Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Gamidarin 2 mg/ml Solution for Injection or Infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml contains 2 mg of Ondansetron (as ondansetron hydrochloride dihydrate).

Each 2 ml ampoule contains 4 mg Ondansetron (as ondansetron hydrochloride dihydrate)
Each 4 ml ampoule contains 8 mg Ondansetron (as ondansetron hydrochloride dihydrate)

Excipient: Each ml of the solution contains 3.6 mg of Sodium.
For a full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Solution for Injection/Infusion.

A clear, colourless solution.

pH of the solution is between 3.3 - 4.0 and osmolality of the solution is 326 mOsmol/L.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Adults:
Ondansetron is indicated for the 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:
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.

4.2 Posology and method of administration

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:

Adults:

The emetogenic potential of cancer treatment varies according to the doses and combinations of chemotherapy and radiotherapy regimens used. The route of administration and dose of ondansetron should be flexible in the range of 8-32mg a day and selected as shown below.

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

For most patients receiving emetogenic chemotherapy or radiotherapy, ondansetron 8mg should be administered as a slow intravenous injection immediately before treatment, followed by 8mg orally twelve hourly.

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

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

A single dose of 8mg by slow intravenous injection immediately before chemotherapy.

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

A single intravenous dose of 16 mg diluted in 50-100ml of saline or other compatible infusion fluid *(see Pharmaceutical Precautions*) and infused over not less than 15 minutes immediately before chemotherapy.

A single dose greater than 16 mg must not be given due to dose dependant increase of QT-prolongation risk (see sections 4.4, 4.8 and 5.1).

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

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

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

Paediatric Population:

CINV in children aged ≥ 6 months and adolescents

The dose for CINV can be calculated based on body surface area (BSA) or weight – see below. 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 (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 < 1.2 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

For children with a body surface area of greater than 1.2 m2 an initial i.v. dose of 8 mg is administered immediately before chemotherapy, followed by 8 mg orally 12 hours later. 8mg 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 (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 8mg) 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 8mg.

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.

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 8mg should not be exceeded.

Post-Operative Nausea and Vomiting (PONV):

Adults:

For the prevention of PONV ondansetron can be administered orally or by intravenous injection.

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

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

Paediatric population

PONV in children aged ≥1 month and adolescents

For prevention and treatment 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 0.1mg/kg up to a maximum of 4mg either prior to, at or after induction of anaesthesia.

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 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 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.

***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 any component of the preparation.

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.

Rarely, transient ECG changes including QT interval prolongation have been reported in patients receiving ondansetron. In addition, post-marketing cases of Torsade de Pointes have been reported in patients using ondansetron. Ondansetron should be administered with caution to patients who have or may develop prolongation of QTc. These conditions include patients with electrolyte abnormalities, with congenital long QT syndrome, or patients taking other medicinal products that lead to QT prolongation. Therefore, caution should be exercised in patients with cardiac rhythm or conduction disturbances, in patients treated with anti-arrhythmic agents or beta-adrenergic blocking agents and in patients with significant electrolyte disturbances.

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.

Paediatric Population:

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

Oral Lyophilisate only:
Ondansetron formulation contains aspartame and therefore should be taken with caution in patients with phenylketonuria.

Pre-filled Syringe only:
The tip cap of the pre-filled syringe contains dry natural latex rubber that has the potential to cause allergic reactions in latex sensitive individuals.

Tablets only:
Patients with rare hereditary problems of galactose intolerance, Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

CINV

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 (section 5.1).

Ondansetron contains 2.52 mmol (57.6 mg) sodium per maximum daily dose of 32 mg.
This has to be taken into consideration for patients on a controlled sodium diet.

4.5 Interaction with other medicinal products and other forms of interaction

There is no evidence that ondansetron either induces or inhibits the metabolism of other drugs commonly co-administered with it. Specific studies have shown that there are no pharmacokinetic interactions when ondansetron is administered with alcohol, temazepan, 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 (section 4.4).

4.6 Fertility, pregnancy and lactation

Pregnancy
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 (see section 5.3). However as animal studies are not always predictive of human response the use of ondansetron in pregnancy is not recommended.

Lactation
Tests have shown that ondansetron passes into the milk of lactating animals (see section 5.3). 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

Adverse events are listed below by system organ class and frequency. Frequencies are defined as: very common (≥1/10), common (≥1/100 and <1/10), uncommon (≥1/1000 and <1/100), rare (≥1/10,000 and <1/1000) and very rare (<1/10,000) including isolated reports. 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 according to indication and formulation.

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 have been observed without definitive evidence of persistent clinical sequelae.
Rare:	Dizziness during i.v. administration, which in most cases is prevented or resolved by lengthening the infusion period.
Eye disorders	
Rare:	Transient visual disturbances (e.g. blurred vision) during i.v. administration.
Very rare:	Transient blindness predominantly during intravenous administration.
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.	
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. Local burning sensation following insertion of suppositories.
Hepatobiliary disorders	
Uncommon:	Asymptomatic increases in liver function tests#.
#These events were observed commonly in patients receiving chemotherapy with cisplatin.	
General disorders and administration site conditions	
Common:	Local i.v. 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.

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

4.9 Overdose

Symptoms and Signs
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 Undesirable effects*). 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.

Treatment
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.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: antiemetics and antinauseants, serotonin (5HT3) antagonists,
ATC code: A04A A01

Ondansetron is a potent, highly selective 5HT3 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 5HT3 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 5HT3 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/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.

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

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 8mg dose. For doses above 8mg 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. 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).

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 140L. 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 65ng/ml. Following intramuscular administration of ondansetron, peak plasma concentrations of about 25ng/ml are attained within 10 minutes of injection.
Following administration of ondansetron suppository, plasma ondansetron concentrations become detectable between 15 and 60 minutes after dosing. Concentrations rise in an essentially linear fashion, until peak concentrations of 20-30 ng/ml are attained, typically 6 hours after dosing. Plasma concentrations then fall, but at a slower rate than observed following oral dosing due to continued absorption of ondansetron. The absolute bioavailability of ondansetron from the suppository is approximately 60% and is not affected by gender. The half life of the elimination phase following suppository administration is determined by the rate of ondansetron absorption, not systemic clearance and is approximately 6 hours. Females show a small, clinically insignificant, increase in half-life in comparison with males.

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.

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 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.

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 (5.4h). 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.

Elderly
Specific studies in the elderly or patients with renal impairment have been limited to intravenous and oral administration. However, it is anticipated that the half-life of ondansetron after rectal administration in these populations will be similar to that seen in healthy volunteers, since the rate of elimination of ondansetron following rectal administration is not determined by systemic clearance.

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. The pharmacokinetics of ondansetron following administration as a suppository have not been evaluated in patients with hepatic impairment.

5.3 Preclinical safety data

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

Ondansetron and its metabolites accumulate in the milk of rats with a milk:plasma-ratio of 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.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Citric acid monohydrate
Sodium citrate
Sodium chloride
Water for Injections

6.2 Incompatibilities

Gamidarin 2mg/ml Solution for Injection or Infusion should not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf life

Before opening
3 years

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

After dilution of the solution
Chemical and physical in-use stability has been demonstrated for 36 hours at 2-8ºC with the solutions given in section 6.6.
The diluted solutions should be stored protected from light.

From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2 to 8ºC, unless dilution has taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage

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

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

6.5 Nature and contents of container

2 ml type I clear glass ampoules containing 2 ml of solution: pack size of 5 or 25 ampoules.

5 ml type I clear glass ampoules containing 4 ml of solution: pack size of 5 or 25 ampoules.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Compatibility with intravenous fluids: 0.08mg/ml concentration of Ondansetron with each diluents at the storage of 2-8 ºC for 36 hours.The solution must not be sterilised in an autoclave.

The solution is to be visually inspected prior to use (also after dilution). Only clear solutions practically free from particles should be used. Do not use if container is damaged.

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

Gamidarin 2mg/ml Solution for Injection or Infusion should only be mixed with those infusion solutions, which are recommended:

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

Dilutions of Ondansetron in the above mentioned diluents have been demonstrated to be stable in polyvinyl chloride (PVC) infusion bags, Non polyvinyl chloride (Non-PVC) infusion bags, Ph. Eur. Type I glass bottles and polyvinyl chloride (PVC) administration sets.

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.

Compatibility with other drugs:
Gamidarin 2mg/ml Solution for Injection or 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 Gamidarin 2mg/ml Solution for Injection or Infusion giving set for ondansetron concentrations of 16 to 160 micrograms/ml (e.g. 8 mg/500 ml and 8 mg/50 ml respectively);

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

Carboplatin:
Concentrations in the range 0.18 mg/ml to 9.9 mg/ml (e.g. 90 mg in 500 ml to 990 mg in 100 ml), administered over ten minutes to one hour.

Etoposide:
Concentrations in the range 0.14 mg/ml to 0.25 mg/ml (e.g. 72 mg in 500 ml to 250 mg in 1 litres), 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.

7 MARKETING AUTHORISATION HOLDER

Amneal Pharma Europe Limited
70 Sir John Rogerson's Quay
Dublin 2
Ireland

8 MARKETING AUTHORISATION NUMBER

PA1897/005/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of First Authorisation: 6th May 2011

Date of last renewal: 26th September 2013

10 DATE OF REVISION OF THE TEXT

June 2014.