ADOSETRON
(O n d a n s e t r o n)

8mg

Tablet

COMPOSITION

Each film-coated tablet contains:
Ondansetron …… 8mg

THERAPEUTIC INDICATIONS

Ondansetron is indicated for the prevention of nausea and vomiting associated with:

• highly emetogenic cancer chemotherapy, including cisplatin greater than or equal to 50 mg/m^2

• initial and repeat courses of moderately emetogenic cancer chemotherapy

• radiotherapy in patients receiving either total body irradiation, single high-dose fraction to the abdomen, or daily fractions to the abdomen.

Ondansetron is also indicated for the prevention of postoperative nausea and/or vomiting

DOSAGE AND ADMINISTRATION

The recommended dosage regimens for adult and pediatric patients are described in Table 1 and Table 2, respectively.

Table 1: Adult Recommended Dosage Regimen for Prevention of Nausea and Vomiting

Indication	Dosage Regimen
Highly Emetogenic Cancer Chemotherapy	A single 24-mg dose administered 30 minutes before the start of single-day highly emetogenic chemotherapy, including cisplatin greater than or equal to 50 mg/m2.
Moderately Emetogenic Cancer Chemotherapy	8 mg administered 30 minutes before the start of chemotherapy, with a subsequent 8-mg dose 8 hours after the first dose. Then administer 8 mg twice a day (every 12 hours) for 1 to 2 days after completion of chemotherapy.
Radiotherapy	For total body irradiation: 8 mg administered 1 to 2 hours before each fraction of radiotherapy each day. For single high-dose fraction radiotherapy to the abdomen: 8 mg administered 1 to 2 hours before radiotherapy, with subsequent 8-mg doses every 8 hours after the first dose for 1 to 2 days after completion of radiotherapy. For daily fractionated radiotherapy to the abdomen: 8 mg administered 1 to 2 hours before radiotherapy, with subsequent 8-mg doses every 8 hours after the first dose for each day radiotherapy is given.
Postoperative	16 mg administered 1 hour before induction of anesthesia.

Table 2: Pediatric Recommended Dosage Regimen for Prevention of Nausea and Vomiting

Indication	Dosage Regimen
Moderately Emetogenic Cancer Chemotherapy	12 to 17 years of age: 8 mg administered 30 minutes before the start of chemotherapy, with a subsequent 8-mg dose 8 hours after the first dose. Then administer 8 mg twice a day (every 12 hours) for 1 to 2 days after completion of chemotherapy. 4 to 11 years of age: 4 mg administered 30 minutes before the start of chemotherapy, with a subsequent 4-mg dose 4 and 8 hours after the first dose. Then administer 4 mg three times a day for 1 to 2 days after completion of chemotherapy.

Dosage in Hepatic Impairment
In patients with severe hepatic impairment (Child-Pugh score of 10 or greater), do not exceed a total daily dose of 8 mg

Dosage in Renal Impairment
No alteration of daily dosage or frequency of dosing, or route of administration are required.

Method of Administration
The tablets should be swallowed whole with liquid.

CONTRAINDICATIONS

Ondansetron is contraindicated in patients:

known to have hypersensitivity (e.g., anaphylaxis) to ondansetron or any of the components of the formulation

receiving concomitant apomorphine due to the risk of profound hypotension and loss of consciousness

SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Hypersensitivity Reactions

Hypersensitivity reactions, including anaphylaxis and bronchospasm, have been reported in patients who have exhibited hypersensitivity to other selective 5-HT3 receptor antagonists. If hypersensitivity reactions occur, discontinue use of Ondansetron; treat promptly per standard of care and monitor until signs and symptoms resolve.

QT Prolongation

Electrocardiogram (ECG) changes, including QT interval prolongation have been seen in patients receiving ondansetron. 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. ECG monitoring is recommended in patients with electrolyte abnormalities (e.g., hypokalemia or hypomagnesemia), congestive heart failure, bradyarrhythmias, or patients taking other medicinal products that lead to QT prolongation.

Serotonin Syndrome

The development of serotonin syndrome has been reported with 5-HT3 receptor antagonists alone. Most reports have been associated with concomitant use of serotonergic drugs (e.g., selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors (SNRIs), monoamine oxidase inhibitors, mirtazapine, fentanyl, lithium, tramadol, and intravenous methylene blue). Some of the reported cases were fatal. Serotonin syndrome occurring with overdose of Ondansetron alone has also been reported. The majority of reports of serotonin syndrome related to 5-HT3 receptor antagonist use occurred in a post-anesthesia care unit or an infusion center.

Symptoms associated with serotonin syndrome may include the following combination of signs and symptoms: mental status changes (e.g., agitation, hallucinations, delirium, and coma), autonomic instability (e.g., tachycardia, labile blood pressure, dizziness, diaphoresis, flushing, hyperthermia), neuromuscular symptoms (e.g., tremor, rigidity, myoclonus, hyperreflexia, incoordination), seizures, with or without gastrointestinal symptoms (e.g., nausea, vomiting, diarrhea). Patients should be monitored for the emergence of serotonin syndrome, especially with concomitant use of Ondansetron and other serotonergic drugs. If symptoms of serotonin syndrome occur, discontinue Ondansetron and initiate supportive treatment. Patients should be informed of the increased risk of serotonin syndrome, especially if Ondansetron is used concomitantly with other serotonergic drugs.

Masking of Progressive Ileus and Gastric Distension

The use of Ondansetron in patients following abdominal surgery or in patients with chemotherapy-induced nausea and vomiting may mask a progressive ileus and/or gastric distension. Monitor for decreased bowel activity, particularly in patients with risk factors for gastrointestinal obstruction.

Ondansetron is not a drug that stimulates gastric or intestinal peristalsis. It should not be used instead of nasogastric suction

EFFECTS ON ABILITY TO DRIVE

Ondansetron has no or negligible influence on the ability to drive and use machines.

In psychomotor testing ondansetron does not impair performance nor cause sedation. No detrimental effects on such activities are predicted from the pharmacology of ondansetron

FERTILITY, PREGNANCY AND LACTATION

Women of childbearing potential

Women of childbearing potential should consider the use of contraception.

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 not be used during the first trimester of pregnancy.

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.

Fertility

There is no information on the effects of ondansetron on human fertility.

ADVERSE DRUG REACTIONS

Tabulated list of adverse reactions

Adverse events are listed below by system organ class and frequency. Frequencies are defined as:

very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000) and very rare (<1/10,000). 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. 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)[1].
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 IV administration [2].
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 [3].

1. Observed without definitive evidence of persistent clinical sequelae.

2. 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.

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

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at pv@searlecompany.com

OVERDOSE

Symptoms and Signs

There is limited experience of ondansetron overdose. In the majority of cases, symptoms were similar to those already reported in patients receiving recommended doses. Manifestations that have been reported include visual disturbances, severe constipation, hypotension and a vasovagal episode with transient second-degree AV block Ondansetron prolongs the QT interval in a dose-dependent fashion. ECG monitoring is recommended in cases of overdose.

Paediatric population

Paediatric cases consistent with serotonin syndrome have been reported after inadvertent oral overdoses of ondansetron (exceeded estimated ingestion of 4 mg/kg) in infants and children aged 12 months to 2 years.

Management

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

Further management should be as clinically indicated or as recommended by the national poisons centre, where available.

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.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamic properties

Pharmacotherapeutic group: Serotonin (5HT3) antagonist, ATC code: A04AA01

Mechanism of action

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.

Pharmacokinetic properties

Absorption

Following oral administration, ondansetron is passively and completely absorbed from the gastrointestinal tract and undergoes first pass metabolism. 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. Mean bioavailability in healthy male subjects, following the oral administration of a single 8 mg tablet, is approximately 55 to 60%. Bioavailability, following oral administration, is slightly enhanced by the presence of food but unaffected by antacids.

The disposition of ondansetron following oral, intramuscular (IM) and intravenous (IV) dosing is similar with a terminal half life of about 3 hours and steady state volume of distribution of about 140 L. Equivalent systemic exposure is achieved after IM and IV administration of ondansetron.

A 4mg 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 concentrations of about 25 ng/mL are attained within 10 minutes of injection.

Following administration of ondansetron suppository, plasma ondansetron concentrations become detectable between 15 and 60 minutes after dosing. Concentrations rise in an essentially linear fashion, until peak concentrations of 20-30 ng/mL are attained, typically 6 hours after dosing. Plasma concentrations then fall, but at a slower rate than observed following oral dosing due to continued absorption of ondansetron. The absolute bioavailability of ondansetron from the suppository is approximately 60% and is not affected by gender. The half life of the elimination phase following suppository administration is determined by the rate of ondansetron absorption, not systemic clearance and is approximately 6 hours. Females show a small, clinically insignificant, increase in half-life in comparison with males.

Distribution

Ondansetron is not highly protein bound (70-76%).

Biotransformation and Elimination

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.

Special Patient Populations:

Gender

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).

Children and Adolescents (aged 1 month to 17 years)

In paediatric patients aged 1 to 4 months (n=19) undergoing surgery, weight normalised clearance was approximately 30% slower than in patients aged 5 to 24 months (n=22) but comparable to the patients aged 3 to 12 years. The half-life in the patient population aged 1 to 4 month 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. The differences in pharmacokinetic parameters in the 1 to 4 month patient population can be explained in part by the higher percentage of total body water in neonates and infants and a higher volume of distribution for water soluble drugs like ondansetron.

In paediatric patients aged 3 to 12 years undergoing elective surgery with general anaesthesia, the absolute values for both the clearance and volume of distribution of ondansetron were reduced in comparison to values with adult patients. Both parameters increased in a linear fashion with weight and by 12 years of age, the values were approaching those of young adults. When clearance and volume of distribution values were normalised by body weight, the values for these parameters were similar between the different age group populations. Use of weight-based dosing compensates for age-related changes and is effective in normalising systemic exposure in paediatric patients.

Population pharmacokinetic analysis was performed on 428 subjects (cancer patients, surgery patients and healthy volunteers) aged 1 month to 44 years following intravenous administration of ondansetron. Based on this analysis, systemic exposure (AUC) of ondansetron following oral or IV dosing in children and adolescents was comparable to adults, with the exception of infants aged 1 to 4 months. Volume was related to age and was lower in adults than in infants and children. Clearance was related to weight but not to age with the exception of infants aged 1 to 4 months. It is difficult to conclude whether there was an additional reduction in clearance related to age in infants 1 to 4 months or simply inherent variability due to the low number of subjects studied in this age group. Since patients less than 6 months of age will only receive a single dose in PONV a decreased clearance is not likely to be clinically relevant.

Elderly

Early Phase I studies in healthy elderly volunteers showed a slight age-related decrease in clearance, and an increase in half-life of ondansetron. However, wide inter-subject variability resulted in considerable overlap in pharmacokinetic parameters between young (< 65 years of age) and elderly subjects (≥ 65 years of age) and there were no overall differences in safety or efficacy observed between young and elderly cancer patients enrolled in CINV clinical trials to support a different dosing recommendation for the elderly.

Based on more recent ondansetron plasma concentrations and exposure-response modelling, a greater effect on QTcF is predicted in patients ≥75 years of age compared to young adults. Specific dosing information is provided for patients over 65 years of age and over 75 years of age for intravenous dosing.

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). A study in patients with severe renal impairment who required regular hemodialysis (studied between dialyses) showed ondansetron's pharmacokinetics to be essentially unchanged following IV administration.

Hepatic impairment

Following oral, intravenous or intramuscular dosing in patients with severe hepatic impairment, ondansetron's systemic clearance is markedly reduced with prolonged elimination half-lives (15-32 hours) and an oral bioavailability approaching 100% due to reduced pre-systemic metabolism. The pharmacokinetics of ondansetron following administration as a suppository have not been evaluated in patients with hepatic impairment.

Summary of Clinical Studies

Prevention of Chemotherapy-Induced Nausea and Vomiting

Highly Emetogenic Chemotherapy

In 2 randomized, double-blind, monotherapy trials, a single 24-mg oral dose of Ondansetron was superior to a relevant historical placebo control in the prevention of nausea and vomiting associated with highly emetogenic cancer chemotherapy, including cisplatin greater than or equal to 50 mg/m2. Steroid administration was excluded from these clinical trials. More than 90% of patients receiving a cisplatin dose greater than or equal to 50 mg/m^2 in the historical-placebo comparator, experienced vomiting in the absence of antiemetic therapy.

The first trial compared oral doses of ondansetron 24 mg as a single dose, 8 mg every 8 hours for 2 doses, and 32 mg as a single dose in 357 adult cancer patients receiving chemotherapy regimens containing cisplatin greater than or equal to 50 mg/m2. The first or single dose was administered 30 minutes prior to chemotherapy. A total of 66% of patients in the ondansetron 24-mg once-a-day group, 55% in the ondansetron 8-mg twice-a-day group, and 55% in the ondansetron 32-mg once-a-day group, completed the 24-hour trial period with 0 emetic episodes and no rescue antiemetic medications, the primary endpoint of efficacy. Each of the 3 treatment groups was shown to be statistically significantly superior to a historical placebo control.

In the same trial, 56% of patients receiving a single 24-mg oral dose of ondansetron experienced no nausea during the 24-hour trial period, compared with 36% of patients in the oral ondansetron 8-mg twice-a-day group (P = 0.001) and 50% in the oral ondansetron 32-mg once-a-day group. Dosage regimens of Ondansetron 8 mg twice daily and 32 mg once daily are not recommended for the prevention of nausea and vomiting associated with highly emetogenic chemotherapy.

In a second trial, efficacy of a single 24-mg oral dose of Ondansetron for the prevention of nausea and vomiting associated with highly emetogenic cancer chemotherapy, including cisplatin greater than or equal to 50 mg/m2, was confirmed.

Moderately Emetogenic Chemotherapy

A randomized, placebo-controlled, double-blind trial was conducted in the US in 67 patients receiving a cyclophosphamide-based chemotherapy regimen containing doxorubicin. The first 8-mg dose of Ondansetron was administered 30 minutes before the start of chemotherapy, with a subsequent dose 8 hours after the first dose, followed by 8 mg of Ondansetron twice a day for 2 days after the completion of chemotherapy. Ondansetron was significantly more effective than placebo in preventing vomiting. Treatment response was based on the total number of emetic episodes over the 3-day trial period. The results of this trial are summarized in Table.

Table: Emetic Episodes - Treatment Response in Patients Receiving Moderately Emetogenic Chemotherapy (Cyclophosphamide-based Regimen Containing Doxorubicin)

aMedian undefined since at least 50% of the patients were withdrawn or had more than 2 emetic episodes.
bMedian undefined since at least 50% of patients did not have any emetic episodes.

	Ondansetron **(n = 33)**	**Placebo (n = 34)**	***P*-value**
Treatment response			
0 Emetic episodes	20 (61%)	2 (6%)	< 0.001
1 to 2 Emetic episodes	6 (18%)	8 (24%)	
More than 2 emetic episodes/withdrawn	7 (21%)	24 (71%)	< 0.001
Median number of emetic episodes	0.0	Undefineda	
Median time to first emetic episode (hours)	Undefinedb	6.5	

In a double-blind, US trial in 336 patients receiving a cyclophosphamide-based chemotherapy regimen containing either methotrexate or doxorubicin, Ondansetron 8 mg administered twice a day, was as effective as Ondansetron 8 mg administered 3 times a day in preventing nausea and vomiting. Ondansetron 8 mg three times daily is not a recommended regimen for the treatment of moderately emetogenic chemotherapy

Treatment response was based on the total number of emetic episodes over the 3-day trial period. See Table for the details of the dosage regimens studied and results of this trial.

Table: Emetic Episodes - Treatment Response After Ondansetron **Tablets Administered Twice a Day and Three Times a Day**

aThe first 8-mg dose was administered 30 minutes before the start of emetogenic chemotherapy, with a subsequent 8-mg dose 8 hours after the first dose, followed by 8 mg administered twice a day for 2 days after the completion of chemotherapy.
bThe first 8-mg dose was administered 30 minutes before the start of emetogenic chemotherapy, with subsequent 8-mg doses at 4 hours and 8 hours after the first dose, followed by 8 mg administered 3 times a day for 2 days after the completion of chemotherapy.
cMedian undefined since at least 50% of patients did not have any emetic episodes.
dVisual analog scale assessment: 0 = no nausea, 100 = nausea as bad as it can be.

	Ondansetron Tablets	
	8 mg Twice Dailya (n = 165)	**8 mg Three Times a Dayb (n = 171)**
Treatment response		
0 Emetic episodes	101 (61%)	99 (58%)
1-2 Emetic episodes	16 (10%)	17 (10%)
More than 2 emetic episodes/withdrawn	48 (29%)	55 (32%)
Median number of emetic episodes	0.0	0.0
Median time to first emetic episode (h)	Undefinedc	Undefinedc
Median nausea scores (0-100)d	6	6

Re-treatment

In single-arm trials, 148 patients receiving cyclophosphamide-based chemotherapy were re-treated with Ondansetron 8 mg three times daily during subsequent chemotherapy for a total of 396 re-treatment courses. No emetic episodes occurred in 314 (79%) of the re-treatment courses, and only 1 to 2 emetic episodes occurred in 43 (11%) of the re-treatment courses.

Pediatric Trials

Three open-label, single-arm, non-US trials have been performed with 182 pediatric patients aged 4 to 18 years with cancer who were given a variety of cisplatin or noncisplatin regimens. The initial dose of Ondansetron injection ranged from 0.04 to 0.87 mg per kg (total dose of 2.16 mg to 12 mg) followed by the administration of oral doses of Ondansetron ranging from 4 to 24 mg daily for 3 days. In these trials, 58% of the 170 evaluable patients had a complete response (no emetic episodes) on Day 1. In 2 trials, the response rates to Ondansetron 4 mg three times a day in patients younger than 12 years was similar to Ondansetron 8 mg three times daily in patients 12 to 18 years. Prevention of emesis in these pediatric patients was essentially the same as for adults.

Radiation-Induced Nausea and Vomiting

Total Body Irradiation

In a randomized, placebo-controlled, double-blind trial in 20 patients, 8 mg of Ondansetron administered 1.5 hours before each fraction of radiotherapy for 4 days was significantly more effective than placebo in preventing vomiting induced by total body irradiation. Total body irradiation consisted of 11 fractions (120 cGy per fraction) over 4 days for a total of 1,320 cGy. Patients received 3 fractions for 3 days, then 2 fractions on Day 4.

Single High-Dose Fraction Radiotherapy

In an active-controlled, double-blind trial in 105 patients receiving single high-dose radiotherapy (800 to 1,000 cGy) over an anterior or posterior field size of greater than or equal to 80 cm2 to the abdomen, Ondansetron was significantly more effective than metoclopramide with respect to complete control of emesis (0 emetic episodes). Patients received the first dose of Ondansetron (8 mg) or metoclopramide (10 mg) 1 to 2 hours before radiotherapy. If radiotherapy was given in the morning, 8 mg of Ondansetron or 10 mg of metoclopramide was administered in the late afternoon and repeated again before bedtime. If radiotherapy was given in the afternoon, patients took 8 mg of Ondansetron or 10 mg of metoclopramide only once before bedtime. Patients continued the doses of oral medication three times daily for 3 days.

Daily Fractionated Radiotherapy

In an active-controlled, double-blind trial in 135 patients receiving a 1- to 4-week course of fractionated radiotherapy (180 cGy doses) over a field size of greater than or equal to 100 cm2 to the abdomen, Ondansetron was significantly more effective than prochlorperazine with respect to complete control of emesis (0 emetic episodes). Patients received the first dose of Ondansetron (8 mg) or prochlorperazine (10 mg) 1 to 2 hours before the first daily radiotherapy fraction, with subsequent 8-mg doses approximately every 8 hours on each day of radiotherapy.

Postoperative Nausea and Vomiting

In 2 placebo-controlled, double-blind trials (one conducted in the US and the other outside the US) in 865 females undergoing inpatient surgical procedures, Ondansetron 16 mg as a single dose or placebo was administered one hour before the induction of general balanced anesthesia (barbiturate, opioid, nitrous oxide, neuromuscular blockade, and supplemental isoflurane or enflurane), Ondansetron tablets was significantly more effective than placebo in preventing postoperative nausea and vomiting.

No trials have been performed in males.

PRECLINICAL SAFETY DATA

Embryo-fetal development studies in rats and rabbits did not show evidence of harm to the fetus when ondansetron was administered during the period of organogenesis at approximately 6 and 24 times respectively the maximum recommended human oral dose of 24 mg/day, based on body surface area. In a pre- and postnatal developmental toxicity study, there were no effects upon pregnant rats and the pre- and postnatal development of their offspring, including reproductive performance at approximately 6 times the maximum recommended human oral dose of 24 mg/day based on body surface area.

PRESENTATION

Adosetron tablets 8 mg are available in blisters of 2 x 6's.

INSTRUCTIONS

To be sold on prescription of a registered medical practitioner only.

Store below 30°C in a dry place, protect from light.

Keep all medicines out of sight & reach of children.

REGISTRATION NUMBER

Adosetron 8mg Tablet: R.N. 078601

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION – As per registrations letter

Product Complies U.S.P. Specs.

Manufactured by:

Searle IV Solutions (Pvt.) Limited. 1.5 km, Manga Raiwind Road, Manga Mandi, Distt. Lahore - Pakistan.

Marketed by:

The Searle Company Limited, One IBL Centre, 2nd Floor, Plot # 1, Block 7 & 8, D.M.C.H.S, Tipu Sultan Road, Off Shahra-e-Faisal, Karachi - Pakistan.

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