

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Ondansetron 4mg Film-coated Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 4 mg ondansetron (as hydrochloride dihydrate).

Excipient(s) with known effect

Each Ondansetron 4mg Film-coated tablet contains 47 mg of lactose monohydrate.
For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet

White to off-white, round biconvex film-coated tablets with PA engraved on one side and 933 on the other side.

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 PONV in children aged ≥ 1 month.

4.2 Posology and method of administration

Posology

Chemotherapy and radiotherapy induced nausea and vomiting (CINV and RINV):

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 ondansetron should be flexible in the range of 8-32 mg a day and selected as shown below.

Emetogenic chemotherapy and radiotherapy: Ondansetron can be given either by rectal, oral (tablets or syrup), intravenous or intramuscular administration.

The recommended oral dose is: 8 mg 1-2 hours before treatment, followed by 8 mg 12 hours later.

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.

The recommended oral dose is 8 mg to be taken twice daily.

Highly emetogenic chemotherapy: e.g. high-dose cisplatin For patients receiving highly emetogenic chemotherapy, e.g. high-dose cisplatin, ondansetron can be given either by rectal, intravenous or intramuscular administration.

The recommended oral dose is 24 mg taken together with oral dexamethasone sodium phosphate 12 mg, 1 to 2 hours before treatment.

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.

The recommended oral dose is 8 mg to be taken twice daily.

Paediatric Population – Chemotherapy-induced nausea and vomiting (CINV) in children aged ≥ 6 months and adolescents:

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 (see Instructions for Use and Handling) and infused over not less than 15 minutes. Weight-based dosing results in higher total daily doses compared to BSA-based dosing (see section 4.4).

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

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/m². The intravenous dose must not exceed 8 mg.

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

The total daily dose must not exceed adult dose of 32 mg.

Table 1: BSA-based dosing for chemotherapy – children aged ≥ 6 months and adolescents

BSA	Day 1 ^{a,b}	Day 2-6 ^b
$< 0.6 \text{ m}^2$	5 mg/m ² IV 2 mg syrup or tablet after 12 hours	2 mg syrup every 12 hours
$\geq 0.6 \text{ m}^2$	5 mg/m ² IV 4 mg syrup or tablet after 12 hours	4 mg syrup or tablet every 12 hours

a The intravenous dose must not exceed 8 mg.

b The total daily dose must not exceed adult dose of 32 mg.

Dosing by bodyweight

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

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

Two further intravenous dose may be given in 4-hourly intervals. The total daily dose must not exceed adult dose of 32 mg.

Oral dosing can commence twelve hours later and may be continues for up to 5 days (see Table 2 below).

Table 2: Weight-based dosing for chemotherapy – children aged > 6 months and adolescents

Weight	Day 1 ^{a,b}	Days 2-6 ^b
$\leq 10 \text{ kg}$	Up to 3 doses of 0.15 mg/kg at 4-hourly intervals	2 mg syrup every 12 hours
$> 10 \text{ kg}$	Up to 3 doses of 0.15 mg/kg at 4 hourly intervals	4 mg syrup or tablet every 12 hours.

a The intravenous dose must not exceed 8 mg

b The total daily dose must not exceed adult dose of 32 mg.

Elderly:

Ondansetron is well tolerated by patients over 65 years and no alteration of dosage, dosing frequency or route of administration are required.

Patients with renal impairment: No alteration of daily dosage or frequency of dosing, or route of administration are required.

Hepatic Impairment: Clearance of ondansetron is significantly reduced and serum half-life significantly prolonged in subjects with moderate or severe impairment of hepatic function. In such patients a total daily dose of 8 mg should not be exceeded.

Patients with Poor Sparteine/Debrisoquine Metabolism

The elimination half-life of ondansetron is not altered in subjects classified as poor metabolisers of sparteine and debrisoquine. Consequently, in such patients repeat dosing will give drug exposure levels no different from those of the general population. No alteration of daily dosage or frequency of dosing are required.

Post-operative nausea and vomiting (PONV):

Adults:

For the prevention of PONV ondansetron can be administered orally or by intravenous or intramuscular injection.

For prevention of post-operative nausea and vomiting, the recommended oral dose is 16 mg given 1 hour prior to anaesthesia. Alternatively, 8 mg one hour prior to anaesthesia followed by two further doses of 8 mg at eight hourly intervals.

For the treatment of established PONV ondansetron administration by injection is recommended.

Paediatric population – Post-operative nausea and vomiting in children aged ≥ 1 month and adolescents:

No studies have been conducted on the use of orally administered ondansetron in the prevention or treatment of post-operative nausea and vomiting (PONV); slow IV injection (in not less than 30 seconds) is recommended for this purpose.

There are no data on the use of ondansetron in the treatment of PONV in children under 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.

Patients with renal impairment:

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

Hepatic Impairment:

Clearance of ondansetron is significantly reduced and serum half life significantly prolonged in subjects with moderate or severe impairment of hepatic function. In such patients a total daily dose of 8 mg should not be exceeded.

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 active substance exposure levels no different from those of the general population. No alteration of daily dosage or frequency of dosing are required.

Method of administration

For oral use.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Concomitant use with apomorphine is contra-indicated (see section 4.5).

4.4 Special warnings 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 (see section 5.1). 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 or patients taking 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)) (see section 4.5). 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 subacute intestinal obstruction should be monitored following 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 ischaemia.

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/m² 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 (see section 5.1).

Excipients

Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

This medicine contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially 'sodium-free'.

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 most other medicinal products commonly co-administered with it. Specific studies have shown that ondansetron does not interact with alcohol, temazepam, furosemide, alfentanil, tramadol, morphine, lignocaine, 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 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.

Caution should be exercised when ondansetron is co-administered with drugs that prolong the QT interval and/or cause electrolyte abnormalities. (See section 4.4)

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 (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.

Tramadol

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

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.

4.6 Fertility, 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.

Breastfeeding

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 Tablets 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 effects

Tabulated list of adverse reactions

Adverse events are listed below by system organ class and frequency. Frequencies are defined according to the following convention: very common ($\geq 1/10$), common ($\geq 1/100$ to $< 1/10$), uncommon ($\geq 1/1,000$ to $< 1/100$), rare ($\geq 1/10,000$ to $< 1/1,000$), very rare ($< 1/10,000$; including isolated reports), not known (cannot be estimated from the available data). 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. 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 dystonic reactions, oculogyric crisis and dyskinesia)¹

Rare: dizziness during rapid IV administration.

Eye disorders

Rare: transient visual disturbances (e.g. blurred vision) predominantly during intravenous administration

Very rare: transient blindness predominantly after intravenous administration²

Cardiac disorders

Uncommon: bradycardia, arrhythmias, chest pain (with or without ST segment depression)

Rare: QTc prolongation (including Torsade de pointes)

Not known: myocardial ischemia* (see section 4.4)

Vascular disorders

Common: feeling of warmth, flushing

Uncommon: hypotension

Respiratory, thoracic and mediastinal disorders

Uncommon: hiccups

Gastrointestinal disorders

Common: constipation

Hepatobiliary disorders

Uncommon: asymptomatic increases in liver function tests³

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 commonly observed in patients receiving chemotherapy with cisplatin.

* These types of adverse drug reactions have been derived from post-marketing experience with ondansetron via spontaneous case reports and literature cases. Because these reactions are reported voluntarily from a population of uncertain size, it is not possible to reliably estimate their frequency which is therefore categorised as not known.

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 the Yellow Card Scheme at: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

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 (see section 4.8). 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 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.

Management

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 centre, 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 group: Serotonin (5HT₃) antagonists

ATC code: A04AA01

Mechanism 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 probably due to antagonism of 5HT₃ receptors on neurons located both in the peripheral and central nervous system. The mechanisms of action in post-operative nausea and vomiting are not known but there may be common pathways with cytotoxic induced nausea and vomiting.

Ondansetron does not alter plasma prolactin concentrations.

Clinical safety and efficacy

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 blind, 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 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.

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 18 years (S3AB3006). On the days of chemotherapy, patients received either ondansetron 5 mg/m² intravenous and ondansetron 4 mg orally after 8 to 12 hours or ondansetron 0.45 mg/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 the worst day of chemotherapy was 49% (5 mg/m² 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/m² intravenous 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 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 received three 0.15 mg/kg doses of intravenous ondansetron, administered 30 minutes before the start of chemotherapy and then at four and eight 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 emesis	50	47	0.004

CR = no emetic episodes, rescue or withdrawal

5.2 Pharmacokinetic properties

Absorption

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.

The disposition of ondansetron following oral, intramuscular (IM) and intravenous (IV) dosing is similar with a terminal half life of about 3 hours and steady state volume of distribution of about 140 L. Equivalent systemic exposure is achieved after IM and IV 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 6 hours 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.

Distribution

Ondansetron is not highly protein bound (70-76%).

Biotransformation and Elimination

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).

Children and Adolescents (aged 1 month to 17 years)

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 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 (\geq 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 \geq 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.

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 h). A study in patients with severe renal impairment who required regular haemodialysis (studied between dialyses) showed ondansetron's pharmacokinetics to be essentially unchanged following IV 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 (15-32 h) 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

Embryo-foetal development studies in rats and rabbits did not show evidence of harm to the foetus when ondansetron was administered during the period of organogenesis at approximately 6 and 24 times respectively the maximum recommended human oral dose of 24 mg/day, based on body surface area. In a pre- and postnatal developmental toxicity study, there were no effects upon pregnant rats and the pre- and postnatal development of their offspring, including reproductive performance at approximately 6 times the maximum recommended human oral dose of 24 mg/day based on body surface area.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Core:

Microcrystalline cellulose

Lactose monohydrate

Maize starch

Magnesium stearate.

Film-coat:

Hypromellose

Lactose monohydrate

Titanium dioxide E171

Macrogol 4000
Sodium citrate dihydrate E331.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

5 years.

6.4 Special precautions for storage

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

6.5 Nature and contents of container

PVC/Al blister
Packs of 6, 10, 15 or 30 film-coated tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements for disposal.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

PLIVA Pharma Ltd.,
Ridings Point, Whistler Drive,
Castleford, West Yorkshire,
WF10 5HX,
United Kingdom

8 MARKETING AUTHORISATION NUMBER

PL 10622/0100

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

19/05/2009

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