

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Emizof 8 mg Film-coated Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 8mg ondansetron (as ondansetron hydrochloride dihydrate).

Excipient with known effect:

Each tablet contains 169.0 mg of lactose monohydrate.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet.

Pale yellow, round, biconvex, film-coated tablets, embossed with identification marking "42" on one side.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Adults:

Emizof is indicated for the management of nausea and vomiting induced by cytotoxic chemotherapy and radiotherapy, and for the prevention and treatment of post-operative nausea and vomiting (PONV).

For treatment of established PONV, administration by injection is recommended.

Paediatric Population:

Emizof is indicated for the management of chemotherapy-induced nausea and vomiting (CINV) in children aged ≥ 6 months.

No studies have been conducted on the use of orally administered ondansetron in the prevention and treatment of PONV in children aged ≥ 1 month, administration by IV injection is recommended for this purpose.

4.2 Posology and method of administration

Posology

Chemotherapy and radiotherapy induced nausea and vomiting

Adults

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.

Emetogenic chemotherapy and radiotherapy

Emizof can be given either by oral or intravenous administration.

For oral administration: 8 mg taken 1-2 hours before treatment, followed by 8 mg every 12 hours for a maximum of 5 days to protect against delayed or prolonged emesis.

Highly emetogenic chemotherapy

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

(For specific recommendations pertaining to the mode of administration of parenteral forms of ondansetron please refer to the corresponding Summary of Product Characteristics).

To protect against delayed or prolonged emesis after the first 24 hours, oral treatment with Emizof associated with dexamethasone, may be continued for up to 5 days after a course of treatment.

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

Paediatric Population

Chemotherapy-induced nausea and vomiting in children aged \geq 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. 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.

Weight-based dosing results in higher total daily doses compared to BSA-based dosing – (see section 4.4).

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.

Dosing by BSA:

Emizof 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 twelve hours later and may be continued for up to 5 days. See Table 1 below.

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

Table 1: BSA-based dosing for Chemotherapy - Children aged \geq 6 months and adolescents

BSA	Day 1 ^(a,b)	Day 2-6 ^(b)
$< 0.6 \text{ m}^2$	5 mg/m ² IV plus 2 mg syrup after 12 hours	2 mg syrup every 12 hours
$\geq 0.6 \text{ m}^2$ to $\leq 1.2 \text{ m}^2$	5 mg/m ² IV plus 4 mg syrup or tablet after 12 hours	4 mg syrup or tablet every 12 hours
$> 1.2 \text{ m}^2$	5 mg/m ² or 8 mg IV plus 8 mg syrup or tablet after 12 hours.	8 mg syrup or tablet every 12 hours.

^a The intravenous dose must not exceed 8mg.

^b The total daily dose over 24 hours (given as divided doses) 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 (sections 4.4. and 5.1).

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

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

Table 2: Weight-based dosing for Chemotherapy - Children aged \geq 6 months and adolescents

Weight	Day 1 ^(a,b)	Day 2-6 ^(b)
$\leq 10 \text{ Kg}$	Up to 3 doses of 0.15 mg/kg IV every 4 hours	2 mg syrup every 12 hours
$> 10 \text{ Kg}$	Up to 3 doses of 0.15 mg/kg IV every 4 hours	4 mg syrup or tablet every 12 hours

^a The intravenous dose must not exceed 8mg.

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

Elderly:

No alteration of oral dose or frequency of administration is required.
Please refer also to "Special Populations".

Post-operative nausea and vomiting (PONV)

Adults

Prevention of PONV

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

For oral administration: 16 mg taken one hour prior to anaesthesia.

For the treatment of established PONV

Intravenous administration is recommended.

Paediatric Population

PONV in children aged ≥ 1 month and adolescents

Oral formulation:

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

Injection:

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 PONV in children below 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 Emizof is well tolerated in patients over 65 years receiving chemotherapy.

Special Populations

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.

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.

Method of administration

For oral use

4.3 Contraindications

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

Hypersensitivity to other selective 5-HT₃ receptor antagonists (e.g. granisetron, dolasetron).

Concomitant use with apomorphine (see section 4.5).

4.4 Special warnings and precautions for use

Hypersensitivity reactions have been reported in patients who have exhibited hypersensitivity to other selective 5HT₃ receptor antagonists. Respiratory events should be treated symptomatically and clinicians should pay particular attention to them as precursors of hypersensitivity reactions.

QT prolongation

Ondansetron prolongs the QT interval in a dose-dependent manner (see section 5.1). In addition, post-marketing cases of Torsade de Pointes have been reported in patients using ondansetron. Avoid ondansetron in patients with congenital long QT syndrome. Ondansetron should be administered with caution to patients who have or may develop prolongation of QTc, including patients with electrolyte abnormalities, congestive heart failure, bradyarrhythmias, or patients taking other medicinal products that lead to QT prolongation or electrolyte abnormalities.

Hypokalaemia and hypomagnesaemia 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 (SSRIs) 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.

Paediatric Population

Paediatric population 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-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 comparing indicates similar efficacy for both regimens (see section 5.1).

Excipient(s) of known effect:

This medicinal product contains lactose. Patients with rare hereditary problems of galactose intolerance, the total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interactions

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 pharmacokinetic interactions when ondansetron is administered with alcohol, temazepam, furosemide, tramadol, alfentanil, morphine, lidocaine, 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.

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

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

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

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

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 ($\geq 1/100$ to $< 1/10$), uncommon ($\geq 1/1,000$ to $< 1/100$), rare ($\geq 1/10,000$ to $< 1/1,000$) 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 for ondansetron according to indication and formulation.

Adverse Drug Reactions by System Organ Class and Frequency

Immune system disorders

Rare:	Immediate hypersensitivity reactions sometimes severe, including anaphylaxis.
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Nervous system disorders

Very common:	Headache.
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Uncommon:	Seizures, movement disorders (including extrapyramidal reactions such as dystonic reactions, oculogyric crisis and dyskinesia) ¹
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Rare:	Dizziness during rapid IV administration.
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Eye disorders

Rare:	Transient visual disturbances (e.g. blurred vision) predominantly during IV administration.
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Very rare:	Transient blindness predominantly during intravenous administration ² .
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Cardiac disorders

Uncommon:	Arrhythmias, chest pain with or without ST segment depression, bradycardia.
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Rare:	QTc prolongation (including Torsades de Pointes)
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Vascular disorders

Common:	Sensation of warmth or flushing.
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Uncommon:	Hypotension.
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Respiratory, thoracic and mediastinal disorders

Uncommon:	Hiccups.
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Gastrointestinal disorders

Common:	Constipation
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Hepatobiliary disorders

Uncommon:	Asymptomatic increases in liver function tests ³
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Skin and subcutaneous tissue disorders

Very rare:	Toxic skin eruption including toxic epidermal necrolysis
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¹ Observed without definitive evidence of persistent clinical sequelae.

² The majority of the blindness cases reported resolved within 20 minutes. Most patients had received chemotherapeutic agents, which included cisplatin. Some cases of transient blindness were reported as cortical in origin.

³ These events were observed commonly in patients receiving chemotherapy with cisplatin.

Paediatric Population

The adverse event profiles in children and adolescents were comparable to that seen in adults.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via HPRA Pharmacovigilance, 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 manner. ECG monitoring is recommended in cases of overdose.

Paediatric population

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

Treatment

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

Further management should be as clinically indicated or as recommended by the national poisons centre, where available.

The use of ipecacuanha to treat overdose with ondansetron is not recommended as patients are unlikely to respond due to the anti-emetic action of ondansetron itself.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

The role of ondansetron in opiate-induced emesis is not yet established.

QT Prolongation

The effect of ondansetron on the QTc interval was evaluated in a double blind, 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.

Paediatric Population*Chemotherapy-induced nausea and vomiting (CINV)*

The efficacy of ondansetron in the control of emesis and nausea induced by cancer chemotherapy was assessed in a double-blind randomised trial in 415 patients aged 1 to 18 years (S3AB3006). On the days of chemotherapy, patients received either ondansetron 5 mg/m² intravenous + ondansetron 4 mg orally after 8-12 hours or ondansetron 0.45 mg/kg intravenous + 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 intravenous + 4 mg ondansetron 4mg orally) and 41 % (0.45 mg/kg intravenous + placebo orally). Post-chemotherapy, both groups received 4 mg ondansetron syrup twice daily for 3 days. There was no difference in the overall incidence or nature of adverse events between the two treatment groups.

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

- 73% of patients when ondansetron was administered intravenously at a dose of 5 mg/m² intravenous together with 2-4 mg dexamethasone orally
- 71% of the patients when ondansetron was administered as a syrup at a dose of 8 mg + 2-4 mg of dexamethasone orally on the days of chemotherapy.

Post-chemotherapy, both groups received 4 mg ondansetron syrup twice daily for 2 days. There was no difference in the overall incidence or nature of adverse events between the two treatment groups.

The efficacy of ondansetron in 75 children aged 6 to 48 months was investigated in an open-label, non-comparative, single-arm study (S3A40320). All children receive three 0.15 mg/kg doses of intravenous ondansetron, administered 30 minutes before the start of chemotherapy and then four and eight hours after the first dose. Complete control of emesis was achieved in 56% of patients.

Another open-label, non-comparative, single-arm study (S3A239) investigated the efficacy of one intravenous dose of 0.15 mg/kg ondansetron followed by two 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.

Prevention of post-operative nausea and vomiting (PONV)

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

Four double-blind, placebo-controlled studies have been performed in 1469 male and female patients (2 to 12 years of age) undergoing general anaesthesia. Patients were randomised to either single intravenous doses of ondansetron (0.1 mg/kg for paediatric patients weighing 40 kg or less, 4 mg for paediatric patients weighing more than 40 kg; number of patients = 735) or placebo (number of patients = 734). Study drug was administered over at least 30 seconds, immediately prior to or following anaesthesia induction. Ondansetron was significantly more effective than placebo in preventing nausea and vomiting. The results of these studies are summarised in Table 3.

Table 3: Prevention and treatment of PONV in Paediatric Patients – Treatment response over 24 hours

Study	Endpoint	Ondansetron %	Placebo %	p value
S3A380	CR	68	39	≤ 0.001
S3GT09	CR	61	35	≤ 0.001
S3A381	CR	53	17	≤ 0.001
S3GT11	No nausea	64	51	0.004
S3GT11	No emesis	60	47	0.004

CR = no emetic episodes, rescue or withdrawal

5.2 Pharmacokinetic properties

Following oral administration, ondansetron is passively and completely absorbed from the gastrointestinal tract and undergoes first pass metabolism. Peak plasma concentrations of about 30 ng/ml are attained approximately 1.5 hours after an 8 mg dose. For doses above 8 mg the increase in ondansetron systemic exposure with dose is greater than proportional; this may reflect some reduction in first pass metabolism at higher oral doses. Mean bioavailability in healthy male subjects, following the oral administration of a single 8 mg tablet, is approximately 55 to 60%. Bioavailability, following oral administration, is slightly enhanced by the presence of food but unaffected by antacids.

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

A 4 mg intravenous infusion of ondansetron given over 5 minutes results in peak plasma concentrations of about 65 ng/ml. Following intramuscular administration of ondansetron, peak plasma concentrations of about 25 ng/ml are attained within 10 minutes of injection.

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.

Special Patient Populations

Gender

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

Children and Adolescents (aged 1 month to 17 years)

In paediatric patients aged 1 month 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 patients aged 3 to 12 years. The half-life in the patient population aged 1 to 4 months was reported to average 6.7 hours compared to 2.9 hours for patients in the 5 to 24 months and 3 to 12 years age range. The differences in the pharmacokinetic parameters in the 1 to 4 months patient population can be explained in part by a 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 patients) aged 1 month to 44 years following intravenous administration of ondansetron. Based on this analysis, systemic exposure (AUC) of ondansetron following oral or IV dosing in children and adolescents was comparable to adults, with the exception of infants aged 1 to 4 months. Volume was related to age and was lower in adults than in infants and children. Clearance was related to weight but not to age with the exception of infants aged 1 to 4 months.

It is difficult to conclude whether there was an additional reduction in clearance related to age in infants 1 to 4 months or simply inherent variability due to the low number of subjects studied in this age group. Since patients less than 6 months of age will only receive a single dose in PONV a decreased clearance is not likely to be clinically relevant.

Elderly

Early Phase I studies in healthy elderly volunteers showed a slight age-related decrease in clearance, and an increase in half-life of ondansetron. However, wide inter-subject variability resulted in considerable overlap in pharmacokinetic parameters between young (< 65 years of age) and elderly subjects (≥ 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 intravenous dosing.

Renal impairment

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

Hepatic impairment

Following oral, intravenous or intramuscular dosing in patients with severe hepatic impairment, ondansetron's systemic clearance is markedly reduced with prolonged elimination half-lives (15-32 h) and an oral bioavailability approaching 100% due to reduced pre-systemic metabolism.

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.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet Core

Lactose monohydrate
Cellulose, microcrystalline (E460)
Maize starch, pregelatinised
Magnesium stearate (E572)

Tablet Coat

Hypromellose (E464)
Titanium dioxide (E171)
Macrogol (E1520)
Sorbitan oleate (E494)
Sorbic acid (E200)
Vanillin
Quinoline yellow (E104)
Hydroxypropyl cellulose (E463).

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Do not store above 30°C.

6.5 Nature and contents of container

Blister packs of 3, 6, 10, 14, 15, 20, 30, 40, 50, 60, 90, 100, 200, 300, 500 tablets comprising PVC film and aluminium foil lidding.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

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

7 MARKETING AUTHORISATION HOLDER

McDermott Laboratories Ltd., T/A Gerard Laboratories
35/36 Baldoyle Industrial Estate
Grange Road
Dublin 13
Ireland

8 MARKETING AUTHORISATION NUMBER

PA0577/083/002

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 29th September 2006

Date of last renewal: 30th September 2009

10 DATE OF REVISION OF THE TEXT

March 2020