SCHEDULING STATUS:

S4

PROPRIETARY NAME AND DOSAGE FORM:

ZOFRAN® 4 mg or **8 mg TABLETS**

ZOFRAN® 4 mg or **8 mg INJECTION**

ZOFRAN® ZYDIS 4 mg and **ZOFRAN® ZYDIS 8 mg** tablets

COMPOSITION:

ZOFRAN 4 mg TABLETS: Each tablet contains ondansetron 4 mg (as hydrochloride dihydrate). Each tablet contains lactose 81,88 mg.

ZOFRAN 8 mg TABLETS: Each tablet contains ondansetron 8 mg (as hydrochloride dihydrate). Each tablet contains lactose 163,75 mg.

Excipients: Lactose, microcrystalline cellulose, pregelatinised maize starch, magnesium stearate, methyl hydroxypropylcellulose, titanium dioxide and iron oxide.

ZOFRAN 4 mg INJECTION: Ampoules containing ondansetron 4 mg (as hydrochloride dihydrate) in 2 ml aqueous solution for intramuscular or intravenous administration.

ZOFRAN 8 mg INJECTION: Ampoules containing ondansetron 8 mg (as hydrochloride dihydrate) in 4 ml aqueous solution for intramuscular or intravenous administration.

Excipients: Sodium chloride, citric acid monohydrate, sodium citrate and water for injections.

ZOFRAN ZYDIS 4 mg: Each Zydis contains ondansetron 4 mg.

ZOFRAN ZYDIS 8 mg: Each Zydis contains ondansetron 8 mg.

The Zydis has a strawberry flavour with preservatives, sodium methyl hydroxybenzoate 0,041 % *m/m* and sodium propyl hydroxybenzoate 0,05 % *m/m*.

Excipients: Other excipients include gelatin, mannitol, aspartame and strawberry flavour.

PHARMACOLOGICAL CLASSIFICATION:

A 5.10 Medicines affecting autonomic functions. Serotonin antagonists

PHARMACOLOGICAL ACTION:

Pharmacodynamic properties:

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.

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 the drug 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.

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 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.

INDICATIONS:

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

ZOFRAN 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 agent 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.

CONTRA-INDICATIONS:

ZOFRAN is contra-indicated in patients known to have hypersensitivity to any components of the preparation.

Concomitant use with apomorphine is contra-indicated (see WARNINGS AND SPECIAL PRECAUTIONS and INTERACTIONS).

The use of ZOFRAN for post-operative nausea and vomiting is contra-indicated in pregnancy (see PREGNANCY AND LACTATION).

Congenital long QT syndrome.

WARNINGS AND SPECIAL PRECAUTIONS:

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

As ZOFRAN is known to increase large bowel transit time, patients with signs of sub-acute intestinal obstructions should be monitored following administration.

ZOFRAN prolongs the QT interval in a dose-dependent manner (see Pharmacodynamic properties). In addition, post-marketing cases of Torsade de Pointes have been reported in patients using ZOFRAN. Avoid ZOFRAN in patients with congenital long QT syndrome (see CONTRA-INDICATIONS). ZOFRAN 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 medicinal products that lead to QT prolongation or electrolyte abnormalities.

Hypokalaemia and hypomagnesaemia should be corrected prior to ZOFRAN administration.

Patients with hepatic impairment: Clearance of ZOFRAN 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.

Effects on ability to drive and use machines:

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

Excipient warnings:

ZOFRAN tablets contain lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

As ZOFRAN ZYDIS contains aspartame, caution is advised in patients with phenylketonuria.

INTERACTIONS:

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) should be compensated for by other enzymes.

Caution should be exercised when ZOFRAN is co-administered with agents that prolong the QT interval and/or cause electrolyte abnormalities (see WARNINGS AND SPECIAL PRECAUTIONS).

Apomorphine: Cases of profound hypotension and loss of consciousness when ZOFRAN was administered concomitantly with apomorphine hydrochloride have been reported. Concomitant use of ZOFRAN and apomorphine may intensify QT prolongation (see CONTRA-INDICATIONS and WARNINGS AND SPECIAL PRECAUTIONS).

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

Tramadol: ZOFRAN may reduce the analgesic effect of tramadol.

PREGNANCY AND LACTATION:

Pregnancy: Safety in pregnancy has not been established (see CONTRA-INDICATIONS).

Lactation: Tests have shown that ZOFRAN passes into the milk of lactating animals. It is therefore recommended that mothers receiving ZOFRAN should not breastfeed their babies.

DOSAGE AND DIRECTIONS FOR USE:

DO NOT attempt to push ZOFRAN ZYDIS through the lidding foil.

PEEL BACK the lidding foil of one blister and GENTLY remove the ZOFRAN ZYDIS.

Place the Zydis 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.

Adults:

Emetogenic Chemotherapy and Radiotherapy: For most patients receiving emetogenic chemotherapy or radiotherapy, ZOFRAN 8 mg should be administered as a slow IV or IM injection in not less than 30 seconds, immediately before treatment, or orally (as Zydis or tablets) 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, ZOFRAN 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 ZOFRAN 8 mg by slow IV 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 two to four hours apart, or by a constant infusion of 1 mg/hour for up to 24 hours.

OR

A single dose of 16 mg diluted in 50-100 ml of saline or other compatible infusion fluid and infused over not less than 15 minutes immediately before chemotherapy. A single dose greater than 16 mg should not be given (see WARNINGS AND SPECIAL PRECAUTIONS).

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

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

Children: Experience is currently limited but ZOFRAN 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 at doses of ZOFRAN 4 mg every 12 hours for up to 5 days.

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

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, preferably over 2-5 minutes. Alternatively, for the prevention of post-operative nausea and vomiting, 16 mg may be given orally (as Zydis or 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, ZOFRAN may be administered by slow intravenous injection 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, ZOFRAN may be administered by slow intravenous injection at a dose of 0,1 mg/kg up to a maximum of 4 mg.

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

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

Patients with renal/hepatic impairment:

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 ZOFRAN 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.

Injections - Instructions for Handling:

The ampoule formulations are unpreserved and should only be used on a single occasion, injected or diluted immediately after opening, any remaining solution should be discarded.

ZOFRAN injection ampoules should not be autoclaved.

Compatibility with intravenous fluids: ZOFRAN injection should not be administered in the same syringe or infusion as any other medication.

ZOFRAN injection should only be admixed with those infusion solutions which are recommended.

IV admixtures should be inspected for clarity, particulate matter, precipitate discolouration and leakage prior to administration whenever solution and container permit. Solutions showing haziness, particulate matter, or discolouration or leakage should not be used.

Intravenous solutions should be prepared at the time of infusion. However, ZOFRAN injection (unpreserved) has been shown to be stable for seven days at room temperature (below 25 °C) under fluorescent lighting or in a refrigerator with the following intravenous infusion fluids:

Sodium Chloride Intravenous Infusion BP 0,9 % *m/v*.

Glucose Intravenous Infusion BP 5 % *m/v*.

Ringers Intravenous Infusion.

Potassium Chloride 0,3 % *m/v* and Sodium Chloride 0,9 % *m/v* Intravenous Infusion BP.

Potassium Chloride 0,3 % *m/v* and Glucose 5 % *m/v* Intravenous Infusion BP.

Compatibility studies have been undertaken in polyvinyl chloride infusion bags and polyvinyl chloride administration sets. It is considered that adequate stability would also be conferred by the use of polyethylene infusion bags or type 1 glass bottles. Dilution of ZOFRAN in sodium chloride 0,9 % *m/v* or in glucose 5 % *m/v* have been demonstrated to be stable in polypropylene syringes. It is considered that ZOFRAN injection diluted with other compatible infusion fluids would be stable in polypropylene syringes.

Note: Preparation must be under the appropriate aseptic conditions if extended storage periods are required.

However, ZOFRAN injection when diluted with the recommended IV solutions, should be used within 24 hours if stored at room temperature or used within 72 hours if stored in a refrigerator, due to possible microbial contamination during preparation.

Compatibility with other medicines: NOTE: As a general principle it is not recommended to mix medicines for infusion.

ZOFRAN 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 the Y-site of the ZOFRAN giving set for ondansetron concentrations of 16 to 160 µg/ml (e.g. 8 mg/500 ml and 8 mg/50 ml respectively).

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

Dexamethasone: Dexamethasone sodium phosphate 20 mg may be administered as a slow intravenous injection over 2-5 minutes via the Y-site of an infusion set delivering 8 mg of ZOFRAN diluted in 50-100 ml of a compatible infusion fluid over approximately 15 minutes. Compatibility between dexamethasone sodium phosphate and ZOFRAN has been demonstrated supporting administration of these drugs through the same giving set with resulting in-line concentrations in the ranges of 32 µg-2,5 mg/ml for dexamethasone sodium phosphate and 8 µg-1 mg/ml for ZOFRAN.

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 cause precipitation of ZOFRAN. The 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 0,18 mg/ml to 9,9 mg/ml (e.g. 90 mg in 500 ml to 990 mg in 100 ml), administered over ten minutes to one hour.

Etoposide: Concentrations in the range 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 250 mg to 2 000 mg reconstituted with Water for Injections BP, 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 Injections BP, 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 10-100 mg reconstituted with Water for Injections BP, 5 ml per 10 mg doxorubicin, as recommended by the manufacturer, and given as an intravenous bolus injection over approximately five minutes.

SIDE EFFECTS:

Adverse events are listed below by system organ class and frequency.

Frequencies are defined as: very common (≥ 1/10), common (≥ 1/100 and < 1/10), uncommon (≥ 1/1 000 and < 1/100), rare (≥ 1/10 000 and < 1/1 000) 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.

Immune system disorders:

Rare: immediate hypersensitivity reactions sometimes severe, including anaphylaxis, bronchospasm, shortness of breath, hypotension, shock, angioedema, urticaria

Nervous system disorders:

Very common: headache

Uncommon: movement disorders (including extrapyramidal reactions such as oculogyric crisis, dystonic reactions and dyskinesia have been observed without definitive evidence of persistent clinical sequelae), seizures

Rare: dizziness during rapid intravenous administration

Eye disorders:

Rare: transient visual disturbances (e.g. blurred vision) during intravenous administration

Very rare: transient blindness predominantly during intravenous administration

Cardiac disorders:

Uncommon: dysrhythmias. 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

General disorders and administration site conditions:

Common: pain, redness and burning at site of injection.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT:

There is limited experience of ZOFRAN overdose. In the majority of cases symptoms were similar to those already reported in patients receiving recommended doses. See SIDE EFFECTS. Manifestations that have been reported include visual disturbances, severe constipation, hypotension and a vasovagal episode with transient second degree AV block. There is no specific antidote for ondansetron, therefore in cases of suspected overdose, symptomatic and supportive therapy should be given as appropriate.

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

IDENTIFICATION:

ZOFRAN 4 mg TABLETS: Yellow, oval, biconvex film-coated tablet engraved 'GXET3' on one face and plain on the other face.

ZOFRAN 8 mg TABLETS: Yellow, oval, biconvex film-coated tablet engraved 'GXET5' on one face and plain on the other face.

ZOFRAN 4 mg INJECTION: Clear glass ampoules containing a colourless solution.

ZOFRAN 8 mg INJECTION: Clear glass ampoules containing a colourless solution.

ZOFRAN ZYDIS 4 mg: White, round, plano-convex, freeze dried, fast dispersing oral dosage form, with a diameter of 10 mm.

ZOFRAN ZYDIS 8 mg: White, round, plano-convex, freeze dried, fast dispersing oral dosage form, with a diameter of 12 mm.

PRESENTATION:

ZOFRAN 4 mg TABLETS: Cartons containing 3 double aluminium foil blister packs (consisting of PVC/Al/OPA blister film with aluminium lidding foil). Each blister contains 5 tablets, pack size of 15 tablets.

ZOFRAN 8 mg TABLETS: Cartons containing 3 double aluminium foil blister packs (consisting of PVC/Al/OPA blister film with aluminium lidding foil). Each blister contains 5 tablets, pack size of 15 tablets.

ZOFRAN 4 mg INJECTION: Carton containing 5 ampoules.

ZOFRAN 8 mg INJECTION: Carton containing 5 ampoules.

ZOFRAN ZYDIS 4 mg: Carton containing 10 tablets in double foil blister pack.

ZOFRAN ZYDIS 8 mg: Carton containing 10 tablets in double foil blister pack.

STORAGE INSTRUCTIONS:

Store below 30 °C.

Keep out of reach of children.

ZOFRAN INJECTION: Protect from light. Do not freeze. Avoid excessive heat. Store in original package until required for use.

ZOFRAN INJECTION when diluted with the recommended IV solutions should be used within 24 hours if stored at room temperature or used within 72 hours if stored in a refrigerator, due to possible microbial contamination during preparation.

Do not dispose unused medicines in drains or sewerage systems.

REGISTRATION NUMBER:

ZOFRAN 4 mg TABLETS: X/5.10/332

ZOFRAN 8 mg TABLETS: X/5.10/333

ZOFRAN 4 mg INJECTION: X/5.10/331

ZOFRAN 8 mg INJECTION: Y/5.10/170

ZOFRAN ZYDIS 4 mg: 32/5.10/0461

ZOFRAN ZYDIS 8 mg: 32/5.10/0462

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION:

72 Steel Road

Spartan, Kempton Park

South Africa

DATE OF PUBLICATION OF THE PACKAGE INSERT:

7 December 2012

Botswana:

Zofran 4 mg Tablets - Reg No B9304090 S2

Zofran 8 mg Tablets - Reg No B9304095 S2

Zofran 4 mg Injection - Reg No B9304100 S2

Zofran 8 mg Injection - Reg No B9304105 S2

Namibia:

Zofran 4 mg Tablets - Reg No 12/5.10/0240 NS2

Zofran 8 mg Tablets - Reg No 12/5.10/0239 NS2

Zofran 4 mg Injection - Reg No 12/5.10/0238 NS2

Zofran 8 mg Injection - Reg No 12/5.10/0237 NS2

Zofran Zydis 4 mg Tablets - Reg No 04/16.2/0942 NS2

Zofan Zydis 8 mg Tablets - Reg No 04/16.2/0943 NS2

Zimbabwe:
Zofran 4 mg tablets - Reg No 91/16.2/2539 PP
Zofran 8 mg tablets - Reg No 91/16.2/2540 PP
Zofran IV 4 mg injections - Reg No 91/16.2/2538 PP
Zofran IV 8 mg Injection – Reg No 2014/16.2/4888 PP