

Prescribing Information

For the use of Registered Medical Practitioner,
Hospital or a Laboratory Only

TROYSETRON

Ondansetron Injection BP 2mg/mL

COMPOSITION:

Each mL contains:
Ondansetron Hydrochloride Dihydrate BP
Eq. to Ondansetron 2 mg.

DESCRIPTION:

TROYSETRON Ondansetron Injection BP 2 mg/mL (2 mL ampoules) is a clear, colourless solution filled in 2 mL flint ampoule with yellow OPC & yellow ring & Ondansetron Injection BP 2 mg/mL (5mL ampoules having 4 mL fill volume) is a clear, colourless solution filled in 5 mL flint ampoule with pink OPC & pink ring Packed in carton. 5 ampoules are packed in U type plastic Ampoule tray along with package information leaflet.

DESCRIPTION OF THE PRODUCT AFTER DILUTION:

Clear colourless solution, free from visible particle.

INDICATIONS:

Adults:
Ondansetron injection is indicated for the management of nausea and vomiting induced by cytotoxic chemotherapy and radiotherapy.
Ondansetron injection is also indicated for the prevention and treatment of post-operative nausea and vomiting.
Paediatric Population:
Injection formulations
Ondansetron is indicated for the management of nausea and vomiting induced by cytotoxic chemotherapy.
No studies have been conducted on the use of orally administered ondansetron in the prevention or treatment of post-operative nausea and vomiting; IV injection is recommended for this purpose.

ROUTE OF ADMINISTRATION:

For Intramuscular route and Intravenous route.

RECOMMENDED DOSE:

Dosage regimen

CHEMOTHERAPY AND RADIOTHERAPY INDUCED NAUSEA AND VOMITING (CINV and RINV)

The emetogenic potential of cancer treatment varies according to the doses and combinations of chemotherapy and radiotherapy regimens used. The selection of dose regimen should be determined by the severity of the emetogenic challenge.

CINV and RINV in Adults

The recommended intravenous (IV) or intramuscular (IM) dose of TROYSETRON is 8 mg administered immediately before treatment. For highly emetogenic chemotherapy, a maximum initial ondansetron dose of 16 mg IV infused over 15 minutes may be used. A single IV dose greater than 16 mg should not be given. The efficacy of ondansetron in highly emetogenic chemotherapy may be enhanced by the addition of a single IV dose of dexamethasone sodium phosphate 20 mg, administered prior to chemotherapy. IV doses greater than 8 mg and up to a maximum of 16 mg must be diluted in 50 mL to 100 mL of 0.9% Sodium Chloride Injection or 5% Dextrose Injection before administration and infused over not less than 15 minutes (see section INSTRUCTIONS FOR USE). Ondansetron doses of 8 mg or less, do not need to be diluted and may be administered as a slow IM or IV injection in not less than 30 seconds. The initial dose of ondansetron may be followed by 2 additional IV or IM doses of 8 mg by 2 to 4 hours apart, or by a constant infusion of 1 mg/h for up to 24 hours. Oral treatment is recommended to protect against delayed or prolonged emesis after the first 24 hours.

CINV in Children and Adolescents (aged 3 years to 17 years)

The dose for CINV 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 saline or other compatible infusion fluid (see section INSTRUCTIONS FOR USE) and infused over not less than 15 minutes.

Dosing by BSA

Ondansetron should be administered immediately before chemotherapy as a single IV dose of 5 mg/m². The IV dose must not exceed 8 mg. Oral dosing can commence 12 hours later and may be continued for up to 5 days (Table 1). Adult doses must not be exceeded.

Table 1 BSA-based dosing for CINV (aged 3 years to 17 years)

BSA	Day 1	Days 2 - 6
≥ 0.6 m ² to ≤ 1.2 m ²	5 mg/m ² IV plus 4 mg tablet every 12 hours	4 mg tablet after 12 hours
> 1.2 m ²	5 mg/m ² IV or 8 mg IV plus 8 mg tablet after 12 hours	8 mg tablet every 12 hours

Dosing by body weight

Ondansetron should be administered immediately before chemotherapy as a single IV dose of 0.15 mg/kg. The IV dose must not exceed 8 mg. On Day 1, two further IV doses may be given in 4-hourly intervals. Oral dosing can commence 12 hours later and may be continued for up to 5 days (Table 2). Adult doses must not be exceeded.

Table 2 Weight-based dosing for CINV (aged 3 years to 17 years)

Body Weight	Day 1	Days 2 - 6
> 10 kg	Up to 3 doses of 0.15 mg/kg IV every 4 hours	4 mg tablet every 12 hours

There are no dosing recommendations for children with BSA <0.6 m², body weight <10 kg or who are unable to swallow tablets.

CINV and RINV in Elderly

Ondansetron is well tolerated by patients over 65 years of age.
In patients 65 years of age or older, all IV doses should be diluted and infused over 15 minutes and, if repeated, given no less than 4 hours apart.

In patients 65 to 74 years of age, the initial IV dose of ondansetron 8 mg or 16 mg, infused over 15 minutes, may be followed by 2 doses of 8 mg infused over 15 minutes and given no less than 4 hours apart. In patients 75 years of age or older, the initial IV dose of ondansetron should not exceed 8 mg infused over 15 minutes. The initial dose of 8 mg may be followed by 2 doses of 8 mg, infused over 15 minutes and given no less than 4 hours apart.

POST-OPERATIVE NAUSEA AND VOMITING (PONV)

PONV in Adults

For prevention of post-operative nausea and vomiting, the recommended dose of ondansetron injection is a single dose of 4 mg by IM or slow IV injection administered at the induction of anaesthesia.
For treatment of established post-operative nausea and vomiting, a single dose of 4 mg given by IM or slow IV injection is recommended.

PONV in Children and Adolescents (aged 3 years to 17 years)

For prevention and treatment of PONV in paediatric patients having surgery performed under general anaesthesia, ondansetron may be administered by slow IV injection (not less than 30 seconds) at a dose of 0.1 mg/kg up to a maximum of 4 mg either prior to, at or after induction of anaesthesia, or after surgery.

PONV in Elderly

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

Special populations

Renal impairment

No alteration of daily dosage or frequency of dosing, or route of administration are required.

Hepatic impairment

Clearance of ondansetron is significantly reduced and serum half-life significantly prolonged in subjects with moderate or severe impairment of hepatic function. In such patients, a total daily dose of 8 mg IV or oral 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.

CONTRAINDICATION:

Hypersensitivity to the active substance or to any of the excipients
Concomitant use with Apomorphine is contraindicated.

WARNING AND PRECAUTIONS FOR USE:

Hypersensitivity reactions have been reported in patients who have exhibited hypersensitivity to other selective 5HT₃ receptor antagonists.
Respiratory events should be treated symptomatically and clinicians should pay particular attention to them as precursors of hypersensitivity reactions.

Ondansetron prolongs the QT interval in a dose-dependent manner. In addition, post-marketing cases of Torsade de Pointes have been reported in patients using ondansetron. Avoid ondansetron in patients with congenital long QT syndrome. Ondansetron should be administered with caution to patients who have or may develop prolongation of QTc, 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.

There have been post-marketing reports describing patients with serotonin syndrome (including altered mental status, autonomic instability and neuromuscular abnormalities) following the concomitant use of ondansetron and other serotonergic drugs (including selective serotonin reuptake inhibitors (SSRI) and serotonin noradrenaline reuptake inhibitors (SNRIs). If concomitant treatment with ondansetron and other serotonergic drugs is clinically warranted, appropriate observation of the patient is advised.
As ondansetron is known to increase large bowel transit time, patients with signs of sub-acute 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.

TROYSETRON Injection contains less than 1 mmol sodium (23 mg) per dose, i.e. essentially “sodium-free”.

Paediatric Population

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

CINV: When calculating the dose on an mg/kg basis and administering three doses at 4-hour intervals, the total daily dose will be higher than if one single dose of 5 mg/m² 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.

INTERACTION OF OTHER MEDICAMENTS:

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, lidocaine, thiopental, 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.

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

Use of ondansetron with QT prolonging drugs may result in additional QT prolongation. Concomitant use of ondansetron with cardiotoxic drugs (e.g. anthracyclines (such as doxorubicin, daunorubicin) or trastuzumab), antibiotics (such as erythromycin), antifungals (such as ketoconazole), antiarrhythmics (such as amiodarone) and beta blockers (such as atenolol or timolol) may increase the risk of arrhythmias.

Serotonergic Drugs (e.g. SSRIs and SNRIs): There have been post-marketing reports describing patients with serotonin syndrome (including altered mental status, autonomic instability and neuromuscular abnormalities) following the concomitant use of ondansetron and other serotonergic drugs (including SSRIs and SNRIs).

Apomorphine: Based on reports of profound hypotension and loss of consciousness when

ondansetron was administered with apomorphine hydrochloride, concomitant use with apomorphine is contraindicated.

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

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

PREGNANCY AND LACTATION:

Pregnancy

The use of ondansetron in pregnancy is not recommended.

In human epidemiological studies, an increase in orofacial clefts was observed in infants of women administered ondansetron during the first trimester of pregnancy. Regarding cardiac malformations, the epidemiological studies showed conflicting results.

Three epidemiological studies in the US assessed the risk of specific congenital anomalies, including orofacial clefts and cardiac malformations in offspring born to mothers exposed to ondansetron during the first trimester of pregnancy.

One cohort study with 88,467 pregnancies exposed to ondansetron showed an increased risk of oral clefts (3 additional cases per 10,000 women treated, adjusted relative risk (RR), 1.24 (95% CI 1.03-1.48)) without an apparent increase in risk of cardiac malformations. A separately published subgroup analysis of 23,877 pregnancies exposed to intravenous ondansetron did not find an increased risk of either oral clefts or cardiac malformations.

One case-control study using population-based birth defect registries with 23,200 cases across two datasets showed an increased risk of cleft palate in one dataset and no increased risk in the other dataset. There was no increased risk of cardiac malformations in this study.

The second cohort study with 3,733 pregnancies exposed to ondansetron found an increased risk of ventricular septal defect, adjusted RR 1.7 (95%CI 1.0-2.9), but no statistically significant increase in risk of cardiac malformations.

Reproductive studies in rats and rabbits did not show evidence of harm to the fetus.

Pregnancy status should be verified for females of reproductive potential prior to starting the treatment with Ondansetron.

Females of reproductive potential should be advised that it is possible that Ondansetron can cause harm to the developing fetus. Sexually active females of reproductive potential are recommended to use effective contraception (methods that result in less than 1 % pregnancy rates) when using Ondansetron during the treatment and for two days after stopping treatment with Ondansetron.

Breast-feeding: Ondansetron is shown to pass into milk of lactating animals; it is therefore recommended that mothers receiving Ondansetron should not breast feed their babies.

SIDE EFFECTS:

Tabulated list of adverse reactions

Adverse events are listed below by system organ class and frequency. Frequencies are defined as:

Very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1000 to <1/100), rare (≥1/10,000 to <1/1000) and very rare (<1/10,000). 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. 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, oculogyric crisis and dyskinesia)(1).
Rare:	Dizziness predominantly during rapid IV administration.
Eye disorders	
Rare:	Transient visual disturbances (e.g. blurred vision) predominantly during IV administration.
Very rare:	Transient blindness predominantly during IV administration (2).
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
Hepatobiliary disorders	
Uncommon:	Asymptomatic increases in liver function tests (3).
General disorders and administration site conditions	
Common:	Local IV 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.	

SYMPTOMS AND TREATMENT OF OVERDOSE:

Symptoms and Signs

There is limited experience of ondansetron overdose. In the majority of cases, symptoms were similar to those already reported in patients receiving recommended doses. Manifestations that have been reported include visual disturbances, severe constipation, hypotension and a vasovagal episode with transient second-degree AV block.

Ondansetron prolongs the QT interval in a dose-dependent fashion. ECG monitoring is recommended in cases of overdose.

Paediatric population

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

Management

There is no specific antidote for ondansetron, therefore in all cases of suspected overdose, symptomatic and supportive therapy should be given as appropriate. Further management should be as clinically indicated or as recommended by the national poisons centre, where available.

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.

PHARMACOLOGICAL PROPERTIES:

Pharmacodynamic properties:

Pharmacotherapeutic group: Serotonin (5HT₃) antagonist, ATC code: A04AA01

Mechanism of action

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.

Clinical safety and efficacy

The role of ondansetron in opiate-induced emesis is not yet 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. No significant changes were seen in the measured electrocardiographic PR or QRS intervals.

Paediatric population

CINV

The efficacy of ondansetron in the control of emesis and nausea induced by cancer chemotherapy was assessed in a double-blind randomised trial in 415 patients aged 1 to 18 years (S3AB3006). On the days of chemotherapy, patients received either ondansetron 5 mg/m² intravenous and ondansetron 4 mg orally after 8 to 12 hours or ondansetron 0.45 mg/kg intravenous and placebo orally after 8 to 12 hours. Post-chemotherapy both groups received 4 mg ondansetron syrup twice daily for 3 days. Complete control of emesis on worst day of chemotherapy was 49% (5 mg/m² intravenous and ondansetron 4 mg orally) and 41% (0.45 mg/kg intravenous and placebo orally). 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.

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/m² intravenous together with 2 to 4 mg dexamethasone orally.
- 71% of patients when ondansetron was administered as syrup at a dose of 8 mg together with 2 to 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 4 and 8 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 years and 8 mg for children aged ≥ 12 years (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 summarized in Table 1.

Table 1: 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

Pharmacokinetic Properties:

Absorption

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

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 140 L. Equivalent systemic exposure is achieved after intramuscular and intravenous administration of ondansetron.

A 4 mg intravenous infusion of ondansetron given over 5 minute's results in peak plasma concentrations of about 65 ng/ml. Following intramuscular administration of ondansetron, peak plasma concentrations of about 25 ng/ml are attained within 10 minutes of injection.

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.

Distribution

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

Biotransformation and Elimination

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

Gender

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).

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 infant's 1 to 4 months or simply inherent variability due to the low number of subjects studied in this age group. Since patients less than 6 months of age will only receive a single dose in PONV a decreased clearance is not likely to be clinically relevant.

Elderly

Early Phase I studies in healthy elderly volunteers showed a slight age-related decrease in clearance, and an increase in half-life of ondansetron. However, wide inter-subject variability resulted in considerable overlap in pharmacokinetic parameters between young (< 65 years of age) and elderly subjects (≥ 65 years of age) and there were no overall differences in safety or efficacy observed between young and elderly cancer patients enrolled in CINV clinical trials to support a different dosing recommendation for the elderly.

Based on more recent ondansetron plasma concentrations and exposure-response modelling, a greater effect on QTcF is predicted in patient's ≥ 75 years of age compared to young adults. Specific dosing information is provided for patients over 65 years of age and over 75 years of age for IV dosing.

Renal impairment

In patients with renal impairment (creatinine clearance 15-60 ml/min), both systemic clearance and volume of distribution are reduced following IV administration of ondansetron, resulting in a slight, but clinically insignificant, increase in elimination half-life (5.4 hours). 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.

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 to 32 hours) 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.

Effects on Ability to Drive and Use Machine:

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

INSTRUCTIONS FOR USE:

For single-use only.

After opening, unused product should be discarded.

TROYSETRON Injection should not be autoclaved.

Compatibility with intravenous fluids

TROYSETRON is physically and chemically stable with following diluents:

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

Compatibility studies have been undertaken in polyvinyl chloride infusion bags and polyvinyl chloride administration sets. It is considered that adequate stability would also be conferred by the use of polyethylene infusion bags or Type 1 glass bottles. Dilutions of TROYSETRON 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 TROYSETRON injection diluted with other compatible infusion fluids would be stable in polypropylene syringes.

In keeping with good pharmaceutical practice dilutions of TROYSETRON injection in intravenous fluids should be prepared at the time of infusion or stored at 2-8°C or room temperature (below 25°C) for no more than 24 hours before the start of administration.

Method of dilution and duration of infusion

IV doses greater than 8 mg and up to a maximum of 16 mg must be diluted in compatible diluents before administration and infused over not less than 15 minutes. Ondansetron may be administered at concentrations of 16 to 160 micrograms/mL (e.g. 8 mg/500mL and 8 mg/50mL respectively).

Ondansetron doses of 8 mg or less, do not need to be diluted and may be administered as a slow IM or IV injection in not less than 30 seconds.

The initial dose of ondansetron may be followed by 2 additional IV or IM doses of 8 mg by 2 to 4 hours apart, or by a constant infusion of 1 mg/h for up to 24 hours.

Excipients: Sodium Chloride, Citric Acid Monohydrate, Sodium Citrate, Water for Injections

STORAGE CONDITION:

Store below 30°C, protect from light.

Dilutions of TROYSETRON injection in compatible intravenous infusion fluids in PVC Infusion bag with PVC administration set, Polyethylene bag or syringe and Type-I glass bottle are stable under normal room lighting conditions or daylight for at least 24 hours, thus no protection from light is necessary while infusion takes place. Store dilutions of TROYSETRON injection at 2 - 8°C or room temperature (below 25°C).

SHELF LIFE:

36 months (unopened).

24 hours (dilutions stored at 2 - 8°C or room temperature (below 25°C)).

DATE OF REVISION:

04/04/2023

PRODUCT REGISTRATION HOLDER/IMPORTED BY:

Unimed Sdn. Bhd.
No.53, Jalan Tembaga SD5/2B,
Bandar Sri Damansara, 52200 Kuala Lumpur, Malaysia

Manufactured by:



Troikaa Pharmaceuticals Ltd.

C-1, Sara Industrial Estate, Selaqui, Dehradun-248197, Uttarakhand, India

D.I.TY.MALE-01