1. NAME OF THE MEDICINAL PRODUCT

ZOFDAN (Ondansetron Injection BP 2mg/ml)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml contains:

Ondansetron Hydrochloride Dihydrate	BP	
Eq. to Ondansetron		2mg
Water for Injections	BP	q.s.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for Injection

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

Adults

Ondansetron is indicated for the management of nausea and vomiting induced by cytotoxic chemotherapy and radiotherapy, and for the prevention and treatment of post-operative nausea and vomiting (PONV).

Paediatric population

Ondansetron is indicated for the management of chemotherapy-induced nausea and vomiting (CINV) in children aged ≥ 6 months, and for the prevention and treatment of post-operative nausea and vomiting (PONV) in children aged ≥ 1 month.

4.2 Posology and Method of Administration

Posology

Ondansetron 4mg/2ml Solution for Injection / Ondansetron 8mg/4ml Solution for Injection:
For intravenous injection or after dilution for intravenous infusion.

Chemotherapy and radiotherapy induced nausea and vomiting

Adults:

The emetogenic potential of cancer treatment varies according to the doses and combinations of chemotherapy and radiotherapy regimens used. The route of administration and dose of Ondansetron should be flexible in the range of 8-32 mg a day and selected as shown below.
Emetogenic chemotherapy and radiotherapy
For patients receiving emetogenic chemotherapy or radiotherapy Ondansetron can be given either by oral or intravenous administration.

For most patients receiving emetogenic chemotherapy or radiotherapy, Ondansetron 8 mg should be administered as a slow intravenous injection (in not less than 30 seconds) or as a short-time intravenous infusion over 15 minutes immediately before treatment, followed by 8 mg orally twelve hourly.

To protect against delayed or prolonged emesis after the first 24 hours, oral treatment with Ondansetron should be continued for up to 5 days after a course of treatment.

Highly emetogenic chemotherapy:

For patients receiving highly emetogenic chemotherapy, e.g. high-dose cisplatin,

Ondansetron can be given either by oral, rectal or intravenous administration. Ondansetron has been shown to be equally effective in the following dose schedules over the first 24 hours of chemotherapy:

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

• A dose of 8 mg by slow intravenous injection (in not less than 30 seconds) or intramuscular injection immediately before chemotherapy, followed by two further intravenous injections (in not less than 30 seconds) or intramuscular doses of 8 mg four hours apart, or by a constant infusion of 1 mg/hour for up to 24 hours.

• A maximum initial intravenous dose of 16 mg diluted in 50-100 ml of 0.9% Sodium Chloride Injection or other compatible infusion fluid and infused over not less than 15 minutes immediately before chemotherapy. The initial dose of Ondansetron may be followed by two additional 8 mg intravenous doses (in not less than 30 seconds) or intramuscular doses four hours apart.

A single dose greater than 16 mg must not be given due to dose dependent increase of QT-prolongation risk. The selection of dose regimen should be determined by the severity of the emetogenic challenge.

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

To protect against delayed or prolonged emesis after the first 24 hours, oral or rectal treatment with Ondansetron should be continued for up to 5 days after a course of treatment.

Paediatric population

Chemotherapy-induced nausea and vomiting (CINV) in children aged ≥ 6 months to 17 years

The dose for CINV can be calculated based on body surface area (BSA) or weight – see below. In paediatric clinical studies, ondansetron was given by IV infusion diluted in 25 to 50 ml of saline or other compatible infusion fluid and infused over not less than 15 minutes.

Weight-based dosing results in higher total daily doses compared to BSA-based dosing.

Ondansetron injection should be diluted in 5% dextrose or 0.9% sodium chloride or other compatible infusion fluid and infused intravenously over not less than 15minutes.

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

Dosing by BSA

Ondansetron should be administered immediately before chemotherapy as a single intravenous dose of 5 mg/m^2. The single intravenous dose must not exceed 8 mg.

Oral dosing can commence 12 hours later and may be continued for up to 5 days (see Table 1)

The total dose over 24 hours (given as divided doses) must not exceed adult dose of 32 mg.

Table 1: BSA-based dosing for Chemotherapy - Children aged ≥ 6 months to 17 years

BSA	Day 1[a,b]	Day 2-6[b]
<0.6 m^2	5 mg/m^2 IV plus 2 mg syrup after 12 hours	2 mg syrup every 12 hours
≥0.6 m^2 to ≤1.2 m^2	5 mg/m^2 IV plus 4 mg syrup or tablet after 12 hours	4 mg syrup or tablet every 12 hours
>1.2 m^2	5 mg/m^2 or 8 mg IV plus 8 mg syrup or tablet after 12 hours	8 mg syrup or tablet every 12 hours

a The intravenous dose must not exceed 8 mg.

b The total dose over 24 hours (given as divided doses) must not exceed adult dose of 32 mg.

Dosing by bodyweight

Weight-based dosing results in higher total daily doses compared to BSA-based dosing.

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

On Day 1, two further intravenous doses may be given in 4 hourly intervals.

Oral dosing can commence 12 hours later and may be continued for up to 5 days.

The total dose over 24 hours (given as divided doses) must not exceed adult dose of 32 mg.

Table 2: Weight-based dosing for Chemotherapy - Children aged ≥ 6 months to 17 years

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

a. The intravenous dose must not exceed 8 mg.
b. The total dose over 24 hours (given as divided doses) must not exceed adult dose of 32 mg.

Elderly:

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

In patients 75 years of age or older, the initial intravenous dose of Ondansetron 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 and infused over 15 minutes. The initial dose of 8 mg may be followed by two further intravenous doses of 8 mg, infused over 15minutes and given no less than four hours apart.

Post-Operative Nausea and Vomiting (PONV)

Adults:

Prevention of PONV

For the prevention of PONV: Ondansetron can be administered orally or by intravenous injection.

Ondansetron may be administered as a single dose of 4 mg given by slow intravenous or intramuscular injection at induction of anaesthesia.

Treatment of established PONV

For treatment of established PONV: A single dose of 4 mg given by intramuscular or slow intravenous injection is recommended.

Paediatric population:

PONV in children aged ≥ 1 month to 17 years

For prevention of PONV in paediatric patients having surgery performed under general anaesthesia, a single dose of ondansetron may be administered by slow intravenous injection

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

There is no data on the use of Ondansetron in the treatment of PONV in children below 2 years of age.

Elderly:

There is limited experience in the use of Ondansetron in the prevention and treatment of PONV in the elderly, however Ondansetron is well tolerated in patients over 65 years receiving chemotherapy.

Special Populations

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 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 intravenously 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 is required.

Method of administration

IM/ IV Injection

4.3 Contraindications

Hypersensitivity to ondansetron or to other selective 5-HT_3-receptor antagonists (e.g.granisetron, dolasetron) or to any of the excipients.

Based on reports of profound hypotension and loss of consciousness when ondansetron was administered with apomorphine hydrochloride, concomitant use with apomorphine is contraindicated.

4.4 Special Warning and Precautions for Use

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

Cases of myocardial ischemia have been reported in patients treated with ondansetron. In some patients, especially in the case of intravenous administration, symptoms appeared immediately after administration of ondansetron. Patients should be alerted to the signs and symptoms of myocardial ischemia.

There have been post-marketing reports describing patients with potentially life-threatening serotonin syndrome (including altered mental status, autonomic instability, neuromuscular abnormalities and/or gastrointestinal symptoms) following the concomitant use of ondansetron and other serotonergic drugs (including selective serotonin reuptake inhibitors (SSRI) and serotonin noradrenaline reuptake inhibitors (SNRIs) and opioid/opiate medicines (e.g. buprenorphine)). If concomitant treatment with ondansetron and other serotonergic drugs is clinically warranted, appropriate observation of the patient is advised.

As ondansetron is known to increase large bowel transit time, patients with signs of sub-acute 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.

CINV:

When calculating the dose on an mg/kg basis and administering three doses at 4-hour intervals, the total daily dose will be higher than if one single dose of 5 mg/m 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 indicates similar efficacy for both regimens.

4.5 Interaction with other medicinal products and other forms of interaction

There is no evidence that ondansetron either induces or inhibits the metabolism of other drugs commonly co-administered with it. Specific studies have shown that there are no interactions when ondansetron is administered with alcohol, temazepam, furosemide, alfentanil, tramadol, morphine, lidocaine, thiopental 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 metabolizing 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.

Caution should be exercised when ondansetron is coadministered with drugs that prolong the QT interval (including some cytotoxics) and/or cause electrolyte abnormalities.

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 trastuzumab), antibiotics (such as erythromycin), antifungals (such as ketoconazole), antiarrhythmics (such as amiodarone) and beta blockers (such as atenolol or timolol)) may increase the risk of arrhythmias.

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 SSRI sand SNRIs). There are also reports of serotonin syndrome when ondansetron is used concomitantly with opioid/opiate medicines, e.g. buprenorphine.

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 Pregnancy and Lactation

Women of childbearing potential

Women of childbearing potential should consider the use of contraception.

Pregnancy

Based on human experience from epidemiological studies, ondansetron is suspected to cause orofacial malformations when administered during the first trimester of pregnancy.

In one cohort study including 1.8 million pregnancies, first trimester ondansetron use was associated with an increased risk of oral clefts (3 additional cases per 10,000 women treated adjusted relative risk, 1.24, (95% CI 1.03-1.48)).

The available epidemiological studies on cardiac malformations show conflicting results.

Animal studies do not indicate direct or indirect harmful effects with respect to reproductive **toxicity**

Ondansetron should not be used during the first trimester of pregnancy.

Pregnancy testing

Pregnancy status should be verified in women of child-bearing potential prior to starting there treatment with Ondansetron.

Breast-feeding

There is insufficient information on the excretion of ondansetron/metabolites in human milk or the effects of Ondansetron on milk production. Tests have shown that ondansetron passes into the milk of lactating animals. It is therefore recommended that mothers receiving Ondansetron should not breast-feed their babies.

Fertility

There is no information on the effects of ondansetron on human fertility.

4.7 Effects on Ability to Drive and Use Machines

Ondansetron has no or negligible influence on the ability to drive and use machines.

In psychomotor testing ondansetron does not impair performance nor cause sedation. No detrimental effects on such activities are predicted from the pharmacology of ondansetron.

4.8 Undesirable Effecsts

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.

Rare: Dizziness predominantly during rapid IV administration.

Eye Disorders

Rare: Transient visual disturbances (e.g. blurred vision) predominantly during rapid IV administration.

Very rare: Transient blindness predominantly during intravenous administration.

Cardiac disorders

Uncommon: Arrhythmias, chest pain, with or without ST segment depression, bradycardia.

Rare: QTc prolongation (including Torsade de Pointes).

Unknown: Myocardial ischemia.

Vascular disorders

Common: Sensation of warmth or flushing.

Uncommon: Hypotension.

Respiratory, thoracic and mediastinal disorders

Uncommon: Hiccups.

Gastrointestinal disorders

Common: Constipation.

Hepatobiliary disorders

Uncommon: asymptomatic increases in liver function tests.

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.

Paediatric population:

The adverse event profiles in children and adolescents were comparable to that seen in adults.

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.

4.9 Overdose

Symptoms and Signs

There is limited experience of ondansetron overdose. In the majority of cases, symptoms were similar to those already reported in patients receiving recommended doses. Manifestations that have been reported include visual disturbances, severe constipation, hypotension and a vasovagal episode with transient second degree AV block.

Ondansetron prolongs the QT interval in a dose-dependent manner. 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 ondansetron, therefore in all 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 center, where available.

The use of ipecacuanha to treat overdose with Ondansetron is not recommended, as patients are unlikely to respond due to the anti-emetic action of Ondansetron itself.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic Properties

Pharmacotherapeutic groups: Antiemetics and antinauseants, Serotonin ($5HT_3$) antagonists

ATC Code: A04AA01

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 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.

The role of ondansetron in opiate-induced emesis is not yet established.

QT prolongation

The effect of ondansetron on the QTc interval was evaluated in a double bind, randomised, 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 8mg, 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:

CINV

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 18years (S3AB3006). On the days of chemotherapy, patients received either ondansetron 5mg/m intravenous and ondansetron 4 mg orally after 8 to 12 hours or ondansetron 0.45mg/kg intravenous and placebo orally after 8 to 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 intravenous and ondansetron 4 mg orally)

and 41 %(0.45 mg/kg intravenous and 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 intravenous together with 2 to 4 mg dexamethasone orally

•71% of patients when ondansetron was administered as syrup at a dose of 8 mg together with 2 to 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 overall 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 receive three 0.15 mg/kg doses of intravenous ondansetron, administered 30 minutes before the start of chemotherapy and then at 4 and 8 hours 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 intravenous 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.

PONV

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 intravenous 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 PONV 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 nausea	60	47	0.004

CR = no emetic episodes, rescue or withdrawal

5.2 Pharmacokinetic properties

Following oral administration, ondansetron is passively and completely absorbed from the gastrointestinal tract and undergoes first pass metabolism. Peak plasma concentrations of about 30 ng/ml are attained approximately 1.5 hours after an 8 mg dose. For doses above 8 mg the increase in ondansetron systemic exposure with dose is greater than proportional; this may reflect some reduction in first pass metabolism at higher oral doses. Mean bioavailability in healthy male subjects, following the oral administration of a single 8 mg tablet, is approximately 55 to 60%. Bioavailability, following oral administration, is slightly enhanced by the presence of food but unaffected by antacids. Studies in healthy elderly volunteers have shown slight, but clinically insignificant, age-related increases in both oral bioavailability (65%) and half-life (5 hours) of ondansetron.

The disposition of ondansetron following oral, intramuscular and intravenous dosing in adults is similar with a terminal 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.

A 4 mg intravenous infusion of ondansetron given over 5 minutes results in peak plasma concentrations of about 65 ng/ml. Following intramuscular administration of ondansetron, peak plasma concentrations of about 25 ng/ml are attained within 10 minutes of injection.

Following administration of ondansetron suppository, plasma ondansetron concentrations become detectable between 15 and 60 minutes after dosing. Concentrations rise in an essentially linear fashion, until peak concentrations of 20-30 ng/ml are attained, typically 6hours after dosing. Plasma concentrations then fall, but at a slower rate than observed following oral dosing due to continued absorption of ondansetron. The absolute bioavailability of ondansetron from the suppository is approximately 60% and is not affected by gender. The half-life of the elimination phase following suppository administration is determined by the rate of ondansetron absorption, not systemic clearance and is approximately 6 hours. Females show a small, clinically insignificant, increase in half-life in comparison with males.

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.

Special Patient Populations

Gender

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

Children and adolescents (aged 1 month to 17 years)

In paediatric patients aged 1 to 4 months (n=19) undergoing surgery, weight normalized 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 patient population aged 1 to 4 months was reported to average 6.7 hours compared to 2.9 hours for the patients in the 5 to 24 months and 3 to 12 year age range. The differences in the pharmacokinetic parameters in the 1 to 4 months 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 intravenous 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 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 PONV 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 IV dosing.

Renal Impairment

In patients with renal impairment (creatinine clearance 15-60 ml/min), both systemic clearance and volume of distribution are reduced following IV administration of ondansetron, resulting in a slight, but clinically insignificant, increase in elimination half-life (5.4 hours). A study in patients with severe renal impairment who required regular haemodialysis (studied

between dialyses) showed ondansetron's pharmacokinetics to be essentially unchanged following intravenous administration.

Hepatic Impairment

Following oral, intravenous or intramuscular dosing in patients with severe hepatic impairment, ondansetron's systemic clearance is markedly reduced with prolonged elimination half-lives (15 to 32 hours) and an oral bioavailability approaching 100% due to reduced pre-systemic metabolism. The pharmacokinetics of ondansetron following administration as a suppository have not been evaluated in patients with hepatic impairment.

5.3 Preclinical Safety Data

Preclinical data revealed no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity and carcinogenic potential.

Ondansetron and its metabolites accumulate in the milk of rats, milk/plasma-ratio was.

Ondansetron in submicromolar concentrations blocked cloned HERG Potassium channels of the human heart. The clinical relevance of this finding is not clear.

6. PHARMACEUTICAL PARTICULARS

6.1 List of Excipients

- Sodium Chloride BP
- Citric Acid BP
- Sodium Citrate BP
- Water for Injections BP

6.2 Incompatibilities

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

Ondansetron injection should only be mixed with those infusion solutions that are recommended.

6.3 Shelf Life

36 Months

Once opened use immediately.

6.4 Special Precautions for Storage

Store at a temperature not exceeding 25 °C. Protect from light

Keep all medicines out of reach of the children.

6.5 Nature and Contents of Container <and Special Equipment for use, Administration or Implantation>

10 × 2 ml amber colour glass ampoule placed in a plastic tray and such tray packed in a carton along with pack insert.

6.6 Special Precautions for Disposal <and Other Handling>

For single use only. Any unused solution should be discarded.

The solution should be visually inspected prior to use. Only clear and colourless solutions practically free from particles should be used.

Compatibility with other medicinal products

Dexamethasone-21-dihydrogenphosphate disodium:

Dexamethasone sodium phosphate 20 mg may be administered as a slow intravenous injection over 2-5 minutes via the Y-site of an infusion set delivering 8 or 16 mg of ondansetron diluted in 50-100 ml of a compatible infusion fluid over approximately 15 minutes.

Ondansetron may be administered by intravenous infusion by 1 mg/hour. The following medicinal products may be administered only via a Y-site of an infusion set in concentrations of ondansetron of 16 to 160 micrograms/ml (e.g. 8 mg/500 ml and 8 mg/50 ml respectively):

Cisplatin

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

Carboplatin

Concentrations not exceeding the range of 0.18 mg/ml to 9.9 mg/ml (e.g. 90 mg in 500 ml to 990 mg in 100 ml), administered over 10 minutes to 1 hour.

5 -Fluorouracil

Concentrations up to 0.8 mg/ml (e.g. 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 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.

Etoposide

Concentrations not exceeding the range of 0.144 mg/ml to 0.250 mg/ml (e.g. 72 mg in 500 ml to 250 mg in 1 litre), administered over thirty minutes to one hour.

Ceftazidime

Doses in the range of 250 mg to 2000 mg reconstituted with water for injections as recommended by the manufacturer (e.g. 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 of 100 mg to 1 g, reconstituted with water for injections, 5 ml 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 of 10 mg to 100 mg reconstituted with water for injections, 5 ml per 10 mg doxorubicin, as recommended by the manufacturer and given as an intravenous bolus injection over approximately 5 minutes.

7.0 Applicant/Sole Agent

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