

DATA SHEET

ONDANSETRON PFIZER

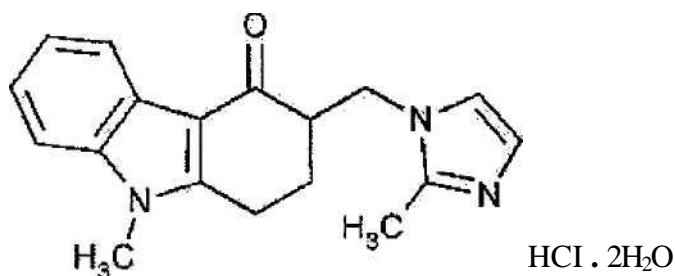
Ondansetron hydrochloride

NAME OF THE MEDICINE

ONDANSETRON PFIZER, Solution for Injection, for Intramuscular (I.M.) or Intravenous (I.V.) use.

Ondansetron hydrochloride has the chemical name (3RS)-9-Methyl-3-[(2-methyl-1H-Imidazole-1-yl)methyl]-1,2,3,9-tetrahydro-4H-carbazol-4-one hydrochloride dihydrate.

It has the chemical formula $C_{18}H_{19}N_3O \cdot HCl \cdot 2H_2O$ with a molecular weight of 365.9. The CAS number is 103639-04-9.



DESCRIPTION

Ondansetron hydrochloride is a white to off-white powder, which is sparingly soluble in water and alcohol.

ONDANSETRON PFIZER, Solution for Injection, is a clear colourless solution containing the equivalent of 2 mg/mL of ondansetron. The pH of the solution is 3.30 - 4.00. The product also contains citric acid monohydrate, sodium citrate, sodium chloride and water for injections.

PHARMACOLOGY

Mode of Action

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 due to antagonism of 5HT₃ receptors on neurones located both in the peripheral and central nervous system. The mechanisms of action in postoperative nausea and vomiting are not known but there may be common pathways with cytotoxic induced nausea and vomiting. In psychomotor testing, ondansetron does not impair performance nor cause sedation. Ondansetron does not alter plasma prolactin concentrations.

A study in cloned, human cardiac ion channels has shown ondansetron has the potential to affect cardiac depolarization via blockade of HERG potassium channels. The clinical relevance of this finding is uncertain.

Pharmacokinetic properties

The disposition of ondansetron following oral, intramuscular or intravenous dosing 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).

In a clinical study, 51 paediatric patients aged 1 to 24 months received either 0.1 or 0.2 mg/kg ondansetron prior to undergoing surgery. Patients aged 1 to 4 months had a clearance when normalised to body weight that was approximately 30% slower than in patients aged 5 to 24 months 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. No dose adjustment is necessary for patients aged 1 to 4 months as only a single i.v. dose of ondansetron is recommended for the treatment of postoperative nausea and vomiting. The differences in pharmacokinetic parameters can be explained in part by the higher volume of distribution in the 1 to 4 month patient population.

In a study of 21 paediatric patients aged between 3 and 12 years undergoing elective surgery with general anaesthesia, the absolute values for both the clearance and volume of distribution of ondansetron following a single intravenous dose of 2mg (3-7 years old) or 4mg (8-12 years old) 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 (0.1mg/kg up to 4mg maximum) compensates for these changes and is effective in normalising systemic exposure in paediatric patients.

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

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

CLINICAL TRIALS

Chemotherapy and Radiotherapy Induced Nausea and

Vomiting Adult Studies

Highly emetogenic chemotherapy:

In a double-blind, randomised study 152 patients were given ondansetron 8 mg I.V. single dose and 173 patients were given 32 mg I.V. single dose 30 minutes prior to cisplatin (>50 mg/m²). No significant difference in terms of emesis control or grade of nausea was demonstrated between 8 mg or 32 mg. However, in some studies conducted in patients

receiving medium (50-90mg/m) or high doses (>100mg/m²) of cisplatin chemotherapy, the 32 mg single dose demonstrated a statistically significant superiority over the 8 mg single dose with regard to control of emesis. In a double-blind, randomised, cross-over

trial, 103 chemotherapy naive patients scheduled to receive cisplatin (50-120 mg/m²) chemotherapy were recruited. Ninety-one patients completed both courses of ondansetron 0.15 mg/kg (8 mg) I.V. x 3 with or without dexamethasone 20 mg I.V. The combination of ondansetron and dexamethasone was shown to be significantly superior to ondansetron alone. In a randomised, double-blind parallel group study, 420 patients were randomised to receive either ondansetron 16 mg suppository prior to cisplatin chemotherapy (>50 mg/m²) on day 1 followed by ondansetron 16 mg suppository once daily for a further 2 days, or ondansetron 8 mg I.V. prior to cisplatin chemotherapy followed by ondansetron 8 mg orally twice daily for a further 2 days. Results from the primary efficacy analysis (i.e. < 2 emetic episodes on day 1) show that the suppository and I.V. and oral combined regimens are equivalent. However, results from the secondary efficacy analyses (e.g. number of emetic episodes on Day 1, the worst day of Days 1-3 and over all of Days 1-3) showed that the suppository was less effective. Patients on the I.V. and oral combined regimen remained free of emesis for significantly longer than patients receiving the suppository.

In a randomised, double-blind, parallel group study 542 patients were randomised to receive either ondansetron tablets (3 x 8mg) plus dexamethasone capsules (2 x 6mg), or I.V. ondansetron hydrochloride 8mg plus I.V. dexamethasone 20mg, prior to cisplatin infusion. 24mg of ondansetron administered orally was as effective as ondansetron 8 mg given I.V. in controlling acute emesis and nausea induced by cisplatin chemotherapy.

Emetogenic Chemotherapy

In a double-blind, parallel group study 82 patients were randomised to either ondansetron 8 mg I.V. prior to cyclophosphamide (>500 mg/m²) based chemotherapy (doxorubicin or epirubicin >40 mg/m²) followed by 8 mg orally three times a day for 3-5 days or metoclopramide 60 mg I.V. prior to chemotherapy followed by 20 mg orally three times a day for 3-5 days. Ondansetron was shown to be significantly superior to metoclopramide.

Paediatric Studies

Three open-label, uncontrolled, non-comparative studies have been performed with 182 patients, aged 4-18 years old with cancer who were given a variety of cisplatin or non-cisplatin regimens. In these trials an initial I.V. dose of ondansetron was followed by oral administration of ondansetron. In these studies, 58% of the 170 evaluable patients had 0 emetic episodes on Day 1.

Post Operative Nausea and Vomiting

The majority of patients included in the post operative nausea and vomiting (PONV) studies using ondansetron have been adult women receiving balanced anaesthesia for gynaecological surgery.

Prevention

Adult Studies

Surgical patients received ondansetron immediately before the induction of general balanced anaesthesia. In a double-blind, placebo controlled study 136 patients given Ondansetron 4 mg I.V. immediately prior to general anaesthesia was significantly more effective than placebo.

The majority of patients included in the PONV studies using ondansetron have been adult women receiving balanced anaesthesia for gynaecological surgery.

Paediatric Studies

Three, large, double-blind, placebo-controlled studies have been performed in 1,049 patients (2 to 12 years of age) undergoing general anaesthesia with nitrous oxide. The surgical procedures included tonsillectomy with or without adenoidectomy, strabismus surgery, hemiorrhaphy, and orchidopexy. Patients were randomised to either single I.V. doses of ondansetron (0.1 mg/kg for children weighing 40 kg or less, a single 4 mg dose for children weighing more than 40 kg) or placebo. Study drug was administered over at least 30 seconds, immediately prior to or following anaesthesia induction. Ondansetron showed significant statistical superiority over placebo in preventing post-operative nausea and vomiting. Repeat dosing was not undertaken in these studies. Children at greater risk of post-operative nausea and vomiting are more likely to benefit from prophylaxis; this includes children with a history of motion sickness or previous post-operative nausea and vomiting. No comparisons with other drugs for the prevention of nausea and/or vomiting are available.

The majority of patients included in the PONV studies using ondansetron have been adult women receiving balanced anaesthesia for gynaecological surgery.

Treatment

Adult Study

Two hundred and twenty one adult surgical patients receiving general balanced anaesthesia, who received no prophylactic anti-emetics and who experienced nausea and/or vomiting within 2 hours post-operatively were evaluated in a double-blind study. Patients who experienced an episode of post-operative nausea and/or vomiting were given ondansetron 4 mg I.V. over 25 minutes, and this was significantly more effective than placebo.

The majority of patients treated in the studies have been adult women receiving balanced anaesthesia for gynaecological surgery.

Paediatric Study

One, large, double-blind, placebo-controlled study was performed in 351 (male and female) outpatients (2 to 12 years of age) who received general anaesthesia with nitrous oxide and no prophylactic anti-emetics. Surgical procedures were restricted. Patients who experienced two or more emetic episodes within 2 hours following discontinuation of nitrous oxide were randomised to a single I.V dose of (0.1 mg/kg for children weighing 40 kg or less, a single 4 mg dose for children weighing more than 40

kg) or placebo administered over at least 30 seconds. Ondansetron demonstrated statistically significant superiority over placebo in preventing further episodes of nausea and vomiting. Repeat dosing was not a feature of this study. No data, involving comparisons with active treatments, have been evaluated.

INDICATIONS

Ondansetron hydrochloride is indicated for:

- the prevention and treatment of nausea and vomiting induced by cytotoxic therapy and radiotherapy
- the prevention and treatment of post-operative nausea and vomiting

CONTRAINDICATIONS

Hypersensitivity to any component of the preparation.

PRECAUTIONS

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

Very rarely and predominantly with I.V. infusion, transient ECG changes including QT interval prolongation have been reported.

As ondansetron increases large bowel transit time, patients with signs of subacute intestinal obstruction should be monitored following administration.

Repeat dosing has not been studied in paediatric patients who experience nausea and/or vomiting despite receiving ondansetron prophylaxis or who continue to experience symptoms after ondansetron treatment.

Use in Pregnancy:

Category B1. Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human foetus having been observed. Studies in animals have not shown evidence of an increased occurrence of foetal damage.

The safety of ondansetron for use in human pregnancy has not been established therefore its use during pregnancy is not recommended.

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 or peri-natal and post-natal development. However animal studies are not always predictive of human response.

Use in Lactation:

Tests have shown that ondansetron is excreted in the breast milk of rats. It is therefore recommended that mothers receiving ondansetron should not breast-feed their babies.

Carcinogenicity/Genotoxicity/Impairment of Fertility:

No evidence for carcinogenic activity was found in two year studies at ondansetron doses up to 10mg/kg/day by gavage in rats or up to 30mg/kg/day via drinking water in mice. Ondansetron did not induce mutations in *Salmonella typhimurium*, *Escherichia coli* or Chinese Hamster Ovary cells in the presence or absence of metabolic activation, and showed no potential for causing chromosomal damage in vitro in peripheral human lymphocytes or in vivo in a mouse micronucleus assay. No evidence for DMA damage was observed with ondansetron in a yeast mitotic gene conversion assay. Oral doses of ondansetron up to 15 mg/kg/day in rats had no effect on male or female fertility.

Interactions with Other Medicines

There is no evidence that ondansetron either induces or inhibits the metabolism of other drugs commonly co-administered with it; specific studies have been limited to alcohol, temazepam, and alfentanil to date.

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.

In patients treated with potent inducers of CYP3A4 e.g. phenytoin, carbamazepine, and rifampicin, the oral clearance of ondansetron was increased and ondansetron blood concentrations were decreased.

Following a single 8mg tablet dose of ondansetron, a threefold to fourfold decrease in the systemic exposure has been seen in adult epileptic subjects maintained on chronic doses of carbamazepine (n=8) or phenytoin (n=8) and not receiving chemotherapy. The effect of these enzyme inducing agents on intravenous ondansetron has not been assessed, but the absence of any first pass effects would be expected to result in a smaller change in exposure than seen following oral dosing. Due to the limited efficacy data in subjects on antiepileptics and the many variables that may influence exposure and response, the clinical significance of this drug interaction in cancer patients receiving chemotherapy is not known.

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

ADVERSE 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 ($<1/10,000$), 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 ondansetron according to indication and formulation.

Immune system disorders

Rare: Immediate hypersensitivity reactions, sometimes severe, including anaphylaxis.

Nervous system disorders

Very common: Headache.

Uncommon: Extrapyramidal reactions (such as oculogyric crisis/dystonic reactions) have been observed without definitive evidence of persistent clinical sequelae, seizures.

Rare: Dizziness during rapid I.V. administration.

Eye disorders

Rare: Transient visual disturbances (e.g. blurred vision) predominantly during I.V. administration.

Very rare: Transient blindness predominantly during I.V. 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, xerostomia.

Hepatobiliary disorders

Uncommon: Asymptomatic increases in liver function tests. However these events were observed commonly in patients receiving chemotherapy with cisplatin.

General disorders and administration site conditions

Common: Local I.V. injection site reactions.

To date there has been limited safety experience in controlled trials following intramuscular administration.

Of 7,400 patients who have received intravenous ondansetron during clinical trials, 11 experienced major cardiovascular events, including 3 fatalities, which were considered to be drug-related by the investigators (1 probable, 10 possible). It is well known that cardiovascular events, especially of a vascular occlusive nature are not uncommon among patients with cancer, and these events are further increased with cytotoxic chemotherapy, particularly cisplatin.

Table 1 shows adverse events occurring in > 5% of paediatric patients (either group) in three pivotal clinical trials for prevention of post-operative nausea and vomiting. Ondansetron appears to be as well tolerated as placebo.

Table 1 -Adverse events occurring in >1% of paediatric patients in three pivotal clinical trials for prevention of post-operative nausea and vomiting

	Placeb (n=548)	Ondansetron (n=542)
Total patients with AE	56% (309)	53% (289)
Eye disorder	16% (86)	19% (102)
Wound problem	13% (72)	13% (70)
Anxiety/agitation	7% (36)	8% (42)
Drowsiness/sedation	8% (44)	6% (34)
Nausea and/or vomiting	11% (62)	6% (33)
Headache	6% (32)	6% (32)
Pyrexia	4% (22)	4% (21)
Disease: lower respiratory	1% (6)	3% (16)

Arrhythmia	3%	(15)	3%	(14)
Expectoration	3%	(16)	2%	(13)
Cough	2%	(13)	2%	(13)
Dizziness	2%	(11)	2%	(01)
Laryngospasm	2%	(10)	2%	(11)
Disturbance of conduct/behaviour	1%	(8)	2%	(10)
Hypoxia	1%	(6)	1%	(8)
Visual disturbance	2%	(11)	1%	(6)
Bradycardia	<1%	(2)	1%	(6)
Throat disorder	<1%	(2)	1%	(6)
Bronchospasm / asthma	2%	(10)	<1%	(5)
Swollen periocular area	1%	(6)	<1%	(5)
Gastric symptoms	1%	(8)	<1%	(4)
Poor oral intake	1%	(8)	<1%	(4)
Pain	1%	(6)	<1%	(4)
Haemorrhage	1%	(8)	<1%	(3)
Ear disorder	1%	(6)	<1%	(2)

The overall incidence of adverse events was similar for ondansetron (53%) and placebo (56%). The most commonly reported adverse events were eye disorders) as a result of ophthalmic operations, wound problems at the surgical site, nausea and/or vomiting, drowsiness/sedation, anxiety/agitation and headache. These events are not unexpected in patients undergoing surgery and there was little difference of these between treatment groups. However the incidence of nausea and/or vomiting reported as an adverse event was significantly higher in patients who had received placebo (11%) compared to those who had received ondansetron (6%).

Table 2 - Adverse events occurring in >1% of paediatric patients in one pivotal clinical trial for treatment of post-operative nausea and vomiting.

	Placebo (n=183)	Ondansetron (n=192)
Nausea and/or vomiting	15% (27)	9% (18)
Wound problem	8% (14)	6% (11)
Pyrexia	10% (19)	5% (10)
Headache	6% (11)	5% (9)
Drowsiness/sedation	7% (12)	4% (7)
Anxiety/agitation	6% (01)	4% (7)
Disturbed behaviour	2% (3)	2% (4)
Hypoxia	<1% (1)	2% (4)
Cough	3% (5)	2% (3)

Fewer adverse events were reported with ondansetron (36%) than with placebo (47%). The most common adverse events were similar to those reported in clinical trials for the prevention of post-operative nausea and vomiting.

Occasionally local reactions at the site of intravenous injection have been reported.

Table 3- Adverse events occurring in >1% of adult patients receiving either ondansetron or placebo I.V. for the prevention or treatment of post-operative nausea and vomiting

	Placebo (n = 842)	Ondansetron I.V. (n=1998)
Headache	10% (82)	11% (220)
Dizziness	9% (73)	8% (144)
Constipation	3% (25)	4% (82)
Bradycardia	2% (19)	3% (60)
Drowsiness	2% (18)	3% (59)
Dysuria/Urinary Tract Infection	2% (15)	3% (53)
Injection Site Reaction	2% (21)	2% (47)
Shivering	2% (20)	2% (43)
Nausea/Vomiting	2% (15)	2% (34)
Pruritis	1% (9)	2% (33)
Anxiety	1% (12)	1% (29)
Sleep Disturbance	<1% (5)	1% (29)
Cough	<1% (6)	1% (26)
Urinary retention	1% (10)	1% (24)
Rash	1% (9)	1% (21)
Abdominal Pain	1% (9)	<1% (20)
Hypotension	2% (14)	<1% (19)
Flatulence	1% (9)	<1% (19)

The overall incidence rate was 45% in the placebo group and 47% in the ondansetron group.

The neurological body system was associated with the highest incidence of adverse events (placebo approximately 23%; ondansetron 24%). These events were predominantly headache, dizziness and drowsiness.

Cardiovascular adverse events (bradycardia and hypotension) occurred in approximately 4% in both placebo and ondansetron groups; gastrointestinal adverse events (constipation, nausea/vomiting, flatulence and abdominal pain) occurred in approximately 7% of patients both receiving placebo and I.V. ondansetron.

The incidence rates were generally similar in both treatment groups for all body systems.

DOSAGE AND ADMINISTRATION

The emetogenic potential of cancer treatment varies according to the doses and combinations of chemotherapy and radiotherapy regimens used. The dose of Ondansetron hydrochloride should be flexible in the range of 8-32 mg a day and selected as indicated below. The lowest effective dose should be used.

In order to reduce microbiological contamination hazards, the diluted solutions should be prepared immediately prior to use and infusion commenced as soon as practicable after preparation of the mixture. The diluted infusion solution should be stored under refrigeration (2-8 °C) and used within 24 hours. The product is for single use in one patient only. Any residue should be discarded.

Adults:

Emetogenic chemotherapy and radiotherapy

For the control of chemotherapy or radiotherapy induced emesis or nausea in adults, a single dose of 8mg of ondansetron should be administered as a slow intravenous injection, immediately before treatment.

Highly emetogenic chemotherapy.

A single dose of ondansetron 8 mg by slow intravenous injection immediately before chemotherapy has been shown to be effective in many patients. Higher doses may be required in some patients, particularly those on high dose cisplatin, and the doses should be adjusted according to the severity of the emetogenic challenge. If required, additional intravenous doses may be given up to a maximum of 32 mg in 24 hours.

Intravenous doses of more than 8 mg should be given by slow intravenous infusion over at least 15 minutes, since rapid intravenous administration of ondansetron has been associated with a higher incidence of transient visual disturbances.

Post-operative Nausea and Vomiting

For prevention of post-operative nausea and vomiting in adults, ondansetron may be administered as a single dose of 4 mg, given by intramuscular or slow intravenous injection at induction of anaesthesia.

For treatment of established post-operative nausea and vomiting, a single dose of 4 mg given by intramuscular or slow intravenous injection is recommended in most patients. If necessary, the dose may be increased to 8 mg.

Children:***Emetogenic chemotherapy and radiotherapy***

Experience is currently limited but ondansetron was effective and well tolerated in children over the age of 4 years, when given intravenously at a dose of 5 mg/m² over 15 minutes, immediately before chemotherapy. It may be necessary to provide ongoing medication using an appropriate oral dose form. The dose of 5 mg/m² is based on limited data.

Post-operative Nausea and Vomiting

For prevention of post-operative nausea and vomiting in children aged 2 to 12 years having surgery under general anaesthesia, ondansetron may be administered by slow intravenous 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.

For treatment of established post-operative nausea and vomiting, ondansetron may be administered by slow intravenous injection at a dose of 0.1 mg/kg up to a maximum of 4 mg.

Repeat dosing has not been studied in paediatric patients who experience nausea and/or vomiting despite receiving ondansetron prophylaxis or who continue to experience symptoms after ondansetron treatment.

Elderly Patients:***Emetogenic chemotherapy and radiotherapy***

Efficacy and tolerance in patients aged over 65 years was similar to that seen in younger adults indicating no need to alter dosage or route of administration in the elderly.

Post-operative Nausea and Vomiting

There is limited experience in the use of ondansetron in the prevention and treatment of postoperative nausea and vomiting in the elderly.

Impaired Renal Function:

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

Impaired Hepatic Function:

A study which investigated the effect of hepatic impairment on the pharmacokinetics of ondansetron in 24 subjects showed that the plasma clearance of ondansetron is reduced to about 20% of normal, and the serum half-life is significantly prolonged in subjects with severe impairment of hepatic function.

The results in patients with only mildly or moderately impaired hepatic function were less clear. The study showed that in this group the plasma clearance of ondansetron fell to about 50% of that seen in healthy volunteers. Subjects with mild and moderate

impairment were not distinguishable from each other for any parameter. This was believed to be partly due to the lack of sensitivity of the Pugh classification system in distinguishing between patients with mild or moderate impairment.

It is recommended that a total daily dose of 8mg should not be exceeded for patients with moderate or severe hepatic dysfunction. For optimum clinical effect it is recommended that this total daily dose be administered before chemotherapy or radiotherapy.

The severity of the liver disease was assessed according to Pugh's modification of Child's classification (Pugh et al, Brit J. Surg. 1973, 60 (8), 646-649). Patients with a Pugh score of 5 or less were considered to have good hepatic function. A patient with a score of 6 was graded as having mild hepatic impairment, 7 to 9 as moderate hepatic impairment and 10 or more as severe hepatic impairment. The clinical features used in the grading and the weighting system applied are shown in the table below:

Clinical and Biochemical Measurements	Points scored for increasing abnormality		
	1	2	3
Encephalopathy (grade) *	None	1 and 2	3 and 4
Ascites	Absent	Slight	Moderate
Bilirubin (μmol per Litre)	17.1-34.2	34.2-51.3	>51.3
Albumin (g per Litre)	35	28-35	<28
Prothrombin time (seconds prolonged)	1-4	4-6	>6
For primary biliary cirrhosis:-Bilirubin (μmol per Litre)	17.1-68.4	68.4-171	>171

* According to grading of Trey, Bums, and Saunders (1966)

Patients with Poor Sparteine/Debrisoquine Metabolism

There were no significant differences among poor and extensive debrisoquine categorised metabolisers with regard to ondansetron disposition (area under the curve, total systemic clearance, elimination half-life) following a single 8mg intravenous dose. The effect of repeated dosing was not investigated, nevertheless dosage adjustments will probably not be required in patients receiving ondansetron.

Compatibility with Other Medicines:

Administration recommendations: slow intravenous injection from an infusion bag or syringe pump. The following medicines may be administered via the Y-site of the ondansetron giving set for ondansetron concentrations of 16 to 160 micrograms/mL (i.e. 8 mg/500 mL and 8 mg/50 mL respectively).

Cisplatin:

Concentrations up to 0.48 mg/mL (i.e. 240 mg in 500 mL) administered over 1 - 8 hours.

Fluorouracil:

Concentrations up to 0.8 mg/mL (i.e. 2.4 g in 3 litres or 400 mg in 500 mL) administered at a rate of at least 20 mL per hour (500 mL per 24 hours). Higher concentrations of fluorouracil may cause precipitation of ondansetron. The 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 (i.e. 90 mg in 500 mL to 990 mg in 100 mL), administered over ten minutes to one hour.

Etoposide:

Concentrations in the range 0.14 mg/mL to 0.25 mg/mL (i.e. 72 mg in 500 mL to 250 mg in 1 litre), administered over thirty minutes to one hour.

Ceftazidime:

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

Cyclophosphamide:

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

Doxorubicin:

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

Pharmaceutical Precautions

Ondansetron hydrochloride should not be administered in the same syringe or infusion as any other medication.

Ondansetron hydrochloride should only be admixed with the infusion solutions recommended below. It is stable for 36 hours in these infusion solutions when kept under refrigeration (2-8°C).

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

Ringer's 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 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. Dilutions of ondansetron in sodium chloride 0.9% w/v or in glucose 5% w/v have been demonstrated to be stable in polypropylene syringes. It is considered that ondansetron injection diluted with other compatible infusion fluids would be stable in polypropylene syringes.

In order to reduce microbiological contamination hazards, the diluted solutions should be prepared immediately prior to use and infusion commenced as soon as practicable after preparation of the mixture. The diluted infusion solution should be stored under refrigeration (2-8 °C) and used within 24 hours. Any residue should be discarded.

Diluted solutions which are hazy, discoloured or contain visible particulate matter must be discarded.

The product is for single use in one patient only. Any residue should be discarded.

OVERDOSAGE

Little is at known about overdosage with ondansetron, however, a limited number of patients have received overdoses. 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. There is no specific antidote for ondansetron. In cases of suspected overdose, symptomatic and supportive therapy should be given as appropriate. For more information contact the Poisons Information Centre (0800 POISON, 0800 764 766).

PRESENTATION AND STORAGE CONDITIONS

Each ampoule of ONDANSETRON PFIZER 4 mg/2 mL contains Ondansetron hydrochloride equivalent to Ondansetron 4 mg.

Each pack contains 5 ampoules.

Each ampoule of ONDANSETRON PFIZER 8 mg/4 mL contains Ondansetron hydrochloride equivalent to ondansetron 8 mg.

Each pack contains 5 ampoules.

Store below 30°C. Protect from light. Do not freeze.

NAME AND ADDRESS OF THE SPONSOR

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Toll Free Number: 0800 736 363

POISON SCHEDULE

S4 Prescription Only Medicine

DATE OF PREPARATION

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