Ondansetron

QUALITATIVE AND QUANTITATIVE COMPOSITION
Each suppository contains 16 mg of ondansetron.

PHARMACEUTICAL FORM
White torpedo shaped suppositories.

CLINICAL PARTICULARS

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

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

CHEMOTHERAPY AND RADIOTHERAPY INDUCED NAUSEA AND VOMITING
The emetogenic potential of cancer treatment varies according to the doses and combinations of chemotherapy and radiotherapy regimens used. The selection of dose regimen should be determined by the severity of the emetogenic challenge.

• Adults
EMETOCYTOGENIC CHEMOTHERAPY AND RADIOTHERAPY
The recommended dose of ZOFRAN suppositories is one 16 mg suppository given 1 to 2 h before treatment. To protect against delayed or prolonged emesis after the first 24 h, oral or rectal treatment with ZOFRAN should be continued for up to five days after a course of treatment. The recommended daily dose of ZOFRAN suppositories is one 16 mg suppository.

HIGHLY EMETOCYTOGENIC CHEMOTHERAPY e.g. high-dose cisplatin
ZOFRAN can be given by oral, i.v., i.m. or rectal administration.

The recommended dose of ZOFRAN suppositories is one 16 mg suppository given 1 to 2 h before treatment. The efficacy of ZOFRAN in highly emetogenic chemotherapy may be enhanced by the addition of a single i.v. dose of dexamethasone sodium phosphate, 20 mg administered prior to chemotherapy. To protect against delayed or prolonged emesis after the first 24 h, oral or rectal treatment with ZOFRAN should be continued for up to five days after a course of treatment. The recommended daily dose of ZOFRAN suppositories is one 16 mg suppository.

• Children
The use of ZOFRAN suppositories in children is not recommended. The usual method of administration is i.v. followed by oral therapy (see Children – Oral Formulations and Injection above).

• 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 and therefore parenteral or oral administration is recommended.

• 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 are required.
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 in 10
- common: ≥1 in 100 and <1 in 10
- uncommon: ≥1 in 1,000 and <1 in 100
- rare: ≥1 in 10,000 and <1 in 1,000
- 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).
Rare: Dizziness during rapid i.v. administration.

**Contraindications**
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.

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.

**Interactions**
There is no evidence that ZOFRAN either induces or inhibits the metabolism of other drugs commonly coadministered 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.
**Eye disorders**
Rare: Transient visual disturbances (eg. blurred vision) during rapid i.v. administration.

**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. 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.

**General disorders and administration site conditions**
Common: Local i.v. injection site reactions.

**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 5HT3 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 5HT3 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 5HT3 receptors on neurons located both in the peripheral and central nervous system.

Ondansetron does not alter plasma prolactin concentrations.

**Pharmacokinetics**
The pharmacokinetic properties of ondansetron are unchanged on repeat dosing.

**Absorption**
Following administration of an Ondansetron Suppository, plasma ondansetron concentrations become detectable between 15 and 60 mins after dosing. Concentrations rise in an essentially linear fashion, until peak concentrations of 20 to 30 nanograms/ml are attained, typically 6h after dosing. Plasma concentrations then fall, but at a slower rate than observed following oral dosing due to continued absorption of ondansetron.

The absolute bioavailability of ondansetron from the suppository is approximately 60%.

**Distribution**
Ondansetron is not highly protein bound (70 to 76%).

**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.
Pre-clinical Safety Data
No additional data of relevance.

PHARMACEUTICAL PARTICULARS

List of Excipients
Witepsol S58.

Incompatibilities
None reported.

Shelf Life
The expiry date is indicated on the packaging.

Special Precautions for Storage
Store below 30oC.

Nature and Contents of Container
As registered locally.

Instructions for Use/Handling
Do not swallow this medicine.
Empty your bowels if necessary.
Wash your hands.
Remove the suppository from its packaging.
You may find that insertion of the suppository will be easier if you squat or bend forward.
Insert the suppository into the back passage (rectum).
Wash your hands.
Try not to empty your bowels within 1 h of inserting the suppository.

Version number: GDS27/IPI03
Date of issue: 22 July 2005
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The half-life of the elimination phase is determined by the rate of ondansetron absorption, not systemic clearance, and is approximately 6 h.

Special Patient Populations

• Gender
Absolute bioavailability is not affected by gender. Females show a small, clinically insignificant, increase in half-life in comparison with males.

• Elderly
Studies in healthy elderly volunteers show slight age-related increases in both oral bioavailability and half-life of ondansetron.
Specific studies in the elderly or patients with renal impairment have been limited to i.v. and oral administration. However, it is anticipated that the half-life of ondansetron in elderly patients will be similar to that seen in healthy volunteers since the rate of elimination of ondansetron following administration of a suppository is not determined by systemic clearance.

• 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 i.v. administration of ondansetron, resulting in a slight, but clinically insignificant, increase in elimination half-life (5.4 h). A study in patients with severe renal impairment who required regular haemodialysis (studied between dialyses) showed ondansetron’s pharmacokinetics to be essentially unchanged following i.v. administration.
Specific studies in patients with renal impairment have been limited to IV and oral administration. However, it is anticipated that the half-life of ondansetron in patients with renal impairment will be similar to that seen in healthy volunteers since the rate of elimination of ondansetron following administration of a suppository is not determined by systemic clearance.

• Hepatic Impairment
The pharmacokinetics of ondansetron following administration as a suppository have not been evaluated in patients with hepatic impairment.