ONDANSETRON SZ ODT

orally-disintegrating tablets 4mg/8mg

NAME OF THE MEDICINE

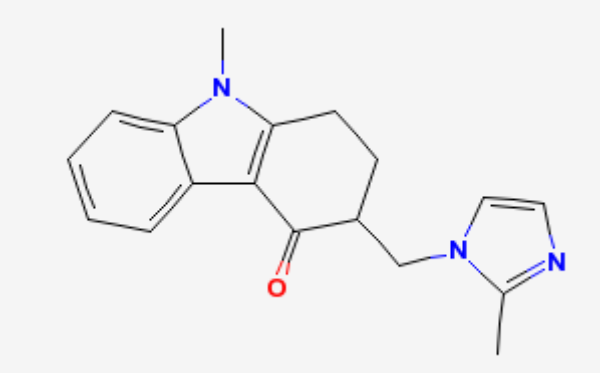
Ondansetron

Chemical name: 1,2,3,9-tetrahydro-9-methyl-3- [2-methyl-1H-imidazol-1-yl)methyl]- 4H-carbazol-4-one

Molecular formula: C_{18} H_{19} N_3 O. MW:293.4

CAS: 99614-02-5

Chemical Structure:



DESCRIPTION

Ondansetron is a white to off white powder with a melting point of approximately 230°C. It is insoluble in water. It is soluble in chloroform and acetic acid. The pKa of ondansetron is 10.4 at 30°C (Diluent: water and methanol in the ratio of 35:65).

Each ONDANSETRON SZ ODT tablet contains 4 mg or 8 mg of ondansetron as the active ingredient. It also contains the following inactive ingredients: Microcrystalline cellulose, mannitol, pregelatinised maize starch, crospovidone, aspartame, guar gum, colloidal anhydrous silica, magnesium stearate, sodium lauryl sulphate, Strawberry Guarana 586997 AP0551

PHARMACOLOGY

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 -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 due to antagonism of $5HT_3$-receptors on neurons located both in the peripheral and central nervous system. The mechanisms of action in postoperative nausea and vomiting are not known but there may be common pathways with cytotoxic induced nausea and vomiting. In psychomotor testing, ondansetron does not impair performance or cause sedation. Ondansetron does not alter plasma prolactin concentrations.

A study in cloned human cardiac ion channels has shown ondansetron has the potential to affect cardiac repolarisation via blockade of HERG potassium channels. The clinical relevance of this finding is uncertain.

Pharmacokinetics

Absorption

Following oral dosing with ondansetron, peak plasma concentrations are achieved in approximately 1.5 hours. For doses above 8 mg the increase in ondansetron systemic exposure with dose is greater thanproportional; this may reflect some reduction in first-pass metabolism at higher doses. The absolute bioavailability of the ondansetron tablet is approximately 60% (range 36 to 112%).

Distribution
The plasma protein binding is 70% to 76%. The volume of distribution is 1.8 L/kg.

Metabolism
Ondansetron is extensively metabolised in humans, with approximately 5% of a radiolabelled dose recovered as the parent compound from the urine. The primary metabolic pathway is hydroxylation on the indole ring followed by glucuronide or sulfate conjugation. Although some nonconjugated metabolites have pharmacological activity, these are not found in plasma concentrations likely to significantly contribute to the biological activity of ondansetron. Ondansetron is a substrate for multiple human hepatic cytochrome P450 enzymes including CYP1A2, CYP2D6 and CYP3A4. This multiplicity of metabolic enzymes capable of metabolising ondansetron means that inhibition or loss of one enzyme (e.g. CYP2D6 genetic deficiency) results in little change in overall rates of ondansetron elimination.

Elimination
The terminal elimination half-life of ondansetron after oral dosing is 4.1 to 11.6 hours. The half-life may be prolonged in the elderly. In patients with severe hepatic impairment, systemic clearance is markedly reduced with prolonged elimination half-lives (15 to 32 hours) and an oral bioavailability approaching 100% because of reduced presystemic metabolism.

Children
In a study of 21 children aged 3 to 12 years receiving elective surgery with general anaesthesia, the clearance and volume of distribution of ondansetron following a single intravenous dose of 2 mg (3 to 7 years old) or 4 mg (8 to 12 years old) were reduced. The size of the change was age related with clearance falling from about 300 mL/minute at 12 years of age to 100 mL/minute at 3 years. Volume of distribution fell from about 75 L at 12 years to 17 L at 3 years.

The clinical safety of ondansetron in children under 2 years has not been established. Increased incidence of mortality with no specific target organ toxicity has been observed in young rats with immature drug metabolising enzymes.

CLINICAL TRIALS

Chemotherapy and radiotherapy induced nausea and vomiting.
Adult studies.
Highly emetogenic chemotherapy
In a double blind, randomised study 152 patients were given ondansetron 8 mg intravenously as a single dose and 173 patients were given 32 mg intravenously as a single dose 30 minutes prior to cisplatin (greater than or equal to 50 mg/m^2). No significant difference in terms of emesis control or grade of nausea was demonstrated between 8 mg or 32 mg.

However, in some studies conducted in patients receiving medium (50 to 90 mg/m^2) or high doses (greater than or equal to 100 mg/m^2) of cisplatin chemotherapy, the 32 mg single dose has demonstrated a statistically significant superiority over the 8 mg single dose with regard to control of emesis (see **DOSAGE AND ADMINISTRATION**).

In a double blind, randomised, crossover trial, 103 chemotherapy naive patients scheduled to receive cisplatin (50 to 120 mg/m^2) chemotherapy were recruited. 91 patients completed both courses of ondansetron 0.15 mg/kg (8 mg) intravenously (three doses) with or without dexamethasone 20 mg intravenously. The combination of ondansetron and dexamethasone was shown to be significantly superior to ondansetron alone.

In a randomised, double blind parallel group study, 420 patients were randomised to receive either a ondansetron 16 mg suppository prior to cisplatin chemotherapy (greater than or equal to 50 mg/m^2) on day 1 followed by a ondansetron 16 mg suppository once daily for a further two days, or ondansetron 8 mg intravenously prior to cisplatin chemotherapy followed by ondansetron 8 mg orally twice daily for a further two days. Results from the primary efficacy analysis (i.e. less than or equal to two emetic episodes on day 1) show that an ondansetron suppository and combined ondansetron intravenous and oral regimens are equivalent.

However, results from the secondary efficacy analyses (e.g. number of emetic episodes on day 1, the worst day of days 1 to 3 and overall of days 1 to 3) showed that the ondansetron suppository was less effective.

Patients on a combined ondansetron intravenous and oral regimen remained free of emesis for significantly longer than patients receiving ondansetron suppository.

In a randomised double blind, parallel group study 542 patients were randomised to receive either ondansetron tablets (3 x 8 mg) plus dexamethasone capsules (2 x 6 mg), or intravenous ondansetron 8 mg plus intravenous dexamethasone 20 mg, prior to cisplatin infusion. Ondansetron 24 mg administered orally was as effective as ondansetron 8 mg given intravenously in controlling acute emesis and nausea induced by cisplatin chemotherapy. One ondansetron 24 mg tablet has been shown to be bioequivalent to three ondansetron 8 mg tablets.

There are no studies on the use of suppositories in radiation induced nausea and vomiting.

Emetogenic chemotherapy
In a double blind, parallel group study 82 patients were randomised to either ondansetron 8 mg intravenously prior to cyclophosphamide (greater than or equal to 500 mg/m^2) based chemotherapy (doxorubicin or epirubicin greater than or equal to 40 mg/m^2) followed by 8 mg orally three times a day for three to five days or metoclopramide 60 mg intravenously prior to chemotherapy followed by 20 mg orally three times a day for three to five days. Ondansetron was shown to be significantly superior to metoclopramide.

In a randomised, single blind study, ondansetron 8 mg orally twice daily in 155 patients was compared with ondansetron 8 mg orally three times daily in 153 patients for three to five days following chemotherapy. Ondansetron 8 mg intravenously was given prior to cyclophosphamide (greater than or equal to 500 mg/m^2) based chemotherapy (doxorubicin or epirubicin > 40 mg/m^2) on day 1. Ondansetron 8 mg given orally twice daily was as effective as ondansetron 8 mg given orally three times daily.

In a randomised double blind parallel group study, 406 patients were randomised to receive either a ondansetron 16 mg suppository once daily for three days or ondansetron 8 mg orally twice daily for three days. The first administration of the suppository and tablet began two hours and one to two hours respectively prior to cyclophosphamide chemotherapy (greater than or equal to 500 mg/m^2) on day 1. Results from the primary efficacy analysis (less than or equal to two emetic episodes on the worst day of days 1 to 3) show that the ondansetron suppository treatment is equivalent to the ondansetron oral treatment. The ondansetron suppository was less effective than ondansetron oral treatment for a number of other secondary efficacy criteria (complete control of emesis on the worst day of days 1 to 3, total number of emetic episodes days 1 to 3 and number of emetic episodes on worst day of days 1 to 3).

Paediatric studies
Three open label, uncontrolled, noncomparative studies have been performed with 182 patients aged 4 to 18 years with cancer who were given a variety of cisplatin or noncisplatin regimens. In these trials an initial intravenous dose of ondansetron was followed by oral administration of ondansetron. In these studies, 58% of the 170 evaluable patients had no emetic episodes on day 1.

INDICATIONS

Prevention and treatment of nausea and vomiting induced by cytotoxic therapy and radiotherapy.

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 (see **PRECAUTIONS**).

PRECAUTIONS

Hypersensitivity reactions have been reported in patients who have exhibited hypersensitivity to other selective $5HT_3$ -receptor antagonists.

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.

Hypokalemia and hypomagnesemia should be corrected prior to ondansetron administration.

Serotonin syndrome has been described following the concomitant use of ondansetron and other serotonergic drugs (see **INTERACTIONS WITH OTHER MEDICINES**). 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.

ONDANSETRON SZ ODT orally disintegrating tablets contain aspartame and therefore should be taken with caution in patients with phenylketonuria.

Repeat dosing has not been studied in paediatric patients who experience nausea and/or vomiting despite receiving ondansetron prophylaxis or who continue to experience symptoms after ondansetron treatment.

Use in pregnancy (Category B1)[1]
The safety of ondansetron for use in human pregnancy has not been established. Evaluation of experimental animal studies does not indicate direct or indirect harmful effects with respect to the development of the embryo or fetus, the course of gestation, and perinatal and postnatal development. However, as animal studies are not always predictive of human response, the use of ondansetron in pregnancy is not recommended.

[1] *Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human foetus having been observed. Studies in animals have not shown evidence of an increased occurrence of foetal damage*

Use in lactation
Tests have shown that ondansetron is excreted in the breast milk of rats. It is therefore recommended that mothers receiving ondansetron should not breastfeed their babies.

Carcinogenicity
No evidence for carcinogenic activity was found in two year studies at ondansetron doses up to 10 mg/kg/day by gavage in rats or up to 30 mg/kg/day via drinking water in mice.

Paediatric use
Experience is currently limited but ondansetron was effective and well tolerated in children over 4 years of age (see **DOSAGE AND ADMINISTRATION**).

Use in the elderly
Efficacy and tolerance in patients aged over 65 years was similar to that seen in younger adults, indicating no need to alter dosage or route of administration in the elderly.

Genotoxicity
Ondansetron did not induce mutations in *Salmonella typhimurium, Escherichia coli* or Chinese hamster ovary cells in the presence or absence of metabolic activation, and showed no potential for causing chromosomal damage *in vitro* in peripheral human lymphocytes or *in vivo* in a mouse micronucleus assay. No evidence for DNA damage was observed with ondansetron in a yeast mitotic gene conversion assay.

Effects on Fertility
Oral doses of ondansetron up to 15 mg/kg/day in rats had no effect on male or female fertility.

INTERACTIONS WITH OTHER MEDICINES

There is no evidence that ondansetron either induces or inhibits the metabolism of other drugs commonly coadministered with it. Specific studies have been limited to alcohol, temazepam, alfentanil, furosemide, tramadol or propofol.

Ondansetron is metabolised by multiple hepatic cytochrome P450 drug enzymes: CYP3A4, CYP2D6 and CYP1A2. Due to the multiplicity of metabolic enzymes capable of metabolising ondansetron, enzyme inhibition or reduced activity of one enzyme (e.g. CYP2D6 genetic deficiency) is normally compensated by other enzymes and should result in little or no significant change in overall ondansetron clearance or dose requirement.

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

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

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.

Following a single 8 mg tablet dose of ondansetron, a three to fourfold decrease in the systemic exposure has been seen in adult epileptic subjects maintained on chronic doses of carbamazepine (n = 8) or phenytoin (n = 8) and not receiving chemotherapy. The effect of these enzyme inducing agents on intravenous ondansetron has not been assessed, but the absence of any first pass effects would be expected to result in a smaller change in exposure than seen following oral dosing.

Due to the limited efficacy data in subjects on antiepileptics and the many variables that may influence exposure and response, the clinical significance of this drug interaction in cancer patients receiving chemotherapy is not known.

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

Serotonergic Drugs (e.g., SSRIs and SNRIs)

Serotonin syndrome (including altered mental status, autonomic instability and neuromuscular abnormalities) has been described following the concomitant use of ondansetron and other serotonergic drugs, including selective serotonin reuptake inhibitors (SSRIs) and serotonin noradrenaline reuptake inhibitors (SNRIs) (see **PRECAUTIONS**).

ADVERSE EFFECTS

Adverse events are listed below by system organ class and frequency. Frequencies are defined as: very common (greater than or equal to 1/10), common (greater than or equal to 1/100 and < 1/10), uncommon (greater than or equal to 1/1,000 and < 1/100), rare (greater than or equal to 1/10,000 and < 1/1,000) 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 postmarketing spontaneous data.

The following frequencies are estimated at the standard recommended doses of ondansetron according to indication and formulation.

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
Rare: transient visual disturbances (e.g. blurred vision) predominantly during intravenous administration.
Very rare: transient blindness predominantly during intravenous administration.

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,
xerostomia,

Hepatobiliary disorders
Uncommon: asymptomatic increases in liver function tests[#].
[#]These events were observed commonly in patients receiving chemotherapy with cisplatin.

Skin and subcutaneous tissue disorders. Very rare: toxic skin eruption, including toxic epidermal necrolysis.

DOSAGE AND ADMINISTRATION

The emetogenic potential of cancer treatment varies according to the doses and combinations of chemotherapy and radiotherapy regimens used. The route of administration and dose of ondansetron should be flexible in the range of 8 to 32 mg a day and selected as shown below. The lowest effective dose should be used.

The orally disintegrating tablet is administered by placing it on top of the tongue where it dissolves within seconds, and is swallowed.

Adults
Emetogenic chemotherapy and radiotherapy
For the control of chemotherapy or radiotherapy induced emesis or nausea in adults, two oral doses of 8 mg each at 12 hourly intervals may be given (tablets or orally disintegrating tablets), the first dose being administered two hours prior to chemotherapy or radiotherapy. To protect against delayed emesis after the first 24 hours, ondansetron should be continued orally at a dosage of 8 mg twice daily, for up to five days after a course of treatment.

Use in children
Emetogenic chemotherapy and radiotherapy
Experience is currently limited but ondansetron was effective and well tolerated in children over 4 years of age, when given intravenously at a dose of 5 mg/m^2 over 15 minutes immediately before chemotherapy, followed by oral therapy at doses of 4 mg twice daily for up to five days. The dose of 5 mg/m^2 is based on limited data.

Use in the elderly
Emetogenic chemotherapy and radiotherapy
Efficacy and tolerance in patients aged over 65 years was similar to that seen in younger adults, indicating no need to alter dosage or route of administration in the elderly.

Impaired renal function
No alteration of daily dosage, frequency of dosing or route of administration is required.

Impaired hepatic function
A study which investigated the effect of hepatic impairment on the pharmacokinetics of ondansetron in 24 subjects showed that the plasma clearance of ondansetron is reduced to about 20% of normal and the serum half-life is significantly prolonged in subjects with severe impairment of hepatic function.

The results in patients with only mildly or moderately impaired hepatic function were less clear. The study showed that in this group the plasma clearance of ondansetron fell to about 50% of that seen in healthy volunteers. Subjects with mild and moderate impairment were not distinguishable from each other for any parameter. This was believed to be partly due to the lack of sensitivity of the Pugh classification system in distinguishing between patients with mild or moderate impairment.

It is recommended that a total daily dose of 8 mg should not be exceeded for patients with moderate or severe hepatic dysfunction. For optimum clinical effect it is recommended that this total daily dose be administered before chemotherapy or radiotherapy.

The severity of the liver disease was assessed according to Pugh's modification of Child's classification (Pugh *et al., Brit. J. Surg.* 1973; 60 (8): 646-649). Patients with a Pugh score of 5 or less were considered to have good hepatic function. A patient with a score of 6 was graded as having mild hepatic impairment, 7 to 9 as moderate hepatic impairment and 10 or more as severe hepatic impairment. The clinical features used in the grading and the weighting system applied are shown in Table 1.

Table 1: Grading of hepatic impairment

Clinical and biochemical measurements	**Points scored for increasing abnormality**		
	1	**2**	**3**
Encephalopathy (grade)*	None	1 and 2	3 and 4
Ascites	Absent	Slight	Moderate
Bilirubin (micromol/L)	17.1 - 34.2	34.2 - 51.3	> 51.3
Albumin (g/L)	35	28 - 35	< 28
Prothrombin time (seconds prolonged)	1 - 4	4 - 6	> 6
For primary biliary cirrhosis			
Bilirubin (micromol/L)	17.1 - 68.4	68.4 - 171	> 171

* According to grading of Trey, Burns and Saunders (1966)

Patients with poor sparteine/debrisoquine metabolism
There were no significant differences among poor and extensive debrisoquine categorised metabolisers with regard to ondansetron disposition (area under the curve, total systemic clearance, elimination half-life) following a single 8 mg intravenous dose. The effect of repeated dosing was not investigated, nevertheless dosage adjustments will probably not be required in patients receiving ondansetron by the oral route.

OVERDOSAGE

Symptoms
Little is known at present about overdosage with ondansetron, however, a limited number of patients have received overdoses. Manifestations that have been reported include visual disturbances, severe constipation, hypotension and a vasovagal episode with transient second degree AV block. In all instances, the events resolved completely.

Contact the Poisons Information Centre (13 11 26) for information regarding the management of overdose.

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

PRESENTATION AND STORAGE CONDITIONS

ONDANSETRON SZ ODT tablets contain 4mg or 8mg of ondansetron

ONDANSETRON SZ ODT 4 mg orally disintegrating tablets: White to off-white, round, biconvex, uncoated tablets embossed '4' on one side and 'O' on the other side.
Available in blister packs of 4, 6 or 10 orally disintegrating tablets (Al/Al blister pack).

ONDANSETRON SZ ODT 8 mg orally disintegrating tablets: White to off-white, round, biconvex, uncoated tablets embossed '8' on one side and 'O' on the other side.
Available in blister packs 4, 6 or 10 (Al/Al blister pack).

Not all strengths and pack sizes may be available.

Store below 30°C

NAME AND ADDRESS OF THE SPONSOR

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Supplier

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POISON SCHEDULE OF THE MEDICINE

S4 – Prescription Only Medicine

Date of first inclusion in the Australian Register of Therapeutic Goods: 22nd November 2010

Date of most recent amendment: 5 October 2016