ZOFRAN™ TABLETS
Ondansetron hydrochloride dihydrate

QUALITATIVE AND QUANTITATIVE COMPOSITION

ZOFRAN tablets 8 mg: Each tablet contains ondansetron 8 mg as hydrochloride dihydrate.

PHARMACEUTICAL FORM

ZOFRAN tablets 8 mg: Yellow, oval, film-coated tablet engraved with ‘GXET5’ on one face and plain on the other face.

CLINICAL PARTICULARS

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

Injection and oral 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 and Administration

ZOFRAN is available for oral and parenteral use to allow the route of administration and dosing to be flexible.

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 m² ondansetron is administered as a single i.v. dose of 5 mg/m² 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.

- 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.

POST-OPERATIVE NAUSEA AND VOMITING (PONV)

• PONV in Adults

For prevention of post-operative nausea and vomiting, the recommended oral dose is 16 mg given 1 hour prior to anaesthesia.

For treatment of established post-operative nausea and vomiting, 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.

• 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.

• 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.

Hypersensitivity to any component of the preparation.

**Warnings and Precautions**

Hypersensitivity reactions have been reported in patients who have exhibited hypersensitivity to other selective 5HT₃ receptor antagonists.

Ondansetron prolongs the QT interval in a dose-dependent manner (see Pharmacodynamic Effects). 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.

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 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.

**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 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 Warnings and Precautions*).

**Tramadol**

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

**Pregnancy and Lactation**

**Pregnancy**

The safety of ZOFRAN for use in human pregnancy has not been established. Evaluation of experimental animal studies does not indicate direct or indirect harmful effects with respect to the development of the embryo, or foetus, the course of gestation and peri- and post-natal development. However as animal studies are not always predictive of human response the use of ZOFRAN in pregnancy is not recommended.

**Lactation**

Tests have shown that ondansetron passes into the milk of lactating animals. It is therefore recommended that mothers receiving ZOFRAN should not breast-feed their babies.

**Effects on Ability to Drive and Use Machines**

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

**Adverse Reactions**

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.

General disorders and administration site conditions

Common: Local IV injection site reactions.

Overdose

Symptoms and Signs

There is limited experience of ZOFRA\text{N} overdose. In the majority of cases symptoms were similar to those already reported in patients receiving recommended doses (see Adverse 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.

Treatment

There is no specific antidote for ZOFRA\text{N}, therefore in cases of suspected overdose, symptomatic and supportive therapy should be given as appropriate.

The use of ipecacuanha to treat overdose with ZOFRA\text{N} is not recommended as patients are unlikely to respond due to the anti-emetic action of ondansetron itself.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamics

Mechanism of Action

Ondansetron is a potent, highly selective 5HT\text{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\text{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\text{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.

**Pharmacodynamic Effects**

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**

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 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.

- **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 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.
Pre-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 Pharmacodynamic Effects– QT prolongation).

PHARMACEUTICAL PARTICULARS

List of Excipients

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

Special Precautions for Storage

Store below 30°C.

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