Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Ondran 8 mg film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

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

Excipients with known effect
Each film-coated tablet contains 169 mg lactose monohydrate.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet

8 mg: pale yellow, round biconvex, film-coated tablet embossed "42" on one side, diameter 9.2 mm.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

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

Paediatric population
Management of chemotherapy-induced nausea and vomiting (CINV) in children aged ≥ 6 months.
Prevention and treatment of post-operative nausea and vomiting in children aged ≥ 1 month.

4.2 Posology and method of administration

Posology

For the different dose regimens appropriate strengths and formulations are available**.**

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 route of administration and dose of Ondansetron should be flexible and selected as shown below.

Emetogenic chemotherapy and radiotherapy
For patients receiving emetogenic chemotherapy or radiotherapy ondansetron can be given either by oral or intravenous administration.

For most patients receiving emetogenic chemotherapy or radiotherapy, ondansetron should initially be administered intravenously immediately before treatment, followed by 8 mg orally twelve hourly.

For oral administration: 8 mg 1-2 hours before treatment, followed by 8 mg orally 12 hours later.

To protect against delayed or prolonged emesis after the first 24 hours, oral treatment with ondansetron should be continued for up to 5 days after a course of treatment. The recommended oral dose is 8 mg to be taken twice daily.

Highly emetogenic chemotherapy
For patients receiving highly emetogenic chemotherapy, e.g. high-dose cisplatin, ondansetron can be given by intravenous administration.

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

To protect against delayed or prolonged emesis after the first 24 hours, oral treatment with ondansetron should be continued for up to 5 days after a course of treatment. The recommended dose for oral administration is 8 mg twice daily.

Paediatric population

Chemotherapy-induced nausea and vomiting in children aged ≥ 6 months and adolescents
The dose for chemotherapy-induced nausea and vomiting can be calculated based on body surface area (BSA) or weight – see below. Weight-based dosing results in higher total daily doses compared to BSA-based dosing -see sections 4.4 and 5.1.
There are no data from controlled clinical trials on the use of ondansetron in the prevention of 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:
Ondansetron should be administered immediately before chemotherapy as a single intravenous dose of 5 mg/m^2. The intravenous dose must not exceed 8 mg.
Oral dosing can commence twelve hours later and may be continued for up to 5 days –(see Table 1 below).
The total daily dose must not exceed adult dose of 32 mg.

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

BSA BSA	Day 1 [a,b]	Days 2-6[b]
< 0.6 m^2	5 mg/m^2 i.v. 2 mg syrup after 12 hrs	2 mg syrup or tablet every 12 hours
≥0.6 m^2	5 mg/m^2 i.v. 4 mg syrup or tablet after 12 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

Dosing by bodyweight:
Weight-based dosing results in higher total daily doses compared to BSA-based dosing (see sections 4.4. and 5.1).

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

Two further intravenous doses may be given in 4-hourly intervals. The total daily dose must not exceed adult dose of 32 mg.

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

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

Weight	Day 1 [a,b]	Days 2-6[b]
≤10 kg	Up to 3 doses of 0.15 mg/kg at 4-hourly intervals	2 mg syrup or tablet every 12 hours
> 10 kg	Up to 3 doses of 0.15 mg/kg at 4 hourly intervals	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
Ondansetron is well tolerated by patients over 65 years and no alteration of dose, dosing frequency or route of administration is required.

Patients with renal impairment
No alteration of daily dose or frequency of dosing, or route of administration is required.

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

Patients with poor sparteine / debrisoquine metabolism
The elimination half-life of ondansetron is not altered in subjects classified as poor metabolisers of sparteine and debrisoquine. Consequently, in such patients repeat dosing will give medicinal product exposure levels no different from those of the general population. No alteration of daily dose or frequency of dosing is required.

Post-operative nausea and vomiting (PONV)

Adults

Prevention of post-operative nausea and vomiting:
For the prevention of PONV ondansetron can be administered orally or by intravenous injection.

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

Alternatively, 8 mg one hour prior to anaesthesia followed by two further doses of 8 mg at eight hourly intervals.

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

Paediatric population

Post-operative nausea and vomiting in children aged ≥ 1 month and adolescents
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 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 (PONV) in the elderly. However, ondansetron is well tolerated in patients over 65 years receiving chemotherapy.

Patients with renal impairment
No alteration of daily dose or frequency of dosing, or route of administration is required.

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

Patients with poor sparteine/debrisoquine metabolism
The elimination half-life of ondansetron is not altered in subjects classified as poor metabolisers of sparteine and debrisoquine. Consequently, in such patients repeat dosing will give medicinal product exposure levels no different from those of the general population. No alteration of daily dose or frequency of dosing is 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 Interactions with other medicinial productsand other forms of interaction).

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.

Rarely transient ECG changes including QT interval prolongation have been reported in patients receiving ondansetron. Ondansetron prolongs the QT interval in a dose-dependent manner (see Pharmacodynamic properties). In addition, post-marketing cases of Torsade de Pointes have been reported in patients using ondansetron. Avoid ondansetron in patients with congenital long QT syndrome. Ondansetron should be administered with caution to patients who have or may develop prolongation of QTc. These conditions include patients with electrolyte abnormalities, congestive heart failure, bradyarrhythmias or patients taking other medicinal products that lead to QT prolongation or electrolyte abnormalities. Therefore caution should be exercised in patients with cardiac rhythm or conduction disturbances, in patients treated with anti-arrhythmic agents or beta-adrenergic blocking agents and in patients with significant electrolyte disturbances.

Hypokalemia and hypomagnesemia should be corrected prior to ondansetron administration.

There have been post-marketing reports describing patients with serotonin syndrome (including altered mental status, autonomic instability and neuromuscular abnormalities) following the concomitant use of ondansetron and other serotonergic medicinal products (including selective serotonin reuptake inhibitors (SSRI) and serotonin noradrenaline reuptake inhibitors (SNRIs)). If concomitant treatment with ondansetron and other serotonergic medicinal products is clinically warranted, appropriate observation of the patient is advised.

As ondansetron is knownto increase large bowel transit time, patients with signs of subacuteintestinal obstruction should be monitored following administration.

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

Since there is little experience to date of the use of ondansetron in cardiac patients, caution should be exercised if ondansetron is coadministered with anaesthetics to patients with arrhythmias or cardiac conduction disorders or to patients who are being treated with antiarrhythmic agents or beta-blockers.

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.

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

<u>Paediatric population</u>
Paediatric patientsreceiving ondansetron with hepatotoxic chemotherapeutic agents should bemonitored closely for impaired hepatic function.

<u>Chemotherapy-induced nausea and vomiting (CINV)</u>
When calculating the dose on an mg/kg basis and administering three doses at 4-hour intervals, the total daily dose will be higher than if one single dose of 5 mg/m^2 followed by an oral dose is given. The comparative efficacy of these two different dosing regimens has not been investigated in clinical trials. Cross-trial comparison indicates similar efficacy for both regimens (see section 5.1).

4.5 Interaction with other medicinal products and other forms of interactions

There is no evidence that ondansetron either induces or inhibits the metabolism of other medicinal products commonly coadministered with it. Specific studies have shown that ondansetron does not interact with alcohol, temazepam, furosemide, alfentanil, tramadol, morphine, 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.

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.

Use of ondansetron with QT prolonging medicinal products may result in additional QT prolongation. Concomitant use of ondansetron with cardiotoxic medicinal products (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).

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 medicinal products (including SSRIs and SNRIs). (See Special warnings and precautions for use).

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

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 (see section 5.3). It is therefore recommended that mothers receiving ondansetron should not breast-feed their babies.

4.7 Effects on ability to drive and use machines

Ondansetron has no ornegligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Adverse events are listed below by system organ class and frequency. Frequencies are defined as: very common (≥ 1/10), common (≥ 1/100 to <1/10), uncommon (≥ 1/,000 to <1/100), rare (≥ 1/10,000 to <1/1,000) very rare (<1/10,000) and not known (cannot beestimated from the available data) including isolated reports. Very common, common and uncommon events were generally determined from clinical trial data. The incidence in placebo was taken into account. Rare and very rare events were generally determined from post-marketing spontaneous data.
The following frequencies are estimated at the standard recommended doses of ondansetron according to indication and formulation.

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 during rapid IV administration.

Eye disorders
Rare: Transient visual disturbances (eg. 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:*Transient ECG changes including QT interval prolongation (including Torsade de Pointes)
Not known: Myocardial ischemia (see section 4.4).

Vascular disorders
Common: Sensation of warmth or flushing.
Uncommon: Hypotension.

Respiratory, thoracic and mediastinal disorders
Uncommon: Hiccups.

Gastrointestinal disorders
Common: Constipation.

Hepatobiliary disorders
Uncommon: Asymptomatic increases in liver function tests[3].

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.

Paediatric population

The adverse event profile in children and adolescents was 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. (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. In all instances, the events resolved completely.

Ondansetron prolongs the QT interval in a dose-dependent manner. ECG monitoring is recommended in cases of overdose.

Treatment

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

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

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

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antiemetics and antinauseants, Serotonin (5-HT_3) antagonists

ATC code: A04AA01

Mechanism of action
Ondansetron is a potent, highly selective 5-HT_3 receptor-antagonist.

Its precise antiemetic and antinauseal mechanism of action is not known. Chemotherapeutic agents and radiotherapy may cause release of 5-HT in the small intestine initiating a vomiting reflex by activating vagal afferents via 5-HT_3 receptors. Ondansetron blocks the initiation of this reflex. Activation of vagal afferents may also cause a release of 5-HT in the area postrema, located on the floor of the fourth ventricle, and this may also promote emesis through a central mechanism. Thus, the effect of ondansetron in the management of the nausea and vomiting induced by cytotoxic chemotherapy and radiotherapy is probably due to antagonism of 5-HT3 receptors on neurons located both in the peripheral and central nervous system. The mechanisms of action in post-operative nausea and vomiting are not known but there may be common pathways with cytotoxic induced nausea and vomiting.

In a pharmaco-psychological study in volunteers ondansetron has not shown a sedative effect.

Ondansetron does not alter plasma prolactin concentrations.

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

Clinical studies

Paediatric population

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

A double-blindrandomised placebo-controlled trial in 438 patients aged 1 to 17 yearsdemonstrated complete control of emesis on worst day of chemotherapy in 73% ofpatients when ondansetron was administered intravenously at a dose of 5 mg/m^2 i.v. together with 2-4 mg dexamethasone p.o. and in 71% of patients when ondansetron was administered as syrup at a dose of 8 mg + 2 - 4 mg dexamethasone p.o. on the days of chemotherapy. Post-chemotherapy both groups received 4 mg ondansetron syrup twice daily for 2 days.

The efficacy ofondansetron in 75 children aged 6 to 48 months was investigated in anopen-label, non-comparative, single-arm study. All children received three 0.15mg/kg doses of intravenous ondansetron, administered 30 minutes before thestart 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 investigated the efficacy of one intravenousdose of 0.15 mg/kg ondansetron followed by two oral ondansetron doses of 4 mgfor 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
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 ≥ 3kg). Included subjects werescheduled to undergo elective surgery under general anaesthesia and had an ASAstatus ≤III. A single dose ofondansetron 0.1 mg/kg was administered within five minutes following inductionof anaesthesia. The proportion ofsubjects who experienced at least one emetic episode during the 24-hourassessment period (ITT) was greater for patients on placebo than those receiving ondansetron (28% vs. 11%, p<0.0001).

5.2 Pharmacokinetic properties

Absorption
Following oral administration, ondansetron is passively and completely absorbed from the gastrointestinal tract and undergoes first pass metabolism (bioavailability is about 60%). Peak plasma concentrations of about 30 ng/mL are attained approximately 1.5 hours after an 8 mg dose. For doses above 8 mg the increase in ondansetron systemic exposure with dose is greater than proportional; this may reflect some reduction in first pass metabolism at higher oral doses. Bioavailability, following oral administration, is slightly enhanced by the presence of food but unaffected by antacids. Studies in healthy elderly volunteers have shown slight, but clinically insignificant, age-related increases in both oral bioavailability (65%) and half-life (5 hours) of ondansetron. Gender differences were shown in the disposition of ondansetron, with females having a greater rate and extent of absorption following an oral dose and reduced systemic clearance and volume of distribution (adjusted for weight).

Distribution
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 140 L. Equivalent systemic exposure is achieved after IM and IV administration of ondansetron.

Biotransformation and elimination
The protein binding of ondansetron is 70-76%. A direct effect of plasma concentration and anti-emetic effect has not been established. Ondansetron is cleared from the systemic circulation predominantly by hepatic metabolism through multiple enzymatic pathways. Less than 5% of the absorbed dose is excreted unchanged in the urine. The absence of the enzyme CYP2D6 has no effect on ondansetron's pharmacokinetics. The pharmacokinetic properties of ondansetron are unchanged on repeat dosing.

Special populations

Paediatric population

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

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

Population pharmacokinetic analysis was performed on 74 paediatric cancer patients aged 6 to 48 months and 41 surgery patients aged 1 to 24 months following intravenous administration of ondansetron. Based on the population pharmacokinetic parameters for patients aged 1 month to 48 months, administration of the adult weight based dose (0.15 mg/kg intravenously

every 4 hours for 3 doses) would result in a systemic exposure (AUC) comparable to that observed in paediatric surgery patients (aged 5 to 24 months), paediatric cancer patients (aged 4 to 18 years), and surgical patients (aged 3 to 12 years), at similar doses, as shown in Table C. This exposure (AUC) is consistent with the exposure-efficacy relationship described previously in paediatric cancer subjects, which showed a 50% to 90% response rate with AUC values ranging from 170 to 250 ng.h/mL.

Table C. Pharmacokinetics in Paediatric Patients 1 Month to 18 Years of age

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

[1] Ondansetron single intravenous dose: 0.1 or 0.2 mg/kg
[2] Population PK Patients: 64% cancer patients and 36% surgery patients.
[3] Population estimates shown; AUC based on dose of 0.15 mg/kg.
[4] Ondansetron single intravenous dose: 2 mg (3 to 7 years) or 4 mg (8 to 12 years)

Patients withhepatic 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

Nonclinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity and carcinogenic potential.

Ondansetron and its metabolites accumulate in the milk of rats, milk/plasma-ratio was 5.2.1.
A study in cloned human cardiac ion channels has shown that ondansetron has the potential to affect cardiac repolarisation via blockade of HERG potassium channels. The clinical relevance of this finding is uncertain.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:
Cellulose, microcrystalline
Lactose monohydrate
Starch, pregelatinised (maize)
Magnesium stearate

Film coating:
Hypromellose
Hydroxypropylcellulose
Propylene glycol (E1520)
Sorbitan oleate
Sorbic acid (E200)

Vanillin
Titanium dioxide (E171)
Quinoline yellow (E104)

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 precautions.

6.5 Nature and contents of container

Blister (PVC/Al)
8 mg: 6, 10, 15, 30, 50 and 100 film coated tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Pinewood Laboratories Ltd,
Ballymacarbry
Clonmel
Co. Tipperary
Ireland

8 MARKETING AUTHORISATION NUMBER

PA0281/127/002

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 22 December 2005
Date of last renewal: 27 September 2009.

10 DATE OF REVISION OF THE TEXT

June 2022