Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Ondansetron 8 mg film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

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

Excipient(s) with known effect:
Each film-coated tablet contains 177.6 mg lactose monohydrate

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet.
Yellow, oblong film coated tablet debossed 8 on one side and scoreline on the other.
The score line is only to facilitate breaking for ease of swallowing and not to divide into equal doses.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Adults
- Nausea and vomiting induced by cytotoxic chemotherapy and radiotherapy
- Prevention of post-operative nausea and vomiting

Children and adolescents

- Ondansetron is indicated for the management of nausea and vomiting induced by cytotoxic chemotherapy for 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; intravenous (IV) injection may be recommended for this purpose.

4.2 Posology and method of administration

Posology

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 route of administration and dose regimen should be determined by the severity of the emetogenic challenge.

Adults

The recommended oral dose is 8 mg taken 1-2 hours before chemotherapy or radiation treatment, followed by 8 mg every 12 hours for a maximum of 5 days.

For patients receiving highly emetogenic chemotherapy e.g. high-dose cisplatin a single oral dose of up to 24 mg ondansetron taken together with 12 mg oral dexamethasone sodium phosphate or equivalent, 1 to 2 hours before chemotherapy, may be used.
After the first 24 hours, oral treatment with ondansetron may be continued for up to 5 days after a course of treatment.

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

Paediatric population *(aged 6 month to 17 years)*
The dose for CINV can be calculated based on body surface area (BSA) or weight – see below. In paediatric clinical studies, ondansetron was given by IV infusion diluted in 25 to 50 ml of saline or other compatible infusion fluid and infused over not less than 15 minutes Weight-based dosing results in higher total daily doses compared to BSA-based dosing

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

Dosing by Body surface area
Ondansetron should be administered immediately before chemotherapy as a single intravenous dose of 5 mg/m^2. The intravenous dose must not exceed 8 mg.
Oral dosing can commence twelve hours later and may be continued for up to 5 days (see Table 1 below).
The total daily dose must not exceed adult dose of 32 mg.

Table 1: BSA-based dosing for 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 hours	2 mg syrup every 12 hours
≥ 0.6 m^2 to ≤ 1.2 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 m^2	5 mg/m^2 IV 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 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

Ondansetron should be administered immediately before chemotherapy as a single intravenous dose of 0.15 mg/kg. The intravenous dose must not exceed 8 mg.
Two further intravenous doses may be given in 4-hourly intervals.

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

The total dose over 24 hours 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 at 4-hourly intervals	2 mg syrup every 12 hours
> 10 kg	Up to 3 doses of 0.15 mg/kg IV at 4 hourly intervals	4 mg syrup or 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.

Elderly
No alterations of oral dosage or frequency of administration is required.

For other special populations refer to 'Post-Operative Nausea And Vominting (PONV)'.

Post-Operative Nausea And Vomiting (PONV)

Adults
For prevention of PONV: ondansetron can be administered orally or by intravenous injection.

For prevention of PONV, the recommended oral dose is 16 mg given 1 hour prior to anaesthesia.

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

Paediatric population (aged 6 month to 17 years)

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

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 (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 dally 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 is required.

Method of administration
Oral use.

4.3 Contraindications

Concomitant use with apomorphine (see section 4.5).

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

Must not be used in children with a body surface area of less than 0.6 m^2 or with a body weight up to 10 kg. More suitable dosage forms with a lower active ingredient content are available for this patient group.

4.4 Special warnings and precautions for use

Hypersensitivity reactions have been reported in patients who have exhibited hypersensitivity to other selective 5-HT_3-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 or patients taking 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 ischemia.

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.

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

Excipient(s)

Lactose
Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

Sodium
This medicinal product contains less than 1 mmol sodium (23 mg) per film-coated tablet, 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, tramadol, alfentanil, morphine, lignocaine, 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.

Use of ondansetron with QT prolonging drugs may result in additional QT prolongation. Concomitant use of ondansetron with cardiotoxic drugs (e.g. anthracyclines) may increase the risk of arrhythmias. The concomitant use of ondansetron with drugs that cause QT interval prolongation and/or electrolyte disturbances should be done with caution (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.

SerotonergicDrugs(e.g.,SSRIsandSNRIs)
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).

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.

Breast-feeding
Tests have shown that ondansetron passes into the milk of lactating animals. It is therefore recommended that mothers receiving ondansetron should not breast-feed their babies.

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

List of adverse reactions

The frequencies of adverse events are ranked according to the following: very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1000 to < 1/100), rare (≥ 1/10 000 to < 1/1000), very rare (<1/10 000; including isolated reports), not known (cannot be estimated from the available date).

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.

Immune system disorders
Rare: immediate hypersensitivity reactions, sometimes severe including anaphylaxis.

Anaphylaxis may be fatal.Hypersensitivity reactions were also observed in patients who were sensitive to other selective 5-HT3 antagonists.

Nervous system disorders
Very common: headache
Uncommon: seizures, movement disorders (including extrapyramidal reactions such as dystonic reactions, acute critical disturbances of the oculomotoric system with view deviation [oculogyric crisis] and dyskinesia)[1] which, however, remained without proven lasting clinical consequences
Rare: dizziness predominantly during rapid intravenous administration

Eye disorders
Rare: transient visual disturbances (e.g. blurred vision) predominantly during intravenous administration
Very rare: transient blindness predominantly after 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: feeling of warmth, 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

[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 commonly observed 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
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.

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

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

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

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antiemetics and antinauseants, Serotonin (5HT3) antagonists.
ATC code: A04AA01

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.

Clinical efficacy and safety
In a pharmaco-psychological study in volunteers ondansetron has not shown a sedative effect.

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 randomized trial in 415 patients aged 1 to 18 years (S3AB3006). On the days of chemotherapy, patients received either ondansetron 5 mg/m^2 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/m^2 intravenous + ondansetron 4 mg 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 randomized 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 2-4 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 intravenous ondansetron, administered 30 minutes before the start of chemotherapy and then at four and eight hours after the first dose. Complete control of emesis was achieved in 56% of patients.

Another open-label, non-comparative, single-arm 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 randomized, 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 randomized 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 summarized 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

Absorption
The average bioavailability in healthy volunteers after administration of a single 8 mg tablet is approximately 55-60%. Peak plasma concentrations are attained approximately 1.6 hr after an oral dose. There is no direct correlation between plasma levels and antiemetic effect.

Distribution
Plasma protein binding (in vitro) is 70 to 76 %.

Biotransformation
Ondansetron is metabolised via several hepatic cytochrome P450 isozymes - CYP3A4, CYP2D6 and CYP1A2. Deficiency of the enzyme CYP2D6 (debrisoquine polymorphism) does not affect the pharmacokinetic behaviour of ondansetron. The pharmacokinetic properties of ondansetron are unchanged with repeated administration.

Elimination
Clearance of ondansetron occurs predominantly via hepatic metabolism. The metabolites are excreted in the urine and faeces. The elimination half-life is approximately 3 hours.

Special patient populations

Children and adolescents (aged 1 month to 17 years)
In paediatric patients aged 1 to 4 months (n = 19) undergoing surgery, weight normalized clearance was approximately 30% slower than in patients aged 5 to 24 months (n = 22) but comparable to the patients aged 3 to 12 years. The half-life in the patient population aged 1 to 4 months was reported to average 6.7 hours compared to 2.9 hours for patients in the 5 to 24 month and 3 to 12 year age range. The differences in pharmacokinetic parameters in the 1 to 4 month patient population can be explained in part by the higher percentage of total body water in neonates and infants and a higher volume of distribution for water soluble drugs like ondansetron.

In paediatric patients aged 3 to 12 years undergoing elective surgery with general anaesthesia, the absolute values for both the clearance and volume of distribution of ondansetron were reduced in comparison to values with adult patients. Both parameters increased in a linear fashion with weight and by 12 years of age, the values were approaching those of young adults. When clearance and volume of distribution values were normalized by body weight, the values for these parameters were similar between the different age group populations. Use of weight-based dosing compensates for age-related changes and is effective in normalizing systemic exposure in paediatric patients.

Population pharmacokinetic analysis was performed on 428 subjects (cancer patients, surgery patients and healthy volunteers) aged 1 month to 44 years following intravenous administration of ondansetron. Based on this analysis, systemic exposure (AUC) of ondansetron following oral or IV dosing in children and adolescents was comparable to adults, with the exception of infants aged 1 to 4 months. Volume was related to age and was lower in adults than in infants and children. Clearance was related to weight but not to age with the exception of infants aged 1 to 4 months. It is difficult to conclude whether there was an additional reduction in clearance related to age in infants 1 to 4 months or simply inherent variability due to the low

number of subjects studied in this age group. Since patients less than 6 months of age will only receive a single dose in 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 to approximately 5 hr. 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. For intravenous administration, specific dose information is given for patients over 65 years of age and for patients over 75 years of age (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 following IV administration of ondansetron, resulting in a slight, but clinically insignificant, increase in elimination half-life (5.4h). A study in patients with severe renal impairment who required regular haemodialysis (studied between dialyses) showed ondansetron's pharmacokinetics to be essentially unchanged.

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

Preclinical data revealed no special hazard for humans based on conventional studies of repeated dose toxicity, genotoxicity and carcinogenic potential.

Reproductive toxicology studies
Reproductive toxicology studies with rats and rabbits revealed no indications of a harmful effect for the foetus when ondansetron was respectively administered during organogenesis at approximately 6-fold and 24-fold the maximum recommended human oral dose of 24 mg/day, based on body surface area.
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 body surface area.

Ondansetron and its metabolites accumulate in the milk of rats, milk/plasma-ratio was 5.2 : 1.

A study in cloned human cardiac ion channels has shown ondansetron has the potential to affect cardiac repolarisation via blockade of hERG potassium channels at clinically relevant concentrations. Dose-dependent QT prolongation has been observed in a thorough QT study in human volunteers.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:
Lactose monohydrate
Sodium starch glycolate – Type A

Microcrystalline cellulose
Pregelatinised starch (maize)
Magnesium stearate

Coating:
Hypromellose
Titanium dioxide (E171)
Macrogol 400
Macrogol 6000
Iron oxide yellow(E172).

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Transparent & white opaque PVC/PVdC aluminium blisters.
Blister packs of 2, 4, 5, 6, 9, 10, 15, 18, 30, 50, 100 & 500 tablets.
Hospital packs of 10 x 1 and 50 x 1 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements for disposal.

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

7 MARKETING AUTHORISATION HOLDER

Teva Pharma B.V.
Swansweg 5
2031GA Haarlem
Netherlands

8 MARKETING AUTHORISATION NUMBER

PA0749/009/002

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 29 April 2005
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10 DATE OF REVISION OF THE TEXT

December 2023