HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use ONDANSETRON safely and effectively. See full prescribing information for ONDANSETRON injection, USP
Ondansetron Injection, USP for intravenous use
Initial U.S. Approval: 1991

RECENT MAJOR CHANGES

Dosage and Administration, Prevention of Nausea and Vomiting Associated with Initial and Repeat Courses of Emetogenic Chemotherapy – Removal of 32 mg single intravenous dose (2.1)	11/2012
Warnings and Precautions, QT Prolongation (5.2)	11/2012

INDICATIONS AND USAGE

Ondansetron Injection is a 5-HT_3 receptor antagonist indicated:

- Prevention of nausea and vomiting associated with initial and repeat courses of emetogenic cancer chemotherapy. (1.1)
- Prevention of postoperative nausea and/or vomiting. (1.2)

DOSAGE AND ADMINISTRATION

Prevention of nausea and vomiting associated with initial and repeat courses of emetogenic cancer chemotherapy (2.1):

- Adults and Pediatric patients (6 months to 18 years): Three 0.15 mg/kg doses, up to a maximum of 16 mg per dose, infused intravenously over 15 minutes. The first dose should be administered 30 minutes before the start of chemotherapy. Subsequent doses are administered 4 and 8 hours after the first dose.

Prevention of Postoperative Nausea and/or Vomiting (2.2):

Population	Age	Ondansetron Injection Dosage	Intravenous Infusion Rate
Adults	> 12 yrs	4 mg x 1	over 2 - 5 min
Pediatrics (> 40 kg)	1 mo. – 12 yrs	4 mg x 1	over 2 - 5 min
Pediatrics (≤ 40 kg)	1 mo. – 12 yrs	0.1 mg/kg x 1	over 2 - 5 min

- In patients with severe hepatic impairment, a total daily dose of 8 mg should not be exceeded. (2.4)

DOSAGE FORMS AND STRENGTHS

Ondansetron Injection (2 mg/mL): 20 mL multidose vials. (3)

CONTRAINDICATIONS

- Patients known to have hypersensitivity (e.g., anaphylaxis) to this product or any of its components. (4)
- Concomitant use of apomorphine. (4)

WARNINGS AND PRECAUTIONS

- Hypersensitivity reactions including anaphylaxis and bronchospasm, have been reported in patients who have exhibited hypersensitivity to other selective 5-HT_3 receptor antagonists. (5.1)
- QT prolongation occurs in a dose-dependent manner. Cases of Torsade de Pointes have been reported. Avoid Ondansetron in patients with congenital long QT syndrome. (5.2)
- Use in patients following abdominal surgery or in patients with chemotherapy-induced nausea and vomiting may mask a progressive ileus and/or gastric distention. (5.3) (5.4)

ADVERSE REACTIONS

Chemotherapy-Induced Nausea and Vomiting –

- The most common adverse reactions (≥ 7%) in adults are diarrhea, headache, and fever. (6.1)

Postoperative Nausea and Vomiting –

- The most common adverse reaction (≥ 10%) which occurs at a higher frequency compared to placebo in adults is headache. (6.1)
- The most common adverse reaction (≥ 2%) which occurs at a higher frequency compared to placebo in pediatric patients 1 to 24 months of age is diarrhea. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Heritage Pharmaceuticals Inc. at 1-866-901-DRUG (3784) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

To report SUSPECTED ADVERSE REACTIONS, contact at or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch

DRUG INTERACTIONS

- Apomorphine – profound hypotension and loss of consciousness. Concomitant use with ondansetron is contraindicated. (7.2)

See 17 for PATIENT COUNSELING INFORMATION

Revised: 01/2013

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FULL PRESCRIBING INFORMATION

1 INDICATIONS & USAGE

1.1 Prevention of Nausea and Vomiting Associated with Initial and Repeat Courses of Emetogenic Cancer Chemotherapy

Ondansetron Injection is indicated for the prevention of nausea and vomiting associated with initial and repeat courses of emetogenic cancer chemotherapy, including high-dose cisplatin *[see Clinical Studies (14.1)]*.
Ondansetron is approved for patients aged 6 months and older.

1.2 Prevention of Postoperative Nausea and/or Vomiting

Ondansetron Injection is indicated for the 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 in whom nausea and/or vomiting must be avoided postoperatively, Ondansetron Injection is recommended even when the incidence of postoperative nausea and/or vomiting is low. For patients who do not receive prophylactic Ondansetron Injection and experience nausea and/or vomiting postoperatively, Ondansetron Injection may be given to prevent further episodes *[see Clinical Studies (14.3)]*.
Ondansetron is approved for patients aged 1 month and older.

2 DOSAGE & ADMINISTRATION

2.1 Prevention of Nausea and Vomiting Associated with Initial and Repeat Courses of Emetogenic Chemotherapy

Ondansetron Injection should be diluted in 50 mL of 5% Dextrose Injection or 0.9% Sodium Chloride Injection before administration.
Adults: The recommended adult intravenous dosage of ondansetron is three 0.15-mg/kg doses up to a maximum of 16 mg per dose *[see Clinical Pharmacology (12.2)]*. The first dose is infused over 15 minutes beginning 30 minutes before the start of emetogenic chemotherapy. Subsequent doses (0.15 mg/kg up to a maximum of 16 mg per dose) are administered 4 and 8 hours after the first dose of ondansetron.
Pediatrics: For pediatric patients 6 months through 18 years of age, the intravenous dosage of ondansetron is three 0.15-mg/kg doses up to a maximum of 16 mg per dose *[see Clinical Studies (14.1) and Clinical Pharmacology (12.2 and 12.3)]*. The first dose is to be administered 30 minutes before the start of moderately to highly emetogenic chemotherapy. Subsequent doses (0.15 mg/kg up to a maximum of 16 mg per dose) are administered 4 and 8 hours after the first dose of ondansetron. The drug should be infused intravenously over 15 minutes.

2.2 Prevention of Postoperative Nausea and Vomiting

Ondansetron Injection should not be mixed with solutions for which physical and chemical compatibility have not been established. In particular, this applies to alkaline solutions as a precipitate may form.
Adults: The recommended adult intravenous dosage of ondansetron is 4 mg *undiluted* administered intravenously in not less than 30 seconds, preferably over 2 to 5 minutes, immediately before induction of anesthesia, or postoperatively if the patient did not receive prophylactic antiemetics and experiences nausea and/or vomiting occurring within 2 hours after surgery. Alternatively, 4 mg *undiluted* may be administered intramuscularly as a single injection for adults. While recommended as a fixed dose for patients weighing more than 40 kg, few patients above 80 kg have been studied. In patients who do not achieve adequate control of postoperative nausea and vomiting following a single, prophylactic, preinduction, intravenous dose of ondansetron 4 mg, administration of a second intravenous dose of 4 mg ondansetron postoperatively does not provide additional control of nausea and vomiting.
Pediatrics: For pediatric patients 1 month through 12 years of age, the dosage is a single 0.1-mg/kg dose for patients weighing 40 kg or less, or a single 4-mg dose for patients weighing more than 40 kg. The rate of administration should not be less than 30 seconds, preferably over 2 to 5 minutes immediately prior to or following anesthesia induction, or postoperatively if the patient did not receive prophylactic antiemetics and experiences nausea and/or vomiting occurring shortly after surgery. Prevention of further nausea and vomiting was only studied in patients who had not received prophylactic ondansetron.

2.3 Stability and Handling
After dilution, do not use beyond 24 hours. Although Ondansetron Injection is chemically and physically stable when diluted as recommended, sterile precautions should be observed because diluents generally do not contain preservative.
Ondansetron Injection is stable at room temperature under normal lighting conditions for 48 hours after dilution with the following intravenous fluids: 0.9% Sodium Chloride Injection, 5% Dextrose Injection, 5% Dextrose and 0.9% Sodium Chloride Injection, 5% Dextrose and 0.45% Sodium Chloride Injection, and 3% Sodium Chloride Injection.
Note: Parenteral drug products should be inspected visually for particulate matter and discoloration before administration whenever solution and container permit.
Precaution: Occasionally, ondansetron precipitates at the stopper/vial interface in vials stored upright. Potency and safety are not affected. If a precipitate is observed, resolubilize by shaking the vial vigorously.

2.4 Dosage Adjustment for Patients with Impaired Hepatic Function
In patients with severe hepatic impairment (Child-Pugh score of 10 or greater), a single maximal daily dose of 8 mg infused over 15 minutes beginning 30 minutes before the start of the emetogenic chemotherapy is recommended. There is no experience beyond first-day administration of ondansetron in these patients *[see Clinical Pharmacology (12.3)]*.

3 DOSAGE FORMS & STRENGTHS
Ondansetron Injection, USP 2 mg/mL is a clear, colorless, nonpyrogenic, sterile solution available as a 20 mL multidose vial.

4 CONTRAINDICATIONS
Ondansetron Injection, USP is contraindicated for patients known to have hypersensitivity (e.g., anaphylaxis) to this product or any of its components. Anaphylactic reactions have been reported in patients taking ondansetron. *[See Adverse Reactions (6.2)]*.
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.

5 WARNINGS AND PRECAUTIONS

5.1 Hypersensitivity Reactions
Hypersensitivity reactions, including anaphylaxis and bronchospasm, have been reported in patients who have exhibited hypersensitivity to other selective 5-HT_3 receptor antagonists.

5.2 QT Prolongation
Ondansetron prolongs the QT interval in a dose-dependent manner *[see Clinical Pharmacology (12.2)]*. 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.

5.3 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 gastric distention.

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

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice. The following adverse reactions have been reported in clinical trials of adult patients treated with ondansetron, the active ingredient of intravenous ondansetron across a range of dosages. A causal relationship to therapy with ondansetron was unclear in many cases.

Chemotherapy-Induced Nausea and Vomiting

Table 1. Adverse Reactions Reported in > 5% of Adult Patients Who Received Ondansetron at a Dosage of Three 0.15-mg/kg Doses

*Cardiovascular:*Rare cases of angina (chest pain), electrocardiographic alterations, hypotension, and tachycardia have been reported.
*Gastrointestinal:*Constipation has been reported in 11% of chemotherapy patients receiving multiday ondansetron.
*Hepatic:*In comparative trials in cisplatin chemotherapy patients with normal baseline values of aspartate transaminase (AST) and alanine transaminase (ALT), these enzymes have been reported to exceed twice the upper limit of normal in approximately 5% of patients. 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.
*Integumentary:*Rash has occurred in approximately 1% of patients receiving ondansetron.
*Neurological:*There have been rare reports consistent with, but not diagnostic of, extrapyramidal reactions in patients receiving ondansetron Injection, and rare cases of grand mal seizure.
*Other:*Rare cases of hypokalemia have been reported.

Postoperative Nausea and Vomiting:

The adverse reactions in Table 2 have been reported in ≥ 2% of adults receiving ondansetron at a dosage of 4 mg intravenous over 2 to 5 minutes in clinical trials.

Table 2. Adverse Reactions Reported in ≥ 2% (and With Greater Frequency than the Placebo Group) of Adult Patients Receiving Ondansetron at a Dosage of 4 mg Intravenous over 2 to 5 Minutes

Adverse Reaction*†	n = 547 patients	n = 547 patients

Pediatric Use: Rates of adverse reactions were similar in both the ondansetron and placebo groups in pediatric patients receiving ondansetron (a single 0.1-mg/kg dose for pediatric patients weighing 40 kg or less, or 4 mg for pediatric patients weighing more than 40 kg) administered intravenously over at least 30 seconds. Diarrhea was seen more frequently in patients taking ondansetron (2%) compared to placebo (<1%) in the 1 month to 24 month age group. These patients were receiving multiple concomitant perioperative and postoperative medications.

6.2 Postmarketing Experience

The following adverse reactions have been identified during post-approval use of ondansetron. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. The reactions have been chosen for inclusion due to a combination of their seriousness, frequency of reporting, or potential causal connection to ondansetron.

Cardiovascular:Arrhythmias (including ventricular and supraventricular tachycardia, premature ventricular contractions, and atrial fibrillation), bradycardia, electrocardiographic alterations (including second-degree heart block, QT/QTc interval prolongation, and ST segment depression), palpitations, and syncope. Rarely and predominantly with intravenous ondansetron, transient ECG changes including QT/QTc interval prolongation have been reported *[see Warnings and Precautions (5.2)]*.

General:Flushing. Rare cases of hypersensitivity reactions, sometimes severe (e.g., anaphylatic reactions, angioedema, bronchospasm, cardiopulmonary arrest, hypotension, laryngeal edema, laryngospasm, shock, shortness of breath, stridor) have also been reported. A positive lymphocyte transformation test to ondansetron has been reported, which suggests immunologic sensitivity to ondansetron.
Hepatobiliary:Liver enzyme abnormalities have been reported. Liver failure and death have been reported in patients with cancer receiving concurrent medications including potentially hepatotoxic cytotoxic chemotherapy and antibiotics.
Local Reactions:Pain, redness, and burning at site of injection.
Lower Respiratory:Hiccups
Neurological:Oculogyric crisis, appearing alone, as well as with other dystonic reactions. Transient dizziness during or shortly after intravenous infusion.
Skin:Urticaria
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. Transient blurred vision, in some cases associated with abnormalities of accommodation, have also been reported.

7 DRUG INTERACTIONS

7.1 Drugs Affecting Cytochrome P-450 Enzymes
Ondansetron does not appear to induce or inhibit the cytochrome P-450 drug-metabolizing enzyme system of the liver . 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 *[see Clinical Pharmacology (12.3)]*. On the basis of limited available data, no dosage adjustment is recommended for patients on these drugs.

7.2 Apomorphine
Based on reports of profound hypotension and loss of consciousness when apomorphine was administered with ondansetron, the concomitant use of apomorphine with ondansetron is contradindicated *[see Contraindications (4)]*.

7.3 Phenytoin, Carbamazepine, and Rifampin
In patients treated with potent inducers of CYP3A4 (i.e., phenytoin, carbamazepine, and rifampin), 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 *[see Clinical Pharmacology (12.3)]*.

7.4 Tramadol
Although there are no data on pharmacokinetic drug interactions between ondansetron and tramadol, data from two small studies indicate that concomitant use of ondansetron may result in reduced analgesic activity of tramadol. Patients on concomitant ondansetron self administered tramadol more frequently in these studies, leading to an increased cumulative dose in patient controlled administration (PCA) of tramadol.

7.5 Chemotherapy
In humans, carmustine, etoposide, and cisplatin do not affect the pharmacokinetics of ondansetron.
In a crossover study in 76 pediatric patients, intravenous ondansetron did not increase blood levels of high-dose methotrexate.

7.6 Temazepam
The coadministration of ondansetron had no effect on the pharmacokinetics and pharmacodynamics of temazepam.

7.7 Alfentanil and Atracurium
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.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy
Pregnancy Category B. Reproduction studies have been performed in pregnant rats and rabbits at intravenous doses up to 4 mg/kg per day (approximately 1.4 and 2.9 times the recommended human intravenous dose of 0.15 mg/kg given three times a day, respectively, based on body surface area) 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.

8.3 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.

8.4 Pediatric Use

Little information is available about the use of ondansetron in pediatric surgical patients younger than 1 month of age. *[See Clinical Studies (14.2)]*. Little information is available about the use of ondansetron in pediatric cancer patients younger than 6 months of age. *[See Clinical Studies (14.1) and Dosage and Administration (2)]*.
The clearance of ondansetron in pediatric patients 1 month to 4 months of age is slower and the half-life is ~2.5 fold longer than patients who are > 4 to 24 months of age. As a precaution, it is recommended that patients less than 4 months of age receiving this drug be closely monitored. *[See Clinical Pharmacology (12.3)]*.

8.5 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, 862 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 (12.3)]*.

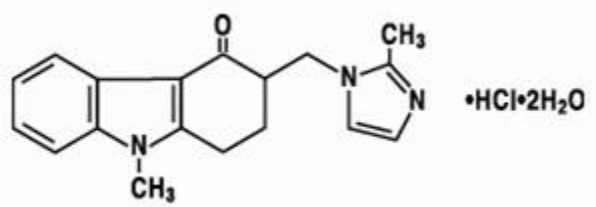
8.6 Hepatic Impairment
In patients with severe hepatic impairment (Child-Pugh score of 10 or greater), clearance is reduced and apparent volume of distribution is increased with a resultant increase in plasma half-life *[see Clinical Pharmacology (12.3)]*. In such patients, a total daily dose of 8 mg should not be exceeded *[see Dosage and Administration (2.3)]*.

8.7 Renal Impairment
Although plasma clearance is reduced in patients with severe renal impairment (creatinine clearance < 30 mL/min), no dosage adjustment is recommended *[see Clinical Pharmacology (12.3)]*.

9 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.

10 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 reactions 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 one patient that was administered 72 mg of ondansetron intravenously as a single dose. Hypotension (and faintness) occurred in another patient that took 48 mg of ondansetron hydrochloride 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.

11 DESCRIPTION
The active ingredient of Ondansetron Injection, USP is ondansetron hydrochloride, a selective blocking agent of the serotonin 5-HT_3 receptor type. Its chemical name 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 $C_{18}H_{19}N_3O{\bullet}HCl{\bullet}2H_2O$, representing a molecular weight of 365.9.
Ondansetron HCl is a white to off-white powder that is soluble in water and normal saline.
Each 1 mL of aqueous solution in the 20 mL multidose vial contains 2 mg of ondansetron as the hydrochloride dihydrate; 8.3 mg of sodium chloride, USP; 0.5 mg of citric acid monohydrate, USP and 0.25 mg of sodium citrate dihydrate, USP as buffers; and 1.2 mg of methylparaben, NF and 0.15 mg of propylparaben, NF as preservatives in Water for Injection, USP.
Ondansetron Injection, USP is a clear, colorless, nonpyrogenic, sterile solution for intravenous use. The pH of the injection solution is 3.3 to 4.0.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Ondansetron is a selective 5-HT_3 receptor antagonist. While ondansetron's mechanism of action has not been fully characterized, it is not a dopamine-receptor antagonist.

12.2 Pharmacodynamics

QTc interval prolongation was studied in a double blind, single intravenous dose, placebo- and positive-controlled, crossover study in 58 healthy subjects. The maximum mean (95% upper confidence bound) difference in QTcF from placebo after baseline-correction was 19.5 (21.8) ms and 5.6 (7.4) ms after 15 minute intravenous infusions of 32 mg and 8 mg ondansetron, respectively. A significant exposure-response relationship was identified between ondansetron concentration and ΔΔQTcF. Using the established exposure-response relationship, 24 mg infused intravenously over 15 min had a mean predicted (95% upper prediction interval) ΔΔQTcF of 14.0 (16.3) ms. In contrast, 16 mg infused intravenously over 15 min using the same model had a mean predicted (95% upper prediction interval) ΔΔQTcF of 9.1 (11.2) ms.

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. In another study in six normal male volunteers, a 16-mg dose infused over 5 minutes showed no effect of the drug on cardiac output, heart rate, stroke volume, blood pressure, or electrocardiogram (ECG). Multiday administration of ondansetron has been shown to slow colonic transit in normal volunteers. Ondansetron has no effect on plasma prolactin concentrations. In a gender-balanced pharmacodynamic study (n = 56), ondansetron 4 mg administered intravenously or intramuscularly was dynamically similar in the prevention of nausea and vomiting using the ipecacuanha model of emesis.

12.3 Pharmacokinetics

In normal adult volunteers, the following mean pharmacokinetic data have been determined following a single 0.15-mg/kg intravenous dose.

Table 3. Pharmacokinetics in Normal Adult Volunteers

Absorption: A study was performed in normal volunteers (n = 56) to evaluate the pharmacokinetics of a single 4-mg dose administered as a 5-minute infusion compared to a single intramuscular injection. Systemic exposure as measured by mean AUC were equivalent, with values of 156 [95% CI 136, 180] and 161 [95% CI 137, 190] ng•h/mL for intravenous and intramuscular groups, respectively. Mean peak plasma concentrations were 42.9 [95% CI 33.8, 54.4] ng/mL at 10 minutes after intravenous infusion and 31.9 [95% CI 26.3, 38.6] ng/mL at 41 minutes after intramuscular injection.

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

Metabolism: 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. The metabolites are observed in the urine.

In vitro metabolism studies have shown that ondansetron is a substrate for multiple human hepatic cytochrome P-450 enzymes, including CYP1A2, CYP2D6, and CYP3A4. In terms of overall ondansetron turnover, CYP3A4 plays a predominant role while formation of the major in vivo metabolites is apparently mediated by CYP1A2. The role of CYP2D6 in ondansetron in vivo metabolism is relatively minor.

The pharmacokinetics of intravenous ondansetron did not differ between subjects who were poor metabolisers of CYP2D6 and those who were extensive metabolisers of CYP2D6, further supporting the limited role of CYP2D6 in ondansetron disposition in vivo.

Elimination: In adult cancer patients, the mean ondansetron elimination half-life was 4.0 hours, and there was no difference in the multidose pharmacokinetics over a 4-day period. In a dose proportionality study, systemic exposure to 32 mg of ondansetron was not proportional to dose as measured by comparing dose-normalized AUC values to an 8-mg dose. This is consistent with a small decrease in systemic clearance with increasing plasma concentrations.

Geriatrics: 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.

Pediatrics: Pharmacokinetic samples were collected from 74 cancer patients 6 to 48 months of age, who received a dose of 0.15 mg/kg of intravenous ondansetron every 4 hours for 3 doses during a safety and efficacy trial. These data were combined with sequential pharmacokinetics data from 41 surgery patients 1 month to 24 months of age, who received a single dose of 0.1 mg/kg of intravenous ondansetron prior to surgery with general anesthesia, and a population pharmacokinetic analysis was performed on the combined data set. The results of this analysis are included in Table 4 and are compared to the pharmacokinetic results in cancer patients 4 to 18 years of age.

Table 4. Pharmacokinetics in Pediatric Cancer Patients 1 Month to 18 Years of Age

1 month to 48 months of age	N = 115	0.582	Vd_{ss} (L/kg)	$T_{½}$ (h)

Based on the population pharmacokinetic analysis, cancer patients 6 to 48 months of age who receive a dose of 0.15 mg/kg of intravenous ondansetron every 4 hours for 3 doses would be expected to achieve a systemic exposure (AUC) consistent with the exposure achieved in previous pediatric studies in cancer patients (4 to 18 years of age) at similar doses.
In a study of 21 pediatric patients (3 to 12 years of age) who were undergoing surgery requiring anesthesia for a duration of 45 minutes to 2 hours, a single intravenous dose of ondansetron, 2 mg (3 to 7 years) or 4 mg (8 to 12 years), was administered immediately prior to anesthesia induction. Mean weight-normalized clearance and volume of distribution values in these pediatric surgical patients were similar to those previously reported for young adults. Mean terminal half-life was slightly reduced in pediatric patients (range, 2.5 to 3 hours) in comparison with adults (range, 3 to 3.5 hours).
In a study of 51 pediatric patients (1 month to 24 months of age) who were undergoing surgery requiring general anesthesia, a single intravenous dose of ondansetron, 0.1 or 0.2 mg/kg, was administered prior to surgery. As shown in Table 5, the 41 patients with pharmacokinetic data were divided into 2 groups, patients 1 month to 4 months of age and patients 5 to 24 months of age, and are compared to pediatric patients 3 to 12 years of age.

Table 5. Pharmacokinetics in Pediatric Surgery Patients 1 Month to 12 Years of Age

In general, surgical and cancer pediatric patients younger than 18 years tend to have a higher ondansetron clearance compared to adults leading to a shorter half-life in most pediatric patients. In patients 1 month to 4 months of age, a longer half-life was observed due to the higher volume of distribution in this age group.
In a study of 21 pediatric cancer patients (4 to 18 years of age) who received three intravenous doses of 0.15 mg/kg of ondansetron at 4-hour intervals, patients older than 15 years of age exhibited ondansetron pharmacokinetic parameters similar to those of adults.
Renal Impairment: 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 mean plasma clearance was reduced by about 41% 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.
Hepatic Impairment: 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 those without hepatic impairment. In patients with severe hepatic impairment (Child-Pugh 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.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis & Mutagenesis & Impairment Of Fertility

Carcinogenic effects were not seen in 2-year studies in rats and mice with oral ondansetron doses up to 10 and 30 mg/kg per day, respectively (approximately 3.6 and 5.4 times the recommended human intravenous dose of 0.15 mg/kg given three times a day, based on body surface area).
Ondansetron was not mutagenic in standard tests for mutagenicity.
Oral administration of ondansetron up to 15 mg/kg per day (approximately 3.8 times the recommended human intravenous dose, based on body surface area) did not affect fertility or general reproductive performance of male and female rats.

14 CLINICAL STUDIES

The clinical efficacy of ondansetron hydrochloride, the active ingredient of ondansetron injection, USP, was assessed in clinical trials as described below.

14.1 Chemotherapy-Induced Nausea and Vomiting

Adults: In a double-blind study of three different dosing regimens of ondansetron Injection, 0.015 mg/kg, 0.15 mg/kg, and 0.30 mg/kg, each given three times during the course of cancer chemotherapy, the 0.15-mg/kg dosing regimen was more effective than the 0.015-mg/kg dosing regimen. The 0.30-mg/kg dosing regimen was not shown to be more effective than the 0.15-mg/kg dosing regimen.

Cisplatin-Based Chemotherapy: In a double-blind study in 28 patients, Ondansetron Injection (three 0.15-mg/kg doses) was significantly more effective than placebo in preventing nausea and vomiting induced by cisplatin-based chemotherapy. Therapeutic response was as shown in Table 6.

Table 6. Therapeutic Response in Prevention of Chemotherapy-Induced Nausea and Vomiting in Single-Day Cisplatin Therapy[1] in Adults

Global satisfaction with control of nausea and vomiting (0-100)[§]	8 (57%) 2 (14%)	0 (0%) 1 (7%)	*P* Value[*]

3-5 Emetic episodes	2 (14%)	13 (93%)	
More than 5 emetic episodes/ rescued			

Ondansetron injection (0.15-mg/kg x 3 doses) was compared with metoclopramide (2 mg/kg x 6 doses) in a single-blind trial in 307 patients receiving cisplatin ≥ 100 mg/m^2 with or without other chemotherapeutic agents. Patients received the first dose of ondansetron or metoclopramide 30 minutes before cisplatin. Two additional ondansetron doses were administered 4 and 8 hours later, or five additional metoclopramide doses were administered 2, 4, 7, 10, and 13 hours later. Cisplatin was administered over a period of 3 hours or less. Episodes of vomiting and retching were tabulated over the period of 24 hours after cisplatin. The results of this study are summarized in Table 7.

Table 7. Therapeutic Response in Prevention of Vomiting Induced by Cisplatin (≥ 100 mg/m^2) Single-Day Therapy[2] in Adults

More than 5 emetic episodes/	19 (14%)	18 (13%)	0.009
rescued	29 (21%)	49 (36%)	

Cyclophosphamide-Based Chemotherapy: In a double-blind, placebo-controlled study of Ondansetron Injection (three 0.15-mg/kg doses) in 20 patients receiving cyclophosphamide (500 to 600 mg/m^2) chemotherapy, Ondansetron Injection was significantly more effective than placebo in preventing nausea and vomiting. The results are summarized in Table 8.

Table 8. Therapeutic Response in Prevention of Chemotherapy-Induced Nausea and Vomiting in Single-Day Cyclophosphamide Therapy[3] in Adults

3-5 Emetic episodes	0 (0%)	2 (20%)	
More than 5 emetic episodes/ rescued	2 (20%) 1 (10%)	4 (40%) 4 (40%)	0.131

Re-treatment:

In uncontrolled trials, 127 patients receiving cisplatin (median dose, 100 mg/m^2) and ondansetron who had two or fewer emetic episodes were re-treated with ondansetron and chemotherapy, mainly cisplatin, for a total of 269 re-treatment courses (median, 2; range, 1 to 10). No emetic episodes occurred in 160 (59%), and two or fewer emetic episodes occurred in 217 (81%) re-treatment courses.

Pediatrics: Four open-label, noncomparative (one US, three foreign) trials have been performed with 209 pediatric cancer patients 4 to 18 years of age given a variety of cisplatin or noncisplatin regimens. In the three foreign trials, the initial ondansetron Injection dose ranged from 0.04 to 0.87 mg/kg for a total dose of 2.16 to 12 mg. This was followed by the oral administration of ondansetron ranging from 4 to 24 mg daily for 3 days. In the US trial, ondansetron was administered intravenously (only) in three doses of 0.15 mg/kg each for a total daily dose of 7.2 to 39 mg. In these studies, 58% of the 196 evaluable patients had a complete response (no emetic episodes) on day 1. Thus, prevention of vomiting in these pediatric patients was essentially the same as for patients older than 18 years of age.

An open-label, multicenter, noncomparative trial has been performed in 75 pediatric cancer patients 6 to 48 months of age receiving at least one moderately or highly emetogenic chemotherapeutic agent. Fifty-seven percent (57%) were females; 67% were white, 18% were American Hispanic, and 15% were black patients. Ondansetron was administered intravenously over 15 minutes in three doses of 0.15 mg/kg. The first dose was administered 30 minutes before the start of chemotherapy, the second and third doses were administered 4 and 8 hours after the first dose, respectively. Eighteen patients (25%) received routine prophylactic dexamethasone (i.e., not given as rescue). Of the 75 evaluable patients, 56% had a complete response (no emetic episodes) on day 1. Thus, prevention of vomiting in these pediatric patients was comparable to the prevention of vomiting in patients 4 years of age and older.

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1Chemotherapy was high dose (100 and 120 mg/m2; Ondansetron Injection n = 6, placebo n = 5) or moderate dose (50 and 80 mg/m2; Ondansetron Injection n = 8, placebo n = 9). Other chemotherapeutic agents included fluorouracil, doxorubicin, and cyclophosphamide. There was no difference between treatments in the types of chemotherapy that would account for differences in response.

2In addition to cisplatin, 68% of patients received other chemotherapeutic agents, including cyclophosphamide, etoposide, and fluorouracil. There was no difference between treatments in the types of chemotherapy that would account for differences in response.

3Chemotherapy consisted of cyclophosphamide in all patients, plus other agents, including fluorouracil, doxorubicin, methotrexate, and vincristine. There was no difference between treatments in the type of chemotherapy that would account for differences in response.

14.2 Prevention of Postoperative Nausea and/or Vomiting

Adults: Adult surgical patients who received ondansetron immediately before the induction of general balanced anesthesia (barbiturate: thiopental, methohexital, or thiamylal; opioid: alfentanil or fentanyl; nitrous oxide; neuromuscular blockade: succinylcholine/curare and/or vecuronium or atracurium; and supplemental isoflurane) were evaluated in two double-blind US studies involving 554 patients. Ondansetron Injection (4 mg) intravenous given over 2 to 5 minutes was significantly more effective than placebo. The results of these studies are summarized in Table 9.

Table 9. Therapeutic Response in Prevention of Postoperative Nausea and Vomiting in Adult Patients

The study populations in Table 9 consisted mainly of females undergoing laparoscopic procedures.

In a placebo-controlled study conducted in 468 males undergoing outpatient procedures, a single 4-mg intravenous ondansetron dose prevented postoperative vomiting over a 24-hour study period in 79% of males receiving drug compared to 63% of males receiving placebo ($P < 0.001$).

Two other placebo-controlled studies were conducted in 2,792 patients undergoing major abdominal or gynecological surgeries to evaluate a single 4-mg or 8-mg intravenous ondansetron dose for prevention of postoperative nausea and vomiting over a 24-hour study period. At the 4-mg dosage, 59% of patients receiving ondansetron versus 45% receiving placebo in the first study ($P < 0.001$) and 41% of patients receiving ondansetron versus 30% receiving placebo in the second study ($P = 0.001$) experienced no emetic episodes. No additional benefit was observed in patients who received intravenous ondansetron 8 mg compared to patients who received intravenous ondansetron 4 mg.

Pediatrics: Three double-blind, placebo-controlled studies have been performed (one US, two foreign) in 1,049 male and female patients (2 to 12 years of age) undergoing general anesthesia with nitrous oxide. The surgical procedures included tonsillectomy with or without adenoidectomy, strabismus surgery, herniorrhaphy, and orchidopexy. Patients were randomized to either single intravenous doses of ondansetron (0.1 mg/kg for pediatric patients weighing 40 kg or less, 4 mg for pediatric patients weighing more than 40 kg) or placebo. Study drug was administered over at least 30 seconds, immediately prior to or following anesthesia induction. Ondansetron was significantly more effective than placebo in preventing nausea and vomiting. The results of these studies are summarized in Table 10.

Table 10. Therapeutic Response in Prevention of Postoperative Nausea and Vomiting in Pediatric Patients 2 to 12 Years of Age

Treatment Response Over 24 Hours	Ondansetron n (%)	Placebo n (%)	*P* Value

Study 1*	205	210	≤ 0.001
Failure	140 (68%)	82 (39%)	
Failure*	65 (32%)	128 (61%)	≤ 0.001
	68 (61%)	38 (35%)	
	44 (39%)	72 (65%)	
None	83 (40%)	110 (53%)	

A double-blind, multicenter, placebo-controlled study was conducted in 670 pediatric patients 1 month to 24 months of age who were undergoing routine surgery under general anesthesia. Seventy-five percent (75%) were males; 64% were white, 15% were black, 13% were American Hispanic, 2% were Asian, and 6% were “other race” patients. A single 0.1-mg/kg intravenous dose of ondansetron administered within 5 minutes following induction of anesthesia was statistically significantly more effective than placebo in preventing vomiting. In the placebo group, 28% of patients experienced vomiting compared to 11% of subjects who received ondansetron ($P \leq 0.01$). Overall, 32 (10%) of placebo patients and 18 (5%) of patients who received ondansetron received antiemetic rescue medication(s) or prematurely withdrew from the study.

14.3 Prevention of Further Postoperative Nausea and Vomiting

Adults: Adult surgical patients receiving general balanced anesthesia (barbiturate: thiopental, methohexital, or thiamylal; opioid: alfentanil or fentanyl; nitrous oxide; neuromuscular blockade: succinylcholine/curare and/or vecuronium or atracurium; and supplemental isoflurane) who received no prophylactic antiemetics and who experienced nausea and/or vomiting within 2 hours postoperatively were evaluated in two double-blind US studies involving 441 patients. Patients who experienced an episode of postoperative nausea and/or vomiting were given Ondansetron Injection (4 mg) intravenous over 2 to 5 minutes, and this was significantly more effective than placebo. The results of these studies are summarized in Table 11.

Table 11. Therapeutic Response in Prevention of Further Postoperative Nausea and Vomiting in Adult Patients

	Ondansetron 4 mg Intravenous	Placebo	*P*Value
Study 1			
Emetic episodes:	104	117	< 0.001
Number of patients	49 (47%)	19 (16%)	
Treatment response 24 h after	12 (12%)	9 (8%)	
study drug	43 (41%)	89 (76%)	
0 Emetic episodes	55.0	43.0	
1 Emetic episode			
More than 1 emetic episode/ rescued			
Median time to first emetic			
episode (min)*			
Nausea assessments:	98	102	
Number of patients	1.7	3.1	
Mean nausea score over 24-h			
postoperative period†			
Study 2			
Emetic episodes:	112	108	0.006
Number of patients	49 (44%)	28 (26%)	
Treatment response 24 h after	14 (13%)	3 (3%)	
study drug	49 (44%)	77 (71%)	
0 Emetic episodes	60.5	34.0	
1 Emetic episode			
More than 1 emetic episode/ rescued			

Median time to first emetic episode (min)*			
Nausea assessments:	105	85	
Number of patients	1.9	2.9	
Mean nausea score over 24-h postoperative period†			

*After administration of study drug.
†Nausea measured on a scale of 0-10 with 0 = no nausea, 10 = nausea as bad as it can be.

The study populations in Table 11 consisted mainly of women undergoing laparoscopic procedures.
Repeat Dosing in Adults: In patients who do not achieve adequate control of postoperative nausea and vomiting following a single, prophylactic, preinduction, intravenous dose of ondansetron 4 mg, administration of a second intravenous dose of ondansetron 4 mg postoperatively does not provide additional control of nausea and vomiting.
Pediatrics: One double-blind, placebo-controlled, US study was performed in 351 male and female outpatients (2 to 12 years of age) who received general anesthesia with nitrous oxide and no prophylactic antiemetics. Surgical procedures were unrestricted. Patients who experienced two or more emetic episodes within 2 hours following discontinuation of nitrous oxide were randomized to either single intravenous doses of ondansetron (0.1 mg/kg for pediatric patients weighing 40 kg or less, 4 mg for pediatric patients weighing more than 40 kg) or placebo administered over at least 30 seconds. Ondansetron was significantly more effective than placebo in preventing further episodes of nausea and vomiting. The results of the study are summarized in Table 12.

Table 12. Therapeutic Response in Prevention of Further Postoperative Nausea and Vomiting in Pediatric Patients 2 to 12 Years of Age

0 Emetic episodes	96 (53%)	29 (17%)	≤ 0.001
Failure*	84 (47%)	142 (83%)	

16 HOW SUPPLIED/STORAGE AND HANDLING

Ondansetron Injection, USP, 2 mg/mL, is supplied as follows:
NDC 23155-168-31 20-mL multidose vials (Singles)
Storage: Store at 25°C (77°F), excursions permitted to 15-30°C (59-86°F). [See USP Controlled Room Temperature]. Protect from light.

17 PATIENT COUNSELING INFORMATION

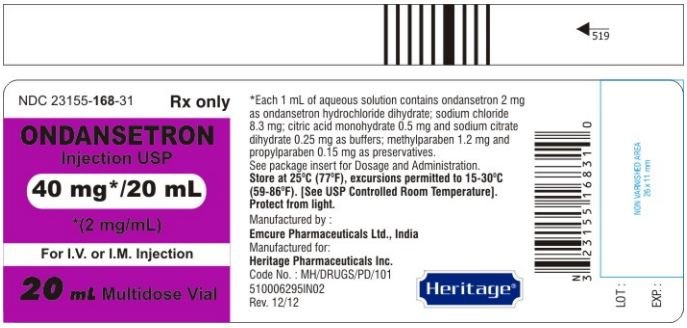
- Patients should be informed that ondansetron may cause serious cardiac arrhythmias such as QT prolongation. Patients should be instructed to tell their health care provider right away if they perceive a change in their heart rate, if they feel lightheaded, or if they have a syncopal episode.
- Patients should be informed that the chances of developing severe cardiac arrhythmias such as QT prolongation and Torsade de Pointes are higher in the following people:
  - Patients with a personal or family history of abnormal heart rhythms, such as congenital long QT syndrome;
  - Patients who take medications, such as diuretics, which may cause electrolyte abnormalities
  - Patients with hypokalemia or hypomagnesemia

Ondansetron should be avoided in these patients, since they may be more at risk for cardiac arrhythmias such as QT prolongation and Torsade de Pointes.
- Inform patients that ondansetron may cause hypersensitivity reactions, some as severe as anaphylaxis and bronchospasm. The patient should report any signs and symptoms of hypersensitivity reactions, including fever, chills, rash, or breathing problems.
- The patient should report the use of all medications, especially apomorphine, to their health care provider. Concomitant use of apomorphine and ondansetron may cause a significant drop in blood pressure and loss of consciousness.
- Inform patients that ondansetron may cause headache, drowsiness/sedation, constipation, fever and diarrhea.

Manufactured by:
Emcure Pharmaceuticals Ltd., India
Manufactured for:
Heritage Pharmaceuticals Inc.
Edison, NJ 08837,USA
1.866.901.DRUG (3784)
Rev. 11/12

PACKAGE LABEL PRINCIPAL DISPLAY PANEL - LABEL

ONDANSETRON Injection USP
40 mg*/20 mL
***(2 mg/mL)**
For I.V. or I.M. Injection
NDC 23155-**168**-31
Rx only
***20 mL* Multidose Vial**
***Each 1 mL of aqueous solution contains ondansetron 2 mg as ondansetron hydrochloride dihydrate; sodium chloride 8.3 mg; citric acid monohydrate 0.5 mg and sodium citrate dihydrate 0.25 mg as buffers; methylparaben 1.2 mg and propylparaben 0.15 mg as preservatives.
See package insert for Dosage and Administration.
Store at 25°C (77°F), excursions permitted to 15-30°C (59-86°F). [See USP Controlled Room Temperature]. Protect from light.
Manufactured by :
Emcure Pharmaceuticals Ltd ., **India**
Manufactured for:
Heritage Pharmaceuticals Inc.



PACKAGE LABEL PRINCIPAL DISPLAY PANEL - CARTON
ONDANSETRON Injection USP
40 mg*/20 mL
***(2 mg/mL)**
NDC 23155-**168**-31
Rx only
For Intravenous or Intramuscular Injection
Sterile
***20 mL* Multidose Vial**
*Each 1 mL of aqueous solution contains ondansetron 2 mg as ondansetron hydrochloride dihydrate; sodium chloride 8.3 mg; citric acid monohydrate 0.5 mg and sodium citrate dihydrate 0.25 mg as buffers; methylparaben 1.2 mg and propylparaben 0.15 mg as preservatives.
See package insert for Dosage and Administration.
Store at 25°C (77°F), excursions permitted to 15-30°C (59-86°F). [See USP Controlled Room Temperature].
Protect from light.
Retain vial in carton until time of use.
Manufactured by :
Emcure Pharmaceuticals Ltd., India
Manufactured for:
Heritage Pharmaceuticals Inc.
Edison, NJ 08837, USA
1.866.901.DRUG (3784)

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*Each 1 mL of aqueous solution contains ondansetron 2 mg as ondansetron hydrochloride dihydrate; sodium chloride 8.3 mg; citric acid monohydrate 0.5 mg and sodium citrate dihydrate 0.25 mg as buffers; methylparaben 1.2 mg and propylparaben 0.15 mg as preservatives.

See package insert for Dosage and Administration.

Store at 25°C (77°F), excursions permitted to 15-30°C (59-86°F). [See USP Controlled Room Temperature].

Protect from light.

Retain vial in carton until time of use.

Code No. : MH/DRUGS/PD/101
Rev. 12/12

NDC 23155-**168**-31 **Rx only**

ONDANSETRON
Injection USP
40 mg*/20 mL
*(2 mg/mL)
20 mL Multidose Vial
Heritage

NON VARNISHED AREA
38 x 35 mm

N 3 23155 16831 0

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NDC 23155-**168**-31 **Rx only**

ONDANSETRON
Injection USP
40 mg*/20 mL
*(2 mg/mL)
20 mL Multidose Vial
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520