Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Ondansetron 2 mg/ml Solution for Injection and Infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

The solution for injection and infusion contains 2 mg/ml ondansetron, as ondansetron hydrochloride dihydrate.

Excipient:
The solution for injection and infusion contains 0.15 mmol/ml sodium.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for injection and infusion.

Clear colourless solution.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

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

Paediatric Population:
- management of chemotherapy-induced nausea and vomiting (CINV) in children aged ≥ 6 months
- prevention and treatment of PONV in children aged ≥ 1 month.

4.2 Posology and method of administration

For intravenous injection or for intravenous infusion after dilution.

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

Ondansetron is also available for oral use to allow the route of administration and dosing to be flexible.

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 dose range of Ondansetron solution for injection and infusion is 8 to 32 mg a day and selected as shown below:-

Emetogenic chemotherapy and radiotherapy
The recommended intravenous dose of ondansetron is 8 mg administered as a slow injection immediately before treatment.

Oral treatment is recommended to protect against delayed or prolonged emesis after the first 24 hours.

Highly emetogenic chemotherapy
For patients receiving highly emetogenic chemotherapy, e.g. high-dose cisplatin. Ondansetron may be administered as a single 8mg intravenous or intramuscular dose immediately before chemotherapy. Doses of greater than 8 mg and up to 32 mg of ondansetron may only be given by intravenous infusion diluted in 50-100 ml saline or other compatible infusion fluid (see *Pharmaceutical Precautions*) and infused over not less than 15 minutes.

Alternatively a dose of 8 mg of ondansetron may be administered by slow intravenous or intramuscular injection immediately before chemotherapy, followed by two further intravenous or intramuscular doses of 8mg two to four hours apart, or by constant infusion of 1mg/hour for up to 24 hours.

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.

Oral treatment is recommended to protect against delayed or prolonged emesis after the first 24 hours.

Paediatric Population

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

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

BSA	**Day 1 [a,b]**	**Days 2-6[b]**
< 0.6 m^2	5 mg/m^2 i.v. 2 mg syrup after 12 hrs	2 mg syrup every 12 hrs
≥ 0.6 m^2 < 1.2 m^2	5 mg/m^2 i.v. 4 mg syrup or tablet after 12 hrs	4 mg syrup or tablet every 12 hrs

[a] The intravenous dose must not exceed 8mg.
[b] The total daily dose must not exceed adult dose of 32 mg

For children with a body surface area of greater than 1.2 m^2 an initial i.v. dose of 8 mg is administered immediately before chemotherapy, followed by 8 mg orally 12 hours later. 8 mg ondansetron, orally twice daily can be continued for up to five days after a course of treatment.

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

In children aged 6 months or older, ondansetron is administered as a single i.v. dose of 0.15 mg/kg (not to exceed 8 mg) immediately before chemotherapy. This dose may be repeated every four hours for a total of three doses. 4 mg orally twice daily can be continued for up to five days after a course of treatment. Adult doses must not be exceeded.

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 syrup every 12 hrs
> 10 kg	Up to 3 doses of 0.15 mg/kg every 4 hrs	4 mg syrup or tablet every 12 hrs

[a] The intravenous dose must not exceed 8 mg.

[b] The total daily dose must not exceed adult dose of 32 mg.

Elderly:-
Ondansetron is well tolerated by patients over 65 years and no alteration of dosage, dosing frequency or route of administration are required.

Post-operative nausea and vomiting
Adults:-
For the prevention of post operative nausea and vomiting, the recommended dose of Ondansetron solution for injection and infusion is a single dose of 4 mg by intramuscular or slow intravenous injection administered at the induction of anaesthesia.

For the treatment of established post-operative nausea and vomiting 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 of 0.1 mg/kg up to a maximum of 4 mg 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 may be administered by slow intravenous injection (not less than 30 seconds) at a dose of 0.1 mg/kg up to a maximum of 4 mg.
There are no data on the use of ondansetron in the treatment of PONV in children below 2 years of age.

Elderly:-
There is limited experience in the use of ondansetron in the prevention and treatment of post-operative nausea and vomiting in the elderly; however ondansetron is well tolerated in patients over 65 years receiving chemotherapy.

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

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

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

4.3 Contraindications

Hypersensitivity to ondansetron or to other selective 5-HT3 receptor antagonists (e.g. granisetron, dolasetron) or to any of the excipients.

4.4 Special warnings and precautions for use

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

The medicinal product should not be used for children younger than two years, as for these patients the experience is limited.

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

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

Very rarely and predominantly with intravenous ondansetron, transient ECG changes including QT interval prolongation have been reported. Caution is advised if patients have received cardiotoxic agents and in patients with a history or family history of prolonged QT syndrome.

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.

This medicinal product contains 2.3 mmol (or 53.5 mg) sodium per 32 mg dose. To be taken into consideration by patients on a controlled sodium diet.

Paediatric Population:

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

Chemotherapy-induced nausea and vomiting: When calculating the dose on an mg/kg basis and administering three doses at 4-hourly 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 medicinal products commonly co-administered with it. Specific studies have shown there are no pharmacokinetic interactions when ondansetron is administered with alcohol, temazepam, furosemide, tramadol 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.

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

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

Use of ondansetron with QT prolonging drugs may result in additional QT prolongation. Concomitant use of ondansetron with cardiotoxic drugs (e.g. anthracyclines) may increase the risk of arrhythmias (see section 4.4).

4.6 Fertility, pregnancy and lactation

The safety of ondansetron for use in human pregnancy has not been established. Evaluation of experimental animal studies does not indicate direct or indirect harmful effects with respect to the development of the embryo, or foetus, the course of gestation and peri- and post-natal development. However as animal studies are not always predictive of human response the use of ondansetron in pregnancy is not recommended.

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

4.7 Effects on ability to drive and use machines

In psychomotor testing ondansetron does not impair performance nor cause sedation.

4.8 Undesirable effects

The following frequency terminology is used:
very common: ≥ 1/10;
common: ≥ 1/100, < 1/10;
uncommon: ≥ 1/1,000, < 1/100;
rare: ≥ 1/10,000,< 1/1,000;
very rare: < 1/10,000 and isolated report.

Immune system disorders
Rare: Immediate hypersensitivity reactions, sometimes severe including anaphylaxis. Anaphylaxis may be fatal.

Hypersensitivity reactions were also observed in patients, who were sensitive to other selective 5-HT_3-antagonists.

Nervous system disorders
Very common: Headache
Uncommon: There have been reports suggestive of involuntary movement disorders such as extrapyramidal reactions, e.g. oculogyric crisis/dystonic reactions and dyskinesia without definitive evidence of persistent clinical sequelae and seizures (e.g. epileptic spasms) have been observed although no known pharmacological mechanism can account for ondansetron causing these effects.
Rare: Dizziness during rapid intravenous administration.
Vary rare: Depression

Opthalmic disorders
Rare: Transient visual disturbances (e.g. blurred vision) during rapid intravenous administration.
Very rare: In individual cases transitory blindness was reported in patients receiving chemotherapeutic agents including cisplatin. Most reported cases were resolved in 20 minutes.

Cardiac disorders
Uncommon: Chest pain with or without ST segment depression, cardiac arrhythmias and bradycardia. Chest pain and cardiac arrhythmias may be fatal in individual cases.
Vary rare: Transitory changes in the electrocardiogram, including prolongation of the QT interval have been observed predominantly after intravenous application of ondansetron.

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

Respiratory, thorax and mediastinum disorders
Uncommon: Hiccups.

Gastrointestinal disorders
Common: Ondansetron is known to increase the large bowel transit time and may cause constipation in some patients.

Hepato-biliary disorders
Uncommon: Asymptomatic increases in liver function tests were observed. These reactions were frequently observed in patients under chemotherapy with cisplatin.

Skin and subcutaneous tissue disorders
Uncommon: Hypersensitivity reactions around the injection site (e.g. rash, urticaria, itching) may occur, sometimes extending along the drug administration vein.

General disorders and administration site conditions
Common: Local reactions at the I.V. injection site.

Paediatric population

The adverse event profile in children and adolescents was comparable to that seen in adults.

4.9 Overdose

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

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

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

ATC Code: A04AA01

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 the 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.

Ondansetron does not alter plasma prolactin concentrations.

Clinical Studies

Paediatric population:

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

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/m^2 intravenous together with 2-4 mg dexamethasone orally
- 71 % of patients when ondansetron was administered as syrup at a dose of 8 mg + 2-4 mg dexamethasone orally on the days of chemotherapy.

Post-chemotherapy both groups received 4 mg ondansetron syrup twice daily for 2 days.
The efficacy of ondansetron in 75 children aged 6 to 48 months was investigated in an open-label, non-comparative, single-arm study (S3A40320). All children received three 0.15 mg/kg doses of intravenous ondansetron, administered 30 minutes before the start of chemotherapy and then at four and eight hours after the first dose. Complete control of emesis was achieved in 56 % of patients.

Another open-label, non-comparative, single-arm study (S3A239) investigated the efficacy of one intravenous dose of 0.15 mg/kg ondansetron followed by two oral ondansetron doses of 4 mg for children aged < 12 yrs and 8 mg for children aged ≥ 12 yrs (total no. of children n= 28). Complete control of emesis was achieved in 42 % of patients.

Prevention of post-operative nausea and vomiting

The efficacy of a single dose of ondansetron in the prevention of post-operative nausea and vomiting was investigated in a randomised, double-blind, placebo-controlled study in 670 children aged 1 to 24 months (post-conceptual age ≥ 44 weeks, weight ≥ 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 nausea	60	47	0.004

CR = no emetic episodes, rescue or withdrawal

5.2 Pharmacokinetic properties

The disposition of ondansetron following oral, intramuscular and intravenous dosing is similar with a terminal half life of about 3 hours and steady state volume of distribution of about 140 L. Equivalent systemic exposure is achieved after intramuscular and intravenous administration of ondansetron. Ondansetron is not highly protein bound (70-76%). 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. Studies in healthy elderly volunteers have shown slight, but clinically insignificant, age-related increases in both oral bioavailability and half-life of ondansetron.

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

In a study of 21 paediatric patients aged between 3 and 12 years undergoing elective surgery with general anaesthesia, the absolute values for both the clearance and volume of distribution of ondansetron following a single intravenous dose of 2 mg (3-7 years old) or 4 mg (8-12 years old) were reduced. The magnitude of the change was age-related, with clearance falling from about 300 ml/min at 12 years of age to 100 ml/min at 3 years. Volume of distribution fell from about 75 L at 12 years to 17 L at 3 years. Use of weight-based dosing (0.1 mg/kg up to 4 mg maximum) compensates for these changes and is effective in normalising systemic exposure in paediatric patients.

In patients with moderate renal impairment (creatinine clearance 15-60 ml/min), both systemic clearance and volume of distribution are reduced, resulting in a slight, but clinically insignificant, increase in elimination half-life (5.4 h). A study in patients with severe renal impairment who required regular haemodialysis (studied between dialyses) showed ondansetron's pharmacokinetics to be essentially unchanged. In patients with severe hepatic impairment, ondansetron systemic clearance is markedly reduced with prolonged elimination half-lives (15 - 32 h) and an oral bioavailability approaching 100 % due to reduced pre-systemic metabolism.

Special Patient Populations

Children and Adolescents (aged 1 month to 17 years)

In paediatric patients aged 1 to 4 months (n=19) undergoing surgery, weight 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 normalized by body weight, the values for these parameters were similar between the different age group populations. Use of weight-based dosing compensates for age-related changes and is effective in normalizing systemic exposure in paediatric patients.

Population pharmacokinetic analysis was performed on 428 subjects (cancer patients, surgery patients and healthy volunteers) aged 1 month to 44 years following intravenous administration of ondansetron. Based on this analysis, systemic exposure (AUC) of ondansetron following oral or IV dosing in children and adolescents was comparable to adults, with the exception of infants aged 1 to 4 months. Volume was related to age and was lower in adults than in infants and children. Clearance was related to weight but not to age with the exception of infants aged 1 to 4 months. It is difficult to conclude whether there was an additional reduction in clearance related to age in infants 1 to 4 months or simply inherent variability due to the low number of subjects studied in this age group. Since patients less than 6 months of age will only receive a single dose in PONV a decreased clearance is not likely to be clinically relevant.

5.3 Preclinical safety data

A study in cloned human cardiac ion channels has shown ondansetron has the potential to affect cardiac repolarisation via blockade of HERG potassium channels. The clinical relevance of this finding is uncertain.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium chloride
Citric acid monohydrate
Sodium citrate
Water for injections

6.2 Incompatibilities

Ondansetron solution for injection and infusion should not be administered in the same syringe or infusion as any other medication (see section 6.6).

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.
Chemical and physical in-use stability has been demonstrated for 24 hours at 2-8°C.

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 2-8 °C, unless dilution has taken place in controlled and validated aseptic conditions.

After opening / dilution: 24 hours stored in a refrigerator (2-8ºC). Diluted solutions should be stored protected from light.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

For storage after opening/dilution see section 6.3.

6.5 Nature and contents of container

Amber type I glass ampoules containing 2 ml or 4 ml of solution, in an outer carton.

Packs of 5 ampoules.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

For single use only. Any unused solution should be disposed of in accordance with local requirements.

Compatibility with Intravenous fluids:
Ondansetron solution for injection and infusion should only be mixed 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

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 I 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 solution for injection and infusion diluted with other compatible infusion fluids would be stable in polypropylene syringes.

Compatibility with other drugs:
Ondansetron solution for injection and infusion 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 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. 2.4 g 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 100ml), administered over ten 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 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 2 g ceftazidime) and given as an intravenous bolus injection over approximately five minutes.

Cyclophosphamide
Doses in the range 100 mg to 1 g, 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 five minutes.

Dexamethasone
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 or 32 mg of ondansetron diluted in 50−100 ml of the following infusion fluids:

- Sodium Chloride Intravenous Infusion BP 0.9% w/v
- Glucose Intravenous Infusion BP 5% w/v
- Sodium Chloride Intravenous Infusion 0.9% w/v and Glucose Intravenous Infusion BP 5% w/v 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 − 1 mg/ml for ondansetron.

7 MARKETING AUTHORISATION HOLDER

Wockpharma Ireland Limited
41 Central Chambers
Dame Court
Dublin 2
Ireland

8 MARKETING AUTHORISATION NUMBER

PA 1448/1/1

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 11th November 2011

10 DATE OF REVISION OF THE TEXT