Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Ondansetron 2 mg/ml Solution for injection/infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

1 ml solution for injection/infusion contains 2mg ondansetron as ondansetron hydrochloride dihydrate and 3.56 mg of sodium as sodium citrate and sodium chloride.
Each 2 ml ampoule contains 4 mg of ondansetron (as ondansetron hydrochloride dihydrate)
Each 4 ml ampoule contains 8 mg of ondansetron (as ondansetron hydrochloride dihydrate)

For full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for injection/infusion.

Glass amber ampoule containing a colourless clear liquid, practically odourless, free of particles.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Adults:
Management of nausea and vomiting induced by cytotoxic chemotherapy and radiotherapy
Prevention and treatment of post-operative nausea and vomiting (PONV).

Paediatric Population:
Management of chemotherapy-induced nausea and vomiting in children aged ≥ 6 months
Prevention and treatment of post-operative nausea and vomiting in children aged ≥ 1 month.

4.2 Posology and method of administration

For intravenous injection or after dilution for intravenous infusion.

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 of Ondansetron should be flexible 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 should initially be administered intravenously 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
Either 8 mg as a slow intravenous bolus injection or as a short-term infusion lasting 15 minutes immediately before chemotherapy. If this initial dose has insufficient effect it can be supplemented by either 8 mg (intravenous bolus or 15 minutes' infusion) every 4th hour, at most twice, or continuous infusion of 1 mg/hour for 24 hours.

A single intravenous dose of 16mg diluted in 50- 100ml of saline or other compatible infusion fluid and infused over not less than 15 minutes immediately before chemotherapy. A single dose greater than 16 mg must not be given due to dose dependent increase of QT-prolongation risk (see sections 4.4, 4.8 and 5.1).

For management of highly emetogenic chemotherapy, a dose of 8 mg of ondansetron may be administered by slow IV in not less than 30 seconds immediately before chemotherapy, followed by 2 further IV doses of 8 mg 2 to 4 hours apart, or by a constant infusion of 1 mg/h for up to 24 hours.

The effect of ondansetron may be enhanced by the simultaneous administration of 20 mg dexamethasone intravenously or an equally potent dose of other glucocorticoids for intravenous use.

Paediatric Population
Chemotherapy-induced nausea and vomiting in children aged ≥ 6 months and adolescents:
The dose for chemotherapy-induced nausea and vomiting can be calculated based on body surface area (BSA) or weight – see below. Weight-based dosing results in higher total daily doses compared to BSA-based dosing – see sections 4.4.and 5.1.
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 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]	**Days 2-6**[b]
< 0.6 m^2	5 mg/m^2 i.v. 2 mg syrup after 12 hrs	2 mg syrup every 12 hrs
≥0.6 m^2	5 mg/m^2 i.v. 4 mg syrup or tablet after 12 hrs	4 mg syrup or tablet every 12 hrs

[a] The intravenous dose must not exceed 8mg.
[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 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 twelve hours later and may be continued 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]
≤10 kg	Up to 3 doses of 0.15 mg/kg every 4 hrs	2 mg syrup every 12 hrs
> 10 kg	Up to 3 doses of 0.15 mg/kg every 4 hrs	4 mg syrup or tablet every 12 hrs

[a] The intravenous dose must not exceed 8mg.

[b] The total daily dose 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 saline or other compatible infusion fluid (see section 6.6) and infused over 15 minutes.

In patients 75 years of age or older, the initial intravenous dose of 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 four hours apart. (see section 5.2)

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 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 medicinal product 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 post-operative nausea and vomiting (PONV) ondansetron can be administered orally or intramuscular or by slow intravenous injection at the induction of anesthesia.

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

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

Paediatric population
Post-operative nausea and vomiting in children aged ≥ 1 month and adolescents
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 0.1mg/kg up to a maximum of 4mg either prior to, at or after induction of anaesthesia.

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

There are no data on the use of ondansetron in the treatment of post-operative nausea and vomiting in children under 2

years of age.

Elderly
There is limited experience in the use of ondansetron in the prevention and treatment of post-operative nausea and vomiting (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.

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

4.3 Contraindications

Concomitant use with apomorphine (see section4.5).
Hypersensitivity to ondansetron or to other selective 5-HT3-receptor antagonists (e.g. granisetron, dolasetron) or to any component of the preparation listed in section 6.1.

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.

Rarely transient ECG changes including QT interval prolongation have been reported in patients receiving ondansetron. Ondansetron prolongs the QT interval in a dose-dependent manner (see Clinical Pharmacology). 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. These conditions include patients with electrolyte abnormalities, congestive heart failure, bradyarrhythmias or patients taking other medicinal products that lead to QT prolongation or electrolyte abnormalities. Therefore caution should be exercised in patients with cardiac rhythm or conduction disturbances, in patients treated with anti-arrhythmic agents or beta-adrenergic blocking agents and in patients with significant electrolyte disturbances.

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 subacute intestinal obstruction should be monitored following administration.

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

Since there is little experience to date of the use of ondansetron in cardiac patients, caution should be exercised if

ondansetron is coadministered with anaesthetics to patients with arrhythmias or cardiac conduction disorders or to patients who are being treated with antiarrhythmic agents or beta-blockers.

The solution for injection contains less than 1 mmol sodium (23 mg) per ampoule, i.e. essentially ‘sodium- free’.

Paediatric Population

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

Chemotherapy-induced nausea and vomiting (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 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 -see 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, alfentanil, tramadol, 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).

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. If it is absolutely necessary that ondansetron be given caution should be exercised when prescribing to pregnant women especially in the first trimester. A careful risk/benefit assessment should be performed.

Lactation
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 (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1000 to <1/100), rare (≥1/10,000 to <1/1000) and very rare (<1/10,000) including isolated reports. Very common, common and uncommon events were generally determined from clinical trial data. The incidence in placebo was taken into account. Rare and very rare events were generally determined from post-marketing spontaneous data.

The following frequencies are estimated at the standard recommended doses of ondansetron according to indication and formulation. 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, (such as oculogyric crisis, dystonic reactions and dyskinesia) [1]
Rare:	Dizziness during rapid intravenous administration.
Eye disorders	
Rare:	Transient visual disturbances (e.g. blurred vision) during rapid intravenous administration.
Very rare:	Transient blindness predominantly during intravenous administration[2]
Cardiac disorders	
Uncommon:	Arrhythmias, chest pain with or without ST segment depression, Bradycardia.
Rare:	Transient ECG changes including QT interval prolongation (including Torsade de Pointes).
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[3].
General disorders and administration site conditions	
Common:	Local intravenous injection site reactions.

1. Observed without definitive evidence of persistent clinical sequelae.
2. The majority of the blindness cases reported resolved within 20 minutes. Most patients had received chemotherapeutic agents, which included cisplatin. Some cases of transient blindness were reported as cortical in origin.
3. These events were observed commonly in patients receiving chemotherapy with cisplatin.

Reporting of suspected adverse reactions

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

Paediatric population

The adverse event profile in children and adolescents was comparable to that seen in adults.

4.9 Overdose

Symptoms and Signs
Little is known at present about overdosage with ondansetron, however, a limited number of patients received overdoses. 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 manner. ECG monitoring is recommended in cases of overdose.

Treatment
There is no specific antidote for ondansetron, therefore in all 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: A04AA01

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.

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 baselinecorrection 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.

Clinical Studies

Paediatric population:

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

A double-blind randomised placebo-controlled trial 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 i.v.together with 2 - 4 mg dexamethasone p.o.and in 71% of patients when ondansetron was administered as syrup at a dose of 8 mg + 2 - 4 mg dexamethasone p.o. on the days of chemotherapy. Post-chemotherapy both groups received 4 mg ondansetron syrup twice daily for 2 days.

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 (S3A239) study 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.

Prevention of post-operative nausea and vomiting

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

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 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.

The protein binding of ondansetron is 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 has no effect on ondansetron's pharmacokinetics. The pharmacokinetic properties of ondansetron are unchanged on repeat dosing.

Special Patient Populations:

Paediatric population

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 patient population aged 1 to 4 month 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 normalized 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 normalizing systemic exposure in paediatric patients.

Population pharmacokinetic analysis was performed on 74 paediatric cancer patients aged 6 to 48 months and 41 surgery patients aged 1 to 24 months following intravenous administration of ondansetron. Based on the population pharmacokinetic parameters for patients aged 1 month to 48 months, administration of the adult weight based dose (0.15 mg/kg intravenously every 4 hours for 3 doses) would result in a systemic exposure (AUC) comparable to that observed in paediatric surgery patients (aged 5 to 24 months), paediatric cancer patients (aged 4 to 18 years), and surgical patients (aged 3 to 12 years), at similar doses, as shown in Table C. This exposure (AUC) is consistent with the

exposure-efficacy relationship described previously in paediatric cancer subjects, which showed a 50% to 90% response rate with AUC values ranging from 170 to 250 ng.h/mL.

Table 3. Pharmacokinetics in Paediatric Patients 1 Month to 18 Years of Age

Study	Patient Population (Intravenous dose)	Age	N	AUC (ng.h/L)	CL (L/h/kg)	Vd_n (L/kg)	$T_{1/2}$ (h)
				Geometric Mean			Mean
S3A40319[1]	Surgery (0.1 or 0.2mg/kg)	1 to 4 months	19	360	0.401	3.5	6.7
S3A40319[2]	Surgery (0.1 or 0.2mg/kg)	5 to 24 months	22	236	0.581	2.3	2.9
S3A40320 & S3A40319 Pop PK [2,3]	Cancer/ Surgery (0.15mg/kg q4h/ 0.1 or 0.2mg/kg)	1 to 48 months	115	257	0.582	3.65	4.9
S3KG02[4]	Surgery (2 mg or 4 mg)	3 to 12 years	21	240	0.439	1.65	2.9
S3A-150	Cancer (0.15 mg/kg q 4h)	4 to 18 years	21	247	0.599	1.9	2.8

[1] Ondansetron single intravenous dose: 0.1 or 0.2 mg/kg

[2] Population PK Patients: 64% cancer patients and 36% surgery patients.

[3] Population estimates shown; AUC based on dose of 0.15 mg/kg.

[4] Ondansetron single intravenous dose: 2 mg (3 to 7 years) or 4 mg (8 to 12 years)

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

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).

Patients with hepatic impairment
Following oral or intravenous 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 : 1.

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
Citric Acid Monohydrate.
Sodium Citrate.
Water for injections.

6.2 Incompatibilities

Ondansetron injection and infusion should not be administered in the same syringe or infusion as any other medication except the recommended infusion diluents mentioned in section 6.6.

This medicinal product must only be mixed with those infusion solutions that are mentioned in section 6.6.

6.3 Shelf life

Unopened 3 years.

After first opening the Injection':
The product should be used immediately after opening. The injection is intended for single-dose use only with any remaining solution discarded immediately after initial use.

After dilution for intravenous infusion:
From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2 to 8^{o}C, unless reconstitution/dilution (etc) has taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage

Keep in the outer container to protect from light.

This medicinal product does not require any special storage precautions.

From a microbiological point of view, unless the method of opening/reconstitution/dilution precludes the risk of microbial contamination, the product should be used immediately.

If not used immediately, in-use storage times and conditions are the responsibility of the user

For storage conditions of the diluted medicinal product see section 6.3.

6.5 Nature and contents of container

Amber glass ampoules, type 1, containing 2 ml or 4 ml solution
Packs of 1, 5 x 1, 5 and 5 x 5 ampoule(s).

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Injection:
Ondansetron injection ampoules should not be autoclaved.
For single use only. Any unused solution should be discarded.

The solution is to be visually inspected prior to use (also after dilution). Only clear solutions practically free from particles should be used.

Infusion:
May be diluted with solution for infusion containing:

- **sodium chloride 9 mg/ml (0.9%),**
- **glucose 50 mg/ml (5 %),**
- **mannitol 100 mg/ml (10 %)**
- **potassium chloride 3 mg/ml (0.3%) + sodium chloride 9 mg/ml (0.9 %)**
- **potassium chloride 3 mg/ml (0.3%) + glucose 50 mg/ml (5 %)**
- **Ringer's solution for infusion.**

Should not be mixed with other pharmaceutical products.

7 MARKETING AUTHORISATION HOLDER

Mercury Pharmaceuticals Ltd
No. 1 Croydon
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United Kingdom

8 MARKETING AUTHORISATION NUMBER

PA0899/030/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 3rd October 2008

Date of last renewal: 29th November 2010

10 DATE OF REVISION OF THE TEXT

April 2016