NOVARTIS

TRADE NAME

Zofran™

DESCRIPTION AND COMPOSITION

Pharmaceutical form

ZOFRAN tablets 8 mg: Yellow, oval, film-coated tablet engraved with 'GXET5' on one face and plain on the other face. Each tablet contains ondansetron 8 mg as hydrochloride dihydrate.

Active substance

Ondansetron

Excipients

Lactose
Microcrystalline cellulose
Pregelatinised maize starch
Magnesium stearate
Methyl hydroxypropylcellulose
Titanium dioxide (E171)
Iron oxide (E172)

INDICATIONS

Adults

ZOFRAN oral formulations are indicated for the management of nausea and vomiting induced by cytotoxic chemotherapy and radiotherapy.

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

Paediatric Population

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

Dosing 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.

Adults

EMETOGENIC CHEMOTHERAPY AND RADIOTHERAPY

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 later for a maximum of 5 days.

To protect against delayed or prolonged emesis after the first 24 hours, oral treatment with *ZOFRAN* should be continued for up to 5 days after a course of treatment. The recommended oral dose is 8 mg to be taken twice daily.

HIGHLY EMETOGENIC CHEMOTHERAPY e.g. high-dose cisplatin

ZOFRAN can be given by oral, intravenous (IV), or intramuscular (IM) administration.

ZOFRAN has been shown to be equally effective in the following dose schedules over the first 24 hours of chemotherapy:

- A single dose of 8 mg by slow intravenous injection immediately before chemotherapy.
- A dose of 8 mg by slow intravenous injection immediately before chemotherapy, followed by two further intravenous dose of 8 mg two to four hours apart, or by a constant infusion of 1 mg/hour for up to 24 hours. Doses of greater than 8 mg up to 16 mg of *ZOFRAN* may only be given by IV infusion 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 due to dose-dependent increase of QT-prolongation risk (*see Warnings and Precautions, Adverse Reactions, Pharmacodynamic Effects*).

The efficacy of *ZOFRAN* in highly emetogenic chemotherapy may be enhanced by the addition of a single intravenous dose of dexamethasone sodium phosphate 20 mg administered prior to chemotherapy.

To protect against delayed or prolonged emesis after the first 24 hours, oral treatment with *ZOFRAN* should be continued for up to 5 days after a course of treatment. The recommended oral dose is 8 mg to be taken twice daily.

CINV in Children and Adolescents (aged 2 years and over)

In children with a body surface area of 0.6 to 1.2 m^2 ondansetron is administered as a single i.v. dose of 5 mg/m^2 immediately before chemotherapy, followed by 4 mg orally 12 hours later. 4 mg orally twice daily can be continued for up to 5 days after a course of treatment.

CINV and RINV in Elderly

No alteration of oral dose, or frequency of administration is required.

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 anesthesia.

For treatment of established post-operative nausea and vomiting, *ZOFRAN* administration by injection is recommended.

PONV in Children and Adolescents (aged 2 years and over)

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 *ZOFRAN* in the prevention and treatment of post-operative nausea and vomiting in the elderly, however *ZOFRAN* 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.

Methods of administration

The tablets should be swallowed whole with liquid.

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 sections WARNINGS AND PRECAUTIONS and 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.

Therefore, caution should be exercised in patients with cardiac rhythm or conduction disturbances, in patients treated with anti-arrhythmic agents or beta-adrenergic blocking agents and in patients with significant electrolyte disturbances.

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 ondansetron administration.

Serotonin syndrome has been described following the concomitant use of *ZOFRAN* and other serotonergic drugs (see section INTERACTIONS). If concomitant treatment with *ZOFRAN* and other serotonergic drugs is clinically warranted, appropriate observation of the patient is advised.

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

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 pains 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.

Local burning sensation following insertion of suppositories.

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.

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/Zydis 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. Adverse drug reactions are listed according to system organ classes in MedDRA.

Cardiac disorders

Myocardial ischemia

INTERACTIONS

There is no evidence that *ZOFRAN* 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 *ZOFRAN* is administered with alcohol, temazepam, furosemide, tramadol or propofol.

Ondansetron is metabolised by multiple hepatic cytochrome P-450 enzymes: CYP3A4, CYP2D6 and CYP1A2. Due to the multiplicity of metabolic enzymes capable of metabolising ondansetron, enzyme inhibition or reduced activity of one enzyme (e.g. CYP2D6 genetic deficiency) is normally compensated by other enzymes and should result in little or no significant change in overall ondansetron clearance or dose requirement.

Use of *ZOFRAN* with QT prolonging drugs and/or drugs that cause electrolyte abnormalities may result in additional QT prolongation. Concomitant use of *ZOFRAN* with cardiotoxic drugs (e.g. anthracyclines) may increase the risk of arrhythmias. Therefore, caution should be exercised when ondansetron is co-administered with drugs that prolong the QT interval and/or cause electrolyte abnormalities and/or cardiotoxic drugs (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 *ZOFRAN* 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 *ZOFRAN* 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(see Human data). Regarding cardiac malformations the epidemiological studies showed conflicting results.

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 reported 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, adjusted RR 1.3 (95% CI 0.86-1.8).

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 ondansetron is transferred into human milk. There are no data on the effects of ondansetron on the breastfed child or the effects of ondansetron 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 *ZOFRAN* 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

Symptoms and Signs

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 section ADVERSE DRUG REACTIONS). Manifestations that have been reported include visual disturbances, severe constipation, hypotension and a vasovagal episode with transient second degree AV block. In all instances, the events resolved completely.

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 *ZOFRAN*, therefore in cases of suspected overdose, symptomatic and supportive therapy should be given as appropriate.

The use of ipecacuanha to treat overdose with *ZOFRAN* is not recommended as patients are unlikely to respond due to the anti-emetic action of ondansetron itself.

CLINICAL PHARMACOLOGY

Pharmacotherapeutic group, ATC Code

Serotonin ($5HT_3$) antagonist, A04AA01

Mechanism of Action

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, 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. No significant changes were seen in the measured electrocardiographic PR or QRS intervals.

Pharmacokinetics (PK)

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).

Children and Adolescents (aged 2 years and over)

In pediatric patients aged 3 to 12 years undergoing elective surgery with general anesthesia, 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 pediatric patients.

Elderly

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.

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 hemodialysis (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.

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 – QT Prolongation).

Reproductive toxicity

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

PHARMACEUTICAL INFORMATION

Incompatibilities

None reported.

Storage

Store below 30°C.

Instructions for use and handling

None.

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TM = Trademark

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