set, with resulting in-line concentrations in the ranges of 32 µg to 2,5 mg/mL for dexamethasone sodium phosphate and 8 µg to 1 mg/mL for ZOFER.

5-Fluorouracil: Concentrations up to 0,8 mg/mL (e.g. 2.4 g in 3 litres, or 400 mg in 500 mL) administered at a rate of at least 20 mL per hour (500 mL per 24 hours). Higher concentrations of 5-fluorouracil infusion may contain up to 0,045 % m/v magnesium chloride in addition to other excipients shown to be compatible.

Carboplatin: Concentrations in the range of 0,18 mg/mL to 9,9 mg/mL (e.g. 90 mg in 500 mL to 990 mg in 100 mL), administered over 10 minutes to one hour.

Etoposide: Concentrations in the range of 0,14 mg/mL to 0,25 mg/mL (e.g. 72 mg in 500 mL to 250 mg in 1 litre), administered over thirty minutes to one hour.

Ceftazidime: Doses in the range of 250 mg to 2 000 mg reconstituted with water for injection, as recommended by the manufacturer (e.g. 2,5 mL for 250 mg and 10 mL for 2 g ceftazidime), and given as an intravenous bolus injection over approximately five minutes.

Cyclophosphamide: Doses in the range 100 mg to 1 g, reconstituted with water for injection, 5 mL per 100 mg cyclophosphamide, as recommended by the manufacturer, and given as an intravenous bolus injection over approximately five minutes.

Doxorubicin: Doses in the range 10 to 100 mg, reconstituted with water for injection, 5 mL per 10 mg doxorubicin, as recommended by the manufacturer, and given as an intravenous bolus injection over approximately five minutes.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Ranbaxy Pharmaceuticals (Pty) Ltd

14 Lautre Road

Stormill, Ext. 1, Roodepoort

Johannesburg 1724

Sign:

8. REGISTRATION NUMBERS

ZOFER® 4 mg TABLETS:	A39/5.10/0413
ZOFER® 8 mg TABLETS:	A39/5.10/0414
ZOFER® RAPITAB 4:	42/5.10/0662
ZOFER® RAPITAB 8:	42/5.10/0663
ZOFER® 4 mg INJECTION:	A39/5.10/0448
ZOFER® 8 mg INJECTION:	A39/5.10/0449

9. DATE OF FIRST AUTHORISATION

ZOFER 4 mg and 8 mg TABLETS:	25 November 2005
ZOFER RAPITAB 4 and 8:	09 October 2009
ZOFER 4 mg and 8 mg INJECTION:	25 November 2005

10. DATE OF REVISION OF THE TEXT

21 May 2025

Namibia registration details:

Scheduling status: NS2

ZOFER® 4 mg TABLETS:	06/5.10/0330
ZOFER® 8 mg TABLETS:	06/5.10/0331
ZOFER® RAPITAB 4:	13/5.10/0032
ZOFER® RAPITAB 8:	13/5.10/0033
ZOFER®4 mg INJECTION:	06/5.10/0328
ZOFER® 8 mg INJECTION:	06/5.10/0329

Sign: