Baxter **Baxter Pharmaceuticals India Private Limited**

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Barcode Information:

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Date: 31/03/21

Baxter

Ondansetron Baxter 2 mg/ml

1. NAME OF THE MEDICINAL PRODUCT

Ondansetron Baxter 2 mg/ml,

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml contains 2 mg Ondansetron USP.

For a full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

A clear and colourless solution for injection.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Adults:
Ondansetron Baxter 2mg/ml is indicated for the management of nausea and vomiting induced by cytotoxic chemotherapy and radiotherapy. Ondansetron Baxter 2mg/ml is indicated for the prevention and treatment of post-operative nausea and vomiting (PONV).

Paediatric Population:
Ondansetron Baxter 2mg/ml is indicated for the management of chemotherapy-induced nausea and vomiting (CINV) in children aged ≥6 months, and for the prevention and treatment of PONV in children aged ≥ 1 month.

4.2 Posology and method of administration

Chemotherapy and Radiotherapy: induced nausea and vomiting (CINV and RINV)

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 Baxter 2mg/ml should be flexible in the range of 8-32mg a day and selected as shown below.

Emetogenic chemotherapy and radiotherapy:
Ondansetron Baxter 2mg/ml can be given either by tablets, intravenous or intramuscular administration.

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

To protect against delayed or prolonged emesis after the first 24 hours, oral treatment with Ondansetron Baxter 2mg/ml 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 Baxter 2mg/ml can be given either by oral, intravenous or intramuscular administration. Ondansetron Baxter 2mg/ml has been shown to be equally effective in the following dose schedules over the first 24 hours of chemotherapy:

- A single dose of 8mg by slow intravenous injection (in not less than 30 seconds) or intramuscular injection immediately before chemotherapy.
- A dose of 8mg by slow intravenous injection (in not less than 30 seconds) or intramuscular injection immediately before chemotherapy, followed by two further intravenous injection(in not less than 30 seconds) or intramuscular doses of 8mg four hours apart, or by a constant infusion of 1mg/hour for up to 24 hours.
- A maximum initial intravenous dose of 16mg diluted in 50-100mL 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 Baxter 2mg/ml may be followed by two additional 8mg 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 Baxter 2mg/ml in highly emetogenic chemotherapy may be enhanced by the addition of a single intravenous dose of dexamethasone sodium phosphate, 20mg administered prior to chemotherapy.

To protect against delayed or prolonged emesis after the first 24 hours, oral or treatment with Ondansetron Baxter 2mg/ml 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.
Weight-based dosing results in higher total daily doses compared to BSA-based dosing (sections 4.4.and 5.1).

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

Dosing by BSA:
Ondansetron Baxter 2mg/ml 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 i.v. plus 2 mg p.o. after 12 hrs	2 mg p.o. every 12 hrs
≥0.6 m^2	5 mg/m^2 i.v. plus 4 mg p.o. after 12 hrs	4 mg p.o. every 12 hrs

a The intravenous dose must not exceed 8mg.
b The total dose over 24 hours (given as divided doses) must not exceed adult dose of 32mg

Dosing by bodyweight:
Weight-based dosing results in higher total daily doses compared to BSA-based dosing.
Ondansetron Baxter 2mg/ml 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 twelve 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	Day 1[a,b]	Days 2-6[b]
≤10 kg	Up to 3 doses of 0.15 mg/kg every 4 hrs	2 mg p.o. every 12 hrs
>10 kg	Up to 3 doses of 0.15 mg/kg every 4 hrs	4 mg p.o. every 12 hrs

a The intravenous dose must not exceed 8mg.
b The total dose over 24 hours (given as divided doses) must not exceed adult dose of 32mg

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 Baxter 2mg/ml 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 are required.

Patients with Hepatic Impairment:
Clearance of Ondansetron Baxter 2mg/ml 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 8mg 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 4mg given by intramuscular or slow intravenous injection at induction of anaesthesia.

For treatment of established PONV a single dose of 4mg 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 Baxter 2mg/ml may be administered by slow intravenous injection (not less than 30 seconds) at a dose of 0.1mg/kg up to a maximum of 4mg either prior to, at or after induction of anaesthesia.

For the treatment of PONV after surgery in paediatric patients having surgery performed under general anaesthesia, a single dose of Ondansetron Baxter 2mg/ml may be administered by slow intravenous injection (not less than 30 seconds) at a dose of 0.1mg/kg up to a maximum of 4mg.

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

Elderly:
There is limited experience in the use of Ondansetron in the prevention and treatment of PONV in the elderly; however Ondansetron is well tolerated in patients over 65 years receiving chemotherapy.

Patients with Renal Impairment:
No alteration of daily dosage or frequency of dosing or route of administration are required.

Patients with Hepatic Impairment:
Clearance of Ondansetron Baxter 2mg/ml 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 8mg 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.

4.3 Contra-indications
Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
Concomitant use with apomorphine (see section 4.5).

4.4 Special Warnings and Precautions for Use

Hypersensitivity reactions have been reported in patients who have exhibited hypersensitivity to other selective 5HT$_3$ receptor antagonists.

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

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

Hypokalaemia and hypomagnesaemia should be corrected prior to ondansetron administration.

The development of serotonin syndrome has been reported with 5-HT$_3$ receptor antagonists. Most reports have been associated with concomitant use of serotonergic drugs (e.g., selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors (SNRIs), monoamine oxidase inhibitors, mirtazapine, fentanyl, lithium, tramadol, and intravenous methylene blue). Some of the reported cases were fatal. Serotonin syndrome occurring with overdose of Ondansetron Baxter 2mg/ml alone has also been reported. The majority of reports of serotonin syndrome related to 5-HT receptor antagonist use occurred in a post-anaesthesia care unit or an infusion centre.
Symptoms associated with serotonin syndrome may include the following combination of signs and symptoms: mental status changes (e.g., agitation, hallucinations, delirium, and coma), autonomic instability (e.g., tachycardia, labile blood pressure, dizziness, diaphoresis, flushing, hyperthermia), neuromuscular symptoms (e.g., tremor, rigidity, myoclonus, hyperreflexia, incoordination), seizures, with or without gastrointestinal symptoms (e.g., nausea, vomiting, diarrhea). Patients should be monitored for the emergence of serotonin syndrome, especially with concomitant use of Ondansetron Baxter 2mg/ml and other serotonergic drugs. If symptoms of serotonin syndrome occur, discontinue Ondansetron Baxter 2mg/ml and initiate supportive treatment. Patients should be informed of the increased risk of serotonin syndrome, especially if Ondansetron Baxter 2mg/ml is used concomitantly with other serotonergic drugs (see Sections 4.5 and 4.9).

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

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

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

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 5mg/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 (section 5.1).

4.5 Interactions with other medicinal productsand 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, temazepan, furosemide, alfentanil, tramadol, morphine, lidocaine, thiopental, or propofol.

Ondansetron is metabolised by multiple hepatic cytochrome P-450 enzymes: CYP3A4, CYP2D6 and CYP1A2. Due to the multiplicity of metabolic enzymes capable of metabolising ondansetron, enzyme inhibition or reduced activity of one enzyme (e.g. CYP2D6 genetic deficiency) is normally compensated by other enzymes and should result in little or no significant change in overall ondansetron clearance or dose requirement.
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: Serotonin syndrome (including altered mental status, autonomic instability, and neuromuscular symptoms) has been described following the concomitant use of 5-HT$_3$ receptor antagonists and other serotonergic drugs, including selective serotonin reuptake inhibitors (SSRIs) and serotonin and noradrenaline reuptake inhibitors (SNRIs). (See section 4.4).

Apomorphine: Based on reports of profound hypotension and loss of consciousness when ondansetron was administered with apomorphine hydrochloride, concomitant use with apomorphine is contraindicated.
Phenytoin, Carbamazepine and Rifampicin: In patients treated with potent inducers of CYP3A4 (i.e. phenytoin, carbamazepine, and rifampicin), the oral clearance of ondansetron was increased and ondansetron blood concentrations were decreased.

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

4.6 Fertility, Pregnancy and Lactation

Pregnancy
Based on human experience of epidemiological studies, ondansetron is suspected to cause orofacial malformations when administered during 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 to 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. The use of ondansetron in pregnancy is not recommended.
Breast-feeding
Tests have shown that ondansetron passes into the milk of lactating animals. It is therefore recommended that mothers receiving Ondansetron Baxter 2mg/ml should not breast-feed their babies.
Fertility
There is no information on the effects of ondansetron on human fertility.

4.7 Effects on Ability to Drive and Use Machines
Ondansetron 2 mg/ml has no or negligible influence on the ability to drive and use machines.
In psychomotor testing ondansetron does not impair performance nor cause sedation. No detrimental effects on such activities are predicted from the pharmacology of ondansetron.

4.8 Undesirable Effects

Adverse events are listed below by system organ class and frequency. Frequencies are defined as: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1000 to <1/100), rare (≥1/10,000 to <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. The adverse event profiles in children and adolescents were comparable to that seen in adults.

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 dystonic reactions, oculogyric crisis and dyskinesia)[1].
Rare: Dizziness during rapid IV administration.
Eye disorders
Rare: Transient visual disturbances (e.g. blurred vision) predominantly during IV administration.
Very rare: Transient blindness predominantly during intravenous administration.[2]

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

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.
Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form https://sideeffects.health.gov.il

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.
Manifestations that have been reported include visual disturbances, severe constipation,

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Packing: 5ml Amp	**Plant Location : Injectable**
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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.

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.
Reported symptoms included somnolence, agitation, tachycardia, tachypnea, hypertension, flushing, mydriasis, diaphoresis, myoclonic movements, horizontal nystagmus, hyperreflexia, and seizure.

Patients required supportive care, including intubation in some cases, with complete recovery without sequelae within 1 to 2 days.

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 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.

5.0 Pharmacological Properties

5.1 Pharmacodynamic Properties
Pharmacotherapeutic group: Serotonin (5HT3) antagonist, 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 $5HT_3$ 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.

Ondansetron does not alter plasma prolactin concentrations.

Clinical safety and efficacy
The role of ondansetron in opiate-induced emesis is not yet established.

QT Prolongation
The effect of ondansetron on the QTc interval was evaluated in a double blind, 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/m2 intravenous and ondansetron 4 mg orally after 8 to 12 hours or ondansetron 0.45 mg/kg intravenous and placebo orally 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% (5 mg/m2 intravenous and ondansetron 4 mg orally) and 41% (0.45 mg/kg intravenous and placebo orally). Post-chemotherapy both groups received 4 mg ondansetron syrup twice daily for 3 days. There was no difference in the overall incidence or nature of adverse events between the two treatment groups.

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

- 73% of patients when ondansetron was administered intravenously at a dose of 5 mg/m2 intravenous together with 2 to 4 mg dexamethasone orally
- 71% of patients when ondansetron was administered as syrup at a dose of 8 mg and 2 to 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 received three 0.15 mg/kg doses of intravenous ondansetron, 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) investigated the efficacy of one intravenous dose of 0.15 mg/kg ondansetron followed by two oral ondansetron doses of 4 mg for children aged < 12 years and 8 mg for children aged ≥ 12 years (total no. of children n= 28). Complete control of emesis was achieved in 42% of patients.

PONV

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

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

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

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

CR = no emetic episodes, rescue or withdrawal

5.2 Pharmacokinetic Properties

Absorption

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

The disposition of ondansetron following oral, intramuscular and intravenous dosing in adults 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 intramuscular and intravenous administration of ondansetron.

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

Distribution

Ondansetron is not highly protein bound (70-76%).

Biotransformation and Elimination

Ondansetron is cleared from the systemic circulation predominantly by hepatic metabolism through multiple enzymatic pathways. Less than 5% of the absorbed dose is excreted unchanged in the urine. The absence of the enzyme CYP2D6 (the debrisoquine polymorphism) has no effect on ondansetron's pharmacokinetics. The pharmacokinetic properties of ondansetron are unchanged on repeat dosing.

Special Patient Populations

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

Children and Adolescents (aged 1 month to 17 years)
In paediatric patients aged 1 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 drugs like ondansetron.

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

Population pharmacokinetic analysis was performed on 428 subjects (cancer patients, surgery patients and healthy 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.

Elderly
Early Phase I studies in healthy elderly volunteers showed a slight age-related decrease in clearance, and an increase in half-life of ondansetron. However, wide inter-subject variability resulted in considerable overlap in pharmacokinetic parameters between young (< 65 years of age) and elderly subjects (≥ 65 years of age) and there were no overall differences in safety or efficacy observed between young and elderly cancer patients enrolled in CINV clinical trials to support a different dosing recommendation for the elderly.
Based on more recent ondansetron plasma concentrations and exposure-response modelling, a greater effect on QTcF is predicted in patients ≥75 years of age compared to young adults. Specific dosing information is provided for patients over 65 years of age and over 75 years of age (see section 4.2).

Renal Impairment
In patients with 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 following intravenous administration.

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

5.3 Preclinical Safety Data

Embryo-fetal development studies in rats and rabbits, did not show evidence of harm to the fetus when ondansetron was administered during the period of organogenesisat approximately 6 and 24 times respectively the maximum recommended human oral dose of 24 mg/day, based on body surface area. In a pre- and postnatal developmental toxicity study, there were no effects upon the pregnant rats and the pre- and postnatal development of their offspring, including reproductive performance at approximately 6 times the maximum recommended human oral dose of 24 mg/day based on body surface area.

6.0 Pharmaceutical Particulars

6.1 List of Excipients

Sodium Chloride, Citric acid monohydrate, Sodium Citrate dihydrate, Water for Injections.

6.2 Incompatibilities

Ondansetron Baxter 2mg/ml should not be administered in the same syringe or infusion as any other medication.
Ondansetron Baxter 2mg/ml should only be mixed with those infusion solutions that are recommended.

6.3 Shelf Life

The expiry date of the product is indicated on the packaging materials.

6.4 Special Precautions for Storage

Store below 30°c. Store the vial in the box in order to protect from light.
After dilution: chemical and physical in-use stability has been demonstrated for 36 hours at 2°C to 8°C protected from light.
From 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.

6.5 Nature and content of container

Type I glass ampoules.
5 ampoules are packed in a carton.
10 ampoules are packed in a carton.
25 ampoules are packed in a carton.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Ondansetron Baxter 2mg/ml should not be autoclaved.
Compatibility with intravenous fluids;
Ondansetron Baxter 2mg/ml should only be mixed with those infusion solutions which are recommended:

a) Sodium chloride Intravenous Infusion BP 0.9 % w/v
b) Glucose Intravenous Infusion BP 5% w/v
c) Mannitol Intravenous Infusion BP 10% w/v
d) Ringers Intravenous Infusion
e) Potassium Chloride 0.3%w/v and Sodium Chloride 0.9%w/v Intravenous Infusion BP
f) Potassium Chloride 0.3%w/v and Glucose 5%w/v Intravenous Infusion BP

Compatibility studies have been undertaken in polyvinyl chloride infusion bags and polyvinyl chloride administration sets. It is considered that adequate stability would also be conferred by the use of polyethylene infusion bags or Type 1 glass bottles. Dilutions of Ondansetron in sodium chloride 0.9%w/v or in glucose 5%w/v have been demonstrated to be stable in polypropylene syringes. It is considered that Ondansetron diluted with other compatible infusion fluids would be stable in polypropylene syringes.

Compatibility with other drugs:
Ondansetron Baxter 2mg/ml may be administered by intravenous infusion 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 Baxter 2mg/ml 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.

5-Fluorouracil:
Concentrations up to 0.8 mg/mL (e.g. 2.4g in 3 litres or 400 mg in 500 mL) administered at a rate of at least 20 mL per hour (500 mL per 24 hours). Higher concentrations of 5- fluorouracil may cause precipitation of ondansetron. The 5-fluorouracil infusion may contain up to 0.045%w/v 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 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 10-100 mg 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 - 2.5mg/ mL for dexamethasone sodium phosphate and 8 microgram - 1mg/mL for ondansetron.

7 MANUFACTURER

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8 MARKETING AUTHORISATION HOLDER

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