Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Ondansetron 2 mg/ml Solution for Injection or Infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml of solution for injection or infusion contains 2mg ondansetron (as ondansetron hydrochloride dihydrate)

Each ampoule with 2ml contains 4mg ondansetron (as ondansetron hydrochloride dihydrate).

Each ampoule with 4ml contains 8mg ondansetron (as ondansetron hydrochloride dihydrate).

Excipient with known effect: 1 ml solution for injection or infusion contains 3.62 mg of sodium as sodium citrate, sodium chloride and sodium hydroxide.

For the full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Solution for Injection or Infusion

Clear colourless solution

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 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

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 in the range of 8-32 mg a day and selected as shown below.

Emetogenic chemotherapy and radiotherapy:
Ondansetron can be given either by rectal, oral (tablets or syrup), intravenous or intramuscular administration.

For most patients receiving emetogenic chemotherapy or radiotherapy, ondansetron 8 mg should be administered as a slow intravenous injection (in not less than 30 seconds) or intramuscular injection, immediately before treatment followed by 8 mg orally twelve hourly.

To protect against delayed or prolonged emesis after the first 24 hours, oral or rectal treatment with ondansetron should be continued for up to 5 days after a course of treatment.

Highly emetogenic chemotherapy: For patients receiving highly emetogenic chemotherapy, e.g. high-dose cisplatin, ondansetron can be given either by oral, rectal, intravenous or intramuscular administration. Ondansetron has been shown to be equally effective in the following dose schedules over the first 24 hours of chemotherapy:

- A single dose of 8 mg by slow intravenous injection (in not less than 30 seconds)or intramuscular injection immediately before chemotherapy.
- A dose of 8 mg by slow intravenous injection (in not less than 30 seconds) or intramuscular doses of 8 mg two to four hours apart, or by a constant infusion of 1 mg/hour for up to 24 hours.
- A maximum initial intravenous dose of 16 mg diluted in 50-100 ml of saline or other compatible infusion fluid (see section 6.6) and infused over not less than 15 minutes immediately before chemotherapy. The initial dose of ondansetron may be followed by two additional 8 mg intravenous doses (in not less than 30 seconds) or intramuscular doses four hours apart.
- A single dose greater than 16 mg must not be given due to dose dependent increase of QT-prolongation risk (see sections 4.4, 4.8 and 5.1)

The selection of dose regimen should be determined by the severity of the emetogenic challenge.

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

To protect against delayed or prolonged emesis after the first 24 hours, oral or rectal treatment with ondansetron should be continued for up to 5 days after a course of treatment.

Paediatric Population:

CINV in children aged ≥6 months and adolescents:

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 – see sections 4.4 and 5.1

Ondansetron hydrochloride should be diluted in 5% dextrose or 0.9% sodium chloride or other compatible infusion fluid (see section 6.6) and infused intravenously over not less than 15 minutes.

There are no data from controlled clinical trials on the use of Ondansetron Injection in the prevention of delayed or prolonged CINV. There are no data from controlled clinical trials on the use of Ondansetron Injection 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 single intravenous dose must not exceed 8 mg.

Oral dosing can commence twelve hours later and may be continued for up to 5 days. (Table 1).

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

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

BSA	Day 1[a,b]	Days 2-6[(b)]
< 0.6 m^2	5 mg/m^2 IV plus 2 mg syrup after 12 hrs	2 mg syrup every 12 hrs
≥0.6 m^2 to ≤ 1.2 m^2	5 mg/m^2 IV plus 4 mg syrup after 12 hrs	4 mg syrup or tablet every 12 hrs
> 1.2 m^2	5 mg/m^2 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 daily dose over 24 hours (given as divided doses) must not exceed adult dose of 32 mg.
Please note: Not all pharmaceutical forms may be available.

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 single intravenous dose must not exceed 8 mg.

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. (Table 2).

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

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

Weight	Day1[(a,b)]	Days 2-6[(b)]
≤10 kg	Up to 3 doses of 0.15 mg/kg IV every 4-hrs.	2 mg syrup every 12 hrs
> 10 kg	Up to 3 doses of 0.15 mg/kg IV every 4-hrs.	4 mg syrup or tablet every 12 hrs

[a] The intravenous dose must not exceed 8 mg.
[b] The total dose over 24 hours (given as divided doses) must not exceed adult dose of 32 mg.
Please note: Not all pharmaceutical forms may be available.

Elderly:
In patients 65 to 74 years of age, the dose schedule for adults can be followed. All intravenous doses should be diluted in 50-100 ml of saline or other compatible infusion fluid (see section 6.6) and infused over 15 minutes.

In patients 75 years of age or older, the initial intravenous dose of Ondansetron should not exceed 8 mg. All intravenous doses should be diluted in 50-100 ml of saline or other compatible infusion fluid (see section 6.6) and infused over 15 minutes.
The initial dose of 8 mg may be followed by two further intravenous doses of 8 mg, infused over 15 minutes and given no less than four hours apart. (see section 5.2)

Patients with renal impairment:
No alteration of daily dosage 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 drug exposure levels no different from those of the general population. No alteration of daily dosage or frequency of dosing is required.

Post-operative nausea and vomiting (PONV):

Adults:
For the prevention of PONV Ondansetron can be administered orally or by intravenous or intramuscular injection.

Ondansetron may be administered as a single dose of 4 mg given by intramuscular or slow intravenous injection at induction of anaesthesia.

For treatment of established PONV A single dose of 4 mg given by intramuscular or slow intravenous injection is recommended.

Paediatric population:

PONV in children aged ≥ 1 month and adolescents.

For prevention of PONV in paediatric patients having surgery performed under general anaesthesia, a single dose of ondansetron may be administered by slow intravenous injection (not less than 30 seconds) at a dose 0.1 mg/Kg up to a maximum of 4 mg either prior to, at or after induction of anaesthesia.

There are no data on the use of Ondansetron in the treatment of PONV children below 2 years of age.

Elderly:
There is limited experience in the use of ondansetron in the prevention and treatment of 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 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 drug exposure levels no different from those of the general population. No alteration of daily dosage or frequency of dosing are required.

Method of administration

For intravenous injection or intramuscular injection or intravenous infusion after dilution.

For instructions on dilution of the product before administration, see section 6.6

Prescribers intending to use ondansetron in the prevention of delayed nausea and vomiting associated with chemotherapy or radiotherapy in adults, adolescents or children should take into consideration current practice and appropriate guidelines.

4.3 Contraindications

Concomitant use with apomorphine (see section 4.5) Hypersensitivity to any component of the preparation.

4.4 Special warnings and precautions for use

Ondansetron is largely metabolised in the liver. Hepatic clearance decreases and half-life increases in patients with impaired liver function. Due to limited experience in such patients, caution is advised in the treatment. The daily dose should be adjusted in these patients (see section 4.2).

Hypersensitivity reactions have been reported in patients who have exhibited hypersensitivity to other selective $5HT_3$ receptor antagonists.

Respiratory events should be treated symptomatically and clinicians should pay particular attention to them as precursors of hypersensitive 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.

Hypokalemia and hypomagnesemia should be corrected prior to ondansetron administration.

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

As ondansetron is known to increase large bowel transit time, patients with signs of subacute intestinal obstruction should be monitored following administration

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

Cases of myocardial ischemia have been reported in patients treated with ondansetron. In some patients, especially in the case of intravenous administration, symptoms appeared immediately after administration of ondansetron. Patients should be alerted to the signs and symptoms of myocardial ischaemia.

This medicinal product contains 7,24 mg sodium per ampoule of 2 ml (or 14,48 mg per ampoule of 4 ml), equivalent to 0,36% (or 0,72%) of the WHO recommended maximum daily intake of 2 g sodium for an adult.

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

CINV:
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 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 pharmacokinetic interactions when ondansetron is administered with alcohol, tramadol, furosemide, propofol, or temazepam..

Ondansetron is metabolised by multiple hepatic cytochrome P-450 enzymes: CYP3A4, CYP2D6 and CYP1A2. Due to the multiplicity of metabolic enzymes capable of metabolising ondansetron, enzyme inhibition or reduced activity of one enzyme (e.g. CYP2D6 genetic deficiency) is normally compensated by other enzymes and should result in little or no significant change in overall ondansetron clearance or dose requirement.

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

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

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

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

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

Tramadol:
Data from small studies indicate that ondansetron may reduce the analgesic effect of tramadol.

Absorption of orally administered ondansetron is not affected by antacids.

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 (see section 5.3).
Ondansetron should not be used during the first trimester of pregnancy.

Breast-feeding
There are no human data on the excretion of ondansetron in human breast milk. 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.

Fertility
There is no information on the effects of ondansetron on human fertility. There is no effect of ondansetron on fertility in test animals (see section 5.3).

4.7 Effects on ability to drive and use machines

Ondansetron has no or negligible 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 and <1/10), uncommon (≥1/1000 to <1/100), rare (≥1/10,000 and <1/1000) and very rare (<1/10,000). Very common, common and uncommon events were generally determined from clinical trial data. The incidence in placebo was taken into account. Rare and very rare events were generally determined from post-marketing spontaneous data.

The following frequencies are estimated at the standard recommended doses of ondansetron.

Immune system disorders
Rare: Immediate hypersensitivity reactions sometimes severe, including anaphylaxis*
Not known: rash, pruritus
*See section 4.4

Nervous system disorders
Very common: Headache.
Uncommon: Seizures, movement disorders (including extrapyramidal reactions such as dystonic reactions, oculogyric crisis and dyskinesia) observed without definitive evidence of persistence clincial sequelae.
Rare: Dizziness during rapid i.v. administration.

Eye disorders

Rare: Transient visual disturbances (eg. blurred vision) predominantly during IV administration.
Very rare: Transient blindness predominantly during intravenous administration[(2)].
The majority of 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.

*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)
*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*
Rare: Diarrhea and abdominal pain*
* See section 4.4

Hepatobiliary disorders
Uncommon: Asymptomatic increases in liver function tests[*#]
*See section 4.4
These events were observed commonly in patients receiving chemotherapy with Cisplatin.

Skin and subcutaneous tissue disorders

Very rare: severe bullous skin reactions including Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN)

General disorders and administration site conditions

Common: local IV injection site reactions
Not known: oedema

Side effects in children and adolescents
Adverse reactions profiles in children and adolescents are similar to those seen in adults.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via HPRA Pharmacovigilance; Website: www.hpra.ie

4.9 Overdose

Symptoms and signs
There is limited experience of ondansetron overdose. In the majority of cases, symptoms were similar to those already reported in patients receiving recommended doses (see section 4.8). Manifestations that have been reported include visual disturbances, severe constipation, hypotension and a vasovagal episode with transient second degree AV block.

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

Cases consistent with serotonin syndrome have been reported in young children following oral overdose.

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

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

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

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

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Serotonin (5HT3) antagonists, ATC code: A04AA01

Mechanism of action

Ondansetron is a potent, highly selective $5HT_3$ 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 $5HT_3$ 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 $5HT_3$ 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.

Research has shown that ondansetron does not interfere with psychomotor functioning and has no sedative effect.

Ondansetron does not alter plasma prolactin concentrations. Clinical studies show that other formulations of ondansetron such as suppositories are less effective in the treatment of cisplatin-induced nausea and vomiting than ondansetron injection/tablets.

QT Prolongation
The effect of ondansetron on the QTc 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.

Paediatric population:
CINV
The efficacy of Ondansetron in the control of emesis and nausea induced by cancer chemotherapy was assessed in a double-blind randomised trial in 415 patients aged 1 to 18 years (S3AB3006). On the days of chemotherapy, patients received either ondansetron 5 mg/m^2 intravenous and ondansetron 4 mg orally after 8to 12 hours or ondansetron 0.45 mg/Kg intravenous and placebo after 8 to 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 % (5mg/m^2 intravenous and ondansetron 4 mg orally) and 41 % (0.45 mg/Kg intravenous and placebo orally).

A double-blind randomised placebo-controlled trial(S3AB4003) in 438 patients aged 1 to 17 years demonstrated complete control of emesis on worst day of chemotherapy in 73% of patients when ondansetron was administered intravenously at a dose of 5mg/m^2 intravenous together with 2-4 mg dexamethasone orally 71% of the patients when ondansetron was administered as a syrup at a dose of 8 mg together with 2to 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 overall incidence or nature of adverse events between the two treatment groups.

The efficacy of ondansetron in 75 children aged 6 to 48 months was investigated in an open-label, non-comparative, single-arm study (S3A40320). All children receive three 0.15 mg/Kg doses of intravenous ondansetron, administered at 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-operative, single-arm study (S3A239) investigated the efficacy of one intravenous dose of 0.15 mg/Kg ondansetron followed by two ondansetron doses of 4mg 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.

PONV

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

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

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

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

CR = no emetic episodes, rescue or withdrawal

Ondansetron does not alter plasma prolactin concentrations.

5.2 Pharmacokinetic properties

The pharmacokinetic properties of ondansetron are unchanged after repeated dosing.

a) General characteristics of ondansetron

Absorption

Following oral administration of 8 mg, a peak plasma concentration of 30 mg/ml is reached after approximately 1.5 hours. With doses above 8 mg, the exposure to ondansetron increases in a greater dose proportional manner.

The mean bioavailability in healthy male volunteers following administration of a single 8 mg tablet is approximately 55 to 60%.

Bioavailability in the presence of food is 17% higher. This increase is not significant.

Following i.v. administration of ondansetron, comparable systemic exposure is obtained.

Distribution

Plasma protein binding is 70 – 76%. The theoretical distribution volume is 2.5 l/kg.

Biotransformation

Ondansetron is metabolized mainly in the liver by various cytochrome P450 enzymes: CYP3A4, CYP1A2 and CYP2D6. The absence of the CYP2D6 enzyme (2D6 'poor metaboliser' phenotype) has no effect on the pharmacokinetics of ondansetron.

Elimination

The metabolites are excreted in the faeces and in the urine. Less than 5% of ondansetronis excreted unchanged in the urine.The terminal half-life of ondansetron after oral or i.v. administration is approximately the same and is is about 3 hours.

The pharmacokinetics of ondansetron are generally linear, with only minor deviations during the accumulation phase up to steady state.

b) Patient characteristics

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 on average 6.7 hours compared to 2.9 hours for patients aged 5 to 24 month and 3 to 12 years. The differences in pharmacokinetic parameters in the 1 to 4 month-old patient population can be explained in part by the higher percentage of otal bodily fluid in neonates and infants and a greater volume of distribution for water soluble drugs like ondansetron.

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

Table 4. Pharmacokinetics in paediatric patients aged between 1 month and 18 years

Study	Patient population (intravenous dose)	Age	N	AUC (ng.u/ml)	CL (l/u/kg)	VD_{ss} (l/kg)	$T_{1/2}$ (u)
				Geometric mean			Mean
S3A40319[1]	Operation (0.1 or 0.2 mg/kg)	1-4 months	19	360	0.401	3.5	6.7
S3A40319[1]	Operation (0.1 or 0.2 mg/kg)	5-24 months	22	236	0.581	2.3	2.9
S3A40320 & S3A40319 Pop PK[2,3]	Cancer/ operation (0.15 mg/kg every 4 h /0.1 or 0.2 mg/kg)	1-48 months	115	257	0.582	3.65	4.9
S3KG02[4]	Operation (2 mg or 4 mg)	3-12 years	21	240	0.439	1.65	2.9
S3A-150	Cancer (0.15 mg/kg every 4 h)	4-18 years	21	247	0.599	1.9	2.8

1 Single intravenous dose of ondansetron: 0.1 or 0.2 mg/kg
2 Population PK: 64% cancer patients and 36% surgical patients
3 Estimated population; AUC based on a dose of 0.15 mg/kg
4 Single intravenous dose of ondansetron: 2 mg (3-7 years) or 4 mg (8-12 years).

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 PONV a decreased clearance is not likely to be clinically relevant.

The elderly

Early Phase I studies in healthy elderly volunteers have showed a slight age-related decrease in clearance, and an increase in half-life of ondansetron. However, wide inter individual variability resulted in considerable overlap in pharmacokinetic parameters between young (< 65 years of age) and elderly subjects (≥ 65 years of age). There were no differences in safety or efficacy observed between young and elderly cancer patients enrolled in CINV clinical trials..

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 after i.v. injection of ondansetron. Specific dosing information is provided for patients aged 65-75 years and over 75 years for the solution for injection(see section 4.2). For the oral formulations and the suppository, no adjustment to the dosing recommendations is necessary.

Patients with hepatic impairment
In patients with severe hepatic impairment clearance is markedly reduced with prolonged elimination half-lives (15-32 hours) and an oral bioavailability approaching 100% due to reduced pre-systemic metabolism.

Renal impairment

In patients with moderate renal impairment (creatinine clearance 31-60 ml/min), both systemic clearance and volume of distribution are reduced, elimination half-life (to 6.5 h after i.v. and 7.1 h after oral administration). This increase is not clinically significant. A study in patients undergoing haemodialysis (creatinine clearance < 15 ml/min) showed unchanged pharmacokinetics of ondansetron (studied between dialyses).

5.3 Preclinical safety data

Preclinical data reveal no special hazard for humans based on conventional studies of repeated-dose toxicity, genotoxicity and carcinogenic potential. Ondansetron and its metabolites accumulate in the milk of rats at a milk: plasma ratio of 5.2:1.

In embryo-foetal development studies in rats and rabbits and in pre- and post-natal developmental toxicity studies in rats there were no significant effects of ondansetron on the maternal animals, development of the offspring, and reproductive performance. The doses were approximately 6 and 24 times the maximum recommended human oral dose, based on body surface area.

A study in cloned human cardiac ion channels has shown ondansetron at clinically relevant concentrations has the potential to affect cardiac repolarisation via blockade of hERG potassium channels. Dose-dependent QT prolongation was observed in a detailed QT study in human volunteers (see section 5.1).

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Citric acid monohydrate
Sodium citrate
Sodium chloride
Sodium hydroxide (for pH adjustment)
Hydrochloric acid, concentrated (for pH adjustment)
Water for injections

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf life

Unopened
3 years

Injection
After first opening the medicinal product should be used immediately.
Infusion

Chemical and physical in-use stability has been demonstrated for 7 days at 25°C and 2-8°C with the solutions given in section 6.6.

From a microbiological point of view, the 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 ampoules in the outer carton in order to protect from light.

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

6.5 Nature and contents of container

Type I clear glass ampoules/amber glass ampoules
2 ml:
Pack sizes: Carton containing 10 ampoules.
Carton containing 5 ampoules.
4 ml:
Pack sizes: Carton containing 10 ampoules.
Carton containing 5 ampoules.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal

The solution must not be sterilised in an autoclave.

Ondansetron Injection should only be admixed with those infusion solutions which are recommended:

Sodium Chloride Intravenous Infusion BP 0.9%w/v
Glucose Intravenous Infusion BP 5%w/v
Mannitol Intravenous Infusion BP 10%w/v
Ringers Intravenous Infusion
Potassium Chloride 0.3%w/v and Sodium Chloride 0.9%w/v Intravenous Infusion BP
Potassium Chloride 0.3%w/v and Glucose 5%w/v Intravenous Infusion BP

The stability of Ondansetron Injection after dilution with the recommended infusion fluids have been demonstrated in concentrations 0.016 mg/ml and 0.64 mg/ml.

Compatibility studies have been undertaken in polyvinyl chloride infusion bags with polyvinyl chloride administration sets, polyethylene infusion bags, Type 1 glass bottles and polypropylene syringes. Dilutions of Ondansetron Injection in 10% mannitol injection, ringer's injection, 0.3% potassium chloride and 0.9% sodium chloride injection, 0.3% potassium chloride and 5% dextrose injection, 0.9% sodium chloride injection and 5% glucose injection have been demonstrated to be stable in polyvinyl chloride infusion bags and polyvinyl chloride administration sets, polyethylene infusion bags, Type 1 glass bottles and polypropylene syringes.

Compatibility with other drugs: Ondansetron Injection may be administered by intravenous infusion using 0.9% sodium chloride and 5% dextrose injection at 1mg/hour, e.g. from an infusion bag or syringe pump. The following drugs may be administered via the Y-site of the Ondansetron Injection giving set for ondansetron concentrations of 16 to 160 micrograms/ml (e.g. 8 mg/500 ml and 8 mg/50 ml respectively);

Cisplatin: Concentrations up to 0.48 mg/ml (e.g. 240 mg in 500 ml) administered over one to eight hours.

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 ten minutes to one hour.

Etoposide: Concentrations in the range 0.14 mg/ml to 0.25 mg/ml (e.g. 72 mg in 500 ml to 250 mg in 1 litre), administered over thirty minutes to one hour.

Ceftazidime: Doses in the range 250 mg to 2000 mg reconstituted with Water for Injections BP as recommended by the manufacturer (e.g. 2.5 ml for 250 mg and 10 ml for 2g ceftazidime) and given as an intravenous bolus injection over approximately five minutes.

Cyclophosphamide: Doses in the range 100 mg to 1g, reconstituted with Water for Injections BP, 5 ml per 100 mg cyclophosphamide, as recommended by the manufacturer and given as an intravenous bolus injection over approximately five minutes.

Doxorubicin: Doses in the range 10-100mg reconstituted with Water for Injections BP, 5 ml per 10 mg doxorubicin, as recommended by the manufacturer and given as an intravenous bolus injection over approximately 5 minutes.

Dexamethasone: Dexamethasone sodium phosphate 20mg may be administered as a slow intravenous injection over 2-5 minutes via the Y-site of an infusion set delivering 8 or 16mg 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 microgram - 2.5 mg/ml for dexamethasone sodium phosphate and 8 microgram – 0.75 mg/ml for ondansetron.

The solution is to be visually inspected prior to use (also after dilution). Only clear solutions practically free from particles should be used.

The diluted solutions should be stored protected from light.
Any unused product or waste material should be disposed of in accordance with local requirements.

6.6 Special precautions for disposal and other handling

The solution must not be sterilised in an autoclave.

Ondansetron Injection should only be admixed with those infusion solutions which are recommended:

Sodium Chloride Intravenous Infusion BP 0.9%w/v
Glucose Intravenous Infusion BP 5%w/v
Mannitol Intravenous Infusion BP 10%w/v
Ringers Intravenous Infusion
Potassium Chloride 0.3%w/v and Sodium Chloride 0.9%w/v Intravenous Infusion BP
Potassium Chloride 0.3%w/v and Glucose 5%w/v Intravenous Infusion BP

The stability of Ondansetron Injection after dilution with the recommended infusion fluids have been demonstrated in concentrations 0.016 mg/ml and 0.64 mg/ml.

Compatibility studies have been undertaken in polyvinyl chloride infusion bags with polyvinyl chloride administration sets, polyethylene infusion bags, Type 1 glass bottles and polypropylene syringes. Dilutions of Ondansetron Injection in 10% mannitol injection, ringer's injection, 0.3% potassium chloride and 0.9% sodium chloride injection, 0.3% potassium chloride and 5% dextrose injection, 0.9% sodium chloride injection and 5% glucose injection have been demonstrated to be stable in polyvinyl chloride infusion bags and polyvinyl chloride administration sets, polyethylene infusion bags, Type 1 glass bottles and polypropylene syringes.

Compatibility with other drugs: Ondansetron Injection may be administered by intravenous infusion using 0.9% sodium chloride and 5% dextrose injection at 1mg/hour, e.g. from an infusion bag or syringe pump. The following drugs may be administered via the Y-site of the Ondansetron Injection giving set for ondansetron concentrations of 16 to 160 micrograms/ml (e.g. 8 mg/500 ml and 8 mg/50 ml respectively);

Cisplatin: Concentrations up to 0.48 mg/ml (e.g. 240 mg in 500 ml) administered over one to eight hours.

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 ten minutes to one hour.

Etoposide: Concentrations in the range 0.14 mg/ml to 0.25 mg/ml (e.g. 72 mg in 500 ml to 250 mg in 1 litre), administered over thirty minutes to one hour.

Ceftazidime: Doses in the range 250 mg to 2000 mg reconstituted with Water for Injections BP as recommended by the manufacturer (e.g. 2.5 ml for 250 mg and 10 ml for 2g ceftazidime) and given as an intravenous bolus injection over approximately five minutes.

Cyclophosphamide: Doses in the range 100 mg to 1g, reconstituted with Water for Injections BP, 5 ml per 100 mg cyclophosphamide, as recommended by the manufacturer and given as an intravenous bolus injection over approximately five minutes.

Doxorubicin: Doses in the range 10-100mg reconstituted with Water for Injections BP, 5 ml per 10 mg doxorubicin, as recommended by the manufacturer and given as an intravenous bolus injection over approximately 5 minutes.

Dexamethasone: Dexamethasone sodium phosphate 20mg may be administered as a slow intravenous injection over 2-5 minutes via the Y-site of an infusion set delivering 8 or 16mg 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 microgram - 2.5 mg/ml for dexamethasone sodium phosphate and 8 microgram – 0.75 mg/ml for ondansetron.

The solution is to be visually inspected prior to use (also after dilution). Only clear solutions practically free from particles should be used.

The diluted solutions should be stored protected from light.

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

7 MARKETING AUTHORISATION HOLDER

Accord Healthcare Ireland Ltd.
Euro House
Euro Business Park
Little Island
Cork T45 K857
Ireland

8 MARKETING AUTHORISATION NUMBER

PA2315/168/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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Date of last renewal: 29 October 2012

10 DATE OF REVISION OF THE TEXT

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