ONDANSETRON (Systemic)

Category

Antiemetic 1.

Indications

Accepted

Nausea and vomiting, cancer chemotherapy-induced (prophylaxis)¾Ondansetron is indicated for the prevention of nausea and vomiting associated with initial and repeat courses of moderately or highly emetogenic cancer chemotherapy 1, 8, 9, 22, 23, 37, 53, 55, 62 , including high-dose cisplatin. 1, 8, 23

Studies done to date comparing ondansetron to high-dose metoclopramide have shown ondansetron to be more effective in preventing nausea and vomiting induced by emetogenic chemotherapy agents during the acute phase lasting 24 hours after the start of chemotherapy. 3, 5, 7, 13, 14, 37, 39, 40, 41, 42, 55, 56

The combination of ondansetron plus dexamethasone has been shown to provide better emetic control over cisplatin-induced emesis than ondansetron alone. 37, 44, 45, 46

Nausea and vomiting, postoperative (prophylaxis and treatment)¾Ondansetron is indicated for the prevention and treatment of postoperative nausea and vomiting. 22, 23, 37, 47, 50, 52, 62, 67 Patients at greatest risk of developing postoperative nausea and vomiting include patients who have previously experienced postoperative nausea, patients predisposed to motion sickness, and patients with high levels of preoperative anxiety. 47 The incidence of postoperative nausea and vomiting is also higher in women 47, 49, 50 and children 47 than in men and adults, respectively. Routine prophylaxis is not recommended for patients in whom there is little expectation that postoperative nausea and vomiting will occur, except in cases in which the stress of vomiting may damage the operation site. 23, 37, 47

Nausea and vomiting, radiotherapy-induced (prophylaxis)¾Ondansetron tablets are indicated for the prevention of nausea and vomiting associated with radiotherapy 22, 37, 57, 62, 69 in patients receiving total body irradiation 57, 60, 62 , or single high-dose fraction or daily fractions to the abdomen. 57, 62, 67, 69, 70

Unaccepted

Ondansetron is not effective in preventing motion-induced nausea and vomiting. 22

Precautions to Consider

Cross-sensitivity and/or related problems

Patients sensitive to granisetron or dolasetron may also be sensitive to ondansetron. 24, 70

Carcinogenicity

Carcinogenic effects were not seen in 2-year studies [39] in rats and mice given ondansetron orally in doses up to 10 and 30 mg per kg of body weight (mg/kg) per day, respectively. [1, 23, 25]

Mutagenicity

Standard tests showed no mutagenic activity of ondansetron. [1, 23, 25, 39]

Pregnancy/Reproduction

Fertility¾Ondansetron had no effect on the fertility or reproductive performance of male and female rats when given in oral doses up to 15 mg/kg per day. [23, 25]

Pregnancy¾Adequate and well-controlled studies in humans have not been done. [1, 22, 23, 25]

Studies in pregnant rats and rabbits given intravenous doses of up to 4 mg/kg per day [1, 23], and oral doses of up to 15 and 30 mg/kg per day, respectively, [25] have not shown that ondansetron causes adverse effects in the fetus.
FDA Pregnancy Category B. [1, 23, 25, 26]

Breast-feeding

It is not known whether ondansetron is distributed into human breast milk. However, ondansetron is distributed into the milk of rats. [1, 22, 23, 25]

Pediatrics

Studies performed to date that included cancer patients 4 to 18 years of age and postoperative patients 2 to 12 years of age have not demonstrated pediatrics-specific problems that would limit the usefulness of ondansetron in children. [1, 23, 25, 52, 67]

Geriatrics

Studies performed to date that included cancer patients over 65 years of age have not demonstrated geriatrics-specific problems that would limit the usefulness of ondansetron in the elderly. [1, 23, 25]

Drug interactions and/or related problems

The following drug interactions and/or related problems have been selected on the basis of their potential clinical significance (possible mechanism in parentheses where appropriate)¾not necessarily inclusive (>> = major clinical significance):
Enzyme inducers, hepatic, cytochrome P450 (see Appendix II) or

Enzyme inhibitors, hepatic, various (see Appendix II)

(because ondansetron is metabolized by hepatic cytochrome P450 enzymes, inducers or inhibitors of these enzymes potentially may alter its clearance and half-life; ondansetron does not appear to induce or inhibit the cytochrome P450 enzyme system of the liver 1, 21, 23, 25)

Laboratory value alterations

The following have been selected on the basis of their potential clinical significance (possible effect in parentheses where appropriate)¾not necessarily inclusive (>> = major clinical significance):
With physiology/laboratory test values

Alanine aminotransferase (ALT [SGPT]) 1, 5, 8, 12, 14, 15, 22, 23, 25, 26, 47 and

Aspartate aminotransferase (AST [SGOT]) 1, 5, 8, 12, 14, 15, 22, 23, 25, 26

(values may be increased; increases reportedly are transient and unrelated to dose or duration of therapy 1, 22, 23, 25)

Bilirubin, serum 5, 8, 15, 26

(concentrations may be increased; increases reportedly are transient and unrelated to dose or duration of therapy 1)

Medical considerations/Contraindications

The medical considerations/contraindications included have been selected on the basis of their potential clinical significance (reasons given in parentheses where appropriate)¾ not necessarily inclusive (>> = major clinical significance).
Risk-benefit should be considered when the following medical problems exist

Hepatic function impairment 7, 21, 71

(use of ondansetron may result in increases in hepatic enzymes; in patients with severe hepatic insufficiency, ondansetron clearance is reduced, plasma half-life is increased, and bioavailability approaches 100%; dosage adjustments are needed)

Phenylketonuria (PKU)

(Zofran brand of ondansetron oral disintegrating tablets contains aspartame, which is metabolized to phenylalanine 71)

Surgery, abdominal 23

(use of ondansetron may mask a progressive ileus and/or gastric distension)

Sensitivity to ondansetron 22, 23, 25 , granisetron 24 , or dolasetron

Side/Adverse Effects

Note: Since ondansetron is used in conjunction with cancer chemotherapeutic agents, it is difficult to attribute some side effects, such as diarrhea and fever, to ondansetron alone. 20

Signs and symptoms consistent with extrapyramidal effects have been reported in a very small number of patients receiving ondansetron 27, 28, 29, 37 ; however, a causal relationship has not been established. 22, 23, 25

The following side/adverse effects have been selected on the basis of their potential clinical significance (possible signs and symptoms in parentheses where appropriate)¾not necessarily inclusive:
Those indicating need for medical attention

Incidence rare

Anaphylaxis 22, 23, 25, 26, 30 hypotension); skin rash, hives, and/or itching); troubled breathing); bronchospasm 1, 22, 23, 25, 30 shortness of breath, tightness in chest, troubled breathing, or wheezing); chest pain 22, 23, 31; injection-site reactions 67 pain, redness, and burning at site of injection)
Those indicating need for medical attention only if they continue or are bothersome

Incidence more frequent

Constipation 1, 3, 6, 12, 13, 15, 22, 23, 25, 26, 32, 37, 39, 53; diarrhea 1, 3, 4, 5, 7, 8, 9, 10, 13, 14, 15, 23, 32, 55; fever 2, 8, 10, 23, 55; headache 1, 2, 3, 4, 5, 7, 8, 9, 10, 12, 13, 14, 15, 22, 23, 25, 26, 32, 37, 39, 47, 53, 55
Incidence less frequent or rare

Abdominal pain or stomach cramps 8, 12, 15, 25, 26; cold sensation 67 (feeling cold); dizziness or lightheadedness 10, 12, 26, 37, 47; drowsiness 3, 5, 10, 14, 15, 32, 37, 47; dryness of mouth 3, 10, 13, 14, 25, 37; paresthesias 67 (burning, tingling, or prickling sensations); pruritus 67 (itching); skin rash 1, 22, 23, 25; unusual tiredness or weakness 3, 8, 13, 25

Overdose

For information on the management of overdose or unintentional ingestion, contact a Poison Control Center (see Poison Control Center Listing).

Clinical effects of overdose

Individual doses as large as 145 mg and total daily dosages as large as 252 mg have been administered intravenously without significant adverse events. 67

Hypotension and faintness occurred in a patient who ingested 48 mg of oral ondansetron. Sudden blindness (amaurosis) of 2 to 3 minutes' duration plus severe constipation occurred in another patient who was administered a single dose of 72 mg of ondansetron intravenously. A vasovagal episode with transient second-degree heart block was observed in another patient following the infusion of 32 mg of ondansetron over a 4-minute period. In all cases, the events resolved completely. 67

Treatment of overdose

There is no specific antidote for ondansetron overdose 67.

Supportive care¾Patients should be managed with appropriate supportive therapy. 67 Patients in whom intentional overdose is confirmed or suspected should be referred for psychiatric evaluation.

Patient Consultation

As an aid to patient consultation, refer to Advice for the Patient, Ondansetron (Systemic) .
In providing consultation, consider emphasizing the following selected information (>> = major clinical significance):
Before using this medication

>> Conditions affecting use, especially:

Sensitivity to ondansetron, granisetron, or dolasetron
Proper use of this medication

Taking additional dose if vomiting occurs within 30 minutes after a dose; checking with doctor if vomiting persists 58

Proper handling/administration of the oral disintegrating tablets 71

>> Proper dosing
Missed dose: Taking missed dose as soon as possible if nausea or vomiting occurs 22, 59

>> Proper storage
Side/adverse effects

Signs of potential side effects, especially anaphylaxis, bronchospasm, chest pain, or injection-site reactions

General Dosing Information

For prophylaxis against nausea and vomiting induced by highly emetogenic chemotherapeutic agents, the parenteral form of ondansetron is recommended. 23 The oral forms of ondansetron are indicated for the prevention of nausea and vomiting induced by moderately emetogenic-chemotherapeutic agents 25.

Zofran brand of oral disintegrating tablets is a freeze-dried formulation of ondansetron that rapidly disintegrates on the tongue and does not require water to aid dissolution or swallowing. 71

Oral disintegrating tablets may contain aspartame, which is metabolized to phenylalanine. This substance must be used with caution in patients with phenylketonuria.

Oral Dosage Forms

ONDANSETRON HYDROCHLORIDE ORAL SOLUTION

Usual adult and adolescent dose

Nausea and vomiting, cancer chemotherapy-induced (prophylaxis)¾
Initial: Oral, 8 mg thirty minutes prior to chemotherapy. 25

Post-chemotherapy: Oral, 8 mg eight hours after the initial dose, followed by 8 mg every twelve hours for one to two days. 62, 64, 65

Nausea and vomiting, postoperative (prophylaxis)¾
Oral, 16 mg one hour prior to induction of anesthesia. 62, 63, 64

Nausea and vomiting, radiotherapy-induced (prophylaxis)¾
Initial: Oral, 8 mg one to two hours prior to radiotherapy. 22, 57

Post-radiotherapy: Oral, 8 mg every eight hours 22, 57, 67, 69, 70.

Note: In patients with hepatic function impairment, the maximum recommended dose of ondansetron is 8 mg a day. 22, 25, 37

Usual pediatric dose

Nausea and vomiting, cancer chemotherapy-induced (prophylaxis)¾
Children up to 4 years of age¾
Dosage has not been established.

Children 4 to 12 years of age¾
Initial¾Oral, 4 mg thirty minutes prior to chemotherapy. 22, 25

Post-chemotherapy¾Oral, 4 mg four and eight hours after the initial dose 22, 25 , followed by 4 mg every eight hours for one to two days. 62

Children 12 years of age and older¾
See Usual adult and adolescent dose. 25

Nausea and vomiting, postoperative (prophylaxis) 62 or
Nausea and vomiting, radiotherapy-induced (prophylaxis) 22, 57, 64¾
Dosage has not been established.

Usual geriatric dose

See Usual adult and adolescent dose. 22, 25, 57, 62

Strength(s) usually available
U.S.¾4 mg per 5 mL (Rx)[Zofran (strawberry flavored) (sorbitol) (citric acid anhydrous) (sodium benzoate) (sodium citrate)]

Canada¾4 mg per 5 mL (Rx)[Zofran (strawberry flavored) (sorbitol) (citric acid anhydrous) (sodium benzoate) (sodium citrate dihydrate)]

Packaging and storage:

Store between 15 and 30 °C (59 and 86 °F), unless otherwise specified by manufacturer. Protect from light. Store bottles upright in cartons 70.

ONDANSETRON HYDROCHLORIDE TABLETS

Usual adult and adolescent dose

See Ondansetron Hydrochloride Oral Solution .

Usual pediatric dose

See Ondansetron Hydrochloride Oral Solution .

Usual geriatric dose

See Ondansetron Hydrochloride Oral Solution .

Strength(s) usually available

U.S.¾4 mg (Rx)[Zofran (lactose) (microcrystalline cellulose) (pregelatinized starch) (hydroxypropyl methylcellulose) (magnesium stearate) (titanium dioxide) (sodium benzoate)]

8 mg (Rx)[Zofran (lactose) (microcrystalline cellulose) (pregelatinized starch) (hydroxypropyl methylcellulose) (magnesium stearate) (titanium dioxide) (iron oxide)]

Canada¾4 mg (Rx)[Zofran (lactose) (microcrystalline cellulose) (pregelatinized starch) (magnesium stearate) (methyl hydroxypropyl cellulose) (Opadry yellow) (Opaspray yellow [containing titanium dioxide and iron oxide yellow])]

8 mg (Rx)[Zofran (lactose) (microcrystalline cellulose) (pregelatinized starch) (magnesium stearate) (methyl hydroxypropyl cellulose) (Opadry yellow) (Opaspray yellow [containing titanium dioxide and iron oxide yellow])]

Packaging and storage:

Store between 2 and 30 °C (36 and 86 °F), unless otherwise specified by manufacturer. Protect from light. 25

ONDANSETRON ORAL DISINTEGRATING TABLETS

Note: Zofran brand of oral disintegrating tablets is a freeze-dried formulation of ondansetron which rapidly disintegrates on the tongue and does not require water to aid dissolution or swallowing. 71

Usual adult and adolescent dose

See Ondansetron Hydrochloride Oral Solution.

71

Usual pediatric dose

See Ondansetron Hydrochloride Oral Solution.

71

Usual geriatric dose

See Ondansetron Hydrochloride Oral Solution.

71

Strength(s) usually available
U.S.¾4 mg (Rx)[Zofran ODT (aspartame [< 0.03 mg]) (gelatin) (mannitol) (methylparaben sodium) (propylparaben sodium) (strawberry flavor)]

8 mg (Rx)[Zofran (aspartame [< 0.03 mg]) (gelatin) (mannitol) (methylparaben sodium) (propylparaben sodium) (strawberry flavor)]

Canada¾Not commercially available.

Packaging and storage:

Store between 2 and 30 °C (36 and 86 °F), unless otherwise specified by manufacturer. Protect from light. 71

Caution:¾Zofran brand of oral disintegrating tablets contains aspartame, which is metabolized to phenylalanine and must be used with caution in patients with phenylketonuria.

Additional information:

Proper handling/administration¾With dry hands, peel back the foil backing of one blister. Do not attempt to push the oral disintegrating tablet through the foil backing. Gently remove the tablet and place it immediately on top of the tongue. It will dissolve in seconds, and should then be swallowed with saliva. 71

Parenteral Dosage Forms

ONDANSETRON INJECTION USP

Usual adult dose

Nausea and vomiting, cancer chemotherapy-induced (prophylaxis)¾

Intravenous, 32 mg administered over fifteen minutes beginning thirty minutes prior to chemotherapy. 22, 23, 55, 56, 66 Alternatively, three doses of 150 mcg (0.15 mg) per kg of body weight, each administered over fifteen minutes, with the initial dose beginning thirty minutes prior to chemotherapy, and subsequent doses administered four and eight hours after the first dose. 1, 22, 23, 55, 56 Or, 8 mg administered over fifteen minutes beginning thirty minutes prior to chemotherapy, followed immediately by a continuous infusion of 1 mg per hour for up to twenty-four hours. 22

Nausea and vomiting, postoperative (prophylaxis)¾
Intravenous, 4 mg administered over not less than thirty seconds and preferably over two to five minutes, beginning immediately prior to induction of anesthesia. 22, 23, 49, 50 Alternatively, 4 mg may be administered undiluted as a single intramuscular injection 67.

Nausea and vomiting, postoperative (treatment)¾
Intravenous, 4 mg administered over not less than thirty seconds and preferably over two to five minutes 22, 33, 51 , given postoperatively if nausea or vomiting occurs. Alternatively, 4 mg may be administered undiluted as a single intramuscular injection 67.

Note: In patients with severe hepatic function impairment, the maximum recommended dose of ondansetron is 8 mg a day, infused over 15 minutes beginning 30 minutes before the start of emetogenic chemotherapy. 19, 22, 23, 37, 67

Usual pediatric dose

Nausea and vomiting, cancer chemotherapy-induced (prophylaxis)¾
Children up to 4 years of age: Dosage has not been established. 1

Children 4 to 18 years of age: Intravenous, three doses of 150 mcg (0.15 mg) per kg of body weight, each administered over fifteen minutes, with the initial dose beginning thirty minutes prior to chemotherapy, and subsequent doses administered four and eight hours after the first dose. 1, 23 Alternatively, 3 to 5 mg per square meter of body surface area administered over fifteen minutes beginning immediately prior to chemotherapy, 22, 37 followed after therapy by oral ondansetron 4 mg every eight hours for up to five days. 22

Nausea and vomiting, postoperative¾
Children up to 2 years of age: Dosage has not been established. 1, 67

Children 2 to 12 years of age: Intravenous, a single dose of 150 mcg (0.15 mg) per kg of body weight for those weighing 40 kg or less, or a single 4-mg dose for those weighing more than 40 kg, administered over not less than thirty seconds and preferably over two to five minutes. 67

Usual geriatric dose

See Usual adult dose.

22, 23

Strength(s) usually available

U.S.¾2 mg per mL (Rx)[Zofran (sodium chloride) (citric acid monohydrate 0.5 mg) (sodium citrate dihydrate 0.25 mg) ([may contain methylparaben 1.2 mg, propylparaben 0.15 mg])]

32 mg per 50 mL (premixed) (Rx)[Zofran (dextrose 2500 mg) (citric acid 26 mg) (sodium citrate 11.5 mg)]

Canada¾2 mg per mL (Rx)[Zofran]

Packaging and storage:

Store between 2 and 30 °C (36 and 86 °F), unless otherwise specified by manufacturer. Protect from light. 1, 22, 23 Do not freeze. 69

Preparation of dosage form:

For intravenous administration¾The manufacturer recommends that the dose of ondansetron be diluted in 50 mL of 5% dextrose injection or 0.9% sodium chloride injection 23, 36 ; however, ondansetron also has been shown to be stable in dextrose and sodium chloride injections, 3% sodium chloride injection 1, 22, 23 , 10% mannitol injection, and Ringer's injection. 22, 36

Stability:

Intravenous infusions of ondansetron retain their potency for 48 hours at room temperature under normal lighting after dilution with 5% dextrose injection, dextrose and sodium chloride injections, 0.9% sodium chloride injection, and 3% sodium chloride injection. 1, 23

Incompatibilities:

The following medications may be incompatible with ondansetron and should be avoided in admixtures: acyclovir, allopurinol, aminophylline, amphotericin B, ampicillin, ampicillin and sulbactam, amsacrine, cefepime, cefoperazone, furosemide, ganciclovir, lorazepam, methylprednisolone, mezlocillin, piperacillin, 19, 26, 36 and sargramostim. 36, 68 In addition, alkaline solutions 23, 26, 35, 36 and fluorouracil in concentrations greater than 0.8 mg per mL 36, 58 have been shown to be physically incompatible with ondansetron.Caution:¾Occasionally, ondansetron precipitates at the stopper/vial interface in vials stored upright. If a precipitate is observed, resolubilize by shaking the vial vigorously. Potency and stability are not affected. 67

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