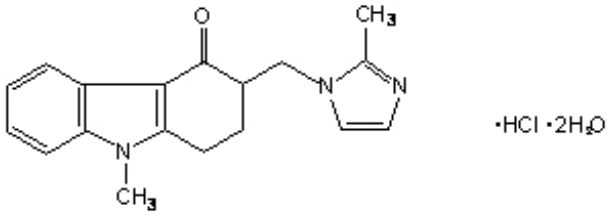
ONDANSETRON- ondansetron tablet, orally disintegrating
Proficient Rx LP

Ondansetron Tablets USP, for oral use
Ondansetron Orally Disintegrating Tablets USP, for oral use

DESCRIPTION

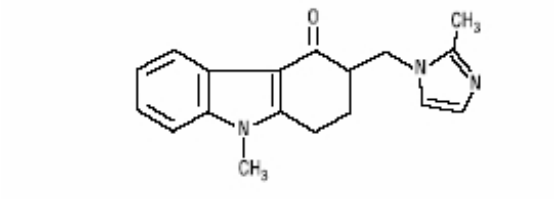
The active ingredient in ondansetron tablets USP is ondansetron hydrochloride (HCl) USP as the dihydrate, the racemic form of ondansetron and a selective blocking agent of the serotonin 5-HT_3 receptor type. Chemically it is (±) 1, 2, 3, 9-tetrahydro-9-methyl-3-[(2-methyl-1H-imidazol-1-yl)methyl]-4H-carbazol-4-one, monohydrochloride, dihydrate. It has the following structural formula:



The empirical formula is $C_{18}H_{19}N_3O \cdot HCl \cdot 2H_2O$, representing a molecular weight of 365.85.

Ondansetron HCl USP dihydrate is a white to off-white powder that is sparingly soluble in water and in alcohol; soluble in methanol, slightly soluble in isopropyl alcohol, and in dichloromethane; very slightly soluble in acetone, in chloroform and in ethyl acetate.

The active ingredient in ondansetron orally disintegrating tablets USP is ondansetron base, the racemic form of ondansetron, and a selective blocking agent of the serotonin 5-HT_3 receptor type. Chemically it is (±) 1, 2, 3, 9-tetrahydro-9-methyl-3-[(2-methyl-1H-imidazol-1-yl)methyl]-4H-carbazol-4-one. It has the following structural formula:



The empirical formula is $C_{18}H_{19}N_3O$ representing a molecular weight of 293.4.

Each 4-mg ondansetron tablet USP for oral administration contains ondansetron HCl USP dihydrate equivalent to 4 mg of ondansetron. Each 8-mg ondansetron tablet USP for oral administration contains ondansetron HCl USP dihydrate equivalent to 8 mg of ondansetron. Each 24-mg ondansetron tablet USP for oral administration contains

ondansetron HCl USP dihydrate equivalent to 24 mg of ondansetron. Each tablet also contains the inactive ingredients colloidal silicon dioxide, hypromellose, iron oxide yellow (8 mg tablet only), iron oxide red (24 mg tablet only), lactose monohydrate, magnesium stearate, microcrystalline cellulose, pregelatinized starch, titanium dioxide and triacetin.

Each 4-mg ondansetron orally disintegrating tablet USP for oral administration contains 4 mg ondansetron base. Each 8-mg ondansetron orally disintegrating tablet USP for oral administration contains 8 mg ondansetron base. Each ondansetron orally disintegrating tablet USP also contains the inactive ingredients aspartame, colloidal silicon dioxide, crospovidone, magnesium stearate, mannitol, sodium stearyl fumarate and strawberry flavor. Ondansetron orally disintegrating tablets USP are an orally administered formulation of ondansetron which rapidly disintegrates on the tongue and does not require water to aid dissolution or swallowing. This product disintegrates in approximately 60 seconds.

CLINICAL PHARMACOLOGY

Pharmacodynamics:

Ondansetron is a selective 5-HT_3 receptor antagonist. While its mechanism of action has not been fully characterized, ondansetron is not a dopamine-receptor antagonist. Serotonin receptors of the 5-HT_3 type are present both peripherally on vagal nerve terminals and centrally in the chemoreceptor trigger zone of the area postrema. It is not certain whether ondansetron's antiemetic action is mediated centrally, peripherally, or in both sites. However, cytotoxic chemotherapy appears to be associated with release of serotonin from the enterochromaffin cells of the small intestine. In humans, urinary 5-HIAA (5-hydroxyindoleacetic acid) excretion increases after cisplatin administration in parallel with the onset of emesis. The released serotonin may stimulate the vagal afferents through the 5-HT_3 receptors and initiate the vomiting reflex.

In animals, the emetic response to cisplatin can be prevented by pretreatment with an inhibitor of serotonin synthesis, bilateral abdominal vagotomy and greater splanchnic nerve section, or pretreatment with a serotonin 5-HT_3 receptor antagonist.

In normal volunteers, single intravenous doses of 0.15 mg/kg of ondansetron had no effect on esophageal motility, gastric motility, lower esophageal sphincter pressure, or small intestinal transit time. Multiday administration of ondansetron has been shown to slow colonic transit in normal volunteers. Ondansetron has no effect on plasma prolactin concentrations.

Ondansetron does not alter the respiratory depressant effects produced by alfentanil or the degree of neuromuscular blockade produced by atracurium. Interactions with general or local anesthetics have not been studied.

Pharmacokinetics:

Ondansetron is well absorbed from the gastrointestinal tract and undergoes some first-pass metabolism. Mean bioavailability in healthy subjects, following administration of a single 8-mg tablet, is approximately 56%.

Ondansetron systemic exposure does not increase proportionately to dose. AUC from a 16-mg tablet was 24% greater than predicted from an 8-mg tablet dose. This may

reflect some reduction of first-pass metabolism at higher oral doses. Bioavailability is also slightly enhanced by the presence of food but unaffected by antacids.

Ondansetron is extensively metabolized in humans, with approximately 5% of a radiolabeled dose recovered as the parent compound from the urine. The primary metabolic pathway is hydroxylation on the indole ring followed by subsequent glucuronide or sulfate conjugation. Although some nonconjugated metabolites have pharmacologic activity, these are not found in plasma at concentrations likely to significantly contribute to the biological activity of ondansetron.

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 metabolizing ondansetron, it is likely that inhibition or loss of one enzyme (e.g., CYP2D6 genetic deficiency) will be compensated by others and may result in little change in overall rates of ondansetron elimination. Ondansetron elimination may be affected by cytochrome P-450 inducers. In a pharmacokinetic study of 16 epileptic patients maintained chronically on CYP3A4 inducers, carbamazepine, or phenytoin, reduction in AUC, C_{max}, and $T_{½}$ of ondansetron was observed.[1] This resulted in a significant increase in clearance. However, on the basis of available data, no dosage adjustment for ondansetron is recommended (see PRECAUTIONS: Drug Interactions).

In humans, carmustine, etoposide, and cisplatin do not affect the pharmacokinetics of ondansetron.

Gender differences were shown in the disposition of ondansetron given as a single dose. The extent and rate of ondansetron's absorption is greater in women than men. Slower clearance in women, a smaller apparent volume of distribution (adjusted for weight), and higher absolute bioavailability resulted in higher plasma ondansetron levels. These higher plasma levels may in part be explained by differences in body weight between men and women. It is not known whether these gender-related differences were clinically important. More detailed pharmacokinetic information is contained in Tables 1 and 2 taken from 2 studies.

Table 1. Pharmacokinetics in Normal Volunteers: Single 8-mg Ondansetron Tablet Dose

Age-group (years)	Mean Weight (kg)	n	Peak Plasma Concentration (ng/mL)	Time of Peak Plasma Concentration (h)	Mean Elimination Half-life (h)	Systemic Plasma Clearance L/h/kg	Absolute Bioavailability
18-40 M F	69 62.7	65	26.2 42.7	2 1.7	3.1 3.5	0.403 0.354	0.483 0.663
61-74 M F	77.5 60.2	66	24.1 52.4	2.1 1.9	4.1 4.9	0.384 0.255	0.585 0.643
≥ 75 M F	78 67.6	56	37 46.1	2.2 2.1	4.5 6.2	0.277 0.249	0.619 0.747

Table 2. Pharmacokinetics in Normal Volunteers: Single 24-mg Ondansetron Tablet Dose

Age-group (years)	Mean Weight (kg)	n	Peak Plasma Concentration (ng/mL)	Time of Peak Plasma Concentration (h)	Mean Elimination Half-life (h)
18-43 M F	84.1 71.8	8 8	125.8 194.4	1.9 1.6	4.7 5.8

A reduction in clearance and increase in elimination half-life are seen in patients over 75 years of age. In clinical trials with cancer patients, safety and efficacy were similar in patients over 65 years of age and those under 65 years of age; there was an insufficient number of patients over 75 years of age to permit conclusions in that age-group. No dosage adjustment is recommended in the elderly.

In patients with mild-to-moderate hepatic impairment, clearance is reduced 2-fold and mean half-life is increased to 11.6 hours compared to 5.7 hours in normals. In patients with severe hepatic impairment (Child-Pugh[2] score of 10 or greater), clearance is reduced 2-fold to 3-fold and apparent volume of distribution is increased with a resultant increase in half-life to 20 hours. In patients with severe hepatic impairment, a total daily dose of 8 mg should not be exceeded.

Due to the very small contribution (5%) of renal clearance to the overall clearance, renal impairment was not expected to significantly influence the total clearance of ondansetron. However, ondansetron oral mean plasma clearance was reduced by about 50% in patients with severe renal impairment (creatinine clearance <30 mL/min). This reduction in clearance is variable and was not consistent with an increase in half-life. No reduction in dose or dosing frequency in these patients is warranted.

Plasma protein binding of ondansetron as measured *in vitro* was 70% to 76% over the concentration range of 10 to 500 ng/mL. Circulating drug also distributes into erythrocytes.

Four-and 8-mg doses of ondansetron orally disintegrating tablets are bioequivalent to corresponding doses of ondansetron tablets and may be used interchangeably. One 24-mg ondansetron tablet is bioequivalent to and interchangeable with three 8-mg ondansetron tablets.

CLINICAL TRIALS

Chemotherapy-Induced Nausea and Vomiting:

Highly Emetogenic Chemotherapy:

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

The first trial compared oral doses of ondansetron 24 mg once a day, 8 mg twice a day,

and 32 mg once a day in 357 adult cancer patients receiving chemotherapy regimens containing cisplatin ≥50 mg/m^2. 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 study 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 oral ondansetron 24 mg once a day experienced no nausea during the 24-hour study 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.

In a second trial, efficacy of the oral ondansetron 24-mg once-a-day regimen in the prevention of nausea and vomiting associated with highly emetogenic cancer chemotherapy, including cisplatin ≥50 mg/m^2, was confirmed.

Moderately Emetogenic Chemotherapy:

In 1 double-blind US study in 67 patients, ondansetron tablets 8 mg administered twice a day were significantly more effective than placebo in preventing vomiting induced by cyclophosphamide-based chemotherapy containing doxorubicin. Treatment response is based on the total number of emetic episodes over the 3-day study period. The results of this study are summarized in Table 3:

Table 3. Emetic Episodes: Treatment Response

	Ondansetron 8-mg b.i.d. ondansetron tablets*	Placebo	*P* Value
Number of patients	33	34	
Treatment response 0 Emetic episodes 1-2 Emetic episodes More than 2 emetic episodes/withdrawn	 20 (61%) 6 (18%) 7 (21%)	 2 (6%) 8 (24%) 24 (71%)	 < 0.001 < 0.001
Median number of emetic episodes	0	Undefined†	
Median time to first emetic episode (h)	Undefined‡	6.5	

* The first dose was administered 30 minutes before the start of emetogenic chemotherapy, with a subsequent dose 8 hours after the first dose. An 8 mg ondansetron tablet was administered twice a day for 2 days after completion of chemotherapy.

† Median undefined since at least 50% of the patients were withdrawn or had more than 2 emetic episodes.

‡ Median undefined since at least 50% of patients did not have any emetic episodes.

In 1 double-blind US study in 336 patients, ondansetron tablets 8 mg administered twice a day were as effective as ondansetron tablets 8 mg administered 3 times a day in

preventing nausea and vomiting induced by cyclophosphamide-based chemotherapy containing either methotrexate or doxorubicin. Treatment response is based on the total number of emetic episodes over the 3-day study period. The results of this study are summarized in Table 4:

Table 4. Emetic Episodes: Treatment Response

Ondansetron		
	8-mg b.i.d. ondansetron tablets*	8-mg t.i.d. ondansetron tablets†
Number of patients	165	171
Treatment response 0 Emetic episodes 1-2 Emetic episodes More than 2 emetic episodes/withdrawn	101 (61%) 16 (10%) 48 (29%)	99 (58%) 17 (10%) 55 (32%)
Median number of emetic episodes	0	0
Median time to first emetic episode (h)	Undefined‡	Undefined‡
Median nausea scores (0-100)§	6	6

* The first dose was administered 30 minutes before the start of emetogenic chemotherapy, with a subsequent dose 8 hours after the first dose. An 8-mg ondansetron tablet was administered twice a day for 2 days after completion of chemotherapy.

† The first dose was administered 30 minutes before the start of emetogenic chemotherapy, with subsequent doses 4 and 8 hours after the first dose. An 8-mg ondansetron tablet was administered 3 times a day for 2 days after completion of chemotherapy.

‡ Median undefined since at least 50% of patients did not have any emetic episodes.

§ Visual analog scale assessment: 0 = no nausea, 100 = nausea as bad as it can be.

Re-treatment:

In uncontrolled trials, 148 patients receiving cyclophosphamide-based chemotherapy were re-treated with ondansetron tablets 8 mg 3 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 Studies:

Three open-label, uncontrolled, foreign trials have been performed with 182 pediatric patients 4 to 18 years old with cancer who were given a variety of cisplatin or noncisplatin regimens. In these foreign trials, the initial dose of ondansetron hydrochloride injection ranged from 0.04 to 0.87 mg/kg for a total dose of 2.16 to 12 mg. This was followed by the administration of ondansetron tablets ranging from 4 to 24 mg daily for 3 days. In these studies, 58% of the 170 evaluable patients had a complete response (no emetic episodes) on day 1. Two studies showed the response rates for patients less than 12 years of age who received ondansetron tablets 4 mg 3 times a day

to be similar to those in patients 12 to 18 years of age who received ondansetron tablets 8 mg 3 times daily. Thus, prevention of emesis in these pediatric patients was essentially the same as for patients older than 18 years of age. Overall, ondansetron tablets were well tolerated in these pediatric patients.

Radiation-Induced Nausea and Vomiting:

Total Body Irradiation:

In a randomized, double-blind study in 20 patients, ondansetron tablets (8 mg given 1.5 hours before each fraction of radiotherapy for 4 days) were 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:

Ondansetron was significantly more effective than metoclopramide with respect to complete control of emesis (0 emetic episodes) in a double-blind trial in 105 patients receiving single high-dose radiotherapy (800 to 1,000 cGy) over an anterior or posterior field size of ≥80 cm^2 to the abdomen. Patients received the first dose of ondansetron tablets (8 mg) or metoclopramide (10 mg) 1 to 2 hours before radiotherapy. If radiotherapy was given in the morning, 2 additional doses of study treatment were given (1 tablet late afternoon and 1 tablet before bedtime). If radiotherapy was given in the afternoon, patients took only 1 further tablet that day before bedtime. Patients continued the oral medication on a 3 times a day basis for 3 days.

Daily Fractionated Radiotherapy:

Ondansetron was significantly more effective than prochlorperazine with respect to complete control of emesis (0 emetic episodes) in a double-blind trial in 135 patients receiving a 1- to 4-week course of fractionated radiotherapy (180 cGy doses) over a field size of ≥100 cm^2 to the abdomen. Patients received the first dose of ondansetron tablets (8 mg) or prochlorperazine (10 mg) 1 to 2 hours before the patient received the first daily radiotherapy fraction, with 2 subsequent doses on a 3 times a day basis. Patients continued the oral medication on a 3 times a day basis on each day of radiotherapy.

Postoperative Nausea and Vomiting:

Surgical patients who received ondansetron 1 hour before the induction of general balanced anesthesia (barbiturate: thiopental, methohexital, or thiamylal; opioid: alfentanil, sufentanil, morphine, or fentanyl; nitrous oxide; neuromuscular blockade: succinylcholine/curare or gallamine and/or vecuronium, pancuronium, or atracurium; and supplemental isoflurane or enflurane) were evaluated in 2 double-blind studies (1 US study, 1 foreign) involving 865 patients. Ondansetron tablets (16 mg) were significantly more effective than placebo in preventing postoperative nausea and vomiting.

The study populations in all trials thus far consisted of women undergoing inpatient surgical procedures. No studies have been performed in males. No controlled clinical study comparing ondansetron tablets to ondansetron hydrochloride injection has been performed.

INDICATIONS AND USAGE

- Prevention of nausea and vomiting associated with highly emetogenic cancer chemotherapy, including cisplatin ≥50 mg/m^2.
- Prevention of nausea and vomiting associated with initial and repeat courses of moderately emetogenic cancer chemotherapy.
- Prevention of nausea and vomiting associated with radiotherapy in patients receiving either total body irradiation, single high-dose fraction to the abdomen, or daily fractions to the abdomen.
- Prevention of postoperative nausea and/or vomiting. As with other antiemetics, routine prophylaxis is not recommended for patients in whom there is little expectation that nausea and/or vomiting will occur postoperatively. In patients where nausea and/or vomiting must be avoided postoperatively, ondansetron tablets USP and ondansetron orally disintegrating tablets USP are recommended even where the incidence of postoperative nausea and/or vomiting is low.

CONTRAINDICATIONS

The concomitant use of apomorphine with ondansetron is contraindicated based on reports of profound hypotension and loss of consciousness when apomorphine was administered with ondansetron.

Ondansetron tablets and ondansetron orally disintegrating tablets are contraindicated for patients known to have hypersensitivity to the drug.

WARNINGS

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

ECG changes including QT interval prolongation has 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.

PRECAUTIONS

General

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

Information for Patients

Phenylketonurics:

Phenylketonuric patients should be informed that ondansetron orally disintegrating tablets contain phenylalanine (a component of aspartame). Each 4 mg and 8 mg orally disintegrating tablet contains 1.5 mg and 3 mg of phenylalanine, respectively.

Patients should be instructed not to remove ondansetron orally disintegrating tablets from the blister until just prior to dosing. The tablet should not be pushed through the foil. With dry hands, the blister backing should be peeled completely off the blister. The tablet should be gently removed and immediately placed on the tongue to dissolve and be swallowed with the saliva. Peelable illustrated stickers are affixed to the product carton that can be provided with the prescription to ensure proper use and handling of the product.

Drug Interactions

Ondansetron does not itself appear to induce or inhibit the cytochrome P-450 drug-metabolizing enzyme system of the liver (see CLINICAL PHARMACOLOGY, Pharmacokinetics). Because ondansetron is metabolized by hepatic cytochrome P-450 drug-metabolizing enzymes (CYP3A4, CYP2D6, CYP1A2), 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.

Apomorphine: Based on reports of profound hypotension and loss of consciousness when apomorphine was administered with ondansetron, concomitant use of apomorphine with ondansetron is contraindicated (see CONTRAINDICATIONS).

Phenytoin, Carbamazepine, and Rifampicin: In patients treated with potent inducers of CYP3A4 (i.e., phenytoin, carbamazepine, and rifampicin), the clearance of ondansetron was significantly increased and ondansetron blood concentrations were decreased. However, on the basis of available data, no dosage adjustment for ondansetron is recommended for patients on these drugs.[1,3]

Tramadol: Although no pharmacokinetic drug interaction between ondansetron and tramadol has been observed, data from 2 small studies indicate that ondansetron may be associated with an increase in patient controlled administration of tramadol.[4,5]

Chemotherapy: Tumor response to chemotherapy in the P-388 mouse leukemia model is not affected by ondansetron. In humans, carmustine, etoposide, and cisplatin do not affect the pharmacokinetics of ondansetron.

In a crossover study in 76 pediatric patients, I.V. ondansetron did not increase blood levels of high-dose methotrexate.

Use in Surgical Patients: The coadministration of ondansetron had no effect on the pharmacokinetics and pharmacodynamics of temazepam.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Pregnancy

Teratogenic Effects

Pregnancy Category B. Reproduction studies have been performed in pregnant rats and

rabbits at daily oral doses up to 15 and 30 mg/kg/day, respectively, and have revealed no evidence of impaired fertility or harm to the fetus due to ondansetron. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers

Ondansetron is excreted in the breast milk of rats. It is not known whether ondansetron is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when ondansetron is administered to a nursing woman.

Pediatric Use

Little information is available about dosage in pediatric patients 4 years of age or younger (see CLINICAL PHARMACOLOGY and DOSAGE AND ADMINISTRATION sections for use in pediatric patients 4 to 18 years of age).

Geriatric Use

Of the total number of subjects enrolled in cancer chemotherapy-induced and postoperative nausea and vomiting in US- and foreign-controlled clinical trials, for which there were subgroup analyses, 938 were 65 years of age and over. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out. Dosage adjustment is not needed in patients over the age of 65 (see CLINICAL PHARMACOLOGY).

ADVERSE REACTIONS

The following have been reported as adverse events in clinical trials of patients treated with ondansetron, the active ingredient of ondansetron tablets and ondansetron orally disintegrating tablets. A causal relationship to therapy with ondansetron tablets and ondansetron orally disintegrating tablets has been unclear in many cases.

Chemotherapy-Induced Nausea and Vomiting:

The adverse events in Table 5 have been reported in ≥5% of adult patients receiving a single 24-mg ondansetron tablet in 2 trials. These patients were receiving concurrent highly emetogenic cisplatin-based chemotherapy regimens (cisplatin dose ≥50 mg/m^2).

Table 1. Principal Adverse Events in US Trials: Single Day Therapy With 24-mg Ondansetron Tablets (Highly Emetogenic Chemotherapy)

Event	Ondansetron 24 mg q.d. n = 300	Ondansetron 8 mg b.i.d. n = 124	Ondansetron 32 mg q.d. n = 117
Headache	33 (11%)	16 (13%)	17 (15%)
Diarrhea	13 (4%)	9 (7%)	3 (3%)

The adverse events in Table 6 have been reported in ≥5% of adults receiving either 8 mg of ondansetron tablets 2 or 3 times a day for 3 days or placebo in 4 trials. These patients were receiving concurrent moderately emetogenic chemotherapy, primarily cyclophosphamide-based regimens.

Table 6. Principal Adverse Events in US Trials: 3 Days of Therapy With 8-mg Ondansetron Tablets (Moderately Emetogenic Chemotherapy)

Event	Ondansetron 8 mg b.i.d. n = 242	Ondansetron 8 mg t.i.d. n = 415	Placebo n = 262
Headache	58 (24%)	113 (27%)	34 (13%)
Malaise/fatigue	32 (13%)	37 (9%)	6 (2%)
Constipation	22 (9%)	26 (6%)	1 (<1%)
Diarrhea	15 (6%)	16 (4%)	10 (4%)
Dizziness	13 (5%)	18 (4%)	12 (5%)

Central Nervous System:

There have been rare reports consistent with, but not diagnostic of, extrapyramidal reactions in patients receiving ondansetron.

Hepatic:

In 723 patients receiving cyclophosphamide-based chemotherapy in US clinical trials, AST and/or ALT values have been reported to exceed twice the upper limit of normal in approximately 1% to 2% of patients receiving ondansetron tablets. The increases were transient and did not appear to be related to dose or duration of therapy. On repeat exposure, similar transient elevations in transaminase values occurred in some courses, but symptomatic hepatic disease did not occur. The role of cancer chemotherapy in these biochemical changes cannot be clearly determined.

There have been reports of liver failure and death in patients with cancer receiving concurrent medications including potentially hepatotoxic cytotoxic chemotherapy and antibiotics. The etiology of the liver failure is unclear.

Integumentary:

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

Other:

Rare cases of anaphylaxis, bronchospasm, tachycardia, angina (chest pain), hypokalemia, electrocardiographic alterations, vascular occlusive events, and grand mal seizures have been reported. Except for bronchospasm and anaphylaxis, the relationship to ondansetron was unclear.

Radiation-Induced Nausea and Vomiting:

The adverse events reported in patients receiving ondansetron tablets and concurrent radiotherapy were similar to those reported in patients receiving ondansetron tablets and concurrent chemotherapy. The most frequently reported adverse events were headache, constipation, and diarrhea.

Postoperative Nausea and Vomiting:

The adverse events in Table 7 have been reported in ≥5% of patients receiving ondansetron tablets at a dosage of 16 mg orally in clinical trials. With the exception of headache, rates of these events were not significantly different in the ondansetron and placebo groups. These patients were receiving multiple concomitant perioperative and postoperative medications.

Table 7. Frequency of Adverse Events From Controlled Studies With Ondansetron Tablets (Postoperative Nausea and Vomiting)

Adverse Event	Ondansetron 16 mg (n = 550)	Placebo (n = 531)
Wound problem	152 (28%)	162 (31%)
Drowsiness/sedation	112 (20%)	122 (23%)
Headache	49 (9%)	27 (5%)
Hypoxia	49 (9%)	35 (7%)
Pyrexia	45 (8%)	34 (6%)
Dizziness	36 (7%)	34 (6%)
Gynecological disorder	36 (7%)	33 (6%)
Anxiety/agitation	33 (6%)	29 (5%)
Bradycardia	32 (6%)	30 (6%)
Shiver(s)	28 (5%)	30 (6%)
Urinary retention	28 (5%)	18 (3%)
Hypotension	27 (5%)	32 (6%)
Pruritus	27 (5%)	20 (4%)

Preliminary observations in a small number of subjects suggest a higher incidence of headache when ondansetron orally disintegrating tablets are taken with water, when compared to without water.

Observed During Clinical Practice:

In addition to adverse events reported from clinical trials, the following events have been identified during post-approval use of oral formulations of ondansetron. Because they are reported voluntarily from a population of unknown size, estimates of frequency cannot be made. The events have been chosen for inclusion due to a combination of their seriousness, frequency of reporting, or potential causal connection to ondansetron.

Cardiovascular: Rarely and predominantly with intravenous ondansetron, transient ECG changes including QT interval prolongation have been reported.

General: Flushing. Rare cases of hypersensitivity reactions, sometimes severe (e.g., anaphylaxis/anaphylactoid reactions, angioedema, bronchospasm, shortness of breath, hypotension, laryngeal edema, stridor) have also been reported. Laryngospasm, shock, and cardiopulmonary arrest have occurred during allergic reactions in patients receiving injectable ondansetron.

Hepatobiliary: Liver enzyme abnormalities

Lower Respiratory: Hiccups

Neurology: Oculogyric crisis, appearing alone, as well as with other dystonic reactions

Skin: Urticaria, Stevens-Johnson syndrome, and toxic epidermal necrolysis.

Special Senses: Eye Disorders:Cases of transient blindness, predominantly during intravenous administration, have been reported. These cases of transient blindness were reported to resolve within a few minutes up to 48 hours.

DRUG ABUSE AND DEPENDENCE

Animal studies have shown that ondansetron is not discriminated as a benzodiazepine nor does it substitute for benzodiazepines in direct addiction studies.

OVERDOSAGE

There is no specific antidote for ondansetron overdose. Patients should be managed with appropriate supportive therapy. Individual intravenous doses as large as 150 mg and total daily intravenous doses as large as 252 mg have been inadvertently administered without significant adverse events. These doses are more than 10 times the recommended daily dose.

In addition to the adverse events listed above, the following events have been described in the setting of ondansetron overdose: “Sudden blindness” (amaurosis) of 2 to 3 minutes’ duration plus severe constipation occurred in 1 patient that was administered 72 mg of ondansetron intravenously as a single dose. Hypotension (and faintness) occurred in a patient that took 48 mg of ondansetron tablets. 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.

DOSAGE AND ADMINISTRATION

Instructions for Use/Handling Ondansetron Orally Disintegrating Tablets USP:

Do not attempt to push ondansetron orally disintegrating tablets USP through the foil backing. With dry hands, PEEL BACK the foil backing of 1 blister and GENTLY remove the tablet. IMMEDIATELY place the ondansetron orally disintegrating tablet USP on top of the tongue where it will dissolve in seconds, then swallow with saliva. Administration with liquid is not necessary.

Prevention of Nausea and Vomiting Associated With Highly Emetogenic Cancer Chemotherapy:

The recommended adult oral dosage of ondansetron is 24 mg given as three 8-mg tablets administered 30 minutes before the start of single-day highly emetogenic chemotherapy, including cisplatin ≥50 mg/m^2. Multiday, single-dose administration of a 24 mg dosage has not been studied.

Pediatric Use:

There is no experience with the use of a 24 mg dosage in pediatric patients.

Geriatric Use:

The dosage recommendation is the same as for the general population.

Prevention of Nausea and Vomiting Associated With Moderately Emetogenic Cancer Chemotherapy:

The recommended adult oral dosage is one 8-mg ondansetron tablet USP or one 8-mg ondansetron orally disintegrating tablet USP given twice a day. The first dose should be administered 30 minutes before the start of emetogenic chemotherapy, with a subsequent dose 8 hours after the first dose. One 8-mg ondansetron tablet USP or one 8-mg ondansetron orally disintegrating tablet USP should be administered twice a day (every 12 hours) for 1 to 2 days after completion of chemotherapy.

Pediatric Use:

For pediatric patients 12 years of age and older, the dosage is the same as for adults. For pediatric patients 4 through 11 years of age, the dosage is one 4-mg ondansetron tablet USP or one 4-mg ondansetron orally disintegrating tablet USP given 3 times a day. The first dose should be administered 30 minutes before the start of emetogenic chemotherapy, with subsequent doses 4 and 8 hours after the first dose. One 4-mg ondansetron tablet USP or one 4-mg ondansetron orally disintegrating tablet USP should be administered 3 times a day (every 8 hours) for 1 to 2 days after completion of chemotherapy.

Geriatric Use:

The dosage is the same as for the general population.

Prevention of Nausea and Vomiting Associated With Radiotherapy, Either Total Body Irradiation, or Single High-Dose Fraction or Daily Fractions to the Abdomen:

The recommended oral dosage is one 8-mg ondansetron tablet USP or one 8-mg ondansetron orally disintegrating tablet USP given 3 times a day.

For total body irradiation, one 8-mg ondansetron tablet USP or one 8-mg ondansetron orally disintegrating tablet USP should be administered 1 to 2 hours before each fraction of radiotherapy administered each day.

For single high-dose fraction radiotherapy to the abdomen, one 8-mg ondansetron tablet USP or one 8-mg ondansetron orally disintegrating tablet USP should be administered 1 to 2 hours before radiotherapy, with subsequent doses every 8 hours after the first dose for 1 to 2 days after completion of radiotherapy.

For daily fractionated radiotherapy to the abdomen, one 8-mg ondansetron tablet USP or one 8-mg ondansetron orally disintegrating tablet USP should be administered 1 to 2 hours before radiotherapy, with subsequent doses every 8 hours after the first dose for each day radiotherapy is given.

Pediatric Use:

There is no experience with the use of ondansetron tablets USP or ondansetron orally disintegrating tablets USP in the prevention of postoperative nausea and vomiting in pediatric patients.

Geriatric Use:

The dosage recommendation is the same as for the general population.

Postoperative Nausea and Vomiting:

The recommended dosage is 16 mg given as two 8-mg ondansetron tablets USP or two 8-mg ondansetron orally disintegrating tablets USP 1 hour before induction of anesthesia.

Pediatric Use:

There is no experience with the use of ondansetron tablets USP or ondansetron orally disintegrating tablets USP in the prevention of postoperative nausea and vomiting in pediatric patients.

Geriatric Use:

The dosage is the same as for the general population.

Dosage Adjustment for Patients With Impaired Renal Function:

The dosage recommendation is the same as for the general population. There is no experience beyond first-day administration of ondansetron.

Dosage Adjustment for Patients With Impaired Hepatic Function:

In patients with severe hepatic impairment (Child-Pugh[2] score of 10 or greater), clearance is reduced and apparent volume of distribution is increased with a resultant increase in plasma half-life. In such patients, a total daily dose of 8 mg should not be exceeded.

HOW SUPPLIED

Ondansetron orally disintegrating tablets USP, 4 mg (as 4 mg ondansetron base) are white, circular, flat faced, uncoated tablets with ‘G’ engraved on one side and ‘4’ on the other side in:

Unit dose packs of 5 tablets (NDC 63187-256-05)

Unit dose packs of 6 tablets (NDC 63187-256-06)

Unit dose packs of 10 tablets (NDC 63187-256-10)

Unit dose packs of 12 tablets (NDC 63187-256-12)

Unit dose packs of 15 tablets (NDC 63187-256-15)

Carton of 20 tablets (contains 2 cards of 10 unit of use blisters) NDC 63187-256-20

Carton of 30 tablets (contains 3 cards of 10 unit of use blisters) NDC 63187-256-30

Ondansetron orally disintegrating tablets USP, 8 mg (as 8 mg ondansetron base) are white, circular, flat faced, uncoated tablets with ‘G’ engraved on one side and ‘8’ on the other side in:

Unit dose packs of 10 tablets (NDC 63187-199-10)

Store at 20° to 25°C (68° to 77°F) [See USP Controlled Room Temperature].

REFERENCES

- Britto MR, Hussey EK, Mydlow P, et al. Effect of enzyme inducers on ondansetron (OND) metabolism in humans. *Clin Pharmacol Ther*. 1997;61:228.
- Pugh RNH, Murray-Lyon IM, Dawson JL, Pietroni MC, Williams R. Transection of the oesophagus for bleeding oesophageal varices. *Brit J Surg*. 1973;60:646-649.
- Villikka K, Kivisto KT, Neuvonen PJ. The effect of rifampin on the pharmacokinetics of oral and intravenous ondansetron. *Clin Pharmacol Ther*. 1999;65:377-381.
- De Witte JL, Schoenmaekers B, Sessler DI, et al. *Anesth Analg*. 2001;92:1319-1321.
- Arcioni R, della Rocca M, Romanò R, et al. *Anesth Analg*. 2002;94:1553-1557.

Manufactured by:

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Manufactured for:

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Relabeled by:

Proficient Rx LP
Thousand Oaks, CA 91320

January 2014

PACKAGE/LABEL PRINCIPAL DISPLAY PANEL

Package/Label Display Panel – Ondansetron Tablets 8 mg Label

ONDANSETRON

ondansetron tablet, orally disintegrating

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:63187-256(NDC:68462-157)
Route of Administration	ORAL		

Active Ingredient/Active Moiety		
Ingredient Name	**Basis of Strength**	**Strength**
ONDANSETRON (UNII: 4AF302ESOS) (ONDANSETRON - UNII:4AF302ESOS)	ONDANSETRON	4 mg

Inactive Ingredients	
Ingredient Name	**Strength**
ASPARTAME (UNII: Z0H242BBR1)	
SILICON DIOXIDE (UNII: ETJ7Z6XBU4)	
CROSPOVIDONE (120 .MU.M) (UNII: 68401960MK)	
MAGNESIUM STEARATE (UNII: 70097M6I30)	
MANNITOL (UNII: 3OWL53L36A)	
SODIUM STEARYL FUMARATE (UNII: 7CV7WJK4UI)	

Product Characteristics			
Color	WHITE	**Score**	no score
Shape	ROUND	**Size**	7mm
Flavor	STRAWBERRY	**Imprint Code**	G;4
Contains			

Packaging				
#	**Item Code**	**Package Description**	**Marketing Start Date**	**Marketing End Date**
1	NDC:63187-256-05	5 in 1 BOX, UNIT-DOSE; Type 0: Not a Combination Product	12/28/2022	
2	NDC:63187-256-06	6 in 1 BOX, UNIT-DOSE; Type 0: Not a Combination Product	01/24/2024	
3	NDC:63187-256-10	10 in 1 BOX, UNIT-DOSE; Type 0: Not a Combination Product	12/28/2022	
4	NDC:63187-256-12	12 in 1 BOX, UNIT-DOSE; Type 0: Not a Combination Product	03/26/2024	
5	NDC:63187-256-15	15 in 1 BOX, UNIT-DOSE; Type 0: Not a Combination Product	12/28/2022	
6	NDC:63187-256-20	20 in 1 BOX, UNIT-DOSE; Type 0: Not a Combination Product	06/01/2017	
7	NDC:63187-256-30	30 in 1 BOX, UNIT-DOSE; Type 0: Not a Combination Product	06/01/2017	

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA078152	06/27/2007	

ONDANSETRON

ondansetron tablet, orally disintegrating

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:63187-199(NDC:68462-158)
Route of Administration	ORAL		

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
ONDANSETRON (UNII: 4AF302ESOS) (ONDANSETRON - UNII:4AF302ESOS)	ONDANSETRON	8 mg

Inactive Ingredients

Ingredient Name	Strength
ASPARTAME (UNII: Z0H242BBR1)	
SILICON DIOXIDE (UNII: ETJ7Z6XBU4)	
CROSPOVIDONE (120 .MU.M) (UNII: 68401960MK)	
MAGNESIUM STEARATE (UNII: 70097M6I30)	
MANNITOL (UNII: 3OWL53L36A)	
SODIUM STEARYL FUMARATE (UNII: 7CV7WJK4UI)	

Product Characteristics

Color	WHITE	**Score**	no score
Shape	ROUND	**Size**	8mm
Flavor	STRAWBERRY	**Imprint Code**	G;8
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:63187-199-10	10 in 1 BOX, UNIT-DOSE; Type 0: Not a Combination Product	10/01/2014	

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA078152	06/27/2007	

Labeler - Proficient Rx LP (079196022)

Establishment

Name	Address	ID/FEI	Business Operations
Proficient Rx LP		079196022	REPACK(63187-199, 63187-256) , RELABEL(63187-199, 63187-256)