Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Ondansetron 2 mg/ml solution for injection/infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml of solution contains ondansetron hydrochloride dihydrate equivalent to 2 mg ondansetron.
Each ampoule with 2 ml solution contains ondansetron hydrochloride dihydrate equivalent to 4 mg ondansetron.
Each ampoule with 4 ml solution contains ondansetron hydrochloride dihydrate equivalent to 8 mg ondansetron.

Excipient with a known effect
Each ml of solution contains 3.52 mg sodium.

For the full list of excipients see section 6.1.

3 PHARMACEUTICAL FORM

Solution for injection/infusion (injection/infusion).
Clear, colourless solution, free from visible particles.
Osmolality 270-310 mOsmol/kg
pH of solution 3.0 – 4.0

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Adults
Ondansetron 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.

Paediatric population
In children over 6 months old and adolescents ondansetron is indicated for the management of chemotherapy-induced nausea and vomiting.
In children over 1 month old and adolescents ondansetron is indicated for the prevention and treatment of post-operative nausea and vomiting.

4.2 Posology and method of administration

Posology

The emetogenic potential of cytostatic or radiotherapy varies depending on the dose level and therapeutic regimen. The selection of dose regimen should be determined by the severity of the emetogenic challenge.

Ondansetron is also available for rectal and/or oral administration and allows the dosage to be individually adjusted. For rectal or oral administration refer to the relevant product information.

Adults

Chemotherapy and radiotherapy induced nausea and vomiting

The recommended dose is 8 mg ondansetron intravenously (IV) or intramuscularly (IM) immediately before chemotherapy or radiotherapy.

In highly emetogenic chemotherapy, a maximum initial dose of 16 mg can be administered as an intravenous infusion over not less than 15 minutes.

A single dose greater than 16 mg must not be given due to dose dependent increase of the risk of QT prolongation (see section 4.4).

The efficacy of ondansetron in highly emetogenic chemotherapy may be enhanced by the addition of a single dose of 20 mg dexamethasone sodium phosphate, administered prior to chemotherapy.

Intravenous doses greater than 8 mg and up to a maximum dose of 16 mg must be diluted in 50-100 ml of 9 mg/ml (0.9%) sodium chloride or 50 mg/ml (5%) glucose solution for infusion or other compatible solution for infusion (see section 6.6) and infused over at least 15 minutes.

Doses of ondansetron 8 mg or less do not need to be diluted and can be administered as a slow intramuscular injection or intravenous infusion over a period of at least 30 seconds.

The initial dose of ondansetron may be followed by two additional 8 mg intravenous or intramuscular doses 2 to 4 hours apart or a continuous infusion of 1 mg/hour for up to 24 hours.

To protect against delayed or prolonged emesis after the first 24 hours, oral or rectal treatment with ondansetron is recommended.

The total maximum daily dose for adults is 32 mg.

Post-operative nausea and vomiting

To prevent postoperative nausea and vomiting, the recommended dose is 4 mg ondansetron as a single dose given by intramuscular or slow intravenous injection at induction of anaesthesia.
For treatment of existing postoperative nausea and vomiting, a single dose of 4 mg given by intramuscular or slow intravenous injection is recommended.

Paediatric population

Chemotherapy-induced nausea and vomiting in children and adolescents form 6 months to 17 years

The dose can be calculated based on body surface area or body weight. In paediatric clinical studies, ondansetron was given by intravenous infusion diluted in 25 to 50 ml of sodium chloride or other compatible infusion fluid (see section 6.6). The infusion must not last less than 15 minutes.

Posology based on 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 12 hours later and may be continued for up to 5 days (see Table 1). The adult dose must not be exceeded.

Table 1 Posology based on body surface area for children and adolescents form 6 months to 17 years

Body surface area	**Day 1**	**Days 2-6**
< 0.6 m^2	5 mg/m^2 IV and 2 mg orally* after 12 hours	2 mg orally* every 12 hours
≥ 0.6 m^2 to ≤ 1.2 m^2	5 mg/m^2 IV and 4 mg orally* after 12 hours	4 mg orally* every 12 hours
> 1.2 m^2	5 mg/m^2 IV or 8 mg IV and 8 mg orally* after 12 hours	8 mg orally* every 12 hours

* Appropriate oral dosage form available (e.g. syrup, oral solution, tablets) should be used

Posology based on body weight

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. On Day 1, two further intravenous doses may be given in 4-hourly intervals. Oral dosing can commence 12 hours later and may be continued for up to 5 days (see Table 2). The adult dose must not be exceeded.

Table 2 Posology based on body weight for children and adolescents form 6 months to 17 years

Body weight	Day 1	Days 2-6
≤ 10 kg	Up to 3 doses of 0.15 mg/kg IV every 4 hours	2 mg orally* every 12 hours
> 10 kg	Up to 3 doses of 0.15 mg/kg IV every 4 hours	4 mg orally* every 12 hours

* Appropriate oral dosage form available (e.g. syrup, oral solution, tablets) should be used

Post-operative nausea and vomiting in children and adolescents from 1 month to 17 years

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

Elderly ≥ 65 years

Chemotherapy and radiotherapy induced nausea and vomiting

In patients 65 years of age or older, all intravenous doses should be diluted and infused over 15 minutes. If repeated dosing is necessary, these should be given at least 4 hours apart.

In patients 65 to 74 years of age, the initial dose of 8 mg or 16 mg may be administered as an infusion over 15 minutes. This may be followed by two further doses of 8 mg, infused over 15 minutes and given no less than 4 hours apart.

In patients 75 years of age or older, the initial dose of ondansetron, administered as an infusion over 15 minutes, must not exceed 8 mg. This may be followed by two further intravenous doses of 8 mg, infused over 15 minutes and given no less than 4 hours apart (see section 5.2).

Post-operative nausea and vomiting

There is limited experience in the use of ondansetron in the prevention and treatment of postoperative nausea and vomiting in the elderly. However, ondansetron is well tolerated by patients over 65 years.

Patients with hepatic impairment
Clearance of ondansetron is significantly reduced and serum half-life significantly prolonged in patients with moderate or severe hepatic impairment. In these patients a total daily dose of 8 mg must not be exceeded.

Patients with renal impairment
No dose adjustment, frequency of administration, or method of administration are required.

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

Compatibility with other drugs

Ondansetron may be administered by intravenous infusion (1 mg/hour). Although ondansetron must not at the same time be mixed with other medicinal products for infusion, the following medicinal products may be administered via the Y-site of the ondansetron giving set for ondansetron concentrations of 16 to 160 mcg/ml (e.g. 8 mg/500 ml and 8 mg/50 ml, respectively).

- **Cisplatin**: Concentrations up to a maximum of 0.48 mg/ml (e.g. 240 mg in 500 ml) can be administered over 1 to 8 hours.
- **5-Fluorouracil** : Concentrations up to a maximum of 0.8 mg/ml (e.g. 2.4 g in 3 litres or 400 mg in 500 ml) administered at a rate of at least 20 ml/hour (500 ml/24 hours). Higher concentrations of 5-fluorouracil may cause precipitation of ondansetron. The 5-fluorouracil infusion may contain up to 0.045% magnesium chloride in addition to other excipients shown to be compatible.

- **Carboplatin**: Concentrations in the range 0.18 mg/ml to 9.9 mg/ml (e.g. 90 mg in 500 ml to 990 mg in 100 ml), administered over 10 minutes to one hour.
- **Etoposide**: Concentrations in the range 0.144 mg/ml to 0.25 mg/ml (e.g. 72 mg in 500 ml to 250 mg in 1000 ml), administered over 30 minutes to one hour.
- **Ceftazidime**: Doses in the range 250 mg to 2000 mg reconstituted with water for injections as recommended by the manufacturer (e.g. 2.5 ml for 250 mg and 10 ml for 2 g ceftazidime) and given as an intravenous bolus injection over approximately 5 minutes.
- **Cyclophosphamide**: Doses in the range 100 mg to 1 g, reconstituted with water for injections (5 ml per 100 mg cyclophosphamide), as recommended by the manufacturer and given as an intravenous bolus injection over approximately 5 minutes.
- **Doxorubicin**: Doses in the range 10-100 mg reconstituted with water for injections (5 ml per 10 mg doxorubicin), as recommended by the manufacturer and given as an intravenous bolus injection over approximately 5 minutes.
- **Dexamethasone sodium phosphate**: Dexamethasone sodium phosphate 20 mg may be administered as a slow intravenous injection over 2-5 minutes via the Y-site of an infusion set delivering 8 mg or 16 mg of ondansetron diluted in 50-100 ml of a compatible infusion fluid over approximately 15 minutes. Compatibility between dexamethasone sodium phosphate and ondansetron has been demonstrated supporting administration of these drugs through the same giving set resulting in concentrations in line of 32 mcg/ml to 2.5 mg/ml for dexamethasone sodium phosphate and 8 mcg/ml to 1 mg/ml for ondansetron.

Method of administration

For intravenous or intramuscular use.
Ondansetron can be administered as a slow intravenous injection or slow intravenous infusion, or intramuscular injection.
For instructions on dilution of the medicinal product before administration and compatible solutions, see section 6.6.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
Severe hypotension and loss of consciousness have been reported to occur when ondansetron was co-administered with apomorphine hydrochloride.
Concomitant use with apomorphine is contraindicated (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 $5HT_3$ receptor antagonists.

If respiratory difficulties occur, these should be treated symptomatically and carefully monitored by the medical staff, as respiratory difficulties may be a sign 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 receiving ondansetron therapy. Ondansetron should be avoided in patients with congenital long QT syndrome. Ondansetron should be administered with caution to patients who have or may develop prolongation of QT, 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 ischaemia.

Hypokalaemia and hypomagnesaemia should be corrected prior to ondansetron administration.
Care should therefore be taken when administering ondansetron to patients with arrhythmias or cardiac conduction disorders as well as to patients treated with antiarrhythmic agents or beta-blockers and patients with significant electrolyte imbalance.

Serotonin syndrome has been described after co-administration of ondansetron and other serotonergic agents (see section 4.5). If concomitant treatment with ondansetron and other serotonergic agents is clinically justified, appropriate observation of the patient is advised.

As ondansetron may increase large bowel transit time, caution is advised in patients with impaired bowel motility (or intestinal obstruction). These patients should be carefully monitored for their bowel function.

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

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

Excipients
This medicinal product contains 3.52 mg sodium per ml, equivalent to 0.18% of the WHO recommended maximum daily intake of 2 g sodium for an adult.

4.5 Interaction with other medicinal products and other forms of interaction

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

Ondansetron is metabolised by multiple hepatic cytochrome P450 enzymes (CYP3A4, CYP2D6 and CYP1A2). As a large number of hepatic enzymes are involved in the degradation of ondansetron, the risk of competitive metabolic interactions is low and enzyme inhibition or reduced activity of enzyme
systems (e.g. genetic CYP2D6 deficiency) is compensated for by other implicated enzyme systems; as
a result, even in these cases, overall clearance of ondansetron is almost unchanged.

Caution should be exercised when ondansetron is co-administered with medicinal products that prolong the QT interval and/or lead to electrolyte imbalances. Use of ondansetron with QT prolonging medicinal products may further prolong the QT interval. 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).

Apomorphine
Severe hypotension and loss of consciousness have been reported to occur when ondansetron was administered with apomorphine hydrochloride. Concomitant use with apomorphine is contraindicated (see section 4.3).

Phenytoin, carbamazepine and rifampicin
In patients treated with highly potent inducers of CYP3A4 (i.e. phenytoin, carbamazepine or rifampicin), the oral clearance of ondansetron was increased and ondansetron blood concentrations were decreased.

Serotonergic agents (e.g. SSRIs and SNRIs)
Serotonin syndrome (including altered mental status, autonomic instability and neuromuscular abnormalities) has been reported after concomitant use of ondansetron and other serotonergic medicinal products including selective serotonin reuptake inhibitors (SSRIs) and serotonin noradrenaline reuptake inhibitors (SNRIs) (see section 4.4).

Tramadol
Two small interaction studies indicate that ondansetron may reduce the analgesic effect of tramadol.

4.6 Fertility, pregnancy and lactation

Pregnancy
Based on human experience from epidemiological studies, ondansetron is suspected to cause orofacial malformations when administered during the first trimester of pregnancy.
In a cohort study including 1.8 million pregnant women, the use of ondansetron in first trimester was associated with an increased risk of cleft lip, jaw and palate (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
It is not known whether ondansetron is excreted in breast milk. No data are available on the influence of ondansetron on the breast-fed child or on the production of breast milk. However, it has been shown that ondansetron is excreted in the breast milk of lactating animals (rats). It is therefore recommended that breast-feeding be discontinued prior to treatment with ondansetron.

Fertility
Ondansetron has no effect on fertility.

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

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 reactions are listed below by system organ class (according to the MedDRA database) and frequency (all reported events). Frequencies are defined as follows: very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100), rare (≥ 1/10,000 to < 1/1,000), very rare (< 1/10,000), not known (cannot be estimated from the available data).

Very common, common and uncommon adverse reactions were generally determined from clinical trial data; the incidence of adverse reactions with placebo was taken into account. Rare and very rare adverse reactions were generally determined on the basis of spontaneous reporting data.

The following frequencies are estimated at the standard recommended doses of ondansetron.
Immune system disorders
Rare: immediate-type hypersensitivity reactions, which can sometimes be serious, including anaphylaxis.

Nervous system disorders
Very common: headache.
Uncommon: seizures, movement disorders (including extrapyramidal symptoms such as dystonic reactions, oculogyric crisis and dyskinesia) observed without definitive evidence of persistent clinical sequelae.
Rare: dizziness, mainly with too rapid IV administration.

Eye disorders
Rare: transient visual disturbances (e.g. blurred vision) mainly with too rapid IV administration.
Very rare: transient blindness, mainly with IV administration.

In the majority of the blindness cases, a full recovery was made within 20 minutes. Most patients had received chemotherapeutic agents, which included cisplatin. Some cases of transient blindness were of cortical origin.

Cardiac disorders
Uncommon: chest pain with or without ST segment depression on ECG, bradycardia and arrhythmias.
Rare: prolongation of the QT interval (including *torsade de pointes*).
Not known: myocardial ischemia (see section 4.4).

Vascular disorders
Common: sensation of warmth or hot flushes.
Uncommon: hypotension.

Respiratory, thoracic and mediastinal disorders
Uncommon: hiccups.

Gastrointestinal disorders

Common: constipation.
Not known: dry mouth.

Hepatobiliary disorders
Uncommon: asymptomatic increases in liver function tests. These events were observed commonly in patients receiving chemotherapy with cisplatin.

Skin and subcutaneous tissue disorders
Common: flushing.
Very rare: toxic skin rash including toxic epidermal necrolysis.

General disorders and administration site conditions
Common: local irritation after IV administration.

Paediatric population
The adverse effect 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, Website: www.hpra.ie

4.9 Overdose

Symptoms and signs
There is limited experience of ondansetron overdose. However, in the event of accidental overdosing the following symptoms of intoxication can be expected: visual disturbances, severe constipation, hypotension and a vasovagal episode with a transient second-degree AV block. In all cases, the events resolved completely.
Ondansetron prolongs the 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.

Management
There is no specific antidote for ondansetron. In cases of suspected overdose, symptomatic and supportive therapy should be given as appropriate.
Further management should be as clinically indicated or as recommended by the national poisons centre, where available.

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

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 mechanism of action in the control of nausea and vomiting is not known.
Chemotherapeutic agents with a cytotoxic effect and radiotherapy may cause release of 5HT (serotonin) in the small intestine initiating a vomiting reflex by activating afferent vagal fibres via 5HT3 receptors. Ondansetron blocks the initiation of this reflex. Activation of the afferent vagal fibres may also cause a release of 5HT (serotonin) in the *area postrema*, which further stimulates vomiting via central mechanisms. Thus, the effect of ondansetron in the management of the nausea and vomiting induced by cytotoxic chemotherapy and radiotherapy is probably due to competitive antagonism of 5HT3 receptors on neurons located both in the peripheral and central nervous system.

The mechanism of action in post-operative nausea and vomiting is not known but it is assumed to follow a similar course to that in chemotherapy-induced nausea and vomiting.

Pharmacodynamic effects
Ondansetron does not alter plasma prolactin concentrations.

QT prolongation
The effect of ondansetron on the QT interval was evaluated in a double blind, randomised, placebo and positive (moxifloxacin) controlled, crossover study in 58 healthy adult men and women.
Ondansetron doses included 8 mg and 32 mg infused intravenously over 15 minutes. At the highest tested dose of 32 mg, the maximum mean (upper limit of 90% CI) difference in QTcF from placebo after baseline-correction was 19.6 (21.5) msec. At the lower tested dose of 8 mg, the maximum mean (upper limit of 90% CI) difference in QTcF from placebo after baseline-correction was 5.8 (7.8) msec. In this study, there were no QTcF measurements greater than 480 msec and no QTcF prolongation was greater than 60 msec. No significant changes were seen in the measured electrocardiographic PR or QRS intervals.

Clinical efficacy

Paediatric population
Chemotherapy-induced nausea and vomiting
The efficacy of ondansetron in the control of vomiting and nausea induced by chemotherapy was investigated in a double-blind randomised clinical trial in 415 patients aged 1 to 18 years (S3AB3006). On the days of chemotherapy, patients received either ondansetron 5 mg/m^2 intravenous and ondansetron 4 mg orally after 8 to 12 hours or ondansetron 0.45 mg/kg body weight intravenous and placebo orally after 8 to 12 hours. Post-chemotherapy both groups received 4 mg ondansetron solution twice daily for 3 days. Complete control of vomiting on worst day of chemotherapy was 49% (5 mg/m^2 intravenous plus 4 mg ondansetron orally) versus 41% (0.45 mg/kg intravenous plus placebo orally).

A double-blind randomised placebo-controlled trial (S3AB4003) in 438 patients aged 1 to 17 years demonstrated complete control of vomiting on worst day of chemotherapy in: 73% of patients when ondansetron was administered intravenously at a dose of 5 mg/m^2 intravenous together with 2 to 4 mg dexamethasone orally; 71% of patients when ondansetron was administered as solution at a dose of 8 mg together with 2 to 4 mg dexamethasone orally on the days of chemotherapy. Post-chemotherapy both groups received 4 mg ondansetron solution twice daily for 2 days. There was no difference in the overall incidence or with regard to the type of adverse reactions was observed between both 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 doses of intravenous ondansetron (0.15 mg/kg body weight each), administered 30 minutes before the start of chemotherapy and then at 4 and 8 hours after the first dose. Complete control of emesis was achieved in 56% of patients.

Another open-label, non-comparative, single-arm study (S3A239) with 28 children investigated the efficacy of one intravenous dose of 0.15 mg/kg body weight ondansetron followed by two oral ondansetron doses of 4 mg for children under 12 years and 8 mg for children aged 12 years and older. Complete control of vomiting 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 double-blind, randomised, placebo-controlled study in 670 children aged 1 to 24 months (post-conceptual age ≥ 44 weeks, weight ≥ 3 kg) (S3A40323). 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 body weight 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 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 medicinal product 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 the table below.

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 medication or study discontinuation

5.2 Pharmacokinetic properties

The pharmacokinetic properties of ondansetron remain unchanged after repeated dosing.

Absorption
Peak plasma concentrations of 30 ng/ml occur approximately 1.5 hours after oral administration of an 8 mg dose. After single intramuscular or intravenous administration of 4 mg ondansetron, equivalent blood levels are achieved within 10 minutes.

Distribution
The steady-state volume of distribution is approximately 140 litres. 70-76% of ondansetron is bound to plasma proteins.

Biotransformation and elimination
Ondansetron is removed from the systemic circulation by hepatic metabolism through multiple pathways. The absence of the enzyme CYP2D6 (the debrisoquine polymorphism) has no effect on ondansetron's pharmacokinetics. Less than 5% of the absorbed dose is excreted unchanged in the urine. The elimination half-life is about 3 to 5 hours.

Special patient populations
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 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 mean half-life in the patient population aged 1 to 4 months was 6.7 hours compared to 2.9 hours for patients aged 5 to 24 months and 3 to 12 years, respectively. 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 fluid in neonates and infants and a higher volume of distribution for water soluble active substances 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 linearly in relation to body 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 groups. Use of body weight-based dosing allows for age-dependent changes and leads to normalisation of 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 after intravenous administration of ondansetron. Based on this analysis, systemic exposure (AUC) of ondansetron after oral or intravenous administration in children and adolescents was comparable to adults, with the exception of infants aged 1 to 4 months. Volume of distribution was related to age and was lower in adults than in infants and children. Clearance was related to weight but not to age with the exception of infants aged 1 to 4 months. It is difficult to conclude whether there was an additional reduction in clearance related to age in infants 1 to 4 months or simply inherent variability due to the low number of subjects studied in this age group. Since patients less than 6 months of age will only receive a single dose for prophylaxis against postoperative 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 the 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). No differences in safety and efficacy were observed between young and elderly cancer patients enrolled in the clinical studies to investigate chemotherapy-induced vomiting and nausea to support a different dose recommendations for the elderly patients.

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

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

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

5.3 Preclinical safety data

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

Reproductive toxicity studies
Reproductive toxicity studies with rats and rabbits did not show evidence of any harmful effect to the foetus when ondansetron was administered during the period of organogenesis at approximately 6 and 24 times, respectively, 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 studies, pregnant rats received oral doses of ondansetron of 15 mg/kg/day from day 17 of gestation up to parturition on day 21. With the exception of a slight reduction in maternal body weight gain, there were no toxic effects of ondansetron in pregnant rats or on the pre- and postnatal development of offspring, including reproductive behaviour in the associated F1 generation. At a dose of 15 mg/kg/day in rats, the maternal dose was approximately 24 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. Transient ECG changes have been reported clinically (see section 4.4).

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium chloride
Citric acid monohydrate
Sodium citrate dihydrate
Water for injections

6.2 Incompatibilities

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

6.3 Shelf life

3 years

After opening ampoule
Once opened the product should be used immediately.

Shelf life after dilution
Chemical and physical in-use stability has been demonstrated for 7 days at 25 °C and 2 to 8 °C.
From a microbiological point of view, the diluted product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2 to 8 °C, unless dilution has taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage

This medicinal product does not require any special temperature storage conditions.
Keep the ampoules in the outer carton in order to protect from light.

For storage conditions after dilution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

2 ml or 4 ml of solution filled in clear glass ampoules with one point cut.
Ampoules are packed in a liner. Liner is placed into outer carton.

Pack sizes:
5, 10 or 25 ampoules

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

For single use only.

The medicinal product should be visually inspected prior to use. The medicinal product should not be used if there are any visible signs of deterioration (e.g. particles or discoloration).

After opening the ampoule the product should be used immediately. Any unused medicinal product or waste material should be disposed of in accordance with local requirements.
Ondansetron should not be autoclaved.

May be diluted with the following intravenous solutions for infusion:

- sodium chloride 9 mg/ml (0.9%) solution;
- glucose 50 mg/ml (5%) solution;
- mannitol 100 mg/ml (10%) solution;
- Ringer's solution;
- potassium chloride 3 mg/ml (0.3%) and sodium chloride 9 mg/ml (0.9%) solution;
- potassium chloride 3 mg/ml (0.3%) and glucose 50 mg/ml (5%) solution;
- Lactated Ringer's solution.

Ondansetron has been shown to be compatible with polypropylene (PP) syringes, Type I glass bottles, polyethylene (PE), polyvinyl chloride (PVC) and ethyl vinyl acetate (EVA) infusion bags, and PVC and PE tubing when diluted with above mentioned solutions for infusion. Undiluted Ondansetron solution for injection/infusion has been shown to be compatible with PP syringes.

Compatibility with other drugs
Ondansetron may be administered by intravenous infusion (at 1 mg/hour). The following medicinal products may be administered via the Y-site of the ondansetron giving set for ondansetron concentrations of 16 to 160 mcg/ml (e.g. 8 mg/500 ml and 8 mg/50 ml, respectively) (see section 4.2).

- Cisplatin
- 5-Fluorouracil
- Carboplatin
- Etoposide
- Ceftazidime
- Cyclophosphamide
- Doxorubicin
- Dexamethasone

7 MARKETING AUTHORISATION HOLDER

AS Kalceks
Krustpils Iela 71e
Riga
1057
Latvia

8 MARKETING AUTHORISATION NUMBER

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