# Ondansetron

## Ondavid
**2 mg/mL Solution for Injection**
**(I.M./I.V.)**

Antiemetic (Serotonin (5HT3) Antagonist)

## DESCRIPTION
Clear, colorless, transparent solution filled in glass ampoule.

## FORMULATION
Each mL contains:
Ondansetron (as hydrochloride) . . . . . 2mg

## ACTIONS AND PHARMACOLOGY
The active substance, ondansetron, is a potent, highly selective $5HT_3$ receptor-antagonist. Its precise mode of action in the control of nausea and vomiting is not known. Chemotherapeutic agents and radiotherapy may cause release of 5HT in the small intestine initiating a vomiting reflex by activating vagal afferents via $5HT_3$ receptors. Ondansetron blocks the initiation of this reflex. Activation of vagal afferents may also cause a release of 5HT in the area postrema, located on the floor of the fourth ventricle, and this may also promote emesis through a central mechanism. Thus, the effect of ondansetron in the management of the nausea and vomiting induced by cytotoxic chemotherapy and radiotherapy is probably due to antagonism of $5HT_3$ receptors on neurons located both in the peripheral and central nervous system.

The mechanisms of action in post-operative nausea and vomiting are not known but there may be common pathways with cytotoxic induced nausea and vomiting.

## 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.

**Adults**

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 minutes results in peak plasma concentrations of about 65 ng/mL. Following intramuscular administration of ondansetron, peak plasma concentration 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 exposure 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

In the elderly, there is a slight, but clinically insignificant, age-related increases in both oral bioavailability (65%) and half-life (5 hours) of ondansetron.

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).

Hepatic impairment

Following oral, intravenous or intramuscular dosing in patients with severe hepatic impairment, and 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.

## INDICATIONS
**Adults**

hovid-Ondansetron injection is indicated for the management of nausea and vomiting induced by cytotoxic chemotherapy and radiotherapy. hovid Ondansetron injection is indicated for the prevention and treatment of post-operative nausea and vomiting (PONV).

**Paediatric Population**

hovid-Ondansetron injection is indicated for the management of chemotherapy-induced nausea and vomiting (CINV) in children aged ≥ 6 months, and for the prevention and treatment of PONV in children aged ≥ 1 month.

## CONTRAINDICATIONS
- Hypersensitivity to the active substance or to any of the excipients listed.
- Concomitant use with apomorphine.

## WARNINGS AND PRECAUTIONS
**Hypersensitivity:** Hypersensitivity reactions have been reported in patients who have exhibited hypersensitivity to other selective $5HT_3$ receptor antagonist. Respiratory events should be treated symptomatically and clinicians should pay particular attention to them as precursors of hypersensitivity reactions.

**QT interval:** Ondansetron prolongs the QT interval in a dose-dependent manner. 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:** Hypokalaemia and hypomagnesaemia should be corrected prior to ondansetron administration.

**Serotonin syndrome:** If concomitant treatment with ondansetron and other serotonergic drugs is clinically warranted, appropriate observation of the patient is advised.

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

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

**Adenotonsillar surgery:** 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.

## PREGNANCY AND LACTATION
**Pregnancy**

The safety of ondansetron for use in human pregnancy has not been established. The use of ondansetron in pregnancy is not recommended.

**Breastfeeding**

It is recommended that mothers receiving ondansetron injection should not breast-feed their babies.

## DRUG INTERACTIONS
There is no evidence that ondansetron either induces or inhibits the metabolism of other drugs commonly co-administered with it. 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. Concomittant use of cardiotoxic drugs (anthracyclines or transtuzumab), antibiotics (erythromycin), antifungals (ketoconazole), antiarrhythmics (amiodarone), beta blockers (atenolol or timolol) may increase the risk of arrhythmias.

**Serotonergic drugs (e.g. SSRIs and SNRIs):** Concomitant use of ondansetron and other serotonergic drugs require appropriate observation of patients.

**Apomorphine:** Concomitant use with apomorphine is contraindicated.

**Phenytoin, Carbamazepine and Rifampicin:** In patients treated with potent inducers of CYP3A4 (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.

## MAIN SIDE/ ADVERSE EFFECTS
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)
*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

## OVERDOSE AND TREATMENT

**Symptoms**

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.

**Management of overdose**

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.

## DOSAGE AND ADMINISTRATION

**Chemotherapy and Radiotherapy Induced Nausea and Vomiting (CINV and RINV)**

Adults

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

Emetogenic Chemotherapy and Radiotherapy

Ondansetron can be given either by rectal, oral (tablets or syrup), intravenous or intramuscular administration. For most patients receiving emetogenic chemotherapy or radiotherapy, ondansetron injection 8 mg should be administered as a slow intravenous injection (in not less than 30 seconds) or intramuscular injection, immediately before treatment, followed by 8 mg orally twelve hourly. To protect against delayed or prolonged emesis after the first 24 hours, oral or rectal treatment with hovid-Ondansetron injection should be continued for up to 5 days after a course of treatment.

Highly Emetogenic Chemotherapy

For patients receiving highly emetogenic chemotherapy, e.g. high dose cisplatin, hovid-Ondansetron injection is equally effective in the following dose schedules over the first 24 hours of chemotherapy:

- A single dose of 8 mg by slow intravenous injection (in not less than 30 seconds) or intramuscular injection immediately before chemotherapy.
- A dose of 8 mg by slow intravenous injection (in not less than 30 seconds) or intramuscular injection immediately before chemotherapy, followed by two further intravenous injection (in not less than 30 seconds) or intramuscular doses of 8 mg four hours apart, or by a constant infusion of 1 mg/hour for up to 24 hours.
- A maximum initial intravenous dose of 16 mg diluted in 50-100 ml of saline or other compatible infusion fluid and infused over not less than 15 minutes immediately before chemotherapy. The initial dose of ondansetron may be followed by two additional 8 mg intravenous doses (in not less than 30 seconds) or intramuscular doses four hours apart.

A single dose greater than 16 mg must not be given due to dose dependent increase of QT-prolongation risk.

The selection of dose regimen should be determined by the severity of the emetogenic challenge. The efficacy of hovid-Ondansetron injection in highly emetogenic chemotherapy may be enhanced by the addition of a single intravenous dose of dexamethasone sodium phosphate, 20 mg administered prior to chemotherapy.

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

Paediatric population

*CINV in children aged ≥ 6 months and adolescents*

The dose for CINV can be calculated based on body surface area (BSA) or weight – see below. Ondansetron can be given by IV infusion diluted in 25 to 50 ml of saline or other compatible infusion fluid and infused over not less than 15 minutes.

hovid-Ondansetron injection should be diluted in 5% dextrose or 0.9% sodium chloride or other compatible infusion fluid and infused intravenously over not less than 15 minutes.

Dosing by BSA

hovid-Ondansetron injection should be administered immediately before chemotherapy as a single intravenous dose of 5 mg/m$^2$. The single intravenous dose must not exceed 8 mg. Oral dosing can commence 12 hours later and may be continued for up to 5 days.

**Table 1:** BSA-based dosing for chemotherapy (children aged ≥ 6 months and adolescents)

| BSA | Day 1 [a,b] | Days 2-6 [b] |
|---|---|---|
| < 0.6 m$^2$ | 5 mg/m$^2$ IV plus 2 mg syrup after 12 hours | 2 mg syrup every 12 hours |
| 0.6 m$^2$ to 1.2 m$^2$ | 5 mg/m$^2$ IV plus 4 mg syrup or tablet after 12 hours | 4 mg syrup or tablet every 12 hours |
| > 1.2 m$^2$ | 5 mg/m$^2$ IV plus 8 mg syrup or tablet after 12 hours | 8 mg syrup or tablet every 12 hours |

a The intravenous dose must not exceed 8 mg.
b The total dose over 24 hours (given as divided doses) must not exceed adult dose of 32 mg.

Dosing by body weight

Weight-based dosing results in higher total daily doses compared to BSA-based dosing.

Ondansetron should be administered immediately before chemotherapy as a single intravenous dose of 0.15 mg/kg. The intravenous dose must not exceed 8 mg. Two further intravenous doses may be given in 4-hourly intervals. The total daily dose must not exceed adult dose of 32 mg. Oral dosing can commence twelve hours later and may be continued for up to 5 days.

**Table 2:** Weight-based dosing for chemotherapy (children aged ≥ 6 months and adolescents)

| Weight | Day 1 [a,b] | Days 2-6 [b] |
|---|---|---|
| ≤ 10 kg | Up to 3 doses of 0.15 mg/kg every 4 hours | 2 mg syrup every 12 hours |
| > 10 kg | Up to 3 doses of 0.15 mg/kg every 4 hours | 4 mg syrup or tablet every 12 hours |

a The intravenous dose must not exceed 8 mg.
b The total dose over 24 hours (given as divided doses) must not exceed adult dose of 32 mg.

Elderly

In patients 65 to 74 years of age, the dose schedule for adults can be followed. All intravenous doses should be diluted in 50–100mL of saline or other compatible infusion fluid and infused over 15 minutes.

In patients 75 years of age or older, the initial intravenous dose should not exceed 8 mg. All intravenous doses should be diluted in 50-100mL of saline or other compatible infusion fluid and infused over 15 minutes. The initial dose of 8 mg may be followed by two further intravenous doses of 8 mg, infused over 15 minutes and given no less than 4 hours apart.

Patients with Renal Impairment

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

Patients with Hepatic Impairment

Clearance of ondansetron is significantly reduced and serum half-life significantly prolonged in subjects with moderate or severe impairment of hepatic function. In such patients a total daily dose of 8 mg should not be exceeded and therefore parenteral or oral administration is recommended.

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. No alteration of daily dosage or frequency of dosing is required.

**Post-Operative Nausea and Vomiting (PONV)**

Adults

For the prevention of PONV: Ondansetron can be administered orally or by intravenous or intramuscular injection. Ondansetron may be administered as a single dose of 4 mg given by intramuscular or slow intravenous injection at induction of anaesthesia.

For treatment of established PONV: A single dose of 4 mg given by intramuscular or slow intravenous injection is recommended.

Paediatric population

*PONV in children aged ≥ 1 month and adolescents*

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

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

There are no data on the use of ondansetron in the treatment of PONV in children below 2 years of age.

Elderly

There is limited experience in the use of Ondansetron in the prevention and treatment of PONV in the elderly, however Ondansetron is well tolerated in patients over 65 years receiving chemotherapy.

Patients with Renal Impairment

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

Patients with Hepatic Impairment

Clearance of ondansetron is significantly reduced and serum half-life significantly prolonged in subjects with moderate or severe impairment of hepatic function. In such patients a total daily dose of 8 mg should not be exceeded and therefore parenteral or oral administration is recommended.

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. No alteration of daily dosage or frequency of dosing are required.

Note: The information given here is limited. For further information, consult your doctor or pharmacist.

Caution: Foods, Drugs, Devices, and Cosmetics Act prohibits dispensing without prescription.

For suspected adverse drug reaction, report to the FDA: www.fda.gov.ph

Seek medical attention immediately at the first sign of any adverse drug reaction.

Storage: Store at temperatures not exceeding 30°C. Protect from light.

Availability: Glass ampoules x 2mL (box of 5's)
Glass ampoules x 4mL (box of 5's)

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