SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

OSETRON 4 mg/2 mL I.V./ I.M. ampoule containing solution for injection

Sterile

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Drug substance:

Each ampoule (2 mL) contains;

5.00 mg of ondansetron hydrochloride dihydrate equivalent to 4 mg ondansetron.

Excipients:

Sodium citrate…….0.5 mg

Sodium chloride…….18.0 mg

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection

Particle free, clear, colorless and odorless solution for injection or infusion

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

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

4.2. Posology and method of administration

Posology /administration frequency and duration

Adults

Chemotherapy and radiotherapy induced nausea and vomiting: Emetogenic potential of cancer treatment depends on the doses of chemotherapy combinations applied and the radiotherapy regimens used. Ondansetron is also available in oral tablet forms which provide application and dosage flexibility. In adults with chemotherapy-induced nausea and vomiting, a low IV dose regimen (0.15 mg / kg three times at 4-hour intervals) may be used. However, the dose of single dose IV ondansetron should not exceed 16 mg due to the risk of QT

prolongation.

Emmetogenic chemotherapy and radiotherapy: Ondansetron can be given by oral or intravenous injection in patients receiving emmetogenic chemotherapy and radiotherapy. A low IV dose regimen (0.15 mg / kg three times at 4-hour intervals) can be used; It is slow intravenous injection just before treatment, but not less than 30 seconds. However, the dose of single dose IV ondansetron should not exceed 16 mg due to the risk of QT prolongation. Oral ondansetron treatment is recommended following the first day of treatment to avoid delayed or prolonged emesis after the first 24 hours.

Highly emetogenic chemotherapy: Patients undergoing high emetogenic chemotherapy, such as high doses of cisplatin, may be used with a low IV dose regimen (0.15 mg / kg three times at 4-hour intervals) immediately before OSETRON chemotherapy. However, the dose of single dose IV ondansetron should not exceed 16 mg due to the risk of QT prolongation. If doses greater than 8 mg are to be given, it should be diluted with 50-100 mL of saline or other infusion fluids and should be given as infusion in not less than 15 minutes.

For administration of highly emetogenic chemotherapy, intravenous injection of 8 mg administered less than 30 seconds not less than chemotherapy or two 8 mg intravenous doses with an interval of 2 to 4 hours following intramuscular injection or up to 24 hours 1 mg/hour continuous infusion. The choice of dosing regimen should be based on the therapeutic potential of the treatment administered (the severity of vomiting and nausea). In extremely emetogenic chemotherapy, the effect of OSETRON may be increased by the addition of a single dose of 20 mg of intravenous dexamethasone sodium phosphate prior to chemotherapy. Oral ondansetron treatment is recommended following the first day of treatment to avoid delayed or prolonged emesis after the first 24 hours.

Postoperative nausea and vomiting: In order to prevent post-operative nausea and vomiting, ondansetron may be given by oral, intramuscular or slow intravenous injection. The recommended dose of OSETRON injection is 4 mg intramuscular or slow intravenous injection in anesthesia induction. In the treatment of started post-operative nausea and vomiting, a single dose of 4 mg intramuscular or slow intravenous injection is administered.

At repeated doses in all adult patients (including the elderly):

- Repeated intravenous doses of ondansetron should be administered at least 4 hours apart.

Adult patients younger than 75 years:

• For the prevention of chemotherapy-induced nausea and vomiting in adults (less than 75 years of age), a single intravenous dose of ondansetron should not exceed **16 mg** (infused over at least 15 minutes).

Method of Administration:

It is administered as intramuscularly or intravenously. (*See also* Section: 6.6).

Additional information on special populations:

Renal impairment:

There is no need to change daily dosage, dosage frequency and route of administration.

Hepatic impairment:

In patients with moderate severe or severe liver dysfunction, OSETRON clearance is significantly reduced and serum half-life is significantly prolonged. In such patients, the total daily dose should not exceed 8 mg.

Pediatric population:

The dose for CINV (nausea and vomiting caused by cytotoxic chemotherapy - from 6 months to 17 years) can be calculated based on body surface area (BSA) or weight. In paediatric clinical studies, ondansetron was given by IV infusion diluted in 25 to 50 mL of serum physiological or other compatible infusion fluid and infused over not less than 15 minutes.

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 dose can be initiated 12 hours later and may be continued for up to 5 days (Table 1). Adult doses should not be exceeded.

Table 1- CINV dose determination according to BSA (from 6 months to 17 years of age)

BSA	**1st Day**	**2-6th Days**
< 0.6 m^2	5 mg / m^2 i.v. + 12 hours later 2 mg syrup	2 mg syrup every 12 hours
≥ 0.6 m^2 and ≤ 1.2 m^2	5 mg / m^2 i.v. + 12 hours later 4 mg syrup or tablet	4 mg syrup or tablet every 12 hours
> 1.2 m^2	5 mg / m^2 i.v. or 8 mg i.v. + 12 hours after 8 mg syrup or tablet	8 mg syrup or tablet every 12 hours

Dosing by body weight

Ondansetron 0.15 mg/kg i.v. should be administered as a single dose just before chemotherapy. I.V. dose should not exceed 8 mg. On the first day, the dose can be given as 2 iv doses with 4 hours interval. Oral dose can be initiated 12 hours later and may be continued for up to 5 days (Table 2). Adult doses should not be exceeded.

Table 2. CINV dose determination based on body weight (from 6 months to 17 years)

Body weight	**1st Day**	**2-6th Days**
≤ 10 kg	Every four hours, up to 3 doses 0.15 mg / kg	2 mg syrup every 12 hours
> 10 kg	Every four hours, up to 3 doses 0.15 mg / kg	4 mg syrup or tablet every 12 hours

Postoperative nausea and vomiting (from 1 month to 17 years of age):

There is no data on the use of ondansetron in the treatment of post-operative nausea and vomiting in children under 2 years of age.

In surgical applications under general anesthesia to prevent post-operative nausea and vomiting in pediatric patients, ondansetron may be administered as a slow iv injection (not less than 30 seconds) up to a maximum of 4 mg at a dose of 0.1 mg / kg or before or after surgery.

Geriatric population:

Emmetogenic chemotherapy and radiotherapy:

Preparation and application of dilution in elderly patients aged 65 and over:

- All intravenous doses should be diluted in 50-100 mL of saline or other compatible liquid and infused over at least 15 minutes.

Elderly patients 75 years and older:

- For the prevention of chemotherapy-induced nausea and vomiting, a single intravenous dose of ondansetron should not exceed **8 mg** (infused over at least 15 minutes).

Postoperative nausea and vomiting:

There are limited studies on the use of ondansetron in the prevention and treatment of post-operative nausea and vomiting in the elderly.

Other:

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 change in daily dosage is required.

4.3. Contraindications

Should not be used in case of hypersensitivity to any of the substances in the composition of the drug product (see Section 6.1).

Concomitant use of ondansetron with apomorphine hydrochloride is contraindicated due to severe hypotension and loss of consciousness (see Section 4.5).

4.4. Special warnings and precautions for use

Hypersensitivity reactions have been reported in patients who have exhibited hypersensitivity to other selective 5-HT_3 receptor antagonists. Respiratory reactions should be treated symptomatically and clinicians should pay special attention to these reactions 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 QT, including patients with electrolyte abnormalities, congestive heart failure, bradyarrhythmias or patients taking other medicinal products that lead to QT prolongation or electrolyte abnormalities.

Hypokalaemia and hypomagnesaemia should be corrected prior to ondansetron administration.

Serotonin syndrome (including altered mental status, autonomic instability and neuromuscular abnormalities) has been described following concomitant use of ondansetron and other serotonergic drugs (including selective serotonin reuptake inhibitors (SSRIs) and serotonin noradrenaline reuptake inhibitors (SNRIs)) (*see Interactions*). Close monitoring of patients is recommended when concomitant therapy with ondansetron and other serotonergic drugs is clinically necessary.

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

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.

Pediatric Population:

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

Chemotherapy-induced nausea and vomiting (CINV): The dose is calculated on a mg/kg basis and when administering three doses 4 hours apart, the total daily dose will be higher compared to a single dose of 5 mg/m^2 followed by an oral dose. The comparative efficacy of these two different dosing regimens has not been studied in clinical studies. Inter-study comparison shows similar efficacy for the two regimens (see section 5.1).

Contains less than 1 mmol sodium (23 mg) per each dose; no side effects related to sodium is expected in that dose.

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 interactions when ondansetron is administered with alcohol, temazepam, furosemide, tramadol, alfentanil, morphine, lidocaine, thiopental and propofol pharmacokinetically.

Ondansetron is metabolised by multiple hepatic cytochrome P-450 enzymes: CYP3A4, CYP2D6 and CYP1A2. Due to the multiplicity of metabolic enzymes capable of metabolising ondansetron, enzyme inhibition or reduced activity of one enzyme (e.g. CYP2D6 genetic deficiency) is normally compensated by other enzymes and should result in little or no significant change in overall ondansetron clearance or dose requirement.

Caution should be exercised when ondansetron is coadministered with drugs that prolong the QT interval and/or cause electrolyte abnormalities. (See section 4.4)

Concomitant use of OSETRON and drugs that cause QT prolongation contributes to QT prolongation. Concomitant use of cardiotoxic drugs (e.g., anthracyclines such as doxorubicin and daunorubicin or trastuzumab), antibiotics (e.g., erythromycin), antifungals (e.g., ketaconazole), antiarrhythmics (e.g., amiodarone) and beta-blockers (e.g., atenolol or timolol) with OSETRON may increase the risk (see section 4.4).

Serotonergic Drugs (eg SSRIs and SNRIs)

Serotonin syndrome (altered mood, autonomic instability, and neuromuscular abnormalities) has been described following concomitant ondansetron and other serotonergic drugs, including selective serotonin reuptake inhibitors (SSRIs) and serotonin noradrenaline reuptake inhibitors (SNRIs) (see Section 4.4).

Apomorphine

Concomitant use of ondansetron with apomorphine hydrochloride is contraindicated due to reports of severe hypotension and loss of consciousness.

Phenytoin, Carbamazepine and Rifampicin

In patients treated with potent inducers of CYP3A4 (e.g., 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.

Additional information for special populations

There is no information.

Pediatric population

There is no information.

4.6 Pregnancy and lactation

General advice

Pregnancy category

In the 1st trimester of pregnancy: D

In the 2nd and 3rd trimester of pregnancy: B

Women with child-bearing potential / Contraception

Pregnancy test:

Pregnancy status should be confirmed in women of childbearing potential before starting ondansetron therapy.

Contraception:

Women of reproductive potential should be informed that ondansetron may harm the developing fetus. It is recommended that sexually active women of reproductive potential use effective contraception (methods that result in a pregnancy rate of less than 1%) during treatment and for two days after stopping treatment with ondansetron.

Pregnancy

Based on human experience from epidemiological studies, ondansetron is suspected to cause orofacial malformations when used during the first trimester of pregnancy.

In a cohort study of 1.8 million pregnancies, first trimester use of ondansetron was

associated with an increased risk of oral cleft (3 additional cases per 10,000 women treated; adjusted relative risk 1.24 (95% CI 1.03-1.48)).

Existing epidemiological studies of cardiac malformations have shown conflicting results.

Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity.

Ondansetron should not be used during the first trimester of pregnancy. The use of ondansetron is not recommended during the second and third trimesters of pregnancy.
Reproduction studies in rats and rabbits showed no evidence of fetal harm (see section 4.6).

Human Data

Three epidemiological studies conducted in the USA evaluated the risks of specific congenital anomalies, including orofacial clefts and cardiac malformations, in infants of mothers exposed to ondansetron during the first trimester of pregnancy.
In a cohort study of 88,467 pregnant women exposed to ondansetron, there was no significant increase in risk of oral clefts (3 additional cases per 10,000 women treated, adjusted relative risk (RR) 1.24 (95% CI 1.03 to 1.48) without a significant increase in cardiac malformations. A separately published subgroup analysis of 23,877 pregnant women exposed to ondansetron intravenously found no increased risk of oral clefts or cardiac malformations.

In a case-control study using population-based birth defects registries of 23,200 cases from the two datasets, an increased risk of cleft palate was demonstrated in one dataset while no increased risk was demonstrated in the other dataset. The risk of cardiac malformation was not increased in this study.
A second cohort study of 3,733 pregnant women exposed to ondansetron found an increased risk of ventricular septal defects with an adjusted RR of 1.7 (95% CI 1.0 to 2.9) but no statistically significant increase in cardiac malformation risk.

Animal Data

In embryo-foetal development studies in rats and rabbits, oral doses of ondansetron up to 15 mg/kg/day and 30 mg/kg/day were administered to pregnant animals during organogenesis, respectively. Apart from a slight decrease in maternal body weight gain in rabbits, ondansetron had no significant effects on the development of maternal animals or offspring. The maternal dose at 15 mg/kg/day in rats and 30 mg/kg/day in rabbits was approximately 6 and 24 times the maximum recommended human oral dose of 24 mg/day,

respectively, based on body surface area. In the pre and postnatal developmental toxicity study, pregnant rats were given oral ondansetron at 15 mg/kg/day from the 17th day of pregnancy to the 21st day of calving. Except for a slight decrease in maternal body weight, pregnant rats and the mated F1 generation had no effect on the pre and postnatal development of the offspring, including reproductive performance. The maternal dose of 15 mg/kg/day in rats was approximately 6 times the maximum recommended human oral dose of 24 mg/day based on BSA.

Lactation

It is not known whether ondansetron passes into breast milk. There are no data on the effects of ondansetron on the breastfed child or the effects of ondansetron on milk production. However, ondansetron has been shown to pass into the milk of lactating animals (rats). Therefore, mothers taking ondansetron should not breastfeed their infants.

Fertility

There is no information on the effects of ondansetron on human fertility.

4.7 Effects on ability to drive and use machines

In psychomotor testing ondansetron does not impair performance nor cause sedation. No detrimental effects on such activities are predicted from the pharmacology of ondansetron.

4.8 Undesirable effects

Frequency class is as follows:

Very common ≥1/10, Common ≥1/100 to <1/10, Uncommon ≥1000 and <1/100, Rare ≥1/10000 and < 1/1000, Very rare <1/10000, Unknown (It can not be estimated from the available data).

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 have been calculated at the standard recommended doses of ondansetron according to indication and formulation. The adverse event profiles in children and adolescents were comparable to that seen in adults.

Immune system disorders

Rare: Immediate hypersensitivity reactions sometimes severe, including anaphylaxis.

Nervous system disorders

Very common:	Headache.
Uncommon:	Seizures, movement disorders (including extrapyramidal reactions such as dystonic reactions, ocular-toxic crises and dyskinesia without persistent clinical sequelae)[1]
Rare:	Dizziness seen throughout rapid iv administration (in many cases, the infusion time is extended or prevented)

Eye disorders

Rare:	Transient visual disturbances (*e.g.*, blurred vision) predominantly during intravenous administration.
Very rare:	Transient blindness predominantly during intravenous ondansetron administration.[2]

Cardiac disorders

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

Vascular disorders

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

Respiratory, thoracic and mediastinal disorders

Uncommon:	Hiccups.

Gastrointestinal disorders

Common:	Constipation.

Hepatobiliary disorders

Uncommon:	Asymptomatic increases in liver function tests[3]

Skin and subcutaneous tissue diseases

Very rare:	Toxic skin rash including toxic epidermal necrolysis

General disorders and administration site conditions

Common: Local I.V. injection site reactions.

1. It has been observed without stable evidence in the direction of persistent clinical sequelae.

2. Most of the reported cases of blindness disappeared within the first 20 minutes. Most patients have previously received chemotherapy agents, including cisplatin. It has been reported that some cases of temporary blindness are cortical in origin.

3. These phenomena have been widely observed in patients undergoing chemotherapy with cisplatin.

Reporting of suspected adverse reactions

If you get any side effects not listed in this leaflet, talk to your doctor or pharmacist. You can also report side effects directly to your doctor or pharmacist. You can also report side effects directly to your country's related health authority. By reporting side effects, you can help provide more information on the safety of this medicine.

4.9 Overdose

Symptoms and Signs

There is limited information available on an overdose of ondansetron. In the vast majority of cases, symptoms are similar to those reported in patients receiving the recommended doses (see section 4.8). Symptoms including blurred vision, severe constipation, hypotension and transient second-degree AV block vasovagal event have been reported.

Onasetron prolongs the QT interval in a dose-dependent manner. In case of overdose, monitoring with ECG is recommended.

Cases consistent with serotonin syndrome have been reported after oral overdose in young children.

Treatment

There is no specific antidote for ondansetron, therefore, in all cases of suspected overdose, symptomatic and supportive treatment should be given as appropriate.

Additional treatment should be as recommended by the national poison center where clinical situation warrants or where available.

In an overdose with ondansetron, the use of golden root is not recommended as patients are unlikely to respond due to the anti-emetic effect of ondansetron.

Pediatric population

Pediatric cases consistent with serotonin syndrome have been reported after accidental oral ondansetron overdoses (over 4 mg/kg estimated intake) in infants and children aged 12 months to 2 years.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic grup: Antiemetics and anti-nausea drugs, Selective $5HT_3$ receptor antagonist

ATC code: A04AA01

Ondansetron; It is a potent, highly selective 5-HT_3 receptor antagonist. The mechanism of action in controlling vomiting and nausea is not fully known.

Chemotherapeutic agents and radiotherapy may cause release of 5HT in the small intestine initiating a vomiting reflex by activating vagal afferents via 5-HT_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 5-HT_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 has not yet been established.

QT Prolongation

The effect of ondansetron on the QTc interval was evaluated in a double blind, randomised, placebo and positive (moxifloxacin) controlled, crossover study in 58 healthy adult men and women. Ondansetron doses included 8 mg and 32 mg infused intravenously over 15 minutes. At the highest tested dose of 32 mg, the maximum mean (upper limit of 90% CI) difference in QTcF from placebo after baseline-correction was 19.6 (21.5) msec. At the lower tested dose of 8 mg, the maximum mean (upper limit of 90% CI) difference in QTcF from placebo after baseline-correction was 5.8 (7.8) msec. In this study, there were no QTcF measurements greater than 480 msec and no QTcF prolongation was greater than 60 msec.

Clinical Trials
Pediatric population

KNBK

The efficacy of ondansetron in controlling nausea and vomiting induced by cancer chemotherapy was evaluated in a double-blind, randomized study in 415 patients aged 1 to 18 years (S3AB3006). On the day of chemotherapy, patients received either ondansetron 5 mg/m2 I.V. and ondansetron 4 mg orally 8 to 12 hours later, or ondansetron 0.45 mg/kg I.V. and placebo orally 8 to 12 hours later. After chemotherapy, both groups used 4 mg of ondansetron syrup twice a day for 3 days. Complete control of vomiting on the worst day of chemotherapy was 49% (5 mg/m2 IV and 4 mg oral ondansetron) and 41% (0.45 mg/kg IV and oral placebo). After chemotherapy, both groups used 4 mg of ondansetron syrup twice a day for 3 days. There was no difference in the overall incidence or nature of adverse events between the two treatment groups.

A double-blind randomized placebo-controlled study (S3AB4003) in 438 patients aged 1 to 17 years showed complete control of vomiting on the worst day of chemotherapy at the following rates:

- 73% of patients when ondansetron was administered intravenously at a dose of 5 mg/m2 with 2 to 4 mg oral dexamethasone.
- 71% of patients when ondansetron was administered as a syrup at a dose of 8 mg in combination with 2 to 4 mg of oral dexamethasone on chemotherapy days.

After chemotherapy, both groups received 4 mg of ondansetron syrup twice a day for 2 days. There was no difference in the incidence or nature of adverse events between the two treatment groups.

The efficacy of ondansetron in 75 children 6 to 48 months of age was investigated in an open-label, non-comparative, single-arm study (S3A40320). All children received three doses of ondansetron, 0.15 mg/kg, administered I.V. at 30 minutes before starting chemotherapy and again 4 and 8 hours after the first dose. Complete control of vomiting was achieved in 56% of patients.

Another open-label, non-comparative, single-arm study (S3A239) investigated the efficacy of an IV dose of 0.15 mg/kg followed by two doses of ondansetron 4 mg for children <12 years old and 8 mg orally for children ≥12 years old. (Total number of children n = 28). Complete control of vomiting was achieved in 42% of patients.

Postoperative nausea and vomiting

The efficacy of a single dose of ondansetron in the prevention of postoperative nausea and

vomiting was investigated in a randomized, double-blind, placebo-controlled study in 670 children aged 1 to 24 months (age ≥44 weeks after cognition, weight ≥3 kg). Included volunteers were scheduled for elective surgery under general anesthesia and had an ASA status of ≤III. A single dose of 0.1 mg/kg ondansetron was administered within five minutes of initiation of anaesthesia. The proportion of subjects experiencing at least one episode of vomiting during the 24-hour evaluation period (ITT) was higher in placebo users than in ondansetron (28% vs. 11%, p<0.0001).

Four double-blind, placebo-controlled studies were conducted in 1469 male and female patients (2 to 12 years) undergoing general anesthesia. Patients were randomized to either single doses of ondansetron (0.1 mg/kg for pediatric patients weighing 40 kg or less, 4 mg for pediatric patients greater than 40 kg; number of patients = 735) or placebo (number of patients = 734). has been done. Study drug was administered immediately before or after the initiation of anesthesia for at least 30 seconds. ondansetron was significantly more effective than placebo in preventing nausea and vomiting. The findings of these studies are summarized in Table 3.

Table 3 Prevention and treatment of postoperative nausea and vomiting in pediatric patients – 24-hour treatment response

Study	End point	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 = episodes of vomiting do not include recovery or discontinuation of therapy.

5.2 Pharmacokinetic properties

General properties

Absorption

Systemic exposure levels after intramuscular or intravenous administration of ondansetron are equivalent.

After oral administration, ondansetron is passively and completely absorbed from the gastrointestinal tract and is subject to first pass metabolism. Peak plasma concentrations of approximately 30 ng/mL are achieved approximately 1.5 hours after an 8 mg dose. For doses above 8 mg, the increase in the systemic exposure of ondansetron with dose is greater than proportional; this may indicate some reduction in first pass metabolism at higher oral doses.

The mean bioavailability following oral administration of 8 mg tablets in healthy volunteers is approximately 55% to 60%. Bioavailability is slightly increased with food after oral administration but is not affected by antacid drugs. Studies in healthy elderly volunteers have shown mild but clinically significant age-related increases in both the bioavailability (65%) and half-life (5 hours) of ondansetron.

Distribution:

The disposition of ondansetron after oral, intravenous, and intramuscular doses is similar, with a terminal half-life of approximately 3 hours and a steady-state volume of distribution of approximately 140 L. Equivalent systemic exposure is achieved after intramuscular and intravenous administration of ondansetron.

4 mg intravenous infusion of ondansetron given over 5 minutes yields peak plasma concentrations of approximately 65 ng/mL. Following intramuscular administration of ondansetron, peak plasma concentrations of approximately 25 ng/mL are achieved within 10 minutes of injection.

Biotransformation:

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.

Elimination:

Ondansetron does not bind to protein at a high rate (70-76%). Ondansetron is cleared from the systemic circulation through multiple enzymatic pathways mainly through hepatic metabolism. Less than 5% of the absorbed dose is excreted unchanged in the urine. The absence of the CYP2D6 enzyme (debrisokuin polymorphism) does not affect the pharmacokinetics of ondansetron. The pharmacokinetic properties of ondansetron do not change with repeated doses.

Linearity/Nonlinearity:

No application

Characteristics of patients

Gender

Gender differences have been shown in the distribution of ondansetron, and absorption is faster and more abundant after oral dosing in women; systemic clearance and volume of distribution (adjusted for weight) are small.

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 depends on weight but is not dependent on age, except in infants 1 to 4 months old. It is difficult to conclude whether there is an additional reduction in clearance due to age in infants 1 to 4 months of age, or whether there is a natural variability due to the small number of individuals. Since patients younger than 6 months of age will only receive a single dose of ondansetron in PSNV (post-surgery nausea and vomiting), clinically relevant low clearance is unlikely.

Elderly:

Early Phase I studies conducted on healthy elderly volunteers showed some age-related decrease in clearance and an increase in the half-life of ondansetron. However, volunteers were selected from different age groups: Younger (<65 years) and elderly volunteers (age≥65 years) have resulted in a conflict between the pharmacokinetic parameters remarkable,

whether KNBK recorded in clinical studies, young and old, efficiency or safety in patients with cancer in support of the proposal for the application of a different dose in the elderly, overall differences were observed.

Based on more up-to-date ondansetron plasma concentrations and exposure-response modeling, a greater effect on QTcF is predicted in patients ≥75 years of age compared to young adults. specific dose administration information for intravenous dosing is provided for patients aged 65 years and over 75 years (see section on Intravenous dosing). Section 4.2 – Nausea and Vomiting Induced by Chemotherapy and Radiotherapy Section - The Elderly)..

Renal impairment

In patients with renal insufficiency (creatinine clearance 15-60 mL/min), the use of ondansetron i.v. after its administration, both systemic clearance and volume of distribution decrease, resulting in a slight but not clinically significant increase in the elimination half-life (5.4 hours). A study conducted with patients with severe renal impairment requiring regular hemodialysis (interdialysis study) shows that the pharmacokinetics of decansetron does not fundamentally change after intravenous administration.

Hepatic impairment

In patients with severe hepatic impairment, oral, intravenous, or intramuscular administration, the systemic clearance of administered after prolonged elimination half-life (15-32 hours) and pre-systemic metabolism due to nearly 100% with oral bioavailability is significantly reduced.

5.3 Preclinical safety data

In a study on transcribed human cardiac ion channels, ondansetron has been shown to have the potential to affect cardiac repolarization by blocking hERG potassium channels at clinically relevant concentrations. Dose-dependent QT prolongation was observed in a comprehensive QT study conducted in human volunteers. *(See, Section 5.1-QT prolongation).*

Reproductive toxicity:

See. Section 4.6

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Citric acid monohydrate

Sodium citrate

Sodium chloride

Sodium hydroxide

Water for injection

6.2 Incompatibilities

Ondansetron injection should not be administered in the same syringe or infusion as any other medication.

Ondansetron injection should only be mixed with those infusion solutions that are recommended.

6.3 Shelf life

24 months

6.4 Special precautions for storage

Store at room temperature below 25 ° C.

The prepared solution should be used immediately.

6.5 Nature and contents of container

2 mL x 1 amber colored type I glass autopul ampoule in carton box

6.6 Special precautions for disposal

Unused products or waste materials must be disposed of in accordance with the "Medical Waste Control Regulation" and "Packaging and Packaging Waste Control Regulation".

Special preparation instructions

Ampoule formulations are not protected and have to be used only once, have to be injected or diluted immediately after opening, holded solutions have to be discarded.

Ampoules containing Ondansetron injection should not be autoclaved.

Compatibility with intravenous solutions: Ondansetron injection should be mixed with only recommended infusion solutions. In keeping with good pharmaceutical practice dilutions of Ondansetron injection in intravenous solutions should be prepared at the time of infusion. In addition, ondansetron injection has been shown to be stable for 7 days at room temperature (below 25 °C), under fluorescent light, or in a cooler with the following intravenous infusion solutions:

Sodium Chloride Intravenous Infusion BP 0.9% w/v,

Glucose Intravenous Infusion BP 5% w/v,

Mannitol Intravenous Infusion BP 10% w/v,

Ringers Intravenous Infusion
Potassium Chloride 0.3% w/v and Sodium Chloride 0.9% w/v Intravenous Infusion BP,
Potassium Chloride 0.2% w/v and Glucose 5% w/v Intravenous Infusion BP.

Compatibility studies have been undertaken in polyvinyl chloride infusion bags and polyvinyl chloride administration sets. It is considered that adequate stability would also be conferred by the use of polyethylene infusion bags or Type 1 glass bottles. Dilutions of Ondansetron in sodium chloride 0.9%w/v or in glucose 5%w/v have been demonstrated to be stable in polypropylene syringes. It is considered that Ondansetron injection diluted with other compatible infusion solutions would be stable in polypropylene syringes.
Note: If it is desired to store injectable mixtures of infusion solutions with OSETRON for a long time after preparation, mixing should be carried out under appropriate aseptic conditions.

Compatibility with other drugs: Ondansetron may be administered by intravenous infusion at 1 mg/hour, e.g. from an infusion bag or syringe pump. The following drugs may be administered via the Y-site of the ondansetron giving set for ondansetron concentrations of 16 to 160 micrograms/mL (e.g. 8 mg/500 mL and 8 mg/50 mL respectively);
-*Cisplatin:* Concentrations up to 0.48 mg/mL (e.g. 240 mg in 500 mL) administered over 1 to 8 hours.
-*5-Fluorouracil:* Concentrations up to 0.8 mg/mL (e.g. 2.4 g in 3 litres or 400 mg in 500 mL) administered at a rate of at least 20 mL per hour (500 mL per 24 hours). Higher concentrations of 5-fluorouracil may cause precipitation of ondansetron. The 5-fluorouracil infusion may contain up to 0.045% w/v magnesium chloride in addition to other excipients shown to be compatible.
-*Carboplatin:* Concentrations in the range 0.18 mg/mL to 9.9 mg/mL (e.g. 90 mg in 500 mL to 990 mg in 100 mL), administered over ten minutes to one hour.
-*Etoposide:* Concentrations in the range 0.144 mg/mL to 0.25 mg/mL (e.g. 72 mg in 500 mL to 250 mg in 1 litre), administered over thirty minutes to one hour.
-*Ceftazidime:* Doses in the range 250 mg to 2000 mg reconstituted with Water for Injections BP as recommended by the manufacturer (e.g. 2.5 mL for 250 mg and 10 mL for 2 g ceftazidime) and given as an intravenous bolus injection over approximately five minutes.
-*Cyclophosphamide:* Doses in the range 100 mg to 1 g, reconstituted with Water for Injections BP, 5 ml per 100 mg cyclophosphamide, as recommended by the manufacturer and given as an intravenous bolus injection over approximately five minutes.
-*Doxorubicin:* Doses in the range 10-100 mg reconstituted with Water for Injections BP, 5 ml

per 10 mg doxorubicin, as recommended by the manufacturer and given as an intravenous bolus injection over approximately 5 minutes.

-*Dexamethasone:* Dexamethasone sodium phosphate 20 mg may be administered as a slow intravenous injection over 2-5 minutes via the Y-site of an infusion set delivering 8 or 16 mg of ondansetron diluted in 50-100 mL of a compatible infusion fluid over approximately 15 minutes. Compatibility between dexamethasone sodium phosphate and ondansetron has been demonstrated supporting administration of these drugs through the same giving set resulting in concentrations in line of 32 microgram - 2.5 mg/mL for dexamethasone sodium phosphate and 8 microgram – 1 mg/mL for ondansetron.

Ampoule opening instructions

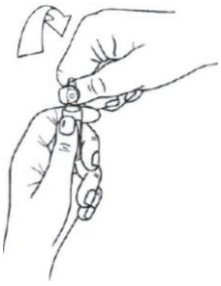
The ampoules are equipped with OPC (One Point Cut) opening system and must be opened according to the following instructions:

• Hold the ampoule at the bottom as shown in figure 1.

• Press on the top of the ring line on the ampoule with the thumb of the other hand as shown in Figure 2.

Figure 1

Figure 2



7. MARKETING AUTHORISATION HOLDER

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