Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Zofran 4mg/2ml Solution for Injection or Infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml contains 2mg ondansetron as hydrochloride dihydrate (4mg/2ml).

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for injection or infusion.
Clear, colourless solution.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Adults

Zofran Solution for Injection or Infusion is indicated for the management of nausea and vomiting induced by cytotoxic chemotherapy and radiotherapy. Zofran Solution for Injection or Infusion is also indicated for the prevention and treatment of post-operative nausea and vomiting.

Paediatric Population

Zofran Solution for Injection or Infusion is indicated for the management of nausea and vomiting induced by cytotoxic chemotherapy in children and adolescents aged from 6 months to 17 years.

IV Zofran injection is indicated for the prevention or treatment of post-operative nausea and vomiting in children and adolescents aged from 1 month to 17 years.

4.2 Posology and method of administration

Zofran is also available for oral and rectal 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.

CINV and RINV in Adults:-
The dose range of Zofran Solution for Injection or Infusion is 8 to 32 mg a day and selected as shown below.

Emetogenic Chemotherapy and Radiotherapy:
For most patients receiving emetogenic chemotherapy or radiotherapy, Zofran 8mg should be administered as a slow intravenous injection (in not less than 30 seconds) or intramuscular injection, immediately before treatment, followed by 8mg orally twelve hourly.

Highly emetogenic chemotherapy:
For patients receiving highly emetogenic chemotherapy, a maximum initial ondansetron dose of 16 mg IV infused over 15 minutes may be used. A single IV dose greater than 16 mg should not be given due to dose dependent increase of QT-prolongation risk (see sections 4.4, 4.8 and 5.1).

- A single dose of 8mg by slow intravenous injection (in not less than 30 seconds) or intramuscular injection immediately before chemotherapy.

- A dose of 8mg by slow intravenous injection (in not less than 30 seconds) or intramuscular injection immediately before chemotherapy, followed by two further intravenous injection (in not less than 30 seconds) or intramuscular doses of 8mg four hours apart, or by a constant infusion of 1mg/hour for up to 24 hours.
- A maximum initial intravenous dose of 16mg diluted in 50-100ml of of 0.9% Sodium Chloride Injection or other compatible infusion fluid (see section 6.6) and infused over not less than 15 minutes immediately before chemotherapy. The initial dose of Zofran may be followed by two additional 8mg intravenous doses (in not less than 30 seconds) or intramuscular doses four hours apart.

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

Oral treatment is recommended to protect against delayed or prolonged emesis after the first 24 hours. The recommended oral dose is 8 mg to be taken twice daily.

The selection of dose regimen should be determined by the severity of the emetogenic challenge.

Paediatric Population

CINV in Children and Adolescents (aged 6 months to 17 years):
The dose of CINV can be calculated based on body surface area (BSA) or weight. Weight-based dosing results in higher total daily doses compared to BSA-based dosing (section 4.4 and 5.1).

There are no data from controlled clinical trials on the use of Zofran in the prevention of chemotherapy-induced delayed or prolonged nausea and vomiting. There are no data from controlled clinical trials on the use of Zofran for radiotherapy-induced nausea and vomiting in children.

In paediatric clinical studies, ondansetron was given by IV infusion diluted in 25 to 50 ml of saline or other compatible infusion fluid (see section 6.6 Instructions for Use and Handling) and infused over not less than 15 minutes.

Dosing by Body Surface Area (BSA)

Ondansetron should be administered immediately before chemotherapy as a single IV dose of 5 mg/m^2. The single IV dose must not exceed 8 mg. Oral dosing can commence twelve hours later and may be continued for up to 5 days (Table 1). The total dose over 24 hours (given as divided doses) must not exceed adult dose of 32mg.

Table 1. BSA-based dosing for CINV (aged 6 months to 17 years)

BSA	Day 1[a,b]	Days 2-6[b]
< 0.6 m^2	5 mg/m^2 IV plus 2 mg syrup after 12 h	2 mg syrup every 12 h
> 0.6 m^2	5 mg/m^2 IV plus 4 mg syrup or tablet after 12 h	4 mg syrup or tablet every 12 h

a The intravenous dose must not exceed 8mg
b the total dose over 24 hours must not exceed adult dose of 32mg

Dosing by bodyweight

Weight-based dosing results in higher total daily doses compared to BSA-based dosing (section 4.4 and 5.1).

Ondansetron should be administered immediately before chemotherapy as a single IV dose of 0.15 mg/kg. The single IV dose must not exceed 8 mg.

On Day 1, two further IV doses may be given in 4-hourly intervals. Oral dosing can commence twelve hours later and may be continued for up to 5 days (Table 2). The total dose over 24 hours (given as divided doses) must not exceed adult dose of 32mg.

Table 2. Weight-based dosing for CINV (aged 6 months to 17 years)

Body Weight	Day 1[a,b]	Days 2-6[b]
≤ 10 kg	Up to 3 doses of 0.15 mg/kg IV every 4 h	2 mg syrup every 12 h
> 10 kg	Up to 3 doses of 0.15 mg/kg IV every 4 h	4 mg syrup or tablet every 12 h

a The intravenous dose must not exceed 8mg
b the total dose over 24 hours must not exceed adult dose of 32mg

CINV and RINV in Elderly:

In patients 65 to 74 years of age, the dose schedule for adults can be followed. All intravenous doses should be diluted in 50-100ml of 0.9% Sodium Chloride Injection or other compatible infusion fluid (see section 6.6) and infused over 15 minutes.

In patients 75 years of age or older, the initial intravenous dose of Zofran should not exceed 8 mg. All intravenous doses should be diluted in 50-100 ml of 0.9% Sodium Chloride Injection or other compatible infusion fluid (see section 6.6) and infused over 15 minutes. The initial dose of 8 mg may be followed by two further intravenous doses of 8 mg, infused over 15 minutes and given no less than four hours apart (see section 5.2).

POST-OPERATIVE NAUSEA AND VOMITING

PONV in Adults:-
For prevention of post-operative nausea and vomiting, the recommended dose of Zofran Solution for Injection or Infusion is a single dose of 4mg by intramuscular or slow intravenous injection administered at the induction of anaesthesia.

For treatment of established post-operative nausea and vomiting a single dose of 4mg given by intramuscular or slow intravenous injection is recommended.

Paediatric Population
PONV in Children and Adolescents (aged 1 month to 17 years):-
For prevention of PONV in paediatric patients having surgery performed under general anaesthesia, a single dose of Zofran may be administered by slow intravenous injection (not less than 30 seconds) at a dose of 0.1mg/kg up to a maximum of 4mg either prior to, at or after induction of anaesthesia.

For the treatment of PONV after surgery in paediatric patients having surgery performed under general anaesthesia, a single dose of Zofran may be administered by slow intravenous injection (not less than 30 seconds) at a dose of 0.1mg/kg up to a maximum of 4mg.

There are no data on the use of Zofran for the treatment of PONV in children under 2 years of age.

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.

PATIENTS WITH RENAL IMPAIRMENT

No alteration of daily dosage or frequency of dosing, or route of administration are required.

PATIENTS WITH HEPATIC IMPAIRMENT

Clearance of Zofran (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 8mg IV or oral should not be exceeded.

PATIENTS WITH POOR SPARTEINE/DEBRISOQUINE METABOLISM

The elimination half-life of Zofran (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.

4.3 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.

4.4 Special warnings and precautions for use

Hypersensitivity reactions have been reported in patients who have exhibited hypersensitivity to other selective $5HT_3$ receptor antagonists. Respiratory events should be treated symptomatically and clinicians should pay particular attention to them as precursors of hypersensitivity reactions.

Ondansetron prolongs the QT interval in a dose-dependent manner (see Section 5.1 Pharmacodynamic Properties). 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, conduction disturbances and in patients taking anti-arrhythmic agents or beta-adrenergic blocking agents or other medicinal products that lead to QT prolongation or electrolyte abnormalities.

Hypokalemia and hypomagnesemia should be corrected prior to ondansetron administration.

There have been post-marketing reports describing patients with serotonin syndrome (including altered mental status, autonomic instability and neuromuscular abnormalities) following the concomitant use of ondansetron and other serotonergic drugs (including selective serotonin reuptake inhibitors (SSRI) and serotonin noradrenaline reuptake inhibitors (SNRIs)). If concomitant treatment with ondansetron 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.

In patients with adenotonsillar surgery prevention of nausea and vomiting with ondansetron may mask occult bleeding. Therefore, such patients should be followed carefully after ondansetron.

Paediatric Population

Paediatric patients receiving ondansetron with hepatotoxic chemotherapeutic agents should be monitored closely for impaired hepatic function.

Chemotherapy-induced nausea and vomiting:-

When calculating the dose on an mg/kg basis and administering three doses at 4-hourly intervals, the total daily dose will be higher than if one single dose of 5 mg/m^2 followed by an oral dose is given. The comparative efficacy of these two different dosing regimens has not been investigated in clinical trials. Cross-trial comparison indicate similar efficacy for both regimens (section 5.1).

4.5 Interaction with other medicinal products and other forms of 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 interactions when Zofran is administered with alcohol, temazepam, frusemide, alfentanil, tramadol, morphine, lignocaine, thiopental or propofol.

Ondansetron is metabolised by multiple hepatic cytochrome P450 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 shouldresult in little or no significant change in overall ondansetron clearance or dose requirement.

Caution should be exercised when ondansetron is coadministered with drugs that prolong the QT interval (including some Cytotoxics) and/or cause electrolyte abnormalities (see Section 4.4 Special Warnings and Precautions for Use).

Use of ondansetron with QT prolonging drugs may result in additional QT prolongation. Concomitant use of ondansetron with cardiotoxic drugs (e.g. anthracyclines such as doxorubicin, daunorubicin or trastuzimab), antibiotics (such as erythromycin or ketoconazole), antiarrhythmics (such as amiodarone) and beta blockers (such as atenolol or timolol) may increase the risk of arrhythmias. (see section 4.4).

Serotonergic Drugs (e.g., SSRIs and SNRIs)
There have been post-marketing reports describing patients with serotonin syndrome (including altered mental status, autonomic instability and neuromuscular abnormalities) following the concomitant use of ondansetron and other serotonergic drugs (including SSRIs and SNRIs) (See section 4.4).

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.

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

4.6 Fertility, pregnancy and lactation

Pregnancy
Safety data of ondansetron in pregnancy are limited, and findings from available pharmaco-epidemiologic studies are inconsistent. Post-marketing reports describe cases of congenital malformations with use of Zofran during pregnancy; however the reports are insufficient to establish a causal relationship.
Reproductive studies in rats and rabbits did not show evidence of harm to the foetus when ondansetron was administered during organogenesis at approximately 6 and 24 times the maximum recommended human oral dose of 24 mg/day, based on body surface area, respectively. However as animal studies are not always predictive of human response, the use of Zofran is not recommended during pregnancy and in women of childbearing potential not using contraception.

Pregnancy testing
Pregnancy status should be verified in women of child-bearing potential prior to starting the treatment with Zofran.

Breastfeeding

There is insufficient information on the excretion of ondasetron/metabolites in human milk or the effects of Zofran on milk production. Available pharmacodynamic/toxicological data in animals have shown excretion of ondansetron/metabolites in milk (for details see 5.3). A risk to the newborns/infants cannot be excluded. Zofran should not be used during breast-feeding.

Fertility
There are no data on the effects of ondansetron on human fertility.

4.7 Effects on ability to drive and use machines

Zofran has no or negligible influence on the 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 ondansetron.

4.8 Undesirable effects

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). 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. 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 oculogyric crisis, dystonic reactions, and dyskinesia)[1]
Rare: Dizziness predominantly during rapid IV administration.

Eye disorders
Rare: Transient visual disturbances (eg. blurred vision) predominantly during rapid intravenous administration.
Very rare: Transient blindness predominantly during intravenous administration[2].

Cardiac disorders
Uncommon: Arrhythmias, chest pain with or without ST segment depression, bradycardia.
Rare: QTc prolongation (including Torsades 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[3].

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.

[1] Observed without definitive evidence of persistent clinical sequelae.

[2] 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.

[3] These events were observed commonly in patients receiving chemotherapy with cisplatin.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via HPRA Pharmacovigilance, Earlsfort Terrace, IRL - Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517. Website: www.hpra.ie; E-mail: medsafety@hpra.ie.

4.9 Overdose

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 4.8 *Undesirable Effects*). Manifestations that have been reported include visual disturbances, severe constipation, hypotension and a vasovagal episode with transient second-degree AV block.

Ondansetron prolongs QT interval in a dose-dependent fashion. ECG monitoring is recommended in cases of overdose.

Paediatric population
Paediatric cases consistent with serotonin syndrome have been reported after inadvertent oral overdoses of ondansetron (exceeded estimated ingestion of 4 mg/kg) in infants and children aged 12 months to 2 years.

Treatment

There is no specific antidote for Zofran, therefore in cases of suspected overdose, symptomatic and supportive therapy should be given as appropriate.

Further management should be as clinically indicated or as recommended by the national poisons centre, where available.

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 Zofran itself.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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 the 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.

Ondansetron does not alter plasma prolactin concentrations.

QT Prolongation
The effect of ondansetron on the QTc interval was evaluated in a double blind, randomized, 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.

Paediatric Population

Chemotherapy induced nausea and vomiting
The efficacy of ondansetron in the control of emesis and nausea induced by cancer chemotherapy was assessed in a double-blind randomised trial in 415 patients aged 1 to 18 years (S3AB3006). On the days of chemotherapy, patients received either ondansetron 5 mg/m^2 IV + ondansetron 4 mg orally after 8-12 hours or ondansetron 0.45 mg/kg IV + placebo orally after 8-12 hours. Post-chemotherapy both groups received 4 mg ondansetron syrup twice daily for 3 days. Complete control of emesis on worst day of chemotherapy was 49% (5 mg/m^2 IV + ondansetron 4 mg orally) and 41% (0.45 mg/kg IV + placebo orally).

Post-chemotherapy both groups received 4 mg ondansetron syrup twice daily for 3 days. There was no difference in the overall incidence or nature of adverse events between the two treatment groups.

A double-blind randomised placebo-controlled trial (S3AB4003) in 438 patients aged 1 to 17 years demonstrated complete control of emesis on worst day of chemotherapy in:

- 73% of patients when ondansetron was administered intravenously at a dose of 5 mg/m^2 IV together with 2-4 mg dexamethasone orally.
- 71% of patients when ondansetron was administered as syrup at a dose of 8 mg + 2-4 mg dexamethasone orally on the days of chemotherapy.

Post-chemotherapy both groups received 4 mg ondansetron syrup twice daily for 2 days. There was no difference in the incidence or nature of adverse events between the two treatment groups.

The efficacy of ondansetron in 75 children aged 6 to 48 months was investigated in an open-label, non-comparative, single-arm study (S3A40320). All children received three 0.15 mg/kg doses of IV ondansetron, administered 30 minutes before the start of chemotherapy and then at four and eight hour after the first dose. Complete control of emesis was achieved in 56% of patients.

Another open-label, non-comparative, single-arm study (S3A239) investigated the efficacy of one IV dose of 0.15 mg/kg ondansetron followed by two oral ondansetron doses of 4 mg for children aged < 12 years and 8 mg for children aged ≥ 12 years (total no. Of children n=28). Complete control of emesis was achieved in 42% of patients.

Post-operative nausea and vomiting
The efficacy of a single dose of ondansetron in the prevention of post-operative nausea and vomiting was investigated in a randomised, double-blind, placebo-controlled study in 670 children aged 1 to 24 months (post-conceptual age ≥ 44 weeks, weight ≥ 3 kg). Included subjects were scheduled to undergo elective surgery under general anaesthesia and had an ASA status ≤ III. A single dose of ondansetron 0.1 mg/kg was administered within five minutes following induction of anaesthesia. The proportion of subjects who experienced at least one emetic episode during the 24-hour assessment period (ITT) was greater for patients on placebo than those receiving ondansetron (28% vs. 11%, p <0.0001).

Four double-blind, placebo-controlled studies have been performed in 1469 male and female patients (2 to 12 years of age) undergoing general anaesthesia. Patients were randomised to either single IV doses of ondansetron (0.1 mg/kg for paediatric patients weighing 40 kg or less, 4 mg for paediatric patients weighing more than 40 kg; number of patients = 735) or placebo (number of patients = 734). Study drug was administered over at least 30 seconds, immediately prior to or following anaesthesia induction.

Ondansetron was significantly more effective than placebo in preventing nausea and vomiting. The results of these studies are summarised in Table 3.

Table 3. Prevention and treatment of post-operative nausea and vomiting in paediatric patients – treatment response over 24 hours

Study	**Endpoint**	**Ondansetron (%)**	**Placebo (%)**	**P value**
S3A380	CR	68	39	≤ 0.001
S3GT09	CR	61	35	≤ 0.001
S3A381	CR	53	17	≤ 0.001
S3GT11	No nausea	64	51	0.004
S3GT11	No emesis	60	47	0.004

CR = no emetic episodes, rescue or withdrawal

5.2 Pharmacokinetic properties

The disposition of ondansetron following oral, intramuscular or intravenous dosing in adults is similar with a terminal elimination half-life of about 3 hours and steady state volume of distribution of about 140L. Equivalent systemic exposure is achieved after intramuscular and intravenous administration of ondansetron. Ondansetron is not highly protein bound (70-76%). Ondansetron is cleared from the systemic circulation predominantly by hepatic metabolism through multiple enzymatic pathways. Less than 5% of the absorbed dose is excreted unchanged in the urine. The absence of the enzyme CYP2D6 (the debrisoquine polymorphism) has no effect on ondansetron's pharmacokinetics. The pharmacokinetic properties of

ondansetron are unchanged on repeat dosing. Studies in healthy elderly volunteers have shown slight, but clinically insignificant, age-related increases in both oral bioavailability and half-life of ondansetron.

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).

Paediatric Population
In paediatric patients aged 1 to 4 months (n=19) undergoing surgery, weight-normalised clearance was approximately 30% slower than in patients aged 5 to 24 months (n=22) but comparable to the patients aged 3 to 12 years. The half-life in the 1 to 4 month patient population was reported to average 6.7 hours compared to 2.9 hours for patients in the 5 to 24 month and 3 to 12 year age range. The differences in pharmacokinetic parameters in the 1 to 4 month patient population can be explained in part by the higher percentage of total body water in neonates and infants and a higher volume of distribution for water soluble drugs like ondansetron.

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.

Population pharmacokinetic analysis was performed on 428 subjects (cancer patients, surgery patients and healthy volunteers) aged 1 month to 44 years following IV administration of ondansetron.

Based on this analysis, systemic exposure (AUC) of ondansetron following oral or IV dosing in children and adolescents was comparable to adults, with the exception of infants aged 1 to 4 months. Volume of distribution was related to age and was lower in adults than in infants and children.

Clearance was related to weight but not to age with the exception of infants aged 1 to 4 months. It is difficult to conclude whether there was an additional reduction in clearance related to age in infants 1 to 4 months or simply inherent variability due to the low number of subjects studied in this age group. Since patients less than 6 months of age will only receive a single dose in post-operative nausea and vomiting a decreased clearance is not likely to be clinically relevant.

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. Specific dosing information is provided for patients over 65 years of age and over 75 years of age for intravenous dosing (see section 4.2).

Renal Impairment
In patients with moderate renal impairment (creatinine clearance 15-60ml/min), both systemic clearance and volume of distribution are reduced, resulting in a slight, but clinically insignificant, increase in elimination half-life (5.4h). A study in patients with severe renal impairment who required regular haemodialysis (studied between dialyses) showed ondansetron's pharmacokinetics to be essentially unchanged.

Hepatic Impairment
In patients with severe hepatic impairment, ondansetron's systemic clearance is markedly reduced with prolonged elimination half-lives (15 - 32 h) and an oral bioavailability approaching 100% due to reduced pre-systemic metabolism.

5.3 Preclinical 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 5.1 Pharmacodynamic Properties – QT prolongation).

In embryo-foetal 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.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium chloride
Citric acid monohydrate
Sodium citrate
Water for injections

6.2 Incompatibilities

Zofran Solution for Injection or Infusion should not be administered in the same syringe or infusion as any other medication *(see Section 6.6 Instructions for Use and Handling)*.
This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf life

Unopened Zofran Solution for Injection on Infusion ampoules have a shelf life of 3 years.
Once opened Zofran Solution for Injection on Infusion has a shelf life of 24 hours when stored at refrigeration temperatures of 2-8°C only.
Dilutions of Zofran injection in compatible intravenous infusion fluids are stable under normal room lighting conditions or daylight for at least 24 hours, thus no protection from light is necessary while infusion takes place.

6.4 Special precautions for storage

Do not store above 30°C. Store in the original container in order to protect from light.

Pharmaceutical precautions: In the interest of good microbiological practice storage of reconstituted or diluted injection solutions is not recommended unless the product is aseptically prepared and even then must not exceed 24 hours at refrigeration temperatures of 2-8°C only.

6.5 Nature and contents of container

Zofran Solution for Injection or Infusion is supplied in Type I clear glass, One-point-cut (OPC) or Snap-ring ampoule sealed by fusion of the glass. Dose volumes of 2 ml are presented in 2 ml ampoules. The ampoules are packed in plastic ampoule like trays in cardboard boxes, five ampoules per box.
Instruction to open the OPC ampoules;

- Flick down any liquid in the ampoule neck.
- Hold the ampoule upright with the coloured dot on the top tag facing you.
- Place thumb over the dot and snap off the top tag.
- Attach syringe directly to the ampoule or insert syringe.
- Withdraw contents using firm consistent pressure.

Instructions to open the Snap-ring ampoules;

- Flick down any liquid in the ampoule neck.
- Hold the ampoule upright.

- Break off the top tag in one quick turn.
- Attach the syringe directly to the ampoule or insert the syringe.
- Withdraw contents using firm consistent pressure.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

Compatibility with intravenous fluids-;

Zofran Solution for Injection or Infusion should only be mixed with those infusion solutions which are recommended.

Sodium Chloride Intravenous Infusion BP 0.9% w/v
Glucose Intravenous Infusion BP 5% w/v
Mannitol Intravenous Infusion BP 10% w/v
Ringers Intravenous Infusion

Potassium Chloride 0.3% w/v and Sodium Chloride 0.9% w/v Intravenous Infusion BP
Potassium Chloride 0.3% w/v and Glucose 5% w/v Intravenous Infusion BP.

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 I glass bottles.

Dilutions of Zofran in sodium chloride 0.9% w/v or in glucose (dextrose) 5% w/v have been demonstrated to be stable in polypropylene syringes. It is considered that Zofran Solution for Injection on Infusion diluted with other compatible infusion fluids would be stable in polypropylene syringes.

Compatibility with other drugs: -
Zofran Solution for Injection or Infusion may be administered by intravenous infusion at 1mg/hour, e.g. 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 160micrograms/ml (e.g. 8mg/500ml and 8mg/50ml respectively);

Cisplatin
Concentrations up to 0.48mg/ml (eg.240mg in 500ml) administered over one to eight hours.

5-fluorouracil
Concentrations up to 0.8mg/ml (eg. 2.4g in 3 litres or 400mg in 500ml) administered at a rate of at least 20ml per hour (500ml per 24 hours). 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 0.18mg/ml to 9.9mg/ml (eg. 90mg in 500ml to 990mg in 100ml), administered over ten minutes to one hour.

Etoposide
Concentrations in the range 0.144mg/ml to 0.25mg/ml (eg.72mg in 500ml to 250mg in 1 litre), administered over thirty minutes to one hour.

Ceftazidime
Doses in the range 250mg to 2000mg reconstituted with Water for Injections BP as recommended by the manufacturer (eg. 2.5ml for 250mg and 10ml for 2g ceftazidime) and given as an intravenous bolus injection over approximately five minutes.

Cyclophosphamide
Doses in the range 100mg to 1g, reconstituted with Water for Injections BP, 5ml per 100mg cyclophosphamide, as recommended by the manufacturer, and given as an intravenous bolus injection over approximately five minutes.

Doxorubicin

Doses in the range 10-100mg reconstituted with Water for Injections BP, 5ml per 10mg doxorubicin, as recommended by the manufacturer and given as an intravenous bolus injection over approximately five minutes.

Dexamethasone
Dexamethasone sodium phosphate 20mg may be administered as a slow intravenous Injection over 2-5 minutes via the Y-site of an infusion set delivering 8 to 16mg of ondansetron diluted in 50-100ml of the following infusion fluids:

Sodium Chloride Intravenous Infusion BP 0.9% w/v
Glucose Intravenous Infusion BP 5% w/v
Sodium Chloride Intravenous Infusion 0.9% w/v and Glucose Intravenous Infusion BP 5% w/v over approximately 15 minutes.
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 microgram - 2.5 mg/ml for dexamethasone sodium phosphate and 8 microgram - 1mg/ml for Ondansetron.

Zofran Solution for Injection or Infusion should not be administered in the same syringe of infusion as any other medication.

7 MARKETING AUTHORISATION HOLDER

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