SM PHARMACEUTICALS SDN BHD

ONDRIN INJECTION 2 ML

DESCRIPTION:
A clear, colourless sterile solution.

After dilution with 50 ml of 5% Dextrose Injection or 0.9% Sodium Chloride Injection at the time of administration, the solution remains clear and colorless without any particulate matter.

Before administration, Ondrin can be diluted with the following diluents:
5% Dextrose Injection
0.9% Sodium Chloride Injection
Note: No diluent is provided along with injection.

COMPOSITION:
Ondansetron 4mg/2ml ampoule: Each ml contains 2 mg Ondansetron (as hydrochloride dihydrate) in aqueous solution.

PHARMACOLOGY (SUMMARY OF PHARMACODYNAMICS AND PHARMACOKINETICS):
Pharmacodynamics:
Ondansetron is a potent, highly selective 5HT3 receptor-antagonist. Its precise mode of action in the control of nausea and vomiting is not known. Chemotherapeutic agents and radiotherapy may cause release of 5HT in the small intestine initiating a vomiting reflex by activating vagal afferents via 5HT3 receptors. Ondansetron blocks the initiation of this reflex. Activation of vagal afferents may also cause a release of 5HT in the area postrema, located on the floor of the fourth ventricle, and this may also promote emesis through a central mechanism. Thus, the effect of Ondansetron in the management of the nausea and vomiting induced by cytotoxic chemotherapy and radiotherapy is probably due to antagonism of 5HT3 receptors on neurons located both in the peripheral and central nervous system. The mechanisms of action in post-operative nausea and vomiting are not known but there may be common pathways with cytotoxic induced nausea and vomiting. Ondansetron does not alter plasma prolactin concentrations. The role of Ondansetron in opiate-induced emesis is not yet established.

Pharmacokinetics:
The pharmacokinetic properties of ondansetron are unchanged on repeat dosing. A direct correlation of plasma concentration and anti-emetic effect has not been established.

Absorption
Following oral administration, ondansetron is passively and completely absorbed from the gastrointestinal tract and undergoes first pass metabolism (Bioavailability is about 60 %.). Peak plasma concentrations of about 30 ng/ml are attained approximately 1.5 hours after an 8 mg dose. For doses above 8 mg the increase in ondansetron systemic exposure with dose is greater than proportional; this may reflect some reduction in first pass metabolism at higher oral doses. Bioavailability, following oral administration, is slightly enhanced by the presence of food but unaffected by antacids.
A 4 mg intravenous infusion of ondansetron given over 5 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.

Distribution
The disposition of ondansetron following oral, intramuscular (IM) and intravenous (IV) dosing is similar with a steady state volume of distribution of about 140 L. Equivalent systemic exposures is achieved after IM and IV administration of ondansetron.
Ondansetron is not highly protein bound (70-76%).

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

Elimination
Less than 5% of the absorbed dose is excreted unchanged in the urine. Terminal half-life is about 3 hours.
Elderly persons
Slight age-related increases in both oral bioavailability (65%) and half-life (5 hours).

Renal impairment
In patients with renal impairment (creatinine clearance 15-60 ml/min), both systemic clearance and volume of distribution are reduced following IV administration of ondansetron, resulting in a slight, but clinically insignificant, increase in elimination half-life (5.4 h). A study in patients with severe renal impairment who required regular haemodialysis (studied between dialyses) showed ondansetron's pharmacokinetics to be essentially unchanged following IV administration.

Hepatic impairment
Following oral, intravenous or intramuscular dosing in patients with severe hepatic impairment, ondansetron's systemic clearance is markedly reduced with prolonged elimination half-lives (15-32 h) and an oral bioavailability approaching 100% due to reduced pre-systemic metabolism.

Gender differences
Gender differences were shown in the disposition of ondansetron, with females having a greater rate and extent of absorption following an oral dose and reduced systemic clearance and volume of distribution (adjusted for weight).

Route of Administration:
IV (Intravenous) or IM (Intramuscular).

INDICATIONS:
Adults
Ondrin injection is indicated for the management of nausea and vomiting induced by cytotoxic chemotherapy and radiotherapy.

Ondrin injection is also indicated for the prevention and treatment of post-operative nausea and vomiting.

Paediatric Population
Ondrin injection 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.

CONTRAINDICATIONS:
Hypersensitivity to the active substance or to other selective 5-HT3 receptor antagonists (e.g. Granisetron, Dolasetron) or to any of the excipients. Concomitant use with Apomorphine.

SIDE EFFECTS / ADVERSE REACTIONS:

Undesirable effects

Immune System Disorder	
Rare:	Immediate hypersensitivity reactions sometimes severe, including anaphylaxis
Nervous System Disorder	
Very common:	Headache
Uncommon:	Seizures, movement disorders (including extrapyramidal reactions such as dystonic reactions, oculogyric crisis and dyskinesia)
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 intravenous administration
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
General disorders and administration site conditions	
Common:	Local IV injection site reactions

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

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

-Ondansetron prolongs the QT interval in a dose-dependent manner (see Pharmacodynamics Effects). 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.

-Hypokalemia and hypomagnesaemia should be corrected prior to ondansetron administration.

-Patients with serotonin syndrome (including altered mental status, autonomic instability and neuromuscular abnormalities) following the concomitant use of ondansetron and other serotonergic drugs (including selective serotonin reuptake inhibitors (SSRI) and serotonin noradrenaline reuptake inhibitors (SNRIs)). If concomitant treatment with ondansetron and other serotonergic drugs is clinically warranted, appropriate observation of the patient is advised.

-As ondansetron is known to increase large bowel transit time, patients with signs of subacute intestinal obstruction should be monitored following administration.

-In patients with adenotonsillar surgery prevention of nausea and vomiting with ondansetron may mask occult bleeding. Therefore, such patients should be followed carefully after ondansetron.

-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-hourly intervals, the total daily dose will be higher than if one single dose of 5mg/m2 followed by an oral dose is given
This medicinal product contains 2.3 mmol (or 53.5 mg) sodium per 32 mg dose. To be taken into consideration by patients on a controlled sodium diet.

EFFECT ON ABILITY TO DRIVE AND USE MACHINE:
Ondansetron 2 mg/ml has no or negligible influence on the ability to drive and use machines.

DRUG INTERACTIONS:
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 ondansetron does not interact with alcohol, temazepam, furosemide, alfentanil, tramadol, morphine, lidocaine, thiopental or propofol.

Ondansetron is metabolized by multiple hepatic cytochrome P-450 enzymes: CYP3A4, CYP2D6 and CYP1A2. Due to the multiplicity of metabolic enzymes capable of metabolizing 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 co-administered with drugs that prolong the QT interval and/or cause electrolyte abnormalities (see warnings and Precautions).

Use of ondansetron with QT prolonging drugs may result in additional QT prolongation. Concomitant use of ondansetron with cardio toxic drugs (e.g. anthracyclines such as doxorubicin, daunorubicin or trastuzimab), antibiotics (such as erythromycin or ketoconazole), antiarrhythmics (such as amiodarone) and beta blockers (such as atenolol or timolol) may increase the risk of arrhythmias. (see warnings and Precautions).
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). (see warnings and Precautions).
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 Ondrin. Females of reproductive potential should be advised that it is possible that Ondrin 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 Ondrin during the treatment and for two days after stopping treatment with Ondrin.

Breast-feeding

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.

RECOMMENDED DOSAGE AND ADMINISTRATION

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.

Populations

- **CINV and RINV in Adult:**

The recommended intravenous (IV) or intramuscular (IM) dose of Ondrin is 8mg administered immediately before the treatment.
For highly emetogenic chemotherapy, a maximum initial ondansetron of 16mg IV infused over 15 minutes may be used. A single IV dose greater than 16 mg should not be given.
The efficacy of Ondrin 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 8mg and up to a maximum of 16mg must be diluted in 50mL to 100mL of 0.9% Sodium Chloride Injection or 5% Dextrose Injection before administration and infused over not less than 15 minutes. Ondrin 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 Ondrin may be followed by 2 additional IV or IM doses of 8mg 2 to 4 hours apart, or by a constant infusion of 1mg/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.

Ondrin can be given by IV infusion diluted in 25 to 50 mL of saline or other compatible infusion fluid (see Instructions for Use and Handling) and infused over not less than 15 minutes.

Dosing by BSA

Ondrin should be administered immediately before chemotherapy as a single IV dose of 5mg/m^2. The IV dose must not exceed 8mg.

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 CINV

BSA	Day1	Days 2-6
≥ 0.6 m^2 to ≤ 1.2 m^2	5mg/m^2 IV Plus 4mg tablet after 12 hours	4 mg tablet every 12 hours
>1.2 m^2	5mg/m^2 IV Plus or 8 mg of IV Plus 8mg tablet after 12 hours	8 mg tablet every 12 hours

Dosing by body weight

Ondrin 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 maybe given in 4-hourly intervals.
Oral dosing can commence 12 hours later and may be continued for up to 5 days (Table 2). Adult dose must not be exceeded.

Table 2. Weight-based dosing CINV

Body Weight	Day 1	Days 2-6
>10kg	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 m^2, 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- 74 years of age, the initial IV dose of Ondrin 8mg 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 Ondrin should not exceed 8mg infused over 15minutes. 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

- **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 patient 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 metabolism of sparteine and debrisoquine. Consequently, in such patients repeat dosing will give drug exposure levels no different from those of the general populations. No alteration of daily dosage or frequency of dosing is required.

POST-OPERATIVE NAUSEA AND VOMITING (PONV)

• PONV in Adults

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

• PONV in Children and Adolescents (aged 3 – 17 years)

For prevention and treatment of PONV in paediatric patients having surgery performed under general anesthesia, Ondrin 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 anesthesia, or after surgery.

• Elderly

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

• 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.

SYMPTOMS AND TREATMENT FOR OVERDOSE AND ANTIDOTE(S):

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.

Treatment

There is no specific antidote for Ondansetron, therefore in all cases of suspected overdose, symptomatic and supportive therapy should be given as appropriate.
The use of 'Ipecacuanha' to treat overdose with ondansetron is not recommended, as patients are unlikely to respond due to the anti-emetic action of ondansetron itself. Further management should be as clinically indicated or as recommended by the national poisons centre, where available.

INSTRUCTION FOR USE

-The solution must not be sterilised in an autoclave.

-Ondansetron Injection should only be admixed with those infusion solutions which are recommended.

-Sodium Chloride Intravenous Infusion BP 0.9% w/v

-Dextrose Intravenous Infusion BP 5% w/v

-The diluted solution should be used within 24 hours after dilution.

- Ondrin Injection if diluted for administration is recommended to be used immediately and should any storage is warranted must be stored below 30° C and must be used within 24 hrs.

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.

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

PACKING / PACK SIZES:

5 x 2 ml ampoules in printed box.

STORAGE CONDITIONS, USER INSTRUCTIONS AND PHARMACEUTICAL PRECAUTIONS:

Store below 30°C, Protect from light.

Storage Condition After Dilution:

Please use within 24 hours after dilution
Store below 30°C

SHELF LIFE:

2 Years.

MANUFACTURER AND PRODUCT REGISTRATION HOLDER:

SM PHARMACEUTICALS SDN BHD (218620-M)
Lot 88, Sungai Petani Industrial Estate
08000 Sungai Petani
Kedah Darul Aman, Malaysia.

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