SANDOZ

# Zofran™

Serotonin ($5HT_3$) antagonist

## DESCRIPTION AND COMPOSITION

### Pharmaceutical form

### Injection:

Ondansetron injection: a clear, colorless, sterile solution for injection or infusion. Each 1 ml of aqueous solution contains 2 mg ondansetron as hydrochloride dihydrate.

### Active substance

Ondansetron/Ondansetron hydrochloride dihydrate

### Excipients

Ampoules contains:

Sodium chloride

Citric acid monohydrate

Sodium citrate

Water for Injection

## INDICATIONS

### Adults

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

ZOFRAN injection is also indicated for the prevention and treatment of post-operative nausea and vomiting.

### Paediatric Population

***Injection formulations:***

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

No studies have been conducted on the use of orally administered ondansetron in the prevention or treatment of post-operative nausea and vomiting; IV injection is recommended for this purpose.

## DOSAGE REGIMEN 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 intravenous (IV) or intramuscular (IM) dose of ZOFRAN is 8 mg administered immediately before treatment. For highly emetogenic chemotherapy, a maximum initial ondansetron dose of 16 mg IV infused over 15 minutes may be used. A single IV dose greater than 16 mg should not be given. The efficacy of ondansetron in highly emetogenic chemotherapy may be enhanced by the addition of a single IV dose of dexamethasone sodium phosphate 20 mg, administered prior to chemotherapy. 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 (see section INSTRUCTIONS FOR USE AND HANDLING). Ondansetron doses of 8 mg or less, do not need to be diluted and may be administered as a slow IM or IV injection in not less than 30 seconds. The initial dose of ondansetron may be followed by 2 additional IV or IM doses of 8 mg by 2 to 4 hours apart, or by a constant infusion of 1 mg/h for up to 24 hours.

Oral treatment is recommended to protect against delayed or prolonged emesis after the first 24 hours.

### 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 (see section INSTRUCTIONS FOR USE AND HANDLING) 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/m$^2$. 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 $m^2$, 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 (see section CLINICAL PHARMACOLOGY).

## POST-OPERATIVE NAUSEA AND VOMITING (PONV)

### PONV in Adults

For prevention of post-operative nausea and vomiting, the recommended dose of ondansetron injection is a single dose of 4 mg by IM or slow IV injection administered at the induction of anaesthesia.

For treatment of established post-operative nausea and vomiting, a single dose of 4 mg given by IM or slow IV injection is recommended.

### PONV in Children and Adolescents (aged 3 years to 17 years)

For prevention and treatment of PONV in paediatric patients having surgery performed under general anaesthesia, ondansetron may be administered by slow IV injection (not less than 30 seconds) at a dose of 0.1 mg/kg up to a maximum of 4 mg either prior to, at or after induction of anaesthesia, or after surgery.

### 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.

## CONTRAINDICATIONS

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 INTERACTIONS).

Hypersensitivity to any component of the preparation (see section WARNINGS AND PRECAUTIONS and section ADVERSE DRUG REACTIONS).

## WARNINGS AND PRECAUTIONS

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

Ondansetron prolongs the QT interval in a dose-dependent manner (see section CLINICAL PHARMACOLOGY). 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 (see section INTERACTIONS). 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.

## ADVERSE DRUG 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 |
| **General disorders and administration site conditions** | |
| Common: | Local IV injection site reactions |

### Adverse drug reactions from spontaneous reports and literature cases (frequency not known)

The following adverse drug reactions have been derived from post-marketing experience with Zofran via spontaneous case reports and literature cases. Because these reactions are reported voluntarily from a population of uncertain size, it is not possible to reliably estimate their frequency which is therefore categorized as not known.

**Table 4 Adverse drug reactions from spontaneous reports and literature (frequency not known)**

| **Cardiac disorders** |
|---|
| Myocardial ischemia |

## 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, frusemide, tramadol 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 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 (see section WARNINGS AND PRECAUTIONS).

### 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) (see section WARNINGS AND PRECAUTIONS).

### Tramadol

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

## PREGNANCY, LACTATION, FEMALES AND MALES OF REPRODUCTIVE POTENTIAL

### Pregnancy

### Risk Summary

In human epidemiological studies, an increase in orofacial clefts was observed in infants of women administered ondansetron during the first trimester of pregnancy. Regarding cardiac malformations, the epidemiological studies showed conflicting results (see Human data).

Reproductive studies in rats and rabbits did not show evidence of harm to the fetus (see Animal data).

The use of ondansetron in pregnancy is not recommended.

### Human Data

Three epidemiological studies in the US assessed the risk of specific congenital anomalies, including orofacial clefts and cardiac malformations in offspring born to mothers exposed to ondansetron during the first trimester of pregnancy.

One cohort study with 88,467 pregnancies exposed to ondansetron showed an increased risk of oral clefts (3 additional cases per 10,000 women treated, adjusted relative risk (RR), 1.24 (95% CI 1.03-1.48)) without an apparent increase in risk of cardiac malformations. A separately published subgroup analysis of 23,877 pregnancies exposed to intravenous ondansetron did not find an increased risk of either oral clefts or cardiac malformations.

One case-control study using population-based birth defect registries with 23,200 cases across two datasets showed an increased risk of cleft palate in one dataset and no increased risk in the other dataset. There was no increased risk of cardiac malformations in this study.

The second cohort study with 3,733 pregnancies exposed to ondansetron found an increased risk of ventricular septal defect, adjusted RR 1.7 (95%CI 1.0-2.9), but no statistically significant increase in risk of cardiac malformations.

### Animal Data

In embryo-fetal development studies in rats and rabbits, pregnant animals received oral doses of ondansetron up to 15 mg/kg/day and 30 mg/kg/day, respectively, during the period of organogenesis. With the exception of a slight decrease in maternal body weight gain in the rabbits, there were no significant effects of ondansetron on the maternal animals or the development of the offspring. At doses of 15 mg/kg/day in rats and 30 mg/kg/day in rabbits, the maternal dose was approximately 6 and 24 times the maximum recommended human oral dose of 24 mg/day, respectively, based on body surface area. In a pre- and postnatal developmental toxicity study, pregnant rats received oral doses of ondansetron up to 15 mg/kg/day from Day 17 of pregnancy to litter Day 21. With the exception of a slight reduction in maternal body weight gain, there were no effects upon the pregnant rats and the pre- and postnatal development of their offspring, including reproductive performance of the mated F1 generation. At a dose of 15 mg/kg/day in rats, the maternal dose was approximately 6 times the maximum recommended human oral dose of 24 mg/day based on BSA.

### Lactation

### Risk Summary

It is not known whether Zofran is transferred into human milk. There are no data on the effects of Zofran on the breastfed child or the effects of Zofran on milk production. However, it has been demonstrated that ondansetron passes into the milk of lactating animals (rats). It is therefore recommended that mothers receiving ondansetron should not breast-feed their babies.

### Females and males of reproductive potential

### Pregnancy testing

Pregnancy status should be verified for females of reproductive potential prior to starting the treatment with Zofran.

### Contraception

Females of reproductive potential should be advised that it is possible that Zofran can cause harm to the developing fetus. Sexually active females of reproductive potential are recommended to use effective contraception (methods that result in less than 1 % pregnancy rates) when using Zofran during the treatment and for two days after stopping treatment with Zofran.

### Infertility

There is no effect of Zofran on fertility.

## OVERDOSAGE

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 ADVERSE DRUG REACTIONS).

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.

## CLINICAL PHARMACOLOGY

### Mechanism of action (MOA)

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 probably due to antagonism of $5HT_3$ 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.

### Pharmacodynamics (PD)

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.

### Pharmacokinetics (PK)

The pharmacokinetic properties of ondansetron are unchanged on repeat dosing.

### Absorption

Equivalent systemic exposure is achieved after IM and IV administration of ondansetron.

### 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)

Early Phase I studies in healthy elderly volunteers showed a slight age-related decrease in clearance, and an increase in half-life of ondansetron. However, wide inter-subject variability resulted in considerable overlap in pharmacokinetic parameters between young (< 65 years of age) and elderly subjects (≥ 65 years of age) and there were no overall differences in safety or efficacy observed between young and elderly cancer patients enrolled in CINV clinical trials to support a different dosing recommendation for the elderly.

Based on more recent ondansetron plasma concentrations and exposure-response modelling, a greater effect on QTcF is predicted in patients ≥75 years of age compared to young adults. Specific dosing information is provided for patients over 65 years of age and over 75 years of age for intravenous dosing (see section DOSAGE REGIMEN AND ADMINISTRATION).

### Paediatric population (aged 3 to 17 years)

The half-life is 2.9 hours for patients 3 to 12 year age range.

In paediatric patients aged 3 to 12 years undergoing elective surgery with general anaesthesia, the absolute values for both the clearance and volume of distribution of ondansetron were reduced in comparison to values with adult patients. Both parameters increased in a linear fashion with weight and by 12 years of age, the values were approaching those of young adults. When clearance and volume of distribution values were normalised by body weight, the values for these parameters were similar between the different age group populations. Use of weight-

based dosing compensates for age-related changes and is effective in normalising systemic exposure in paediatric patients.

Population pharmacokinetic analysis was performed on 428 subjects (cancer patients, surgery patients and healthy volunteers) aged 1 month to 44 years following IV administration of ondansetron. Based on this analysis, systemic exposure (AUC) of ondansetron following oral or IV dosing in children and adolescents was comparable to adults, with the exception of infants aged 1 to 4 months. 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. It is difficult to conclude whether there was an additional reduction in clearance related to age in infants (1 to 4 months) or simply inherent variability due to the low number of subjects studied in this age group. Since patients less than 6 months of age will only receive a single dose in PONV a decreased clearance is not likely to be clinically relevant.

#### Renal impairment

In patients with moderate renal impairment (creatinine clearance 15 to 60 mL/min), both systemic clearance and volume of distribution are reduced following IV administration of ondansetron, 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 following IV administration.

### 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.

## CLINICAL STUDIES

### Children and adolescents (aged 3 to 17 years)

### CINV

The efficacy of ondansetron in the control of emesis and nausea induced by cancer chemotherapy was assessed in a double-blind randomized trial in 415 patients aged 1 to 18 years (S3AB3006). On the days of chemotherapy, patients received either ondansetron 5 mg/m$^2$ IV and ondansetron 4 mg orally after 8 to 12 hours or ondansetron 0.45 mg/kg IV and placebo orally after 8 to 12 hours. Post-chemotherapy both groups received 4 mg ondansetron syrup twice daily for 3 days. Complete control of emesis on worst day of chemotherapy was 49% (5 mg/m$^2$ IV and ondansetron 4 mg orally) and 41% (0.45 mg/kg IV and placebo orally). Post-chemotherapy both groups received 4 mg ondansetron syrup twice daily for 3 days. There was no difference in the overall incidence or nature of adverse events between the two treatment groups.

A double-blind randomized placebo-controlled trial (S3AB4003) in 438 patients aged 1 to 17 years demonstrated complete control of emesis on worst day of chemotherapy in:

- 73% of patients when ondansetron was administered intravenously at a dose of 5 mg/m$^2$ IV together with 2 to 4 mg dexamethasone orally.

- 71% of patients when ondansetron was administered as syrup at a dose of 8 mg together with 2 to 4 mg dexamethasone orally on the days of chemotherapy.

Post-chemotherapy both groups received 4 mg ondansetron syrup twice daily for 2 days. There was no difference in the incidence or nature of adverse events between the two treatment groups.

The efficacy of ondansetron in 75 children aged 6 to 48 months was investigated in an open-label, non-comparative, single-arm study (S3A40320). All children received three 0.15 mg/kg doses of IV ondansetron, administered 30 minutes before the start of chemotherapy and then at 4 and 8 hours after the first dose. Complete control of emesis was achieved in 56% of patients.

Another open-label, non-comparative, single-arm study (S3A239) investigated the efficacy of one IV dose of 0.15 mg/kg ondansetron followed by two oral ondansetron doses of 4 mg for children aged < 12 years and 8 mg for children aged ≥ 12 years (total no. of children n= 28). Complete control of emesis was achieved in 42% of patients.

## PONV

The efficacy of a single dose of ondansetron in the prevention of post-operative nausea and vomiting was investigated in a randomized, double-blind, placebo-controlled study in 670 children aged 1 to 24 months (post-conceptual age ≥44 weeks, weight ≥ 3 kg). Included subjects were scheduled to undergo elective surgery under general anesthesia and had an ASA status ≤ III. A single dose of ondansetron 0.1 mg/kg was administered within five minutes following induction of anesthesia. The proportion of subjects who experienced at least one emetic episode during the 24-hour assessment period (ITT) was greater for patients on placebo than those receiving ondansetron (28% vs. 11%, p <0.0001).Four double-blind, placebo-controlled studies have been performed in 1469 male and female patients (2 to 12 years of age) undergoing general anesthesia. Patients were randomized to either single IV doses of ondansetron (0.1 mg/kg for pediatric patients weighing 40 kg or less, 4 mg for pediatric patients weighing more than 40 kg; number of patients = 735)) or placebo (number of patients = 734). Study drug was administered over at least 30 seconds, immediately prior to or following anesthesia induction. Ondansetron was significantly more effective than placebo in preventing nausea and vomiting. The results of these studies are summarized in Table 5.

**Table 5 Prevention and treatment of PONV in Pediatric Patients – Treatment response over 24 hours**

| Study | Endpoint | Ondansetron (%) | Placebo (%) | p value |
|---|---|---|---|---|
| S3A380 | CR | 68 | 39 | ≤0.001 |
| S3GT09 | CR | 61 | 35 | ≤0.001 |
| S3A381 | CR | 53 | 17 | ≤0.001 |
| S3GT11 | no nausea | 64 | 51 | 0.004 |
| S3GT11 | no emesis | 60 | 47 | 0.004 |

*CR = no emetic episodes, rescue or withdrawal*

## NON-CLINICAL SAFETY DATA

A study in cloned human cardiac ion channels has shown ondansetron has the potential to affect cardiac repolarisation via blockade of hERG potassium channels at clinically relevant concentrations.

Dose-dependent QT prolongation has been observed in a thorough QT study in human volunteers (see section CLINICAL PHARMACOLOGY).

### Reproductive toxicity

See section PREGNANCY, LACTATION, FEMALES AND MALES OF REPRODUCTIVE POTENTIAL.

### Incompatibilities

**Compatibility with IV fluids**

Compatibility studies have shown that unpreserved ondansetron injection is stable for seven days at room temperature (below 25°C) under fluorescent lighting or in a refrigerator with the following IV infusion fluids:

- Sodium Chloride IV Infusion BP 0.9% w/v.
- Glucose IV Infusion BP 5% w/v.
- Mannitol IV Infusion BP 10% w/v.
- Ringers IV Infusion.
- Potassium Chloride 0.3% w/v and Sodium Chloride 0.9% w/v IV Infusion BP.
- Potassium Chloride 0.3% w/v and Glucose 5% w/v IV Infusion BP.

### Compatibility with other drugs

Ondansetron may be administered by IV infusion at 1 mg/h, from an infusion bag or syringe pump. The following drugs may be administered via the Y-site of the ondansetron giving set for ondansetron concentrations of 16 to 160 micrograms/mL (e.g. 8 mg/500mL and 8 mg/50mL respectively):

| | |
|---|---|
| Cisplatin | Concentrations up to 0.48 mg/mL (e.g. 240 mg in 500 mL) administered over one to eight hours. |
| 5-fluorouracil | Concentrations up to 0.8 mg/mL (e.g. 2.4 g in 3 L or 400 mg in 500 mL) administered at a rate of at least 20 mL/h (500 mL per 24 hours). Higher concentrations of 5-fluorouracil may cause precipitation of ondansetron. The 5-fluorouracil infusion may contain up to 0.045 % w/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 10 minutes to 1 hour. |
| Etoposide | Concentrations in the range 0.144 mg/mL to 0.25 mg/mL (e.g. 72 mg in 500 mL to 250 mg in 1L), administered over 30 minutes to 1 hour. |
| Ceftazidime | Doses in the range 250 mg to 2000 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 IV 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 IV bolus injection over approximately 5 minutes. |
| Doxorubicin | Doses in the range 10 to 100 mg reconstituted with Water for Injections BP, 5 mL per 10 mg doxorubicin, as recommended by the manufacturer and given as an IV bolus injection over approximately five minutes. |
| Dexamethasone | Dexamethasone sodium phosphate 20 mg may be administered as a slow IV injection over 2 to 5 minutes via the Y-site of an infusion set delivering 8 to 16 mg of ondansetron diluted in 50 to 100 mL of a compatible infusion fluid over approximately 15 minutes. Compatibility between dexamethasone sodium phosphate and ondansetron has been demonstrated supporting administration of these drugs through the same giving set resulting in concentrations in line of 32 micrograms to 2.5 mg/mL for dexamethasone sodium phosphate and 8 micrograms to 1 mg/mL for ondansetron. |

## STORAGE

### Special precautions for storage

Store below 30°C. Protect from light.
Zofran should not be used after the date marked “EXP” on the pack.

Zofran must be kept out of the reach and sight of children**.**

## Nature and Contents of Container

Zofran injection is available in:

Glass ampoules containing ondansetron 4 mg in 2 ml, packed in boxes of 10's.
Glass ampoules containing ondansetron 8 mg in 4 ml, packed in boxes of 8's.

Not all presentations are available in every country.

## Instructions for use and handling

## Injection:

Ondansetron injection should not be administered in the same syringe or infusion as any other medication (see section INCOMPATIBILITIES).

Ondansetron injection should only be mixed with those infusion solutions which are recommended (see section INCOMPATIBILITIES).

**Solution for injection:**

The solution for injection are unpreserved, should only be used once and injected or diluted immediately after opening. Any remaining solution should be discarded.

Ondansetron injection ampoules should not be autoclaved.

Compatibility studies have been carried out in polyvinyl chloride infusion bags and polyvinyl chloride administration sets. Stability is conferred by the use of polyethylene infusion bags or Type 1 glass bottles.

Dilutions of unpreserved ondansetron injection in sodium chloride 0.9% w/v or in dextrose 5% w/v have been demonstrated to be stable in polypropylene syringes. Therefore, it is considered that unpreserved ondansetron injection diluted with compatible infusion fluids recommended below would also be stable in polypropylene syringes.

In keeping with good pharmaceutical practice, IV solutions should be prepared at the time of infusion, under appropriate aseptic conditions.

## Product Registration Holder:

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## Malaysia Package Leaflet

Information issued: Mar 2021

Revision date: Jan 2024