

HIGHLIGHTS OF PRESCRIBING INFORMATION

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These highlights do not include all the information needed to use ONDANSETRON ORAL SOLUTION safely and effectively. See full prescribing information for ONDANSETRON ORAL SOLUTION

ONDANSETRON oral solution
Initial U.S. Approval: 1991

INDICATIONS AND USAGE

Ondansetron is a 5-HT₃ receptor antagonist indicated for the prevention of:

- nausea and vomiting associated with highly emetogenic cancer chemotherapy, including cisplatin greater than or equal to 50 mg/m². (1)
- nausea and vomiting associated with initial and repeat courses of moderately emetogenic cancer chemotherapy. (1)
- 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. (1)
- postoperative nausea and/or vomiting. (1)

DOSAGE AND ADMINISTRATION

- See full prescribing information for the recommended dosage in adults and pediatrics. (2)
- Patients with severe hepatic impairment: do not exceed a total daily dose of 8 mg. (2.2, 8.6)

DOSAGE FORMS AND STRENGTHS

- Oral Solution: 4 mg/5 mL (3)

CONTRAINDICATIONS

- Patients known to have hypersensitivity (e.g., anaphylaxis) to ondansetron or any components of the formulation. (4)
- Concomitant use of apomorphine. (4)

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- **Hypersensitivity reactions including anaphylaxis and bronchospasm:** Discontinue ondansetron if suspected. Monitor and treat promptly per standard of care until signs and symptoms resolve. (5.1)
- **QT interval prolongation and Torsade de Pointes:** Avoid in patients with congenital long QT syndrome; monitor with electrocardiograms (ECGs) if concomitant electrolyte abnormalities, cardiac failure or arrhythmias, or use of other QT prolonging drugs. (5.2)
- **Serotonin syndrome:** Reported with 5-HT₃ receptor antagonists alone but particularly with concomitant use of serotonergic drugs. If such symptoms occur, discontinue ondansetron and initiate supportive treatment. If concomitant use of ondansetron with other serotonergic drugs is clinically warranted, patients should be made aware of a potential increased risk for serotonin syndrome. (5.3)
- **Masking of progressive ileus and/or gastric distention following abdominal surgery or chemotherapy-induced nausea and vomiting:** Monitor for decreased bowel activity, particularly in patients with risk factors for gastrointestinal obstruction. (5.4)

ADVERSE REACTIONS

The most common adverse reactions in adults for the:

- prevention of chemotherapy-induced (greater than or equal to 5%) are: headache, malaise/fatigue, constipation, diarrhea. (6.1)
- prevention of radiation-induced nausea and vomiting (greater than or equal to 2%) are: headache, constipation, and diarrhea. (6.1)
- prevention of postoperative nausea and vomiting (greater than or equal to 9%) are: headache and hypoxia. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Taro Pharmaceuticals U.S.A., Inc. at 1-866-923-4914 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

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Revised: 05/2019

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

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

- highly emetogenic cancer chemotherapy, including cisplatin greater than or equal to 50 mg/m².
- initial and repeat courses of moderately emetogenic cancer chemotherapy.
- radiotherapy in patients receiving either total body irradiation, single high-dose fraction to the abdomen, or daily fractions to the abdomen.

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

2 DOSAGE AND ADMINISTRATION

2.1 Dosage

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

Corresponding doses of ondansetron tablets and ondansetron oral solution may be used interchangeably.

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

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

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

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

2.2 Dosage in Hepatic Impairment

In patients with severe hepatic impairment (Child-Pugh score of 10 or greater), do not exceed a total daily dose of 8 mg [see Use in Specific Populations (8.6), Clinical Pharmacology (12.3)].

3 DOSAGE FORMS AND STRENGTHS

Ondansetron oral solution USP, 4 mg/5 mL, is a clear, colorless to light yellow liquid with a characteristic strawberry odor available in a 50-mL bottle.

4 CONTRAINDICATIONS

Ondansetron is contraindicated in patients:

- known to have hypersensitivity (e.g., anaphylaxis) to ondansetron or any of the components of the formulation [see Adverse Reactions (6.2)].
- receiving concomitant apomorphine due to the risk of profound hypotension and loss of consciousness.

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-HT₃ receptor antagonists. If hypersensitivity reactions occur, discontinue use of ondansetron; treat promptly per standard of care and monitor until signs and symptoms resolve [see Contraindications (4)].

5.2 QT Prolongation

Electrocardiogram (ECG) changes including QT interval prolongation have been seen in patients receiving ondansetron. In addition, postmarketing 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 [see Clinical Pharmacology (12.2)].

5.3 Serotonin Syndrome

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

Symptoms associated with serotonin syndrome may include the following combination of signs and symptoms: mental status changes (e.g., agitation, hallucinations, delirium, and coma), autonomic instability (e.g., tachycardia, labile blood pressure, dizziness, diaphoresis, flushing, hyperthermia), neuromuscular symptoms (e.g., tremor, rigidity, myoclonus, hyperreflexia, incoordination), seizures, with or without gastrointestinal symptoms (e.g., nausea, vomiting, diarrhea). Patients should be monitored for the emergence of serotonin syndrome, especially with concomitant use of ondansetron and other serotonergic drugs. If symptoms of serotonin syndrome occur, discontinue ondansetron and initiate supportive treatment. Patients should be informed of the increased risk of serotonin syndrome, especially if ondansetron is used concomitantly with other serotonergic drugs [see Drug Interactions (7.1), Overdosage (10)].

5.4 Masking of Progressive Ileus and Gastric Distension

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

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

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 with rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The following adverse reactions have been reported in clinical trials of patients treated with ondansetron, the active ingredient of ondansetron oral solution. A causal relationship to therapy with ondansetron was unclear in many cases.

Prevention of Chemotherapy-induced Nausea and Vomiting

The most common adverse reactions reported in greater than or equal to 4% of 300 adults receiving a single 24-mg dose of ondansetron orally in 2 trials for the prevention of nausea and vomiting associated with highly emetogenic chemotherapy (cisplatin greater than or equal to 50 mg/m²) were: headache (11%) and diarrhea (4%).

The most common adverse reactions reported in 4 trials in adults for the prevention of nausea and vomiting associated with moderately emetogenic chemotherapy (primarily cyclophosphamide-based regimens) are shown in Table 3.

Table 3: Most Common Adverse Reactions in Adults* for the Prevention of Nausea and Vomiting Associated with Moderately Emetogenic Chemotherapy [Primarily Cyclophosphamide-based Regimens]

Adverse Reaction	Ondansetron 8 mg Twice Daily (n = 242)	Placebo (n = 262)
Headache	58 (24%)	34 (13%)
Malaise/fatigue	32 (13%)	6 (2%)
Constipation	22 (9%)	1 (<1%)
Diarrhea	15 (6%)	10 (4%)

* Reported in greater than or equal to 5% of patients treated with ondansetron and at a rate that exceeded placebo.

Less Common Adverse Reactions

Central Nervous System: Extrapyrarnidal reactions (less than 1% of patients).

Hepatic: Aspartate transaminase (AST) and/or alanine transaminase (ALT) values exceeded twice the upper limit of normal in approximately 1% to 2% of 723 patients receiving ondansetron and cyclophosphamide-based chemotherapy in US clinical trials. 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 is unclear.

Liver failure and death has been reported in cancer patients receiving concurrent medications, including potentially hepatotoxic cytotoxic chemotherapy and antibiotics. The etiology of the liver failure is unclear. **Integumentary:** Rash (approximately 1% of patients).

Other (less than 2%): Anaphylaxis, bronchospasm, tachycardia, angina, hypokalemia, electrocardiographic alterations, vascular occlusive events, and grand mal seizures. Except for bronchospasm and anaphylaxis, the relationship to ondansetron is unclear.

Prevention of Radiation-Induced Nausea and Vomiting

The most common adverse reactions (greater than or equal to 2%) reported in patients receiving ondansetron and concurrent radiotherapy were similar to those reported in patients receiving ondansetron and concurrent chemotherapy and were headache, constipation, and diarrhea.

Prevention of Postoperative Nausea and Vomiting

The most common adverse reactions reported in adult(s) in prevention of postoperative nausea and vomiting are shown in Table 4. In these trial(s), patients were receiving multiple concomitant perioperative and postoperative medications in both treatment groups.

Table 4: Most Common Adverse Reactions in Adults* for the Prevention of Postoperative Nausea and Vomiting

Adverse Reaction	Ondansetron 16 mg as a Single Dose (n = 550)	Placebo (n = 531)
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%)
Urinary retention	28 (5%)	18 (3%)
Pruritus	27 (5%)	20 (4%)

* Reported in greater than or equal to 5% of patients treated with ondansetron and at a rate that exceeded placebo.

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.

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 interval prolongation have been reported.

General

Flushing. Rare cases of hypersensitivity reactions, sometimes severe (e.g., anaphylactic 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.

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.

7 DRUG INTERACTIONS

7.1 Serotonergic Drugs

Serotonin syndrome (including altered mental status, autonomic instability, and neuromuscular symptoms) has been described following the concomitant use of 5-HT₃ receptor antagonists and other serotonergic drugs, including selective serotonin reuptake inhibitors (SSRIs) and serotonin and noradrenaline reuptake inhibitors (SNRIs). Monitor for the emergence of serotonin syndrome. If symptoms occur, discontinue ondansetron and initiate supportive treatment [see Warnings and Precautions (5.3)].

7.2 Drugs Affecting Cytochrome P-450 Enzymes

Ondansetron does not itself appear to induce or inhibit the cytochrome P-450 drug-metabolizing enzyme system of the liver [see Clinical Pharmacology (12.3)]. 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. 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)].

7.3 Tramadol

Although no pharmacokinetic drug interaction between ondansetron and tramadol has been observed, data from 2 small trials indicate that when used together, ondansetron may increase patient-controlled administration of tramadol. Monitor patients to ensure adequate pain control when ondansetron is administered with tramadol.

7.4 Chemotherapy

Carmustine, etoposide, and cisplatin do not affect the pharmacokinetics of ondansetron.

In a crossover trial in 76 pediatric patients, intravenous ondansetron did not increase systemic concentrations of high-dose methotrexate.

7.5 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

Risk Summary

Available data do not reliably inform the association of ondansetron and adverse fetal outcomes. Published epidemiological studies on the association between ondansetron and fetal outcomes have reported inconsistent findings and have important methodological limitations hindering interpretation [see Data]. Reproductive studies in rats and rabbits did not show evidence of harm to the fetus when ondansetron was administered during organogenesis at approximately 6 and 24 times the maximum recommended human oral dose of 24 mg/day, based on body surface area, respectively [see Data]. The background risk of major birth defects and miscarriage for the indicated population is unknown. In the US general population, the estimated background risk of major birth defects and miscarriages in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

