PRODUCT MONOGRAPH

[Pr]AVA-ONDANSETRON

Ondansetron Hydrochloride Dihydrate Tablets
8 mg ondansetron

Antiemetic (5-HT_3-receptor antagonist)

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Ava-Ondansetron

Ondansetron (as Hydrochloride Dihydrate)

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form/Strength	Clinically Relevant Nonmedicinal Ingredients
Oral	Tablet 8 mg ondansetron (as hydrochloride dihydrate)	lactose monohydrate For a complete listing see **DOSAGE FORMS, COMPOSITION AND PACKAGING** section.

INDICATIONS AND CLINICAL USE

Ava-Ondansetron is indicated for:

- Prevention of nausea and vomiting associated with emetogenic chemotherapy, including high dose cisplatin and radiotherapy.
- Prevention and treatment of postoperative nausea and vomiting.

Pediatrics (<18 years of age)
Post-Chemotherapy:
Clinical experience of ondansetron hydrochloride dihydrate in children is currently limited, however, ondansetron hydrochloride dihydrate was effective and well tolerated when given to children 4-12 years of age (see **DOSAGE AND ADMINISTRATION**). Ondansetron hydrochloride dihydrate is not indicated for the treatment of children 3 years or younger.

Post-Radiotherapy:
Safety and efficacy of ondansetron hydrochloride dihydrate in any age group in this population following radiotherapy has not been established and is therefore not indicated for use in this population.

Postoperative Nausea and Vomiting:
Safety and efficacy of ondansetron hydrochloride dihydrate in any age group in this population for the prevention and treatment of postoperative nausea and vomiting has not been established and is not indicated for use in this group.

Geriatrics (> 65 years of age)
Post-Chemotherapy and Radiotherapy:
Efficacy and tolerance of ondansetron hydrochloride dihydrate were similar to that observed in younger adults (see **DOSAGE AND ADMINISTARTION**).

Postoperative Nausea and Vomiting:
Clinical experience in the use of ondansetron hydrochloride dihydrate in the prevention and treatment of postoperative nausea and vomiting is limited and is not indicated for use in this population.

CONTRAINDICATIONS

- Ava-Ondansetron is contraindicated in patients with a history of hypersensitivity to the drug or any components of its formulations. For a complete listing, see **DOSAGE FORMS, COMPOSITION AND PACKAGING** section of the Product Monograph.

WARNINGS AND PRECAUTIONS

GENERAL
Cross-reactive hypersensitivity has been reported between different 5-HT_3 antagonists. Patients who have experienced hypersensitivity reactions to one 5-HT_3 antagonist have experienced more severe reactions upon being challenged with another drug of the same class. The use of a different 5-HT_3 receptor antagonist is not recommended as a replacement in cases in which a patient has experienced even a mild hypersensitivity type reaction to another 5-HT_3 antagonist.
Rarely and predominantly with intravenous ondansetron, transient ECG changes, including QT interval prolongation, have been reported (see **POSTMARKET ADVERSE DRUG REACTIONS**).

Ondansetron hydrochloride dihydrate is not effective in preventing motion-induced nausea and vomiting.

HEPATIC
There is no experience in patients who are clinically jaundiced. The clearance of an 8 mg intravenous dose of ondansetron hydrochloride dihydrate was significantly reduced and the serum half-life significantly prolonged in subjects with severe impairment of hepatic function. In patients with moderate or severe impairment of hepatic function, reductions in dosage are therefore recommended and a total daily dose of 8 mg should not be exceeded. This may be given as a single intravenous or oral dose. As ondansetron is known to increase large bowel transit time, patients with signs of subacute intestinal obstruction should be monitored following administration.

Ondansetron does not itself appear to induce or inhibit the cytochrome P_{450} drug-metabolizing enzyme system of the liver. Because ondansetron is metabolised by hepatic cytochrome P_{450}

drug-metabolizing enzymes, inducers or inhibitors of these enzymes may change the clearance and, hence, the half-life of ondansetron. On the basis of available data no dosage adjustment is recommended for patients on these drugs.

SPECIAL POPULATIONS

Pregnant Women: The safety of ondansetron for use in human pregnancy has not been established. Ondansetron is not teratogenic in animals. However, as animal studies are not always predictive of human response, the use of ondansetron in pregnancy is not recommended.

Nursing Women: Ondansetron is excreted in the milk of lactating rats. It is not known if it is excreted in human milk, however, nursing is not recommended during treatment with ondansetron.

Pediatrics (<3 years of age): Insufficient information is available to provide dosage recommendations for children 3 years of age or younger.

ADVERSE REACTIONS

CLINICAL TRIAL ADVERSE DRUG REACTIONS

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

Ondansetron hydrochloride dihydrate has been administered to over 2500 patients worldwide in controlled clinical trials and has been well tolerated.

The most frequent adverse events reported in controlled clinical trials were headache (11%) and constipation (4%). Other adverse events include sensations of flushing or warmth (<1%).

Cardiovascular: There have been rare reports of tachycardia, angina (chest pain), bradycardia, hypotension, syncope and electrocardiographic alterations.

Central Nervous System: There have been rare reports of seizures.

Dermatological: Rash has occurred in approximately 1% of patients receiving ondansetron.

Hypersensitivity: Rare cases of immediate hypersensitivity reactions sometimes severe, including anaphylaxis, bronchospasm, urticaria and angioedema have been reported.

Metabolic: There were transient increases of SGOT and SGPT of over twice the upper limit of normal in approximately 5% of patients. These increases did not appear to be related to dose or duration of therapy. There have been reports of liver failure and death in patients with cancer receiving concurrent medications including potentially hepatotoxic or cytotoxic chemotherapy

and antibiotics. The etiology of the liver failure is unclear. There have been rare reports of hypokalemia.

Other: There have been reports of abdominal pain, weakness and xerostomia.

Special Senses: Rare cases of transient visual disturbances (e.g. blurred vision) have been reported during or shortly after intravenous administration of ondansetron, particularly at rates equal to or greater than 30 mg in 15 minutes.

POSTMARKET ADVERSE DRUG REACTIONS

Over 250 million patient treatment days of ondansetron hydrochloride dihydrate have been supplied since the launch of the product worldwide. The following events have been spontaneously reported during post-approval use of ondansetron hydrochloride dihydrate, although the link to ondansetron cannot always be clearly established.

General Disorders

Rare cases of hypersensitivity reactions, such as laryngeal edema, stridor, laryngospasm and cardiopulmonary arrest have also been reported.

Cardiovascular Disorders

There have been rare reports (<0.01%) of myocardial infarction, myocardial ischemia, angina, chest pain with or without ST segment depression, arrhythmias (including ventricular or supraventricular tachycardia, premature ventricular contractions, and atrial fibrillation), electrocardiographic alterations (including second degree heart block), palpitations and syncope.

Rarely and predominantly with intravenous ondansetron, transient ECG changes, including QT interval prolongation have been reported (see **WARNINGS AND PRECAUTIONS**).

Eye Disorder

There have been very rare cases of transient blindness following ondansetron treatment, generally within the recommended dosing range and mainly during intravenous administration.

The majority of blindness cases reported resolved within 20 minutes. Although most patients had received chemotherapeutic agents, including cisplatin a few cases of transient blindness occurred following ondansetron administration for the treatment of postoperative nausea or vomiting and in the absence of cisplatin treatment. Some cases of transient blindness were reported as cortical in origin.

Hepatobiliary Disorders

Occasional asymptomatic increases in liver function tests have been reported.

Nervous System Disorder

Transient episodes of dizziness (<0.01%) have been reported during or upon completion of IV infusion of ondansetron. Rare reports (<0.01%) suggestive of extrapyramidal reactions such as oculogyric crisis/dystonic reactions (e.g. oro-facial dyskinesia, opisthotonos, tremor, etc.) have been reported without definitive evidence of persistent clinical sequelae.

Respiratory, Thoracic and Mediastinal Disorders
There have also been rare reports of hiccups.

DRUG INTERACTIONS

OVERVIEW
Specific studies have shown that there are no pharmacokinetic interactions when ondansetron is administered with alcohol, temazepam, furosemide, tramadol or propofol.

Ondansetron is metabolised by multiple hepatic cytochrome P-450 enzymes: CYP3A4, CYP2D6 and CYP1A2. Despite the multiplicity of metabolic enzymes capable of metabolising ondansetron which can compensate for an increase or decrease in enzyme activity, it was found that patients treated with inducers of CYP3A4 (i.e. phenytoin, carbamazepine, and rifampicin) demonstrated an increase in oral clearance of ondansetron and a decrease in ondansetron blood concentrations. No effect in ondansetron clearance secondary to enzyme inhibition or reduced activity (i.e. CYP2D6 genetic deficiency) has been identified to date.

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

DRUG-FOOD INTERACTIONS
Interactions with food have not been established.

DRUG-HERB INTERACTIONS
Interactions with herbal products have not been established.

DRUG-LABORATORY TEST INTERACTIONS
Interactions with laboratory tests have not been established.

DOSAGE AND ADMINISTRATION

CHEMOTHERAPY INDUCED NAUSEA AND VOMITING:
DOSING CONSIDERATIONS
- Ava-0ndansetron should be given as an initial dose prior to chemotherapy, followed by a dosage regimen tailored to the anticipated severity of emetic response caused by different cancer treatments.
- The dose of ondansetron hydrochloride dihydrate should be flexible in the range of 8-32 mg a day. The selection of dose regimen should be determined by the severity of the emetogenic challenge as shown below.

RECOMMENDED DOSE AND DOSAGE ADJUSTMENT

Administration

Use in Adults:

HIGHLY EMETOGENIC CHEMOTHERAPY (e.g. regimens containing cisplatin**)**

Ondansetron hydrochloride dihydrate has been shown to be effective in the following dose schedules for the prevention of emesis during the first 24 hours following chemotherapy:

Post-chemotherapy:

After the first 24 hours, Ava-Ondansetron tablets 8 mg orally every 8 hours[i] for up to 5 days.

LESS EMETOGENIC CHEMOTHERAPY (e.g. regimens containing cyclophosphamide, doxorubicin, epirubicin, fluorouracil and carboplatin)

Post-chemotherapy:

Ava-Ondansetron tablets 8 mg orally twice daily for up to 5 days.

Use in Children:

Clinical experience of ondansetron hydrochloride dihydrate in children is currently limited however, ondansetron hydrochloride dihydrate was effective and well tolerated when given to children 4-12 years of age. After therapy, ondansetron tablets 4 mg should be given orally every 8 hours[ii] for up to 5 days. For children 3 years of age and younger, there is insufficient information available to make dosage recommendations (see **INDICATIONS AND CLINICAL USE**).

Use in Elderly:

Efficacy and tolerance in patients aged over 65 years were similar to that seen in younger adults indicating no need to alter dosage schedules in this population.

RADIOTHERAPY INDUCED NAUSEA AND VOMITING

Use in Adults:

Initial Dose:

Ava-Ondansetron tablets 8 mg should be given orally 1 to 2 hours before radiotherapy.

Post-radiotherapy:

Ava-Ondansetron tablets 8 mg should be given orally every 8 hours[i] for up to 5 days after a course of treatment.

Use in Children:

There is no experience in clinical studies in this population.

Use in Elderly:

Efficacy and tolerance in patients aged over 65 years were similar to that seen in younger adults indicating no need to alter dosage schedules in this population.

POSTOPERATIVE NAUSEA AND VOMITING

Use in Adults:

For prevention of postoperative nausea and vomiting Ava-Ondansetron tablets may be given orally as a single dose of 16 mg one hour prior to anæsthesia.

Use in Children:
There is no experience in the use of ondansetron hydrochloride dihydrate in the prevention and treatment of postoperative nausea and vomiting in children (see **INDICATIONS AND CLINICAL USE**).

Use in Elderly:
There is limited experience in the use of ondansetron hydrochloride dihydrate in the prevention and treatment of postoperative nausea and vomiting in the elderly (see **INDICATIONS AND CLINICAL USE**).

PATIENTS WITH RENAL/HEPATIC IMPAIRMENT
Use in Patients with Impaired Renal Function:
No alteration of daily dosage, frequency of dosing, or route of administration is required.

Use in Patients with Impaired Hepatic Function:
The clearance of an 8 mg intravenous dose of ondansetron hydrochloride dihydrate was significantly reduced and the serum half-life significantly prolonged in subjects with severe impairment of hepatic function. In patients with moderate or severe impairment of hepatic function, reductions in dosage are therefore recommended and a total daily dose of 8 mg should not be exceeded.

No studies have been conducted to date in patients with jaundice.

PATIENTS WITH POOR SPARTEINE/DEBRISOQUINE METABOLISM
The elimination half-life and plasma levels of a single 8 mg intravenous dose of ondansetron did not differ between subjects classified as poor and extensive metabolisers of sparteine and debrisoquine. No alteration of daily dosage or frequency of dosing is recommended for patients known to be poor metabolisers of sparteine and debrisoquine.

[ii] The efficacy of twice daily dosage regimens for the treatment of post-chemotherapy emesis has been established only in adult patients receiving less emetogenic chemotherapy. The appropriateness of twice versus three times daily dosage regimens for other patient groups should be based on an assessment of the needs and responsiveness of the individual patient.

OVERDOSAGE

At present there is little information concerning overdosage with ondansetron. Individual doses of 84 mg and 145 mg and total daily doses as large as 252 mg have been administered with only mild side effects. There is no specific antidote for ondansetron, therefore, in cases of suspected overdosage, symptomatic and supportive therapy should be given as appropriate.

The use of Ipecac to treat overdosage with ondansetron is not recommended as patients are unlikely to respond due to the antiemetic action of ondansetron itself.

"Sudden blindness" (amaurosis) of 2 to 3 minutes duration plus severe constipation occurred in one patient who was administered 72 mg of ondansetron intravenously as a single dose. Hypotension (and faintness) occurred in another patient who took 48 mg of oral ondansetron. Following infusion of 32 mg over only a 4-minute period, a vasovagal episode with transient second degree heart block was observed. In all instances, the events resolved completely.

ACTION AND CLINICAL PHARMACOLOGY

MECHANISM OF ACTION

Ondansetron hydrochloride dihydrate is a selective antagonist of the serotonin receptor subtype, 5-HT_3. Its precise mode of action in the control of chemotherapy induced nausea and vomiting is not known. Cytotoxic chemotherapy and radiotherapy are associated with the release of serotonin (5-HT) from enterochromaffin cells of the small intestine, presumably initiating a vomiting reflex through stimulation of 5-HT_3 receptors located on vagal afferents. Ondansetron may block the initiation of this reflex. Activation of vagal afferents may also cause a central release of serotonin from the chemoreceptor trigger zone of the area postrema, located on the floor of the fourth ventricle. Thus, the antiemetic effect of ondansetron is probably due to the selective antagonism of 5-HT_3 receptors on neurons located in either the peripheral or central nervous systems, or both.

The mechanisms of ondansetron's antiemetic action in postoperative nausea and vomiting are not known.

Clinical trial results showing the number and percentage of patients exhibiting a complete response to ondansetron (0 emetic episodes) are shown in the tables below for both postoperative and chemotherapy induced emesis.

PREVENTION OF CHEMOTHERAPY INDUCED EMESIS – RESPONSE OVER 24 HOURS					
DOSE	Ondansetron 3 doses of 0.15 mg/kg	Placebo 3 doses of placebo	Ondansetron 8 mg IV + 1 mg/hr, 24 hours	Ondansetron 8 mg IV	Ondansetron 32 mg IV
# of patients	14	14	168	152	173
Treatment Response 0 emetic episodes 1-2 emetic episodes	 2 (14%) 8 (57%)	 0 (0%) 0 (0%)	 92 (55%) -	 82 (54%) -	 97 (56%) -

PREVENTION OF POSTOPERATIVE EMESIS - RESPONSE OVER 24 HOURS*						
	ORAL PREVENTION			INTRAVENOUS PREVENTION		
DOSE	Ondansetron 16 mg od	Placebo	p Value	Ondansetron 4 mg IV	Placebo	p Value
# of patients	253	250		136	139	
Treatment Response 0 emetic episodes	 126 (50%)	 79 (32%)	 <0.001	 103 (76%)	 62 (46%)	 < 0.001

TREATMENT OF POSTOPERATIVE EMESIS - RESPONSE OVER 24 HOURS*			
	INTRAVENOUS TREATMENT		
DOSE	Ondansetron 4 mg IV	Placebo	p Value
# of patients	104	117	
Treatment Response 0 emetic episodes	 49 (47%)	 19 (16%)	 <0.001

*The majority of patients included in the prevention and treatment of postoperative nausea and vomiting studies using ondansetron have been adult women receiving balanced anaesthesia for gynæcological surgery.

PHARMACOKINETICS

Absorption: Pharmacokinetic studies in human volunteers showed peak plasma levels of 20-30 ng/mL at around 1½ hours after an 8 mg oral dose of ondansetron. An 8 mg infusion of ondansetron resulted in peak plasma levels of 80-100 ng/mL. Repeat dosing of an 8 mg tablet every 8 hours for 6 days increased the peak plasma value to 40 ng/mL. A continuous intravenous infusion of 1 mg/hour after the initial 8 mg loading dose of ondansetron maintained plasma levels over 30 ng/mL during the following 24 hour period.

Distribution: The absolute bioavailability of ondansetron in humans was approximately 60% and the plasma protein binding was approximately 73%.

Metabolism: *In vitro* metabolism studies have shown that ondansetron is a substrate for human hepatic cytochrome P_{450} enzymes, including CYP1A2, CYP2D6 and CYP3A4. In terms of overall ondansetron turnover, CYP3A4 played the predominant role. Because of the multiplicity of metabolic enzymes capable of metabolising ondansetron, it is likely that inhibition or loss of one enzyme (e.g. CYP2D6 enzyme deficiency) will be compensated by others and may result in little change in overall rates of ondansetron clearance.

In a pharmacokinetic study of 16 epileptic patients maintained chronically on carbamazepine or phenytoin, reduction in AUC, C_{max} and $T_{½}$ of ondansetron was observed. This resulted in a significant increase in clearance. However, on the basis of available data, no dosage adjustment is recommended (see **WARNINGS AND PRECAUTIONS**).

Excretion: Following oral or IV administration, ondansetron is extensively metabolised and excreted in the urine and fæces. In humans, less than 10% of the dose is excreted unchanged in the urine. The major urinary metabolites are glucuronide conjugates (45%), sulphate conjugates (20%) and hydroxylation products (10%).

The half-life of ondansetron after either an 8 mg oral dose or intravenous dose was approximately 3-4 hours and may be extended to 6-8 hours in the elderly.

STORAGE AND STABILITY

Ava-Ondansetron tablets should be stored between 15 and 30ºC.

DOSAGE FORMS, COMPOSITION AND PACKAGING

Ava-Ondansetron tablets contain 8 mg of ondansetron base, in the form of ondansetron hydrochloride dihydrate. Ava-Ondansetron tablets also contain the following excipients: cellulose microcrystalline, lactose monohydrate, maize starch (pregelatinised), magnesium stearate, hypromellose, titanium dioxide, ferric oxide yellow.

Ava-Ondansetron 8 mg tablets
Yellow, film-coated tablet, formed like a bean with an embossment “O” on one side and “8" on the other side. Each tablet contains 8 mg ondansetron (as hydrochloride dihydrate). Available in blister packs of 10 tablets.

PART II: SCIENTIFIC INFORMATION

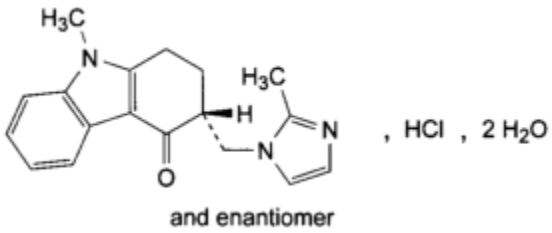
PHARMACEUTICAL INFORMATION

Drug Substance

Proper name: Ondansetron hydrochloride dihydrate

Chemical name: (±)-2,3-Dihydro-9-methyl-3-[(2-methylimidazol-1-yl)methyl]carbazol-4(1 H)-one monohydrochloride dihydrate.

Structural formula:



Molecular formula: $C_{18}H_{19}N_3O \cdot HCl \cdot 2H_2O$ (hydrochloride dihydrate)
Molecular mass: 365.9 g/mol

Physicochemical properties:

Description and Solubility:
Ondansetron hydrochloride dihydrate is a white to off-white powder.

Hydrochloride dihydrate
Sparingly soluble in water and in alcohol, soluble in methanol, slightly soluble in methylene chloride. The melting point of ondansetron hydrochloride dihydrate is about 177° C. pKa is 7.4 and pH of 1% w/v solution in water is approximately 4.6. The distribution coefficient between n-octanol and water is pH dependent:

log D = 2.2 at a pH of 10.60

log D = 0.6 at a pH of 5.95

CLINICAL TRIALS

Please find below the results of the open, randomized, 2 periods, 2-way crossover, bioequivalence study of ondansetron hydrochloride dihydrate (equivalent to 8 mg ondansetron) film-coated tablets (Hexal AG, Germany) and Zofran® 8 mg film-coated tablets (Glaxo

Wellcome GmbH & Co., Germany) administered as a single oral dose of 8 mg in 24 healthy adult male volunteers under fasting conditions.

Summary Table of Comparative Bioavailability Data for a Single-Dose Fasting Study of Ondansetron Hydrochloride (1 x 8 mg) Tablets

Ondansetron (1 x 8 mg) From measured data Geometric Mean Arithmetic Mean (CV%)				
PARAMETER	Ondansteron	Zofran® 8 mg tablet ***	% RATIO OF GEOMETRIC MEANS	90 % CONFIDENCE INTERVALS
AUC_T (ng.h/mL)	204.99 215.64 (32.73)	212.32 221.85 (28.60)	96.12	91.00-101.54
AUC_∞ (ng.h/mL)	215.60 228.73 (34.07)	223.37 234.05 (29.67)	96.52	91.27-102.06
C_{max} (ng/mL)	30.25 31.94 (34.17)	32.14 33.73 (31.64)	94.12	87.99-100.68
T_{max}* (h)	1.50 (1.00-6.00)	1.50 (0.750-4.00)	---	---
$T_{½}$** (h)	5.61 (18.92)	5.51 (17.73)	---	---

* expressed as median (range) only.
** expressed as arithmetic mean (CV%) only.
*** Zofran®, manufactured by Glaxo Wellcome Gmbh & Co.
Country where Zofran® was purchased: Germany.

Please find below the results of the open, randomized, 2 periods, 2-way crossover, bioequivalence study of ondansetron hydrochloride dihydrate (equivalent to 4 mg ondansetron) film-coated tablets and Zofran® 4 mg film-coated tablets (Glaxo Wellcome GmbH & Co., Germany) administered as a single oral dose of 4 mg in 26 healthy adult male volunteers under fasting conditions.

Summary Table of Comparative Bioavailability Data for a Single-Dose Fasting Study of Ondansetron Hydrochloride (1 x 4 mg) Tablets

Ondansetron (1 x 4 mg) From measured data Geometric Mean Arithmetic Mean (CV%)				
PARAMETER	Ondansteron	Zofran® 4 mg tablet ***	% RATIO OF GEOMETRIC MEANS	90 % CONFIDENCE INTERVALS
AUC_T (ng.h/mL)	105.97 111.75 (33.42)	104.26 109.30 (31.73)	101.64	96.25-107.33
AUC_∞ (ng.h/mL)	111.40 117.98 (35.14)	109.37 115.11 (33.51)	101.85	96.18-107.86
C_{max} (ng/mL)	15.05 15.70 (31.01)	14.57 15.29 (32.43)	103.32	97.60-109.36
T_{max}* (h)	1.70 (0.750-3.00)	1.50 (0.750-4.08)	---	---
$T_{½}$** (h)	5.12 (20.47)	5.09 (19.88)	---	---

* expressed as median (range) only.
** expressed as arithmetic mean (CV%) only.
*** Zofran®, manufactured by Glaxo Wellcome Gmbh & Co.
Country where Zofran® was purchased: Germany.

DETAILED PHARMACOLOGY

ANIMAL PHARMACOLOGY

Pharmacodynamics

The ferret provides an excellent model for demonstrating the antiemetic action of drugs. Emesis can be induced by antineoplastic drugs or whole body irradiation. Behavioural changes associated with these treatments are noted in these animals and may also provide a parallel for the human experience of nausea.

The antiemetic action of ondansetron has been evaluated in both male and female ferrets given cisplatin (9-10 mg/kg), cyclophosphamide (200 mg/kg) or irradiation (2 and 8 Gy, 250kV). Intravenous doses of ondansetron (0.1-1 mg/kg) abolished cisplatin-induced emesis for up to 2 hours. In cyclophosphamide-induced emesis, subcutaneous doses of 0.5 mg/kg ondansetron completely eliminated vomiting, significantly reduced retching and delayed the onset of these responses.

The radiation-induced emesis, 0.5 mg/kg ondansetron alone completely and rapidly eliminated retching and vomiting.

The antiemetic effects of ondansetron (0.1 mg/kg) in combination with dexamethasone (2-5 mg/kg) were potentiated in ferrets with cyclophosphamide-induced emesis, compared with

ondansetron alone. Ondansetron with dexamethasone produced a significant reduction in retching (65%) and vomiting (72%).

Serotonin receptors of the $5HT_3$ type are present both peripherally and on vagal nerve terminals. Ondansetron probably acts by preventing activation of these receptors or receptors located in other regions of the central nervous system. Both the peripheral and central nervous systems appear to be involved since both abdominal vagotomy and microinjection of ondansetron and other 5-HT_3 antagonists directly into the area postrema eliminate cisplatin-induced emesis, while 5-HT_1-like (methiothepin maleate) and 5-HT_2 (ketanserin) antagonists have no effect.

Ondansetron is highly selective for 5-HT_3 receptors and shows negligible binding to other receptors such as 5-HT_1-like, 5-HT_2, α1 and α2 adrenoceptors, β1 and β2 adrenoceptors, D_1 and D_2 muscarinic, nicotinic, $GABA_A$, H_1 and H_2 receptors.

The pharmacological specificity of ondansetron may explain the observed lack of extrapyramidal side effects often seen following similar therapy with metoclopramide, which preferentially binds to dopamine receptors of the D_2 subtype.

Among its secondary effects, ondansetron has also been shown to cause a dose-dependent increase in the rate of gastric emptying in the guinea pig which is significant at doses of 0.01-0.1 mg/kg. As gastric stasis is frequently associated with nausea, stimulation of gastric motility may be a beneficial action of ondansetron. In the cat, dog and monkey, ondansetron has little effect on heart rate, blood pressure or ECG at intravenous doses up to 3 mg/kg.

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 concentration at which this effect was seen may be attainable with the 32 mg IV dose, however, the clinical relevance of this finding is uncertain.

Pharmacokinetics

In mice, rats, rabbits and dogs dosed at 1 mg/kg orally and/or intravenously, the plasma half-life of ondansetron was less than 1 hour, but the half-lives of its metabolites were significantly longer. Peak plasma concentrations of ondansetron in rats and dogs ranged from 351 to 419 ng/mL for the IV dose and 8 to 15 ng/mL for the oral dose. Plasma levels were linear over a 30 fold dose range. In repeat dose studies there was no apparent accumulation of ondansetron.

Ondansetron is almost completely absorbed in animals, and is rapidly metabolized by N-demethylation and hydroxylation of the indole ring, followed by conjugation with glucuronic acid and sulphate. There is significant first-pass metabolism after oral doses.

Ondansetron and its metabolites are rapidly and widely distributed in tissues, reaching higher levels than the corresponding plasma levels. In the rat and dog, ondansetron binds reversibly to tissues containing melanin and elastin. In rats and man, plasma protein binding is about 73%, while it is slightly lower in the dog (60%). Ondansetron and its metabolites cross the blood-brain barrier to only a slight extent.

HUMAN PHARMACOLOGY

Pharmacodynamics

In vivo pharmacodynamic studies have investigated the effects of ondansetron on gastric emptying, small bowel transit time and oesophageal motility.

Both oral (16 mg tid) and intravenous (5-10 mg) doses of ondansetron failed to produce a significant effect on gastric emptying in both healthy volunteers and in patients suffering from delayed gastric emptying. However, in one study intravenous doses of 8 mg did increase gastric emptying in over half the volunteers tested.
Intravenous infusion of either 1 mg or 5 mg ondansetron tended to increase small bowel transit times and single intravenous doses of 10 mg ondansetron have been reported to decrease sphincter pressure in the lower oesophagus in some subjects.
In psychomotor testing ondansetron does not impair performance nor cause sedation.

TOXICOLOGY

ACUTE TOXICITY

Single doses of ondansetron up to the LD_{50} in mice and in rats were generally well tolerated. Reactions, including tremor and convulsive behaviour, occurred only at near lethal levels.

Species	LD_{50} (mg/kg)	
	Oral	IV
Mice	10-30	1.0-2.5
Rats	100-150	15-20

All deaths resulted from the acute effects of treatment, the observed clinical signs being consistent with the central nervous system effects associated with behavioural depression. These effects were not associated with any apparent histopathological changes in the brain. No target organ toxicity was identified.

LONG TERM TOXICITY

Subacute Toxicity Studies

Species	Route	Dose (mg/kg/day)	Duration of Study	Results
Rats	Oral	160	7 weeks	Well tolerated
	IV	12	5 weeks	Well tolerated
Dogs	Oral	7.5-25	5 weeks	Transient post-dosing clinical reactions associated with behavioural depression (at highest dose levels)
	IV	2-8	5 weeks	

Maximum daily dose levels in rats were found to be higher when doses were gradually increased. Identical doses were rapidly lethal to rats not previously exposed to ondansetron. Post-dosing

reactions, in both rats and dogs, included ataxia, exophthalmia, mydriasis, tremor and respiratory changes. Increases in liver enzymes (SGPT and SGOT) were noted at high dose levels. Dogs dosed at 6.75 mg/kg/day intravenously exhibited vein irritancy in the form of constriction and thickening, creating resistance to needle penetration. The changes were noted after seven days treatment but were reversed by decreasing the dose concentration.

Chronic Toxicity

Species	Duration	Max. no-effect Dose (mg/kg/day)	Effects
Rat Dogs	18 months 12 months	1 12	Usually transient and restricted to highest dose

Carcinogenicity Studies

Species	Route	Dose (mg/kg/day)	Durations of Study	Results
Mice	Oral	1-40 (max. oral dose 30)	2 years	No treatment related increases in tumour incidence.
Rats	Oral	1-25 (max. oral dose 10)	2 years	Proportion of benign/malignant tumours also remained consistent with the pathological background of the animals studied.

There was no evidence of a tumourigenic effect of ondansetron in any tissue.

MUTAGENICITY STUDIES

No evidence of mutagenicity was observed in microbial mutagen tests using mutant strains of *Salmonella typhimurium*, *Escherichia coli* or *Saccharomyces cerevisiae*, with or without a rat-liver post-mitochondrial metabolizing system.
There was also no evidence of damage to genetic material noted in *in vitro* V-79 mammalian cell mutation studies, *in vitro* chromosome aberration tests using human peripheral lymphocytes, or *in vivo* chromosome aberration assays in mouse bone marrow.

REPRODUCTION AND TERATOLOGY

Ondansetron was not teratogenic in rats and rabbits at dosages up to the maximum non-convulsive level, (rat: 15 mg/kg/day, rabbit: 30 mg/kg/day). No adverse effects on pregnancy or foetal and postnatal development were detected in rats and no fœtal abnormalities were observed in rabbits after oral administration of ondansetron.

A slight maternal toxicity was observed at the highest dose level in intravenous organogenesis (4.0 mg/kg/day) studies in the rabbit. Effects included maternal body weight loss and increased incidence of early fœtal death. In a rat fertility study, there was a dose-related decrease in the proportion of surviving pups of the F2 generation; however, the significance of this is unclear.

Administration of ondansetron to pregnant rats and rabbits, indicated there was fœtal exposure to low levels of ondansetron and its metabolites. Ondansetron is retained in the fœtal eye presumably bound to melanin. In rats, the transfer of ondansetron and its metabolites into breast

milk was extensive. The concentration of unchanged ondansetron in breast milk was higher than in corresponding plasma samples.

Daily administration of ondansetron at dosages up to 15 mg/kg/day to pregnant rats from day 17 of pregnancy to litter day 22 had no effects on pregnancy of the parental generation or on postnatal development and mating of the F1 generation. Fœtal development of the F2 generation was comparable to controls; however, the number of implantations and viable fœtuses was reduced in the highest dosage group when compared with controls.

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PART III: CONSUMER INFORMATION

PR AVA-ONDANSETRON

Ondansetron (as Hydrochloride Dihydrate)

This leaflet is part III of a three-part "Product Monograph" published when Ava-Ondansetron was approved for sale in Canada and is designed specifically for consumers. This leaflet is a summary and will not tell you everything about Ava-Ondansetron. Contact your doctor or pharmacist if you have any questions about the drug.

Ava-Ondansetron can only be obtained with a prescription from your doctor.

ABOUT THIS MEDICATION

What the medication is used for:

The name of your medicine is Ava-Ondansetron tablets (ondansetron hydrochloride dihydrate). This medicine is one of a group called antiemetics.

Ava-Ondansetron is intended to prevent the nausea (feeling of sickness) and vomiting, which can occur while undergoing cancer chemotherapy and radiotherapy, or after receiving general anaesthesia during an operation.

What it does:

These treatments are thought to cause the release of natural substance (serotonin), which can cause you to feel sick and to vomit. Ondansetron stops this from happening and helps prevent you from vomiting or feeling sick.

When it should not be used:

Do not take Ava-Ondansetron tablets:

- If you have a history of hypersensitivity (an allergic reaction) to any ingredient in Ava-Ondansetron (see **What the important nonmedicinal ingredients are**).

What the medicinal ingredient is:

The medicinal ingredient is ondansetron (as hydrochloride dihydrate).

What the important nonmedicinal ingredients are:

Ava-Ondansetron tablets also contain : cellulose microcrystalline, lactose monohydrate, maize starch (pregelatinised), magnesium stearate, hypromellose, titanium dioxide, ferric oxide yellow.

What dosage forms it comes in:

Ava-Ondansetron tablets is supplied as 8 milligrams of ondansetron. Your doctor will decide which strength you need.

WARNINGS AND PRECAUTIONS

BEFORE you use Ava-Ondansetron talk to your doctor or pharmacist if:

- you have a history of hypersensitivity (an allergic reaction) to the drug or any components of its composition.
- you are pregnant or likely to become pregnant.
- you are breast feeding.
- you have liver problems.
- you have signs of intestinal obstruction.
- you have history of heart problems.

If you experience wheezing and tightness of the chest, heart throbbing, swelling of eyelids, face or lips, or develop a skin rash, skin lumps or hives, **contact your doctor immediately. Do not take any more medicine unless your doctor tells you to do so.**

INTERACTIONS WITH THIS MEDICATION

Tell your doctor about all medicines you are taking including those you have bought yourself. If you are taking any medicines containing tramadol, (such as TRAMACET) Ava-Ondansetron tablets may reduce its effectiveness.

PROPER USE OF THIS MEDICATION

The label on the container of your medicine should tell you how often to take your medicine and how many doses you should take each time. If not, or if you are not sure, consult your doctor or pharmacist.

Do not take more doses, or take them more often than your doctor prescribes. If, however, you vomit within one hour of taking your medicine, you should take the same amount of medicine again. If vomiting persists, consult your doctor.

Usual dose:

Chemotherapy Induced Nausea and Vomiting

You will receive Ava-Ondansetron prior to chemotherapy. Based on how likely you are to experience nausea and/or vomiting, caused by your cancer treatment, your doctor will tell you the amount you need to take and how frequently.

Adults: The dose of Ava-Ondansetron will depend on the potential of your chemotherapy treatment to cause you to vomit and /or have nausea.

Children (4 to 12 years old): After chemotherapy, take 4 mg orally every 8 hours for up to 5 days.

Radiotherapy Induced Nausea and Vomiting

Adults: Take 8 mg orally 1 to 2 hours before radiotherapy. After therapy, take 8 mg orally every 8 hours for up to 5 days after a course of treatment.

Prevention of Postoperative Nausea and Vomiting
Adults: Take 16 mg orally one hour before anaesthesia.

If you have a liver problem, your dose may be altered. Please follow the instructions of your doctor.

Overdose:
In the event you accidentally take more doses than prescribed, immediately contact your doctor or hospital emergency department or nearest poison control centre.

Missed Dose:
If you miss a dose and do not feel sick, take the next dose when it is due.
If you forget to take your medicine and feel sick or vomit, take a dose as soon as possible.

If your doctor decides to stop the treatment, do not keep any leftover medicine unless your doctor tells you to.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

You may experience headaches, a feeling of warmness, flushing or constipation, while taking Ava-Ondansetron. There is no need to stop taking your medicine, but you should tell your doctor about these symptoms at your next visit.

If your nausea (feeling of sickness) or vomiting do not improve while taking ondansetron, consult your doctor for further advice.

If you feel unwell or have symptoms that you do not understand, you should contact your doctor immediately.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Frequency	Side Effect/ Symptom	Talk with your doctor or pharmacist	Stop taking the drug and call your doctor or pharmacist
Uncommon	Heart problems such as fast/slow heart beat, chest pain		✓
	Seizures		✓
Rare	Eye problems such as blurred vision	✓	
	Immediate allergic reaction and symptoms such as swelling of the mouth, throat, difficulty in breathing, rash, hives, increased heart rate		✓
Very Rare	Eye problems such as temporary blindness	✓	

This is not a complete list of side effects. For any unexpected effects while taking Ava-Ondansetron tablets*, contact your doctor or pharmacist.*

HOW TO STORE IT

Keep your medicine in a safe place where children cannot reach it. Your medicine may harm them.

Ava-Ondansetron tablets should be kept at room temperature in a well closed container and protected from light. Do not refrigerate or freeze.

REPORTING SUSPECTED SIDE EFFECTS

To monitor drug safety, Health Canada collects information on serious and unexpected effects of drugs. If you suspect you have had a serious or unexpected reaction to this drug you may notify Health Canada by:

Toll-free telephone: 1-866-234-2345
Toll-free fax: 1-866-678-6789
By email: cadrmp@hc-sc.gc.ca

By regular mail:
National AR Centre
Marketed Health Products Safety and Effectiveness Information Division
Marketed Health Products Directorate
Tunney's Pasture, AL 0701C
Ottawa ON K1A 0K9

NOTE: Before contacting Health Canada, you should contact your physician or pharmacist.

MORE INFORMATION

Remember: This medicine is for you. Only a doctor can prescribe it for you. Never give it to someone else. It may harm them even if their symptoms are the same as yours.

This leaflet does not contain the complete information about your medicine. If any questions remain unanswered or you are not sure about something, you should ask your doctor or pharmacist.

You may want to read this leaflet again. **PLEASE DO NOT THROW IT AWA**Y until you have finished your medicine.

This document, plus the full product monograph prepared for health professionals, can be obtained by contacting the sponsor, Avanstra Inc., at: 1-855-708-3678
or
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