

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Ondansetron 4 mg/5 ml syrup

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 5ml syrup contains 4mg ondansetron (as ondansetron hydrochloride dihydrate).

Excipients with known effect:

Each 5ml syrup contains 2100mg of Sorbitol (E420), 6mg of sodium benzoate (E211) and 14.1mg propylene glycol (E1520).

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Syrup

Clear, colourless syrup with strawberry flavour

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Adults

Management of nausea and vomiting induced by cytotoxic chemotherapy and radiotherapy.

Prevention of post-operative nausea and vomiting.

Paediatric Population

Management of nausea and vomiting induced by cytotoxic chemotherapy in children and adolescents aged from 6 months to 17 years.

No studies have been conducted in children on the use of orally administered ondansetron in the prevention or treatment of post-operative nausea and vomiting; IV injection may be recommended for this purpose.

4.2 Posology and method of administration

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.

CINV and RINV in Adults:

The recommended oral dose is 8 mg (10 ml, i.e., two 5 ml spoonfuls) 1-2 hours before treatment, followed by 8 mg (10 ml, i.e., two 5 ml spoonfuls) orally 12 hours later.

Highly emetogenic chemotherapy:

For patients receiving highly emetogenic chemotherapy a single oral dose of up to 24 mg (30 ml, i.e., six 5 ml spoonfuls) ondansetron taken together with 12 mg oral dexamethasone sodium phosphate, 1 to 2 hours before chemotherapy, may be used. After the first 24 hours, oral treatment with ondansetron should be continued for up to 5 days and rectal treatment for up to 3 days after a course of treatment. The recommended oral dose is 8 mg (10 ml, i.e., two 5 ml spoonfuls) to be taken twice daily.

Paediatric Population

CINV in Children and Adolescents (aged 6 months to 17 years):

The dose of 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 (section 4.4 and 5.1).

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

In paediatric clinical studies, ondansetron was given by IV infusion diluted in 25 to 50 ml of saline or other compatible infusion fluid and infused over not less than 15 minutes.

Dosing by Body Surface Area (BSA)

Ondansetron should be administered immediately before chemotherapy as a single IV dose of 5 mg/m². The single IV dose must not exceed 8 mg.

Oral dosing can commence twelve 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 (equivalent to 2.5 mls of syrup or the smaller end of spoon supplied in original pack) after 12 hours	2 mg syrup (equivalent to 2.5 mls of syrup or the smaller end of spoon supplied in original pack) every 12 hours
> 0.6 m ² to ≤ 1.2 m ²	5 mg/m ² IV plus 4 mg syrup (equivalent to 5 mls of syrup or the larger end of spoon supplied in original pack) or one 4 mg tablet after 12 hours	4 mg syrup (equivalent to 5 mls of syrup or the larger end of spoon supplied in original pack) or one 4 mg tablet every 12 hours

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 (section 4.4 and 5.1).

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

On Day 1, two further IV doses may be given in 4-hourly intervals. Oral dosing can commence twelve 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)

Body Weight	Day 1 ^(a, b)	Days 2-6 ^(b)
≤ 10 kg	Up to 3 doses of 0.15 mg/kg IV every 4 hours	2 mg syrup (equivalent to 2.5 mls of syrup or the smaller end of spoon supplied in original pack) every 12 hours
> 10 kg	Up to 3 doses of 0.15 mg/kg IV every 4 hours	4 mg syrup (equivalent to 5 mls of syrup or the larger end of spoon supplied in original pack) every 12 hours

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:

Ondansetron is well tolerated by patients over 65 years of age and no alteration of oral dose or frequency of administration is required.

POST-OPERATIVE NAUSEA AND VOMITING:

PONV in Adults:

For prevention of post-operative nausea and vomiting the recommended oral dose is 16 mg (20 ml, i.e., four 5 ml spoonfuls) given one hour prior to anaesthesia.

For treatment of established post-operative nausea and vomiting ondansetron administration by injection is recommended.

Paediatric Population

PONV in Children and Adolescents (aged 1 month to 17 years):

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

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 in the elderly, however ondansetron is well tolerated in patients over 65 years receiving chemotherapy.

PATIENTS WITH RENAL/HEPATIC IMPAIRMENT:Patients with Renal Impairment:

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

Patients with Hepatic Impairment:

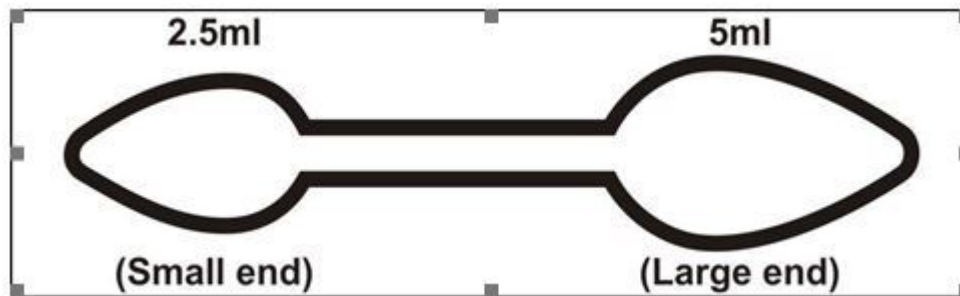
Clearance of ondansetron is significantly reduced and serum half-life significantly prolonged in subjects with moderate or severe impairment of hepatic function. In such patients, a total daily dose of 8 mg IV or oral should not be exceeded.

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 is required.

Method of administration:

- Use the 2.5-5 ml double-ended spoon supplied in the pack (see below) to measure the required dose.
- The solution should be swallowed.
- The spoon should be washed with clean water after taking every dose.
- Once measured, the solution should be consumed within 3 hours

Double-ended Spoon**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 ondansetron 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 QT_c, including patients with electrolyte abnormalities, congestive heart failure, bradyarrhythmias, conduction disturbances and in patients

taking anti-arrhythmic agents or beta-adrenergic blocking agents or other medicinal products that lead to QT prolongation or electrolyte abnormalities.

Hypokalemia and hypomagnesemia should be corrected prior to ondansetron administration.

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.

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.

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/m² followed by an oral dose is given. The comparative efficacy of these two different dosing regimens has not been investigated in clinical trials. Cross-trial comparison indicate similar efficacy for both regimens (section 5.1).

Excipient warnings:

Sorbitol (E420): This medicinal product contains 2100 mg sorbitol in each 5 ml dose which is equivalent to 420 mg/ml. Patients with hereditary fructose intolerance (HFI) should not take/be given this medicinal product. Sorbitol may cause gastrointestinal discomfort and mild laxative effect.

Sodium benzoate (E211): This medicinal product contains 6 mg sodium benzoate in each 5 ml dose which is equivalent to 1.2 mg/ml.

Propylene glycol (E1520): This medicinal product contains 14.1 mg/5 ml propylene glycol in each 5 ml dose which is equivalent to 2.82 mg/ml.

Sodium: This medicinal product contains less than 1 mmol sodium (23 mg) per 5 ml dose, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

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

Ondansetron is metabolised by multiple hepatic cytochrome P450 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 coadministered with drugs 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 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

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 (for details see 5.3). A risk to the newborns/infants cannot be excluded. Ondansetron should not be used during breast-feeding.

Fertility

There are 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 ($\geq 1/10$), common ($\geq 1/100$ and $< 1/10$), uncommon ($\geq 1/1000$ and $< 1/100$), rare ($\geq 1/10,000$ and $< 1/1000$) 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 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 oculogyric crisis, dystonic reactions, and dyskinesia) ¹
Rare:	Dizziness predominantly during rapid IV administration.
Eye disorders	
Rare:	Transient visual disturbances (e.g. blurred vision) predominantly 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:	QTc prolongation (including Torsades de Pointes)
Frequency unknown:	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.
	Local burning sensation following insertion of suppositories.
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 the HPRA Pharmacovigilance, Website: www.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.

Ondansetron prolongs 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: Anti-emetics and Anti-nauseants, (*Serotonin (5HT₃) antagonist*)

ATC code: A04A A01

Mechanism of Action

Ondansetron is a potent, highly selective 5HT₃ receptor-antagonist. Its precise mode of action in the control of nausea and vomiting is not known. Chemotherapeutic agents and radiotherapy may cause release of 5HT in the small intestine initiating a vomiting reflex by activating vagal afferents via 5HT₃ receptors. Ondansetron blocks the initiation of this reflex. Activation of vagal afferents may also cause a release of 5HT in the area postrema, located on the floor of the fourth ventricle, and this may also promote emesis through a central mechanism. Thus, the effect of ondansetron in the management of the nausea and vomiting induced by cytotoxic chemotherapy and radiotherapy is probably due to antagonism of 5HT₃ receptors on neurons located both in the peripheral and central nervous system. The mechanisms of action in post-operative nausea and vomiting are not known but there may be common pathways with cytotoxic induced nausea and vomiting.

Ondansetron does not alter plasma prolactin concentrations.

QT Prolongation

The effect of ondansetron on the QTc interval was evaluated in a double blind, randomized, 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/m² IV + ondansetron 4 mg orally after 8-12 hours or ondansetron 0.45 mg/kg IV + placebo orally after 8-12 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 IV + ondansetron 4 mg orally) and 41% (0.45 mg/kg IV + 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 IV together with 2-4 mg dexamethasone orally.
- 71% of patients when ondansetron was administered as syrup at a dose of 8 mg + 2-4 mg dexamethasone orally on the days of chemotherapy.

Post-chemotherapy both groups received 4 mg ondansetron syrup twice daily for 2 days. There was no difference in the 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 IV ondansetron, administered 30 minutes before the start of chemotherapy and then at four and eight hours after the first dose. Complete control of emesis was achieved in 56% of patients.

Another open-label, non-comparative, single-arm study (S3A239) investigated the efficacy of one IV 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 IV 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	Analyzed Study Population	Ondansetron N (%)	Placebo N (%)	P value
S3A380	CR	Efficacy Subgroup	140/205 (68)	82/210 (39)	≤ 0.001
S3GT09	CR	PP	68/112 (61)	38/110 (35)	≤ 0.001
S3A381	CR	Efficacy Subgroup	96/180 (53)	29/171 (17)	≤ 0.001
S3GT11	No nausea	ITT	135/212 (64)	108/215 (51)	0.004
S3GT11	No emesis	ITT	127/212 (60)	100/215 (47)	0.004

CR = no emetic episodes, rescue or withdrawal

5.2 Pharmacokinetic properties

Following oral administration, ondansetron is passively and completely absorbed from the gastrointestinal tract and undergoes first pass metabolism. Peak plasma concentrations are attained approximately 1.5 hours after dosing.

For doses above 8 mg the increase in ondansetron systemic exposure with dose is greater than proportional; this may reflect some reduction in first pass metabolism at higher oral doses.

Mean bioavailability in healthy male subjects, following the administration of a single 8 mg tablet, is approximately 55 to 60%.

Bioavailability is slightly enhanced by the presence of food but unaffected by antacids. The disposition of ondansetron following oral, intramuscular or intravenous dosing is similar with a terminal elimination half-life of about 3 hours and steady state volume of distribution of about 140 L.

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 (65%) and half-life (5 h) 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 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 IV 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 post-operative nausea and vomiting a decreased clearance is not likely to be clinically relevant.

Elderly

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

Based on more recent ondansetron plasma concentrations and exposure-response modelling, a greater effect on QTcF is predicted in patients $\geq$ 75 years of age compared to young adults.

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 h). 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 resulting in prolonged elimination half-lives (15 - 32 h) 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 Pharmacodynamic Properties - QT prolongation). 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. Potential environmental risk of ondansetron is currently unknown (see section 6.6)

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Citric acid monohydrate (E330)
Sodium citrate (E331)
Sorbitol, liquid (non-crystallising) (E420)
Sodium benzoate (E211)
Strawberry flavour (contains propylene glycol (E1520))
Purified water

6.2 Incompatibilities

Not applicable

6.3 Shelf life

3 years.

Discard 60 days after first opening

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Bottle: Type III Amber glass
Closure: HDPE, EPE wadded, tamper evident, child resistant screw on white plastic polypropylene cap.

Dosing Device: Double ended plastic spoon with 2.5ml and 5ml measuring ends.

Pack size: 50ml, 100ml and 300ml
Not all pack sizes may be marketed

6.6 Special precautions for disposal

Environmental risk of this medicinal product is currently unknown. (see section 5.3)

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

7 MARKETING AUTHORISATION HOLDER

Syri Pharma Limited t/a Thame Laboratories
Floor 0
1 WML
1 Windmill Lane
Dublin 2
D02 F206
Ireland

8 MARKETING AUTHORISATION NUMBER

PA22697/013/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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10 DATE OF REVISION OF THE TEXT

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