

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Ondansetron 2mg/ml Solution for Injection or Infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

1 ml solution for injection contains 2.494 mg ondansetron hydrochloride dihydrate equivalent to 2 mg of ondansetron. One 2 ml ampoule contains 4 mg of ondansetron and one 4 ml ampoule contains 8 mg of ondansetron.

For the full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Solution for injection

Clear and colourless solution.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

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

Ondansetron is available for oral, parenteral and rectal use to allow the route of administration and dosing to be flexible.

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

The emetogenic potential of cancer treatment varies according to the doses and combinations of chemotherapy and radiotherapy regimens used. The selection of dose regimen should be determined by the severity of the emetogenic challenge.

Populations - Adults

The dose range of Ondansetron is 8 to 32 mg a day and selected as shown below.

Emetogenic chemotherapy and radiotherapy

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

Highly emetogenic chemotherapy

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

- A single dose of 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 injection (in not less than 30 seconds) or intramuscular doses of 8 mg four hours apart, or by a constant infusion of 1mg/hour for up to 24 hours.
- A maximum initial intravenous dose of 16 mg diluted in 50 to 100 ml of saline or other compatible infusion fluid (see section 6.6) 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.

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

Oral or rectal treatment is recommended to protect against delayed or prolonged emesis after the first 24 hours and should be continued for up to 5 days after a course of treatment. The recommended dosage of oral ondansetron is 8 mg twice daily. For oral or rectal treatment, other medicinal products are available on the market.

Paediatric Population

Chemotherapy-induced nausea and vomiting (CINV) in children and adolescents (aged 6 months to 17 years)
The dose for chemotherapy induced nausea and vomiting (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 section 6.6) 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 and 5.1).

Ondansetron injection should be diluted in 5% dextrose or 0.9% sodium chloride or other compatible infusion fluid (see section 6.6) 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 single intravenous dose must not exceed 8 mg.

Oral dosing can commence 12 hours later and may be continued for up to 5 days (Table 1). The total daily dose must not exceed adult dose of 32 mg.

Table 1: BSA-based dosing for Chemotherapy - Children and adolescents (aged 6 months to 17 years)

BSA	Day 1(a,b)	Days 2-6(b)
< 0.6 m²	5 mg/m² i.v. plus 2 mg syrup after 12 hours	2 mg syrup every 12 hours
≥ 0.6 m²	5 mg/m² i.v. plus 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 BSA-based dosing (see sections 4.4 and 5.1).

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.

Two further intravenous doses may be given in 4-hourly intervals. The total daily dose must not exceed adult dose of 32 mg. Oral dosing can commence 12 hours later and may be continued for up to 5 days (Table 2).

Table 2: Weight-based dosing for Chemotherapy - Children and adolescents (aged 6 months to 17 years)

Weight	Day 1 (a,b)	Days 2-6(b)
≤10 kg	Up to 3 doses of 0.15 mg/kg every 4 hours	2 mg syrup every 12 hours
> 10 kg	Up to 3 doses of 0.15 mg/kg every 4 hours	4 mg syrup or tablet every 12 hours

- a. The intravenous dose must not exceed 8mg.
- b. The total daily dose must not exceed adult dose of 32 mg.

Populations - Elderly

In patients 65 to 74 years of age, all intravenous doses should be diluted in 50-100 ml of saline or other compatible infusion fluid (see section 6.6) and infused over 15 minutes. Potential further doses should be given no less than 4 hours apart.
For patients aged 65 to 74 years, the initial intravenous dose of ondansetron is 8 mg or 16 mg infused over 15 minutes. The initial dose may be followed by two further doses of 8 mg infused over 15 minutes no less than 4 hours apart.

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 saline or other compatible infusion fluid (see section 6.6) and infused over 15 minutes. The initial dose of 8 mg may be followed by two further intravenous doses of 8 mg, infused over 15 minutes and given no less than 4 hours apart (see section 5.2).

Populations - Renal Impairment

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

Populations - 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.

Populations - 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)

Populations - Adults

For prevention of post-operative nausea and vomiting, the recommended dose of Ondansetron is a single dose of 4 mg by intramuscular or slow intravenous injection administered at the induction of anaesthesia.

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

Paediatric population

Post-operative nausea and vomiting in children and adolescents (aged 1 month to 17 years)

For prevention of PONV in paediatric patients having surgery performed under general anaesthesia, a single dose of ondansetron may be administered by slow IV 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 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 4 mg.

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

Populations - Elderly

There is limited experience in the use of ondansetron in the prevention and treatment of post-operative nausea and vomiting in the elderly, however ondansetron is well tolerated in patients over 65 years receiving chemotherapy.

Populations - Renal Impairment

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

Populations - 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.

Populations - 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.

4.3 Contraindications

Hypersensitivity to the active substance or to other selective 5-HT₃ (serotonin/5-hydroxytryptamine) receptor antagonists (e.g. granisetron, dolasetron) or to any of the excipients listed in section 6.1.

Concomitant use with apomorphine (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 5-HT₃ 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 5.2). 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)). 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.

Ondansetron 2 mg/ml Solution for Injection or Infusion contains sodium. The solutions for injection (ampoules with 2 ml and 4 ml) contain less than 1 mmol sodium (23 mg) each, i.e. essentially "sodium-free".

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-hourly intervals, the total daily dose will be higher than if one single dose of 5mg/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 indicates similar efficacy for both regimens (section 5.1).

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 medicinal products commonly coadministered with it. Specific studies have shown that ondansetron does not interact with alcohol, temazepam, furosemide, tramadol, alfentanil, morphine, lignocaine, propofol and thiopental.

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.

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

Serotonergic Drugs (e.g., SSRIs and SNRIs)

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

Apomorphine

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

Phenytoin, Carbamazepine and Rifampicin

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

Tramadol

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

4.6 Fertility, pregnancy and lactation

Pregnancy

The safety of ondansetron for use in human pregnancy has not been established. Evaluation of experimental animal studies does not indicate direct or indirect harmful effects with respect to the development of the embryo, or foetus, the course of gestation and peri- and post-natal development. However as animal studies are not always predictive of human response the use of ondansetron in pregnancy is not recommended.

Breastfeeding

Tests have shown that ondansetron passes into the milk of lactating animals (see section 5.3). It is therefore recommended that mothers receiving ondansetron should not breast-feed their babies.

4.7 Effects on 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

Adverse events are listed below by system organ class and frequency. Frequencies are defined as: very common ($\geq 1/10$), common ($\geq 1/100$ to $< 1/10$), uncommon ($\geq 1/1000$ to $< 1/100$), rare ($\geq 1/10,000$ to $< 1/1000$) and very rare ($< 1/10,000$). Very common, common and uncommon events were generally determined from clinical trial data. The incidence in placebo was taken into account. Rare and very rare events were generally determined from post-marketing spontaneous data.

The following frequencies are estimated at the standard recommended doses of ondansetron.

	Very common	Common	Uncommon	Rare	Very rare
Immune system disorders				Immediate hypersensitivity reactions sometimes severe, including anaphylaxis.	
Nervous system disorders	Headache.		Seizures, movement disorders (including extrapyramidal reactions such as dystonic reactions, oculogyric crisis and dyskinesia) ¹	Dizziness during rapid IV administration.	
Eye disorders				Transient visual disturbances (e.g. blurred vision) predominantly during IV administration.	Transient blindness predominantly during intravenous administration ² .
Cardiac disorders			Arrhythmias, chest pain with or without ST segment depression, Bradycardia.	QTc prolongation (including Torsade de pointes)	
Vascular disorders		Sensation of warmth or flushing.	Hypotension.		
Respiratory,			Hiccups.		

thoracic and mediastinal disorders					
Gastrointestinal disorders		Constipation.			
Hepatobiliary disorders			Asymptomatic increases in liver function tests ³		
Skin and subcutaneous tissue disorders					Toxic skin eruption, including toxic epidermal necrolysis
General disorders and administration site conditions		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. Healthcare professionals are asked to report any suspected adverse reactions via HPRA Pharmacovigilance, Earlsfort Terrace, IRL - Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517. Website: <http://www.hpra.ie/>; E-mail: medsafety@hpra.ie.

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. In all instances, the events resolved completely.

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

Treatment

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

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.

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.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antiemetics and antinauseants, Serotonin (5-HT₃) antagonists

ATC Code: A 04 AA 01

Ondansetron is a potent, highly selective 5-HT₃ receptor-antagonist. Its precise antiemetic and antinauseal mechanism of action is not known.

Chemotherapeutic agents and radiotherapy may cause release of 5-HT in the small intestine initiating a vomiting reflex by activating vagal afferents via 5-HT₃ receptors. Ondansetron blocks the initiation of this reflex. Activation of vagal afferents may also cause a release of 5-HT 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 5-HT₃ 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.

In a pharmaco-psychological study in volunteers ondansetron has not shown a sedative effect.

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 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.

Clinical Studies

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 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 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 received 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 yrs and 8 mg for children aged ≥ 12 yrs (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	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 (bioavailability is about 60%). 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. 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.

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).

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 4mg 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.

Ondansetron is not highly protein bound (70-76%). A direct effect of plasma concentration and anti-emetic effect has not been established. 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 Populations

Paediatric population (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 watersoluble 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.

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.

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 (see section 4.2).

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.

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 5.2.

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

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium chloride
Sodium citrate
Citric acid monohydrate
Water for injections

6.2 Incompatibilities

Ondansetron 2 mg/ml Solution for Injection or Infusion should not be given in the same syringe or in the same infusion with other medicinal products.

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6

6.3 Shelf life

Unopened: 5 years

Injection

The medicinal product should be used immediately after opening.

Infusion

The medicinal product remains chemically and physically stable for 28 days after dilution in the solutions for infusion presented in section 6.6 when stored at room temperature or refrigerated. For microbiological reasons, the medicinal product should be used immediately after dilution. If the medicinal product is not used immediately, the storage time and conditions before use are the responsibility of the user, and, if the dilution has not been carried out under controlled and validated aseptic conditions, normally must not exceed 24 hours at 2 – 8 °C.

6.4 Special precautions for storage

Keep the ampoules in the outer carton.

For storage after dilution *see section 6.3*.

6.5 Nature and contents of container

Type I clear glass ampoules in a carton.

Pack sizes: 1 x 2 ml, 5 x 2 ml and 50 (10 x 5) x 2 ml
1 x 4 ml, 5 x 4 ml and 50 (10 x 5) x 4 ml

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

The medicinal product is for single use only. Any unused solution should be discarded.

The Ondansetron 2 mg/ml Solution for Injection or Infusion is to be visually inspected prior to use (also after dilution). Only clear solutions practically free from particles should be used.

The ondansetron solution for injection can be added to the following solutions for infusion:
0.9% sodium chloride solution (physiological saline solution), 5% glucose solution, Ringer`s solution and 10% mannitol solution.

Both the glass containers and the polyethylene (PE) infusion bags have been shown to be suitable for dilution.

7 MARKETING AUTHORISATION HOLDER

ROWEX LTD
Bantry
Co Cork

8 MARKETING AUTHORISATION NUMBER

PA 0711/068/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 15 April 2005

Date of last renewal: 6th November 2008

10 DATE OF REVISION OF THE TEXT

April 2016