1.3 SUMMARY OF PRODUCT CHARACTERISTICS, LABELLING AND INSTRUCTIONS FOR MEDICAL USE:

1.3.1. SUMMARY OF PRODUCT CHARACTERISTICS (SmPC)

1.3.1.1 NAME OF MEDICINAL PRODUCT

Product Name: Ondansetron Injection USP

Strength: 8mg/4ml

Pharmaceutical dosage from: Injection

1.3.1.2 QUALITATIVE AND QUANTITATIVE COMPOSITION

The quantitative composition and function of each component in the drug product is listed below in **Table P.1.T01**

Label claim:

Each ml contains:

Ondansetron Hydrochloride Dihydrate USP 2mg

Equivalent to Ondansetron

Water for Injections BP qs

Batch Size:

200 Ltr (47059 Ampoules)

Table P.1.T01:

Sr. No.	Ingredients	Specification	Mg/ml	Std. Qty.	Unit	Uses
1	Ondansetron Hydrochloride Dihydrate Equivalent to Ondansetron (With 5% Overages)	USP	2.62 2.1	524.00 (A)	gm	Active ingredient
2	Sodium Chloride	BP	9.0	1.800	Kg	Isotonic Agent
3	Sodium Citrate	BP	0.25	50.00	gm	Alkalinizing Agent
4	Citric Acid Monohydrate	BP	q.s. pH 3.65	100.00	gm	pH adjustment
5	Water for Injection	BP	q.s. 1.0 ml	q.s. 200	Ltr	Vehicle

Note:

Target fill volume 4.25 ml (17.0 ml for 4 dose in 25 ml graduated cylinder, (limit 16.5 to 17.5 ml))

Actual quantity of Ondansetron Hydrochloride to be issued = $\frac{524.00 \times 100 \times 100}{X \times (100 - (Y-9)}$ = A gm

[Where X = Assay of Ondansetron Hydrochloride on anhydrous basis.....and Y = Water]

1.3.1.3 PHARMACEUTICAL FORM:

Injection

1.3.1.4 CLINICAL PARTICULATE

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

Paediatric Population:

Ondansetron 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.

a) POSOLOGY AND METHOD OF ADMINISTRATION:

For intravenous injection or for intravenous infusion after dilution.

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.

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 or infusion is 8-32 mg a day and selected as shown below.

Emetogenic chemotherapy and radiotherapy

For patients receiving emetogenic chemotherapy or radiotherapy ondansetron can be given either by intravenous or other routes of administration, however this product is for intravenous use only.

The recommended intravenous dose of ondansetron is 8 mg administered as a slow injection (in not less than 30 seconds) or as an infusion over 15 minutes immediately before treatment, followed by treatment with dosage forms other than intravenous.

Treatment with dosage forms other than intravenous 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 can be given by intravenous or other routes of administration, however this product is for intravenous use only.

Ondansetron has been shown to be equally effective in the following intravenous 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) immediately before chemotherapy.

• A dose of 8 mg by slow intravenous injection (in not less than 30 seconds) or as a short-time intravenous infusion over 15 minutes immediately before chemotherapy, followed by two further intravenous doses of 8 mg 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 sodium chloride 9 mg/ml (0.9 % w/v) solution or other compatible infusion fluid (see compatibility with solutions for infusion under 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) four hours apart. A single dose greater than 16 mg must not be given due to dose dependent increase of QT-prolongation risk

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, ondansetron treatment with dosage forms other than intravenous should be continued after a course of treatment.

<u>Paediatric Population:</u>

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.

Ondansetron injection should be diluted in 5% glucose 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/m2. The 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 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. plus 2 mg syrup after 12 hrs	2 mg syrup every 12 hrs
≥ 0.6 m^2	5 mg/m^2 i.v. plus 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

Dosing by bodyweight:

Weight-based dosing results in higher total daily doses compared to BSA-based dosing.

Ondansetron should be administered immediately before chemotherapy as a single intravenous dose of 0.15 mg/kg. The intravenous dose must not exceed 8 mg. Two further intravenous doses may be given in 4-hourly intervals. The total daily dose must not exceed adult dose of 32 mg.

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

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 8mg.

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

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 and infused over 15 minutes.

In patients 75 years of age or older, the initial intravenous dose should not exceed 8 mg. All intravenous doses should be diluted in 50-100 ml of saline or other compatible infusion 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.

Post-operative nausea and vomiting (PONV)

Prevention of PONV

Adults: For the prevention of PONV ondansetron can be administered by intravenous injection or other dosage forms.

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

Treatment of established PONV

For treatment of established PONV a single dose of 4 mg given by 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.

For treatment of established PONV in paediatric patients and adolescents, ondansetron may be administered by slow intravenous injection at a dose of 0.1 mg/kg up to a maximum of 4 mg.

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.

Special Populations

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.

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.

b) CONTRAINDICATIONS:

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

Concomitant use with apomorphine.

c) SPECIAL WARNINGS AND PRECAUTIONS FOR USE:

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

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

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. These conditions include patients with electrolyte abnormalities, congestive heart failure, bradyarrhythmias or patients taking other medicinal products that lead to QT prolongation or electrolyte abnormalities.

Hypokalaemia and hypomagnesaemia 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.

<u>Paediatric Population:</u>

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

<u>CINV</u>

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 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.

This medicine contains less than 1 mmol sodium (23 mg) per ml, that is to say essentially 'sodium-free'.

d) INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION:

Effects of ondansetron on other medicinal products

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

Effects of other medicinal products on ondansetron

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.

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 trastuzimab), antibiotics (such as erythromycin or ketoconazole), antiarrhythmics (such as amiodarone) and beta blockers (such as atenolol or timolol) may increase the risk of arrhythmias.

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).

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.

e) PEGNANCY 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.However Ondansetron should not be used during the first trimester of pregnancy.

Lactation:

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.

f) 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.

g) UNDESIRABLE EFFECTS:

The following frequency terminology is used:

very common: ≥1/10;

common: ≥1/100 to <1/10;

uncommon: ≥1/1,000 to <1/100;

rare: ≥1/10,000 to <1/1,000;

very rare: <1/10,000;

not known: cannot be established from the available data

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 towards other selective 5-HT_3 receptor 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.
Very rare:	Depression.

Eye 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 within 20 minutes. Some cases of transient blindness were reported as cortical in origin.

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.
Rare:	Transitory changes in the electrocardiogram, QTc prolongation (including Torsades de Pointes)

Vascular disorders

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

Respiratory, thoracic and mediastinal disorders

Uncommon:	Hiccups.

Gastrointestinal disorders

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

Hepatobiliary 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 IV injection site.

Paediatric population

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

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.

h) OVERDOSE:

Little is known at present about overdosage with ondansetron, however, a limited number of patients received overdoses. In the majority of cases, symptoms were similar to those already reported in patients receiving recommended doses (see section 4.8). Manifestations that have been reported include visual disturbances, severe constipation, hypotension and a vasovagal episode with transient second degree AV block. In all instances, the events resolved completely. Ondansetron prolongs the QT interval in a dose-dependent fashion. ECG monitoring is recommended in cases of overdose.

There is no specific antidote for ondansetron, therefore in all cases of suspected overdose, symptomatic and supportive therapy should be given as appropriate. The use of ipecacuanha to treat overdose with ondansetron is not recommended, as patients are unlikely to respond due to the anti-emetic action of ondansetron itself.

Paediatric population

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

1.3.1.5 PHARMACOLOGICAL PROPERTIE

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

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 + 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/m2 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 openlabel, 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.

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.

b. PHARMACOKINETIC PROPERTIES:

The pharmacokinetic properties of ondansetron are unchanged on repeat dosing.

A direct correlation of plasma concentration and anti-emetic effect has not been established.

Absorption

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

A 4 mg 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 25 ng/ml are attained within 10 minutes of injection.

Distribution

The disposition of ondansetron following oral, intramuscular (IM) and intravenous (IV) dosing is similar with a steady state volume of distribution of about 140 L. Equivalent systemic exposure is achieved after IM and IV administration of ondansetron.

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

Metabolism

Ondansetron is cleared from the systemic circulation predominantly by hepatic metabolism through multiple enzymatic pathways. The absence of the enzyme CYP2D6 (the debrisoquine polymorphism) has no effect on ondansetron's pharmacokinetics.

Excretion

Less than 5% of the absorbed dose is excreted unchanged in the urine. Terminal half life is about 3 hours.

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 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.

Based on the population pharmacokinetic parameters for subjects aged 1 month to 48 months, administration of a 0.15 mg/kg i.v. dose of ondansetron every 4 hours for 3 doses would result in a systematic exposure (AUC) comparable to that observed in paediatric surgery subjects aged 5 to 24 months and previous paediatric studies in cancer (aged 4 to 18 years) and surgical (aged 3 to 12 years) subjects, at similar doses.

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 persons

Studies in healthy elderly volunteers have shown slight age-related increases in both oral bioavailability (65%) and half-life (5 hours).

Renal impairment

In patients with renal impairment (creatinine clearance 15-60 ml/min), both systemic clearance and volume of distribution are reduced following IV administration of ondansetron, 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 following IV 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 h) and an oral bioavailability approaching 100% due to reduced pre-systemic metabolism.

Gender differences

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).

C PRECLINICAL SAFETY DATA

Preclinical data revealed no special hazard for humans based on conventional studies of safety, pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential and toxicity to reproduction.

Ondansetron and its metabolites accumulate in the milk of rats, milk/plasma-ratio was 5.2:1.

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

1.3.1.6. PHARMACEUTICAL PARTICULARS

a) LIST OF EXCIPIENTS

Sodium chloride

Sodium citrate dihydrate

Citric acid monohydrate

Water for injections

b) INCOMPATIBILITIES

This medicinal product must not be mixed with other medicinal products except

Sodium chloride 9 mg/ml (0.9 % w/v) solution

Glucose 50 mg/ml (5 % w/v) solution

Mannitol 100 mg/ml (10 % w/v) solution

Ringer's lactate solution

c) SHELF LIFE

36 months from date of manufacturing

d) SPECIAL PRECAUTIONS FOR STORAGE

Store at a temperature below 30°C. Protected from light.

e) NATURE AND CONTENTS OF CONTAINER

Five ml amber coloured glass ampoule with snap off, labeled and packed in a plastic tray with five ampoules and such one tray along with packing insert is packed in a carton.

1.3.1.7. MARKETING AUTHORISATION HOLDER

Samarth Life Sciences Pvt. Ltd.

1.3.1.8. MARKETING AUTHORISATION NUMBER(S)

1.3.1.9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION