



APO-ONDANSETRON

1. PRODUCT NAME

APO-ONDANSETRON (4mg and 8mg tablets)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Ondansetron as hydrochloride dihydrate 4mg
Ondansetron as hydrochloride dihydrate 8mg

Excipient of known effect

Apo-Ondansetron contains lactose.

Lactose

If you have been told by your doctor that you have intolerance to some sugars, contact your doctor before taking this medicinal product.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Apo-Ondansetron Tablets 4 mg: Yellow, oval, biconvex, film coated tablets embossed with 'BL' on one face and '4' on the other. Each tablet contains 4 mg of ondansetron as ondansetron hydrochloride dihydrate.

Apo-Ondansetron Tablets 8 mg: Yellow, oval, biconvex, film coated tablets embossed with 'BL' on one face and '8' on the other. Each tablet contains 8 mg of ondansetron as ondansetron hydrochloride dihydrate.

Do not halve the tablets. Dose equivalence when the tablet is divided has not been established. This product is not able to deliver all approved dose regimens

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Ondansetron tablets are indicated for the management of nausea and vomiting induced by cytotoxic chemotherapy and radiotherapy. Ondansetron tablets are also indicated for the prevention of post-operative nausea and vomiting.

4.2 Dose and method of administration

Do not halve the tablets. Dose equivalence when the tablet is divided has not been established. This product is not able to deliver all approved dose regimens

Chemotherapy and Radiotherapy Induced Nausea and Vomiting

Adults

The emetogenic potential of cancer treatment varies according to the doses and combinations of chemotherapy and radiotherapy regimens used.

Emetogenic Chemotherapy and Radiotherapy:

The recommended oral dose is 8mg 1-2 hours before treatment, followed by 8mg orally 12 hours later.

To protect against delayed or prolonged emesis after the first 24 hours, oral treatment with Ondansetron tablets should be continued for up to 5 days after a course of treatment. The recommended oral dose is 8mg to be taken twice daily.

Highly Emetogenic Chemotherapy:

Ondansetron can be given by oral administration.

To protect against delayed or prolonged emesis after the first 24 hours, oral treatment with Ondansetron tablets should be continued for up to 5 days after a course of treatment. The recommended oral dose is 8mg to be taken twice daily.

Children and Adolescents (aged 6 months to 17 years)

In children with a body surface area of 0.6 to 1.2 m² ondansetron is administered as a single intravenous dose (not available in this product range) of 5 mg/m² immediately before chemotherapy, followed by 4 mg orally twelve hours later. 4 mg orally twice daily can be continued for up to 5 days after a course of treatment.

For children with a body surface area of greater than 1.2 m² an initial i.v. dose (not available in this product range) of 8 mg is administered immediately before chemotherapy, followed by 8 mg orally 12 hours later. 8mg orally twice daily can be continued for up to five days after a course of treatment.

Alternatively, in children aged 6 months or older, ondansetron is administered as a single i.v. dose (not available in this product range) of 0.15 mg/kg (not to exceed 8mg) immediately before chemotherapy. This dose may be repeated every four hours for a total of three doses. 4 mg orally twice daily can be continued for up to five days after a course of treatment. Adult doses must not be exceeded.

Elderly

Ondansetron tablets are well tolerated by patients over 65 years and no alteration of dosage, dosing frequency or route of administration are required.

Post-Operative Nausea and Vomiting

Adults

For prevention of post-operative nausea and vomiting, the recommended oral dose is 16mg given one hour prior to anaesthesia.

Children and Adolescents (aged 1 month to 17 years)

No studies have been conducted on the use of orally administered ondansetron in the prevention or treatment of post-operative nausea and vomiting.

Elderly

There is limited experience in the use of Ondansetron tablets in the prevention and treatment of post-operative nausea and vomiting in the elderly, however Ondansetron tablets are 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 tablets 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 8mg 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 are required.

4.3 Contraindications

Based on reports of profound hypotension and loss of consciousness when ondansetron was administered with apomorphine hydrochloride, concomitant use with apomorphine is contraindicated.

Hypersensitivity to any component of the preparation.

4.4 Special warnings and precautions for use

Hypersensitivity reactions have been reported in patients who have exhibited hypersensitivity to other selective 5HT₃ receptor antagonists.

Rarely, transient ECG changes including QT interval prolongation have been reported in patients receiving ondansetron. In addition, post-marketing cases of Torsade de Pointes have been reported in patients using ondansetron. Ondansetron should be administered with caution to patients who have or may develop prolongation of QTc. These conditions include patients with electrolyte abnormalities, with congenital long QT syndrome, or patients taking other medicinal products that lead to QT prolongation.

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

4.5 Interaction with other medicines and other forms of interaction

There is no evidence that ondansetron either induces or inhibits the metabolism of other drugs commonly coadministered with it. Specific studies have shown that there are no pharmacokinetic interactions when ondansetron is administered with alcohol, temazepam, frusemide, tramadol 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.

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.

4.6 Fertility, pregnancy and lactation

Pregnancy

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

In one cohort study including 1.8 million pregnancies, first trimester ondansetron use was associated with an increased risk of oral clefts (3 additional cases per 10 000 women treated; adjusted relative risk, 1.24, (95% CI 1.03-1.48)).

The available epidemiological studies on cardiac malformations show conflicting results.

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

Ondansetron should only be used during the first-trimester of pregnancy if the benefits of use clearly outweigh the risks of harm to the woman and the fetus.

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.

4.7 Effects on ability to drive and use machines

In psychomotor testing ondansetron does not impair performance nor cause sedation.

4.8 Undesirable effects

Adverse events are listed below by system organ class and frequency. Frequencies are defined as: very common ($\geq 1/10$), common ($\geq 1/100$ and $< 1/10$), uncommon ($\geq 1/1000$ and $< 1/100$), rare ($\geq 1/10,000$ and $< 1/1000$) and very rare ($< 1/10,000$) including isolated reports. 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 according to indication and formulation. [10]

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 oculogyric crisis, dystonic reactions and dyskinesia have been observed without definitive evidence of persistent clinical sequelae).

Eye disorders

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.

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#.

#These events were observed commonly in patients receiving chemotherapy with cisplatin.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions <https://nzphvc.otago.ac.nz/reporting/>

4.9 Overdose

Symptoms

There is limited experience of ondansetron overdose. In the majority of cases symptoms were similar to those already reported in patients receiving recommended doses (see Undesirable Effects). There is no specific antidote for ondansetron, therefore in cases of suspected overdose, symptomatic and supportive therapy should be given as appropriate.

Treatment

There is no specific antidote for ondansetron, therefore in 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 tablets itself.

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764 766).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic Properties

Pharmacotherapeutic group: Antiemetic and antinauseant, Serotonin (5HT₃) antagonist

ATC code: not yet assigned

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.

5.2 Pharmacokinetic properties

Following oral administration, ondansetron is passively and completely absorbed from the gastrointestinal tract and undergoes first pass metabolism. Peak plasma concentrations are attained approximately 1.5 hours after dosing. For doses above 8mg 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 is slightly enhanced by the presence of food but unaffected by antacids. The disposition of ondansetron following oral, intramuscular or intravenous dosing is similar with a terminal elimination half-life of about 3 hours and steady state volume of distribution of about 140L. Ondansetron is not highly protein bound (70-76%). 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. Studies in healthy elderly volunteers have shown slight, but clinically insignificant, age-related increases in both oral bioavailability and half-life of ondansetron.

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).

In a clinical study, 51 paediatric patients aged 1 to 24 months received either 0.1 or 0.2 mg/kg ondansetron prior to undergoing surgery. Patients aged 1 to 4 months had a clearance when normalised to body weight that was approximately 30% slower than in patients aged 5 to 24 months but comparable to the patients aged 3 to 12 years. The half-life in the 1 to 4 month patient population 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. No dose adjustment is necessary for patients aged 1 to 4 months as only a single i.v. dose of ondansetron is recommended for the treatment of postoperative nausea and vomiting. The differences in pharmacokinetic parameters can be explained in part by the higher volume of distribution in the 1 to 4 month patient population.

In a study of 21 paediatric patients aged between 3 and 12 years undergoing elective surgery with general anaesthesia, the absolute values for both the clearance and volume of distribution of ondansetron following a single intravenous dose of 2 mg (3-7 years old or 4 mg (8-12 years old) were reduced. The magnitude of the change was age-related, with clearance falling from about 300 mL/min at 12 years of age to 100 mL/min at 3 years. Volume of distribution fell from about 75 L at 12 years to 17 L at 3 years. Use of weight-based dosing (0.1 mg/kg up to 4 mg maximum) compensates for these changes and is effective in normalising systemic exposure in paediatric patients.

In patients with moderate renal impairment (creatinine clearance 15-60 mL/min), both systemic clearance and volume of distribution are reduced, 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. 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.

5.3 Preclinical safety data

Preclinical data revealed no special hazard for humans based on conventional studies of repeated dose toxicity, genotoxicity and carcinogenic potential.

Ondansetron and its metabolites accumulate in the milk of rats, milk/plasma-ratio was 5.2:1.

A study in cloned human cardiac ion channels has shown ondansetron has the potential to affect cardiac repolarisation via blockade of HERG potassium channels.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Apo-Ondansetron tablet contains the following excipients:

- Hypromellose
- Iron oxide yellow
- Lactose
- Magnesium stearate
- Microcrystalline cellulose
- Pregelatinised maize starch
- Purified water
- Titanium dioxide

Gluten free. Contains Lactose.

6.2 Incompatibilities

Not applicable

6.3 Shelf life

3 years when stored at or below 25°C.

6.4 Special precautions for storage

Store at or below 25°C

6.5 Nature and contents of container

Apo-Ondansetron 4mg and 8mg are available in blister pack of 10, 20, 30 & 50 tablets.

Not all pack sizes are available.

6.6 Special precautions for disposal

No special requirements for disposal.

Any unused medicine or waste material should be disposed of in accordance with local requirements.

7. MEDICINE SCHEDULE

Prescription Medicine



APO-ONDANSETRON

8. SPONSOR

Apotex NZ Ltd.
Level 2 Tamariki House
7 Tamariki Ave
Orewa
AUCKLAND 0931

Telephone: (09) 444 2073

E-mail: NZcustomerservice@apotex.com

9. DATE OF FIRST APPROVAL

05 October 2006

10. DATE OF REVISION OF THE TEXT

23 June 2020

SUMMARY TABLE OF CHANGES

Section changed	Summary of new information
4.6 Pregnancy	Revised safety information
5.3 Preclinical Safety Data	Align with other NZ datasheets
8 Sponsor	Updated contact details