SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT
Ondansetron Vianex

2. QUALITATIVE AND QUANTITATIVE COMPOSITION IN ACTIVE SUBSTANCES

Ondansetron Vianex solution for injection 4 mg/2 ml:
Ampoules containing 4 mg ondansetron (as hydrochloride dihydrate) in 2 ml of aqueous solution for intravenous or intramuscular use.

Ondansetron Vianex solution for injection 8 mg/4 ml:
Ampoules containing 8 mg ondansetron (as hydrochloride dihydrate) in 4 ml of aqueous solution for intravenous or intramuscular use

3. PHARMACEUTICAL FORM

Solution for injection

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Adults
Ondansetron solution for injection is indicated for the management of nausea and vomiting induced by cytotoxic chemotherapy and radiotherapy. Ondansetron solution for injection is also indicated for the prevention and treatment of post-operative nausea and vomiting.

Paediatric Population
Ondansetron is indicated for the management of chemotherapy induced nausea and vomiting in children aged ≥ 6months and for the prevention and treatment of post-operative nausea and vomiting in children aged ≥ 1month.

4.2 Posology and route of administration

Intravenously or intramuscularly.

Chemotherapy and Radiotherapy induced Nausea and Vomiting:

Adults:

The emetogenic potential of cancer treatment varies according to the dosage regimens and combinations used in chemotherapy and radiotherapy.
Ondansetron may be given, except for orally, intramuscularly and intravenously and rectally, thus permitting flexibility in the mode of administration and dosage.

Ondansetron injection dosage ranges from 8-32 mg daily and is selected as shown below.

Mild Emetogenic Chemotherapy and Radiotherapy:
For patients receiving emetogenic chemotherapy or radiotherapy, Ondansetron can be used either orally (as tablets or syrup) or rectally or by intravenous or intramuscular injection.

The recommended dose for oral administration is 8 mg 1-2 hours immediately before treatment.

The recommended dose of Ondansetron suppositories is one suppository 16 mg 1-2 hours before treatment.

Ondansetron recommended intravenous or intramuscular dose is 8 mg by slow intravenous or intramuscular injection immediately before treatment.

To protect against delayed or prolonged vomiting after the first 24 hours, oral treatment with ondansetron 8 mg every 12 hours for up to 5 days should be continued or rectally with one ondansetron suppository 16 mg daily for up to 5 days.

Highly Emetogenic Chemotherapy:
For patients receiving highly emetogenic chemotherapy, e.g. high-dose cisplatin, ondansetron can be used either rectally or by intravenous or intramuscular injection.

The recommended dose for oral administration is 24 mg co-administered with 12 mg of dexamethasone sodium phosphate given orally, 1-2 hours prior to chemotherapy.

A single dose of ondansetron 8 mg can be administered by slow intravenous injection immediately before chemotherapy, followed by two further intravenous or intramuscular doses of 8 mg every 2-4 hours or by continuous intravenous infusion of 1mg/hour for up to 24 hours. Alternatively, 32 mg by intravenous infusion for not less than 15 minutes or 1 suppository 16 mg rectally, 1-2 hours before treatment.

Ondansetron doses higher than 8 mg and up to 32 mg are administered only intravenously, diluted in 50-100 ml of saline or other compatible infusion fluid (see Instructions for Use/ Handling) for not less than 15 minutes.

The selection of the dose regimen should be determined based on the severity of the expected emetogenic response.

The efficacy of Ondansetron in highly emetogenic chemotherapy may be enhanced by the administration of a single intravenous dose of dexamethasone sodium phosphate 20 mg before chemotherapy.

To protect against delayed or prolonged vomiting after the first 24 hours, oral treatment with Ondansetron 8 mg every 12 hours for up to 5 days should be continued or rectally with recommended dose of one ondansetron suppository 16 mg daily for up to 5 days.

Paediatric Population:

Chemotherapy induced nausea and vomiting in children aged ≥ 6 months and adolescents

The dose for chemotherapy induced nausea and vomiting 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 (see 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 chemotherapy induced nausea and vomiting. 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 the adult dose of 32 mg.

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

BSA	Day 1[1,2]	Days 2-6 [2]
< 0.6 m^2	5 mg/m^2 IV plus 2 mg syrup after 12 hrs	2 mg syrup every 12 hrs
≥ 0.6 m^2	5 mg/m^2 IV plus 4 mg syrup or tablet after 12 hrs	4 mg syrup or tablet every 12 hrs

[1] The intravenous dose must not exceed 8 mg.
[2] The total daily dose must not exceed the adult dose of 32 mg.

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

Ondansetron should be administered immediately before chemotherapy as a single intravenous dose of 0.15mg/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 the 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 [1,2]	Days 2-6[2]
≤ 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

[1] The intravenous dose must not exceed 8mg.
[2] The total daily dose must not exceed the adult dose of 32 mg.

The use of ondansetron suppositories in children is not recommended.

Elderly:

Ondansetron is well tolerated by patients over 65 years of age and no modification of dosage, frequency of dosing and route of administration is required.

Post – Operative Nausea and Vomiting

Adults:

For the prevention of post-operative nausea and vomiting, Ondansetron can be administered orally (tablets or syrup) or by intravenous or intramuscular injection.

The recommended dose for oral administration is 16 mg one hour prior to anaesthesia or 8 mg one hour prior to anaesthesia followed by two more doses of 8 mg every 8 hours.

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

For the treatment of established post-operative nausea and vomiting, a single dose of 4 mg given by slow intravenous or intramuscular injection is recommended.

Paediatric population:

Post-operative nausea and vomiting in children aged ≥ 1 month and adolescents
For the prevention of post-operative nausea and vomiting 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 4 mg either prior to or after induction of anaesthesia.

For the treatment of post-operative nausea and vomiting 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 4 mg.

There are no data on the use of Ondansetron in the treatment of post-operative nausea and vomiting in children below 2 years of age.

No studies have been conducted on the use of orally administered Ondansetron in the prevention or treatment of post-operative nausea and vomiting. Slow i.v. infusion is recommended (not less than 15 minutes).

The use of ondansetron suppositories in children is not recommended.

Elderly:

There is limited experience for the use of Ondansetron in the prevention and treatment of post-operative nausea and vomiting in the elderly, however, Ondansetron is well tolerated by patients older than 65 years of age receiving chemotherapy.

Patients with renal failure:

No modification of daily dosage, frequency of dosing or route of administration is required.

Patients with hepatic failure:

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

Patients with poor sparteine/debrisoquine metabolism:

The elimination half-life of Ondansetron is not modified in subjects considered to have poor sparteine and debrisoquine metabolism. Consequently, in such patients repeat dosing will give the same blood levels with those of the general population. No modification of daily dosage and frequency of dosing is required.

4.3 Contraindications

Hypersensitivity to any of the components of the preparation.

4.4 Special Warnings and Precautions for Use

Hypersensitivity reactions have been reported in patients who have shown hypersensitivity to other selective $5HT_3$ receptor antagonists.
Adverse events from the respiratory system should be treated symptomatically and clinicians should pay particular attention to them as these can be precursors of hypersensitivity reactions.

Rarely, transient ECG changes including QT interval prolongation have been reported to patients taking Ondansetron. Furthermore, after marketing, incidents of polymorphic ventricular tachycardia (Torsade de Pointes) have been reported to patients taking Ondansetron. Ondansetron should be carefully administered to patients that have or could develop QTc prolongation. These circumstances include patients with electrolytic disturbances, congenital QT prolongation syndrome or patients that receive other medicines that cause QT prolongation.

As Ondansetron increases large intestine transit time, patients with signs of subacute intestinal obstruction should be monitored following its administration.
In patients with adenotonsillar surgery, the prevention of nausea and vomiting with Ondansetron may mask occult bleeding.

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

4.5 Interactions 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 interactions when ondansetron is administered with alcohol, temazepam, furosemide, alfentanil, tramadol, morphine, lignocaine, thiopental or propofol.

Ondansetron is metabolized by various hepatic enzymes of P-450 cytochrome: CYP3A4, CYP2D6 and CYP1A2. Due to the variability of the metabolic enzymes capable of metabolizing ondansetron, enzyme inhibition or reduced activity of one enzyme (i.e. CYP2D6 genetic deficiency) is usually compensated by other enzymes and should result in little or insignificant change in overall Ondansetron clearance or of the required dose.

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

Tramadol
Data from small studies show that Ondansetron may reduce the analgesic effect of tramadol.

The 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 Pregnancy and Lactation

Pregnancy: Ondansetron has no teratogenic effects on animals. The safe use of Ondansetron during pregnancy has not been established. Evaluation of experimental animal studies does not indicate direct or indirect harmful effects with respect to the foetus development, 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 indicated.

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.

4.7 Effects on Ability to Drive and Use Machines

In psychomotor testing Ondansetron does not impair performance of activities nor causes sedation. No harmful effects in such activities are expected based on Ondansetron pharmacology.

4.8 Undesirable effects

The following undesirable effects are listed below per system organ class and frequency. Frequencies are defined as 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). Very common, common and uncommon events were generally calculated from clinical studies data. Frequency with placebo was also considered. Rare and very rare events were generally calculated from post-marketing spontaneous reports.

The following frequencies were calculated at the usual recommended doses of oondansetron according to the indication and pharmaceutical form.

Immune system disorders
Rare: immediate hypersensitivity reactions sometimes severe, including anaphylaxis.

Nervous system disorders
Very common: headache
Uncommon: epileptic seizures, motor disorders (including extrapyramidal reactions such as dystonic reactions, oculogyric crisis and dyskinesia)[1]
Rare: dizziness during rapid intravenous administration

Eye disorders
Rare: transient visual disorders (e.g. blurred vision) mainly during intravenous administration
Very rare: transient blindness mainly during intravenous administration[2]

Cardiac disorders
Uncommon: arrhythmias, chest pain with or without ST segment depression, bradycardia

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 suppository's administration.

Hepatobiliary disorders
Uncommon: asymptomatic increases in liver function tests[3]

General disorders and administration site conditions
Common: local reactions at the intravenous injection site

[1] They have been observed without definite data of clinical symptoms prolongation.
[2]The majority of blindness reported events recovered within 20 minutes. Most of the patients had received chemotherapeutic agents containing cisplatin. Some cases of transient blindness were reported to be of cortical origin.
[3] These events were frequently observed in patients receiving chemotherapy with cisplatin.

Paediatric population
The undesirable effects profile in children and adolescents was comparable to that seen in adults.

4.9 Overdose

There is limited experience with Ondansetron overdose. In most cases the symptoms were similar to those reported in patients receiving the 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.

Two patients who received an intravenous dose of 84 mg and 145 mg respectively reported only mild undesirable effects, not requiring drastic treatment. There is no specific antidote for

Ondansetron, therefore, in cases of suspected overdose, symptomatic and supportive treatment should be given.
In overdose with ondansetron, the use of ipecac is not indicated, since patients may not respond because of the anti-emetic action of Ondansetron itself.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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.
The role of ondansetron in opiate-induced emesis is not yet established.
Ondansetron does not alter plasma prolactin concentrations.

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. There was no difference in the overall incidence or nature of adverse events between the two treatment groups.

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. There was no difference in the overall incidence or nature of adverse events between the two treatment groups.

The efficacy of ondansetron in 75 children aged 6 to 48 months was investigated in an open-label, non-comparative, single-arm study (S3A40320). All children received three 0.15 mg/kg doses of intravenous ondansetron, administered 30 minutes before the start of chemotherapy and then at 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.

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 1.

Table 1 Prevention and treatment of post-operative nausea and vomiting 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 vomiting	60	47	0.004

CR = no emetic episodes, rescue or withdrawal

5.2 Pharmacokinetic properties

Following oral administration, ondansetron is rapidly absorbed with peak plasma concentrations of 26.2 ng/ml in males and 42.72 ng/ml in females attained approximately 2 and 1.7 hours respectively after a single dose of 8 mg, and absolute bioavailability, following oral

administration, of approximately 56%. Following oral administration of ondansetron at a single dose of 24 mg, peak plasma concentrations of 125.8 ng/ml in males and 194.4 ng/ml in females were observed after about 1.9 and 1.6 hours, respectively.

The mean bioavailability in healthy males after the single administration of an 8 mg tablet is approximately 55 to 60%.

Following ondansetron oral, intramuscular or intravenous administration a similar final half-life of about 3 hours is observed and a stable distribution volume of about 140 l. The intravenous infusion of ondansetron 4 mg results in peak plasma concentrations of about 65 ng/ml within 5 minutes. Systemic exposure following the intramuscular or intravenous administration of ondansetron 4 mg is equivalent.

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 six hours after dosing. Plasma concentrations then fall, but at a slower rate than observed following oral dosing due to continued absorption of ondansetron. The half-life of the elimination phase following suppository administration is determined by the rate of ondansetron absorption, not systemic clearance and is approximately six hours.
Females show a small, clinically insignificant, increase in half-life in comparison with males. The absolute bioavailability of ondansetron from the suppository is approximately 60% and is not affected by gender.

Ondansetron plasma protein binding ranges from 70% to 76%. Ondansetron is cleared from the systemic circulation predominantly by hepatic metabolism through multiple enzymatic pathways. Less than 5% of the dose is excreted unchanged in the urine. The lack of the enzyme CYP2D6 (debrisoquine polymorphism) has no effect on ondansetron pharmacokinetics. Ondansetron pharmacokinetic properties are unchanged on repeat dosing.

Gender
It has been observed that ondansetron disposition is different between the two genders, with females having a greater rate and duration of absorption following an oral dose and reduced systemic clearance and volume of distribution (adjusted to the body weight).

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 based clearance was approximately 30% lower than that in patients aged 5 to 24 months (n=22) but comparable to that in patients aged 3 to 12 years. The half-life in the patient population aged 1 to 4 months was reported to be 6.7 hours on average compared to 2.9 hours for patients in the 5 to 24 months and 3 to 12 years age range. The differences in pharmacokinetic parameters in the 1 to 4 months patient population can be partially explained by the higher percentage of total body water in neonates and infants and the higher volume of distribution for water soluble drugs like ondansetron.
In paediatric patients aged between 3 to 12 years undergoing selective surgery with general anaesthesia, the absolute values for both ondansetron clearance and distribution volume were reduced compared to the values of the adult patients. Both parameters increased in a lineal relation to the weight and by the age of 12 years the values were approaching those of young

adults. When clearance and volume of distribution values normalised with respect to the 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) following oral or IV dosing in children and adolescents was comparable to that of adults, with the exception of infants aged 1 to 4 months. Distribution 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 aged 1 to 4 months or simply an 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 post-operative nausea and vomiting a decreased clearance is not likely to be clinically relevant.

Elderly
Studies in healthy elderly volunteers have shown a slight, but clinically insignificant, increase in ondansetron oral bioavailability (65%) and a half-life of 5 hours.

Renal failure
In patients with moderate renal dysfunction (creatinine clearance > 15 to 60 ml/min), both systemic clearance and distribution volume are reduced, resulting in a slight but clinically insignificant, increase in half-life (5.4 hours).
A study in patients with serious renal failure who had undergone regular haemodialysis (studied between dialyses) showed that ondansetron pharmacokinetics does not change.

Hepatic failure
In patients with serious hepatic failure, systemic clearance is markedly reduced with prolonged half-lives (15 - 32 hours) and oral bioavailability approaches 100% due to reduced pre-systemic metabolism.

5.3 Preclinical safety data

Carcinogenic effects have not been observed in 2-year carcinogenic studies in rats and mice for doses up to 10 and 30mg/kg per day, respectively. Ondansetron has not been mutagenic in mutagenicity tests. Oral administration of ondansetron at doses up to 15mg/kg per day did not affect fertility and reproduction of male and female rats.

Additionally for the solution for injection:
A study in cloned ion channels of human heart showed that ondansetron may affect cardiac repolarization by blocking potassium channels type HERG in clinically related concentrations. In vivo, prolongation of the QT interval in cats anaesthetized following an intravenous injection has been observed, but at doses exceeding 100 times the pharmacological effective ones. Similar effects have been observed in cynomologus monkeys. Transitory changes of ECG have been reported in clinical practice (see section 4.4).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Citric acid monohydrate, Sodium citrate, Sodium chloride, Water for injection.

6.2 Incompatibilities

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

Ondansetron solution for injection should be mixed only with the recommended infusion solutions (see section 6.6).

6.3 Shelf life

36 months

6.4 Special precautions for storage

Should be stored at ≤ 25° C.

6.5 Nature and contents of container

- Carton containing 1 ampoule from amber transparent glass, in a plastic tray with a package insert.
- Carton containing 5 ampoules from amber transparent glass, in a plastic tray with a package insert.

6.6 Instructions for Use/Handling

Ampoules:
Ondansetron injection ampoules should not be placed in autoclaves.

Compatibility with intravenous fluids:
Ondansetron injection should be mixed only with the recommended infusion solutions. In accordance with the good pharmaceutical practice, intravenous solutions should be prepared at the time of infusion. However, it has been demonstrated that ondansetron injection is stable for seven days at room temperature (below 25ºC) under fluorescent light or in refrigerator with the following intravenous solutions for infusion:

Sodium chloride 0.9% w/v for intravenous infusion
Glucose 5% w/v for intravenous infusion
Mannitol 10% w/v for intravenous infusion
Ringer solution for intravenous infusion
Potassium chloride 0.3% w/v and sodium chloride 0.9% w/v for intravenous infusion
Potassium chloride 0.3% w/v and glucose 5% w/v for intravenous infusion

Compatibility studies for ondansetron have been performed in polyvinylchloride infusion bags and administration sets. Adequate stability would also be conferred using polyethylene infusion bags or Type I glass bottles.

Ondansetron solutions in sodium chloride 0.9% w/v or glucose 5% w/v are stable in polypropylene syringes.

It is considered that ondansetron injection when mixed with other compatible infusion fluids is stable in polypropylene syringes.

Note: The product should be maintained under appropriate aseptic conditions when prolongation of storage time is required.

Compatibility with other drugs: Ondansetron can be administered by intravenous infusion at 1mg/hour, from an infusion bag or infusion pump. The following drugs can be administered concomitantly with Ondansetron via a Y-type administration 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) are 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 ranging from 0.18 mg/ml to 9.9 mg/ml (e.g. 90 mg in 500 ml to 990 mg in 100 ml), are administered over 10 minutes to one hour.

Etoposide:
Concentrations ranging from 0.14 mg/ml to 0.25 mg/ml (e.g. 72 mg in 500 ml to 250 mg in 1 litre) are administered over 30 minutes to 1 hour.

Ceftazidime:
Doses ranging from 250 mg to 2000 mg diluted in distilled water for injection, 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 ranging from 100 mg to 1 g diluted in distilled water for injection with 100 mg/5 ml cyclophosphamide, as recommended by the manufacturer, and given as an intravenous bolus injection over approximately five minutes.

Doxorubicin:
Doses ranging from 10-100 mg diluted in distilled water for injection with 10 mg/5 ml 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 a Y-type infusion set in combination with 8 or 32 mg Ondansetron diluted in 50-100 ml of a compatible infusion fluid over approximately 15 minutes.

Compatibility between dexamethasone sodium phosphate and ondansetron has been demonstrated via the administration of the two drugs through the same administration set in concentration of 32 mcg – 2.5 mg/ml for dexamethasone sodium phosphate and 8 mcg – 1 mg/ml for ondansetron.

7. MARKETING AUTHORISATION HOLDER

VIANEX S.A., Tatoiou str., 14671 Nea Erythrea, Greece, Tel.: +30.210.8009111

8. MARKETING AUTHORISATION NUMBER

9. DATE OF FIRST AUTHORISATION / DATE OF RENEWAL

10. DATE OF PARTIAL REVISION OF THE TEXT

4-9-2012