10000000035368

ZOFRAN™ TABLETS

Ondansetron

QUALITATIVE AND QUANTITATIVE COMPOSITION

ZOFRAN tablets 4 mg: Each film-coated tablet contains ondansetron 4 mg as hydrochloride dihydrate.

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

Not all presentations are available in every country.

PHARMACEUTICAL FORM

ZOFRAN tablets 4 mg: Yellow, oval, biconvex, film coated tablet embossed with 'GLAXO' on one face and '4' on the other.

ZOFRAN tablets 8 mg: Yellow, oval, biconvex, film coated tablet embossed with 'GLAXO' on one face and '8' on the other.

CLINICAL PARTICULARS

Indications

ZOFRAN tablets are indicated for the management of nausea, retching and vomiting induced by cytostatic therapy and radiotherapy.

ZOFRAN 8 mg is also indicated for the prevention of post-operative nausea, retching and vomiting.

Dosage and Administration

Nausea, retching and vomiting caused by cytostatic therapy and radiotherapy

- **Adults**

Moderately emetogenic chemotherapy protocols, e.g. with cyclophosphamide, doxorubicin, carboplatin :

Immediately before chemotherapy give 8 mg ondansetron by slow intravenous injection or infusion over 15 minutes

or

Give 8 mg ondansetron orally 1-2 hours before chemotherapy.

The treatment is continued for up to a total of 5 days with 8 mg orally every 12 hours (mornings and evenings).

Nausea, retching and vomiting during radiotherapy

Give 8 mg ondansetron orally every 12 hours (mornings and evenings). The first dose should be taken 1-2 hours before the radiation. The length of treatment depends on the length of radiotherapy given.

HIGHLY EMETOGENIC CHEMOTHERAPY e.g. with cisplatin

On the day of chemotherapy according to therapeutic requirements

either

immediately before administration of the chemotherapy inject 8 mg ondansetron slowly by the i.v. route or infuse over 15 minutes. Then continue as a continuous i.v. infusion at a rate of 1 mg/hour for up to 24 hours or give two further doses of 8 mg ondansetron at intervals of 2-4 hours either as a slow i.v. injection or as a 15 minute short infusion.

or

immediately before administration of the chemotherapy give an infusion of 32 mg ondansetron diluted in 50-100 ml physiological saline solution or another compatible infusion solution over at least 15 minutes

or

immediately before administration of the chemotherapy inject 8 mg ondansetron slowly by the intravenous route.

The anti-emetogenic efficacy of Zofran can be increased by a single intravenous dose of 20 mg dexamethasone 21-dihydrogenphosphate disodium salt before the start of chemotherapy, in the case of highly emetogenic chemotherapy. After chemotherapy the treatment is continued for up to 5 days with 8 mg ondansetron orally every 12 hours (mornings and evenings).

- **Children**

Experience is currently limited. In children over the age of 2 years 5 mg/m^2 can be administered by the i.v. route over 15 minutes immediately before chemotherapy followed by oral administration of 4 mg ondansetron every 12 hours (mornings and evenings) over 5 days.

- **Elderly**

ZOFRAN is well tolerated by patients over 65 years and no alteration of dosage, dosing frequency or route of administration are 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 should not be exceeded.

POST-OPERATIVE NAUSEA, RETCHING AND VOMITING

- **Adults**

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

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

- **Elderly**

There is limited experience in the use of *ZOFRAN* in the prevention and treatment of post-operative nausea, retching and vomiting in the elderly, however *ZOFRAN* is well tolerated in patients over 65 years receiving chemotherapy.

- **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 should not be exceeded.

Contraindications

Hypersensitivity to any component of the preparation.

ZOFRAN must not be used in children under the age of 2 years as there is insufficient experience in this age group

Warnings and Precautions

Hypersensitivity reactions have been reported in patients who have exhibited hypersensitivity to other selective 5HT$_3$ receptor antagonists.

Very rarely and predominantly with intravenous ondansetron, transient ECG changes including QT interval prolongation have been reported

As *ZOFRAN* is known to increase large bowel transit time, patients with signs of subacute intestinal obstruction should be monitored following administration.

Patients with the rare hereditary galactose intolerance, lactase deficiency or glucose-galactose malabsorption should not take Zofran film-coated tablets.

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, frusemide, 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.

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.

Tramadol

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

Pregnancy and Lactation

The safety of ondansetron 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.

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.

Adverse Reactions

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 (≥1/1000 and <1/100), rare (≥1/10,000 and <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* according to indication and formulation.

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).

Eye disorders

Rare: Transient visual disturbances (e.g. blurred vision) predominantly during i.v. administration.

Very rare: transient blindness predominantly during intravenous 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.

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.

Overdose

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 Adverse Reactions)*. 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.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamics

Ondansetron is a potent, highly selective 5HT$_3$ receptor-antagonist. Its precise mode of action in the control of nausea, retching 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, retching 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, retching and vomiting are not known but there may be common pathways with cytotoxic induced nausea, retching and vomiting.

Ondansetron does not alter plasma prolactin concentrations.

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.

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, i.m. or i.v. 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, i.m. or i.v. dosing is similar with a terminal elimination half life of about 3 hours.

PHARMACEUTICAL PARTICULARS

List of Excipients

Lactose
Microcrystalline cellulose
Pregelatinised maize starch
Magnesium stearate (Ph. Eur.)
hypromellose
Titanium dioxide (E171)
Iron oxide (E172)

Incompatibilities

None reported.

Shelf Life

The expiry date is indicated on the packaging.

Special Precautions for Storage

Do not store above 30°C.

Instructions for Use/Handling

None.

Version number: GDS 27/IPI04
Date of issue: 22 July 2005

THIS IS A MEDICAMENT

Medicament is a product which affects your health and its consumption contrary to instructions is dangerous for you.

Follow strictly the doctor's prescription, the method of use and the instructions of the pharmacist who sold the medicament.

- The doctor and the pharmacist are the experts in medicines, their benefits and risks.
- Do not by yourself interrupt the period of treatment prescribed.
- Do not repeat the same prescription without consulting your doctor.
- Keep all medicaments out of reach of children.

Council of Arab Health Ministers,
Union of Arab Pharmacists.

GlaxoSmithKline

Packed by
Pharmaline - Lebanon
Licensed by
GlaxoSmithKline Export Limited, U.K.

Rev. 04/2010 905076-A