Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Ondansetron 2mg/ml Solution for Injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 1-mL contains ondansetron hydrochloride dihydrate equivalent to 2 mg of ondansetron.
Each 2-mL ampoule contains 4 mg of ondansetron.
Each 4-mL ampoule contains 8 mg of ondansetron.

Excipients with known effect:
This medicinal product contains 0.313 mmol (7.2 mg) sodium per 2-mL ampoule.
This medicinal product contains 0.626 mmol (14.4 mg) sodium per 4-mL ampoule.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for injection.
Clear and colourless aqueous solution.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Adults
Ondansetron is indicated for the management of nausea and vomiting induced by cytotoxic chemotherapy and radiotherapy.
Ondansetron is also indicated for the prevention and treatment of post-operative nausea and vomiting.

Paediatric population
Ondansetron is indicated for the management of nausea and vomiting induced by cytotoxic chemotherapy in children and adolescents aged from 6 months to 17 years.
Ondansetron injection is indicated for the prevention or treatment of post-operative nausea and vomiting in children and adolescents aged from 1 month to 17 years.

4.2 Posology and method of administration

Chemotherapy and radiotherapyinduced 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.

CINV and RINV in adults
The dose range of Ondansetron is 8 – 32 mg a day and selected as shown below.

The recommended intravenous or intramuscular dose of Ondansetron is 8mg administered immediately before treatment.

Highly emetogenic chemotherapy
For patients receiving highly emetogenic chemotherapy, maximum initial ondansetron dose of 16 mg IV infused over 15 minutes may be used. 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). Ondansetron has been shown to be equally effective in the following dose schedules over the first 24 hours of chemotherapy:

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

- A dose of 8 mg by slow intravenous injection (in not less than 30 seconds) or intramuscular injection immediately before chemotherapy, followed by two further intravenous injections (in not less than 30 seconds) or intramuscular doses of 8 mg four hours apart, or by a constant infusion of 1 mg / h for up to 24 hours.
- A maximum initial intravenous dose of 16 mg diluted in 50 – 100 mL of sodium chloride 0.9% w/v 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 intravenous dose of dexamethasone sodium phosphate, 20 mg administered prior to chemotherapy.

Oral treatment is recommended to protect against delayed or prolonged emesis after the first 24 hours. The recommended oral dose is 8 mg to be taken twice daily.

The selection of dose regimen should be determined by the severity of the emetogenic challenge.

Paediatric population

CINV in children and adolescents (aged 6 months to 17 years)

The dose for CINV can be calculated based on body surface area (BSA) or weight. Weight-based dosing results in higher total daily doses compared to BSA-based dosing (see sections 4.4 and 5.1).

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 Instructions for Use and Handling) and infused over not less than 15 minutes.

There are no data from controlled clinical trials on the use of ondansetron for radiotherapy-induced nausea and vomiting in children.

Dosing by Body Surface Area (BSA)

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

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

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

Table 1: BSA-based dosing for CINV(aged 6 months to 17 years)

BSA	**Day 1** [a,b]	**Days 2 – 6** [b]
< 0.6 m^2	5 mg / m^2 IV plus 2 mg syrup after 12 h	2 mg syrup every 12 h
≥ 0.6 m^2	5 mg / m^2 IV plus 4 mg syrup or tablet after 12 h	4 mg syrup or tablet every 12 h

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

[b] The total dose over 24 hours 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.
On Day 1, two further intravenous doses may be given in 4-hourly intervals.
Oral dosing can commence 12 hours later and may be continued for up to 5 days (Table 2).

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

Table 2: Weight-based dosing for CINV (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 IV every 4 h	2 mg syrup every 12 h
> 10 kg	Up to 3 doses of 0.15 mg / kg IV every 4 h	4 mg syrup or tablet every 12 h

[a] The intravenous dose must not exceed 8 mg.
[b] The total dose over 24 hours must not exceed adult dose of 32 mg.

CINV and RINV in elderly

In patients 65 to 74 years of age, the dose schedule for adults can be followed. All intravenous doses should be diluted in 50-100 mL of 0.9% sodium chloride solution 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 0.9% sodium chloride solution 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).

Post-Operative Nausea and Vomiting (PONV)

PONV in adults
For the prevention of post-operative nausea and vomiting, the recommended dose of ondansetron is a single dose of 4 mg given by intramuscular or slow intravenous injection at induction of anaesthesia.
For treatment of established post-operative nausea and vomiting a single dose of 4 mg given by intramuscular or slow intravenous injection is recommended.

Paediatric population

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

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.

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 IV or oral 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.

4.3 Contraindications

Based on reports of profound hypotension and loss of consciousness when ondansetron was administered with apomorphine hydrochloride, concomitant use with apomorphine is contraindicated (see section 4.5).
Hypersensitivity to the active substance or to any of the excipients 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 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, conduction disturbances and in patients taking anti-arrhythmic agents or beta-adrenergic blocking agents or other medicinal products that lead to QT prolongation or electrolyte abnormalities.

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.

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.

This medicinal product contains less than 1 mmol sodium (23 mg) per ampoule, that is to say 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
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 5 mg / m^2 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 drugs commonly co-administered with it. Specific studies have shown that there are no interactions when ondansetron is administered with alcohol, temazepam, furosemide, alfentanil, tramadol, morphine, lidocaine, thiopental or propofol.

Ondansetron is metabolised by multiple hepatic cytochrome P-450 enzymes: CYP3A4, CYP2D6 and CYP1A2. Due to the multiplicity of metabolic enzymes capable of 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 medicinal products that prolong the QT interval (including some cytotoxics) 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 medicinal products (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

Women of childbearing potential
Women of childbearing potential should consider the use of contraception.

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

In one cohort study including 1.8 million pregnancies, first trimester ondansetron use was associated with an increased risk of oral clefts (3 additional cases per 10 000 women treated; adjusted relative risk, 1.24, (95% CI 1.03-1.48)).
The available epidemiological studies on cardiac malformations show conflicting results.
Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity. Ondansetron should not be used during the first trimester of pregnancy.

Pregnancy testing
Pregnancy status should be verified in women of child-bearing potential prior to starting the treatment with ondansetron.

Breast-feeding
There is insufficient information on the excretion of ondansetron/metabolites in human milk or the effects of ondansetron on milk production. Available pharmacodynamic/toxicological data in animals have shown excretion of ondansetron/metabolites in milk (see section 5.3). A risk to the newborns/infants cannot be excluded. Ondansetron should not be used during breast-feeding.

Fertility
There is no data on the effects of ondansetron on human fertility.

4.7 Effects on ability to drive and use machines

Ondansetron has no or negligible influence on the ability to drive and use machines.
In psychomotor testing ondansetron does not impair performance nor cause sedation.
No detrimental effects on such activities are predicted from the pharmacology of ondansetron

4.8 Undesirable 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 (≥1/1 000 to<1/100); rare: (≥1/10 000 to <1/1 000); very rare: (<1/10 000); 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 predominantly during rapid IV administration.
Eye disorders	
Rare:	Transient visual disturbances (e.g., blurred vision) predominantly during rapid IV administration.
Very rare:	Transient visual disturbances, predominantly during intravenous administration.[(2)]
Cardiac disorders	
Uncommon:	Arrhythmias, chest pain with or without ST segment depression, bradycardia.
Rare:	QTc prolongation (including Torsade de Pointes).
Not known:	Myocardial ischemia (see section 4.4)
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)].
Skin and subcutaneous tissue disorders	
Very rare:	Toxic skin eruption, including toxic epidermal necrolysis.
General disorders and administration site conditions	
Common:	Local IV injection site reactions.

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

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

For IE: HPRA Pharmacovigilance, Website: www.hpra.ie.
For UK: Yellow Card Scheme, Website: 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 the QT interval in a dose-dependent fashion. ECG monitoring is recommended in cases of overdose.

Paediatric population

Paediatric cases consistent with serotonin syndrome have been reported after inadvertent oral overdoses of ondansetron (exceeded estimated ingestion of 4 mg / kg) in infants and children aged 12 months to 2 years.

Treatment
There is no specific antidote for ondansetron, therefore in 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: Antiemetics and antinauseants, Serotonin ($5\text{-}HT_3$) antagonists
ATC Code: A04AA01

Mechanism of action
Ondansetron is a potent, highly selective $5HT_3$ receptor-antagonist. Its precise mode of action in the control of nausea and vomiting is not known. Chemotherapeutic agents and radiotherapy may cause the release of 5HT in the small intestine initiating a vomiting reflex by activating vagal afferents via $5HT_3$ receptors. Ondansetron blocks the initiation of this reflex. Activation of vagal afferents may also cause a release of 5HT in the area postrema, located on the floor of the fourth ventricle, and this may also promote emesis through a central mechanism. Thus, the effect of ondansetron in the management of the nausea and vomiting induced by cytotoxic chemotherapy and radiotherapy is probably due to antagonism of $5HT_3$ receptors on neurons located both in the peripheral and central nervous system. The mechanisms of action in post-operative nausea and vomiting are not known but there may be common pathways with cytotoxic induced nausea and vomiting.
Ondansetron does not alter plasma prolactin concentrations.

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. No significant changes were seen in the measured electrocardiographic PR or QRS intervals.

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 (S3AB3006). On the days of chemotherapy, patients received either ondansetron 5 mg / m^2 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 / m^2 intravenous and ondansetron 4 mg orally) and 41% (0.45 mg / kg intravenous and placebo orally). Post-chemotherapy both groups received 4 mg ondansetron syrup twice daily for 3 days. There was no difference in the overall incidence or nature of adverse events between the two treatment groups.

A double-blind randomised placebo-controlled trial (S3AB4003) in 438 patients aged 1 to 17 years demonstrated complete control of emesis on worst day of chemotherapy in:

- 73% of patients when ondansetron was administered intravenously at a dose of 5 mg / m^2 intravenous together with 2 to 4 mg dexamethasone orally
- 71% of patients when ondansetron was administered as syrup at a dose of 8 mg together with 2 to 4 mg dexamethasone orally on the days of chemotherapy.

Post-chemotherapy both groups received 4 mg ondansetron syrup twice daily for 2 days. There was no difference in the 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 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.

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).

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 post-operative nausea and vomiting 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

The disposition of ondansetron following oral, intramuscular or intravenous dosing in adults is similar with a terminal elimination half life of about 3 hours and steady state volume of distribution of about 140 L. Equivalent systemic exposure is

achieved after intramuscular and intravenous administration of ondansetron.

Ondansetron is not highly protein bound (70 – 76%). Ondansetron is cleared from the systemic circulation predominantly by hepatic metabolism through multiple enzymatic pathways. Less than 5 % of the absorbed dose is excreted unchanged in the urine. The absence of the enzyme CYP2D6 (the debrisoquine polymorphism) has no effect on ondansetron's pharmacokinetics. The pharmacokinetic properties of ondansetron are unchanged on repeat dosing. Studies in healthy elderly volunteers have shown slight, but clinically insignificant, age-related increases in both oral bioavailability and half-life of ondansetron.

Gender differences were shown in the disposition of ondansetron, with females having a greater rate and extent of absorption following an oral dose and reduced systemic clearance and volume of distribution (adjusted for weight).

Paediatric population
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 medicinal products 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 of distribution was related to age and was lower in adults than in infants and children. Clearance was related to weight but not to age with the exception of infants aged 1 to 4 months. It is difficult to conclude whether there was an additional reduction in clearance related to age in infants 1 to 4 months or simply inherent variability due to the low number of subjects studied in this age group. Since patients less than 6 months of age will only receive a single dose in PONV a decreased clearance is not likely to be clinically relevant.

Elderly
Early Phase I studies in healthy elderly volunteers showed a slight age-related decrease in clearance, and an increase in half-life of ondansetron. However, wide inter-subject variability resulted in considerable overlap in pharmacokinetic parameters between young (< 65 years of age) and elderly subjects (≥ 65 years of age) and there were no overall differences in safety or efficacy observed between young and elderly cancer patients enrolled in CINV clinical trials to support a different dosing recommendation for the elderly.

Based on more recent ondansetron plasma concentrations and exposure-response modelling, a greater effect on QTcF is predicted in patients ≥75 years of age compared to young adults. Specific dosing information is provided for patients over 65 years of age and over 75 years of age for IV dosing (see section 4.2).

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

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

5.3 Preclinical safety data

A study in cloned human cardiac ion channels has shown ondansetron has the potential to affect cardiac repolarisation via blockade of hERG potassium channels at clinically relevant concentrations. Dose-dependent QT prolongation has been observed in a thorough QT study in human volunteers (see section 5.1). In embryo-foetal development studies in rats and rabbits, pregnant animals received oral doses of ondansetron up to 15 mg/kg/day and 30 mg/kg/day, respectively, during the period of organogenesis. With the exception of a slight decrease in maternal body weight gain in the rabbits, there were no significant effects of ondansetron on the maternal animals or the development of the offspring. At doses of 15 mg/kg/day in rats and 30 mg/kg/day in rabbits, the maternal dose was approximately 6 and 24 times the maximum recommended human oral dose of 24 mg/day, respectively, based on body surface area. In a pre- and postnatal developmental toxicity study, pregnant rats received oral doses of ondansetron up to 15 mg/kg/day from Day 17 of pregnancy to litter Day 21. With the exception of a slight reduction in maternal body weight gain, there were no effects upon the pregnant rats and the pre- and postnatal development of their offspring, including reproductive performance of the mated F1 generation. At a dose of 15 mg/kg/day in rats, the maternal dose was approximately 6 times the maximum recommended human oral dose of 24 mg/day based on BSA.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Citric acid monohydrate
Sodium citrate dihydrate
Sodium chloride
Water for injections

6.2 Incompatibilities

Ondansetron injection should not be administered in the same syringe or infusion as any other medication. This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf life

Glass ampoules: 2 years
Plastic ampoules overwrapped in individual aluminium foil blisters: 2 years
Plastic ampoules overwrapped with a protective pouch: 2 years
Use within 4 months after opening the protective pouch.

After dilution: Chemical and physical in-use stability has been demonstrated for 24 hours stored at 25°C and 36 hours stored in a refrigerator (2 – 8°C). Dilutions of Ondansetron injection in compatible intravenous infusion fluids are stable under normal room lighting conditions or daylight for at least 24 hours, thus no protection from light is necessary while infusion takes place. From a microbiological point of view, unless the method of opening or 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.

6.4 Special precautions for storage

Store below 25ºC. Store in the original package in order to protect from light. For storage conditions of the diluted medicinal product, see section 6.3.

6.5 Nature and contents of container

2 mL or 4 mL polypropylene blow-fill-sealed ampoules with a twist-off top or clear, colourless glass (Ph. Eur., type I) ampoules. The plastic ampoules are overwrapped in individual aluminium foil blisters and placed in cartons. Alternatively, strips of 5 plastic ampoules are overwrapped with a protective pouch and placed in cartons.The glass ampoules are placed in plastic cases inside cartons.

Packs of 5 glass ampoules or 5, 10 and 50 plastic ampoules are availlable.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Ondansetron should not be autoclaved.

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

Compatibility with intravenous fluids

Ondansetron injection should only be mixed with solutions for infusion which are recommended:

Diluent	**Resulting concentration of ondansetron**
Sodium chloride solution for infusion 0.9%w/v	0.16 mg / mL
Glucose solution for infusion 5%w/v	0.16 mg / mL
Mannitol solution for infusion 10%w/v	0.16 mg / mL
Ringers solution for infusion	0.16 mg / mL
Potassium chloride 0.3%w/v and sodium chloride 0.9%w/v solution for infusion	0.16 mg / mL
Potassium chloride 0.3%w/v and glucose 5%w/v solution for infusion	0.16 mg / mL

In complying with good pharmaceutical practice, dilutions of ondansetron injection in intravenous fluids should be prepared at the time of infusion. However, it has been demonstrated that dilutions of ondansetron in polyethylene bottles with the following intravenous infusion fluids remain stable for 24 hours at room temperature (25 ± 2°C) or for 36 hours in the refrigerator (2 – 8°C).

Compatibility with other medicinal products

Ondansetron may be administered by intravenous infusion at 1 mg / h, e.g., from an infusion bag or syringe pump. The following medicinal products may be administered via the Y-site of an infusion set for ondansetron concentrations of 16 to 160 micrograms / mL (e.g., 8 mg / 500 mL and 8 mg / 50 mL respectively):

Cisplatin:
Concentrations up to 0.48 mg / mL (e.g., 240 mg in 500 mL) administered over one to eight hours.

5-Fluorouracil:
Concentrations up to 0.8 mg / mL (e.g., 2.4 g in 3 litres or 400 mg in 500 mL) administered at a rate of at least 20 mL per hour (480 mL per 24 hours). Higher concentrations of 5-fluorouracil may cause precipitation of ondansetron. The 5-fluorouracil infusion may contain up to 0.045%w/v magnesium chloride in addition to other excipients shown to be compatible.

Carboplatin:
Concentrations in the range 0.18 mg / mL to 9.9 mg / mL (e.g., 90 mg in 500 mL to 990 mg in 100 mL), administered over ten minutes to one hour.

Etoposide:
Concentrations in the range 0.14 mg / mL to 0.25 mg / mL (e.g., 70 mg in 500 mL to 250 mg in 1L), administered over thirty minutes to one hour.

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

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

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

Dexamethasone:
Dexamethasone sodium phosphate 20 mg may be administered as a slow intravenous injection over 2 – 5 minutes via the Y-site of an infusion set delivering 8 or 16 mg of ondansetron diluted in 50-100 mL of the following infusion fluids:
- Sodium chloride 0.9% w/v

- Glucose 5% w/v
-Sodium chloride 0.9% w/v and Glucose solution for infusion 5% w/v over approximately 15 minutes.
Compatibility between dexamethasone sodium phosphate and ondansetron has been demonstrated supporting administration of these drugs through the same giving set resulting in concentrations in line of 32 microgram – 2.5 mg / mL for dexamethasone sodium phosphate and 8 microgram – 1 mg / mL for ondansetron.

Ondansetron should not be administered in the same syringe of infusion as any other medicinal products.

7 MARKETING AUTHORISATION HOLDER

Noridem Enterprises Limited
Evagorou & Makariou
Mitsi Building 3, Office 115
1065 Nicosia
Cyprus

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