ZOFRAN™ INJECTION
GlaxoSmithKline

Ondansetron

QUALITATIVE AND QUANTITATIVE COMPOSITION
Each 1 ml of aqueous solution contains 2 mg ondansetron as hydrochloride dihydrate.

PHARMACEUTICAL FORM
A clear, colourless, sterile solution for injection or infusion.

CLINICAL PARTICULARS
Indications
ZOFRAN injection is indicated for the management of nausea and vomiting induced by cytotoxic chemotherapy and radiotherapy.
ZOFRAN is also indicated for the prevention and treatment of post-operative nausea and vomiting.

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
EMETOGENIC CHEMOTHERAPY AND RADIOTHERAPY
The recommended i.v. or i.m. dose of ondansetron is 8 mg administered as a slow injection immediately before treatment.
Oral or rectal treatment is recommended to protect against delayed or prolonged emesis after the first 24 h.

HIGHLY EMETOGENIC CHEMOTHERAPY e.g. high-dose cisplatin

ZOFRAN can be given by oral, i.v., i.m. or rectal administration.
Ondansetron may be administered as a single 8 mg i.v. or i.m. dose immediately before chemotherapy. Doses of greater than 8 mg and up to 32 mg of ondansetron may only be given by i.v. infusion diluted in 50 to 100 ml of saline or other compatible infusion fluid (see Instructions for Use and Handling) and infused over not less than 15 mins.
Alternatively a dose of 8 mg of ondansetron may be administered by slow i.v. or i.m. injection immediately before chemotherapy, followed by two further i.v. or i.m. doses of 8 mg 2 to 4 h apart, or by a constant infusion of 1 mg/h for up to 24 h.
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.
Oral or rectal treatment is recommended to protect against delayed or prolonged emesis after the first 24 h.

• Children and Adolescents (aged 6 months to 17 years)
In children with a body surface area of less than 0.6 m2 an initial i.v. dose of 5 mg/m2 is administered immediately before chemotherapy, followed by a 2 mg oral dose of ondansetron syrup 12 h later. 2 mg orally twice daily can be continued for up to five days after a course of treatment.
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 h later. 4 mg orally twice daily can be continued for up to five days after a course of treatment.
For children with a body surface area of greater than 1.2 m2 an initial i.v. dose of 8 mg is administered immediately before chemotherapy, followed by 8 mg orally 12 hours later.
8 mg orally twice daily can be continued for up to five days after a course of treatment. Alternatively, in children aged 6 months or older, ondansetron is administered as a single i.v. dose of 0.15 mg/kg (not to exceed 8 mg) immediately before chemotherapy. This dose may be repeated every four hours for a total of three doses. 4 mg orally twice daily can be continued for up to five days after a course of treatment. Adult doses must not be exceeded.

• 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.

POST-OPERATIVE NAUSEA AND VOMITING

• Adults
For prevention of post-operative nausea and vomiting, the recommended dose of ondansetron injection is a single dose of 4 mg by i.m. or slow i.v. injection administered at the induction of anaesthesia. For treatment of established post-operative nausea and vomiting a single dose of 4 mg given by i.m. or slow i.v. injection is recommended.

• Children and Adolescents (aged 1 month to 17 years)
For prevention and treatment of PONV in paediatric patients having surgery performed under general anaesthesia, ondansetron may be administered by slow i.v. injection 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.

• 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 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.

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.

**Phenytin, 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 ondansetron 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 perinatal 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.

**Eye disorders**

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

**Eye disorders**

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.
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. 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. Ondansetron does not alter plasma prolactin concentrations.

### Pharmacokinetics

The pharmacokinetic properties of ondansetron are unchanged on repeat dosing.

**Absorption**

Equivalent systemic exposure is achieved after i.m. and i.v. administration of ondansetron.

**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 h.
Population pharmacokinetic analysis was performed on 74 patients aged 6 to 48 months following administration of 0.15 mg/kg i.v. ondansetron every 4 hours for three doses for the treatment of chemotherapy induced nausea and vomiting and 41 surgery patients aged 1 to 24 months following administration of a single 0.1 mg/kg or 0.2 mg/kg i.v. dose of ondansetron. Based on the population pharmacokinetic parameters for subjects aged 1 month to 48 months, administration of a 0.15 mg/kg i.v. dose of ondansetron every 4 hours for 3 doses would result in a systemic exposure (AUC) comparable to that observed in paediatric surgery subjects aged 5 to 24 months and previous paediatric studies in cancer (aged 4 to 18 years) and surgical (aged 3 to 12 years) subjects, at similar doses.

Elderly
Studies in healthy elderly volunteers show slight age-related increases in both oral bioavailability and half-life of ondansetron.

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.

Hepatic Impairment
In patients with severe hepatic impairment, ondansetron’s systemic clearance is markedly reduced with prolonged elimination half-lives (15 to 32 h) 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. The clinical relevance of this finding is uncertain.
ZOFRAN injection ampoules should not be autoclaved. Compatibility studies have been undertaken in polyvinyl chloride infusion bags and polyvinyl chloride administration sets. It is considered that adequate stability would also be conferred by the use of polyethylene infusion bags or Type 1 glass bottles. Since 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, it is considered that preserved or unpreserved ondansetron injection diluted with compatible infusion fluids recommended above would also be stable in polypropylene syringes.

Note: Preparation must be under the appropriate aseptic conditions if extended storage periods are required.

Compatibility with i.v. fluids
In keeping with good pharmaceutical practice i.v. solutions should be prepared at the time of infusion. However, unpreserved ondansetron injection has been shown to be stable for seven days at room temperature (below 25oC) under fluorescent lighting or in a refrigerator with the following i.v. infusion fluids:
- Sodium Chloride i.v. Infusion BP 0.9%w/v.
- Glucose i.v. Infusion BP 5%w/v.
- Mannitol i.v. Infusion BP 10%w/v.
- Ringers i.v. Infusion.
- Potassium Chloride 0.3%w/v and Sodium Chloride 0.9%/w/v i.v. Infusion BP.
- Potassium Chloride 0.3%/w/v and Glucose 5%/w/v i.v. Infusion BP.

Compatibility with other drugs
ZOFRAN may be administered by i.v. infusion at 1 mg/h, eg. 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 (eg 8 mg/500 ml and 8 mg/50 ml respectively);
- Cisplatin - Concentrations up to 0.48 mg/ml (eg. 240 mg in 500 ml) administered over one to eight h.
- 5-fluorouracil - Concentrations up to 0.8 mg/ml (eg...
2.4 g in 3 litres or 400 mg in 500 ml) administered at a rate of at least 20 ml per h (500 ml per 24 h). 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 (eg. 90 mg in 500 ml to 990 mg in 100 ml), administered over ten mins to one h.
- Etoposide - Concentrations in the range 0.144 mg/ml to 0.25 mg/ml (eg. 72 mg in 500 ml to 250 mg in 1 L), administered over thirty mins to one h.
- Cefazidime - Doses in the range 250 mg to 2000 mg reconstituted with Water for Injections BP as recommended by the manufacturer (eg. 2.5 ml for 250 mg and 10 ml for 2 g cefazidime) and given as an i.v. bolus injection over approximately five mins.
- 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 i.v. bolus injection over approximately five mins.
- 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 i.v. bolus injection over approximately five mins.
- Dexamethasone - Dexamethasone sodium phosphate 20 mg may be administered as a slow i.v. injection over 2 to 5 mins via the Y-site of an infusion set delivering 8 or 32 mg of ondansetron diluted in 50 to 100 ml of a compatible infusion fluid over approximately 15 mins. 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.

**Injection (preserved) multidose vials:** Compatibility studies have been undertaken in poly-vinyl chloride infusion bags and polyvinyl chloride administration sets. It is considered that adequate stability would also be conferred by the use of polyethylene infusion bags or Type 1 glass bottles. Since 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, it is considered that preserved or unpreserved ondansetron injection diluted with compatible infusion fluids recommended above would also be stable in polypropylene syringes.

**Compatibility with i.v. fluids**

In keeping with good pharmaceutical practice i.v. solutions should be prepared at the time of infusion. However, preserved ondansetron injection has been shown to be stable for 48 h at room temperature (below 25°C) with the following i.v. infusion fluids:

- Sodium Chloride i.v. Infusion BP 0.9%w/v.
- Sodium Chloride i.v. Infusion BP 3%w/v.
- Glucose i.v. Infusion BP 5%w/v.
- Sodium Chloride 0.9%w/v and Glucose 5%w/v i.v. Infusion BP.
- Sodium Chloride 0.45%w/v and Glucose 5%w/v i.v. Infusion BP.

Although compatibility studies have not been undertaken, in-line with the unpreserved ampoule formulation (see above) it is considered likely that adequate stability would also be maintained with the following additional i.v. infusion fluids:

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

**Compatibility with other drugs**

Ondansetron diluted in a compatible infusion fluid may be infused at a rate of 1 mg/h, eg. from an infusion bag or syringe pump. The following drugs may be administered via the Y-site of the giving set:
- Cisplatin: Concentrations up to 0.5 mg/ml (eg. 250 mg in 500 ml) given over one to eight h via the Y-site of an infusion set delivering ondansetron concentrations of 3 to 150 micrograms/ml (eg 1.5 mg/500 ml and 7.5 mg/50 ml respectively).

- Dexamethasone sodium phosphate: 20 mg given as a slow i.v. injection over two to five mins via the Y-site of an infusion set delivering ondansetron 8 mg/50 ml.

Not all presentations are available in every country.

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