Ondansetron HCl

(on-**dan**-sah-tron)
Zofran®
5-HT3 Receptor Antagonist (Systemic Drug)

Dosages Dosage Forms Drug Interactions Adverse Effects

Prescriber Highlights

- Serotonin type 3 (5-HT_3) receptor antagonist for severe vomiting.
- Appears to be well tolerated.

Uses / Indications

Ondansetron is an antiemetic used for severe vomiting in dogs and cats. Ondansetron, metoclopramide, and maropitant are equally effective in reducing the frequency of vomiting in dogs with parvoviral enteritis.[1] Ondansetron can be particularly effective for treating chemotherapy-associated vomiting. A study in cats found that ondansetron 0.22 mg/kg IM administered with dexmedetomidine and buprenorphine (in the same syringe) reduced the incidence (≈33%) and severity of nausea and vomiting when compared to ondansetron given 30 minutes before dexmedetomidine and buprenorphine (67%) or when ondansetron was not given (76%).[2]

Pharmacology / Actions

Ondansetron is a 5-HT_3 receptor antagonist. 5-HT_3 receptors are found peripherally on vagal nerve terminals and centrally in the chemoreceptor trigger zone (CRTZ). Ondansetron's effects appear to be mediated by antagonism of these receptors both centrally and peripherally. It has no effect on GI motility or transit time.

Pharmacokinetics

In cats, ondansetron's oral bioavailability is approximately 32% but 75% when injected SC. Elimination half-life is approximately 2 hours (IV), 1.2 hours (PO), and 3.2 hours (SC).[3] Administration of ondansetron 2 mg SC to geriatric cats and cats with renal and hepatic disease revealed reductions in clearance, which were greatest in cats with hepatic disease.[4] Ondansetron in *Lipoderm*® transdermal gel applied to the inner ear pinna of healthy cats resulted in no measurable serum ondansetron levels.[5]

After a single oral dose to healthy dogs, peak levels were reached at 1.1 hours and elimination half-life was approximately 1.3 hours.[6]

In humans, ondansetron is well absorbed from the GI tract but exhibits some first-pass hepatic metabolism. Bioavailability is approximately 50% to 60%. Peak plasma levels occur approximately 2 hours after an oral dose. Ondansetron is extensively metabolized in the liver by several cytochrome P450

enzymes, primarily via CYP3A4. Elimination half-lives are approximately 3 to 4 hours but are prolonged in elderly patients.

Contraindications / Precautions / Warnings

Ondansetron is contraindicated in patients hypersensitive to it or other agents in this class. Ondansetron may mask ileus or gastric distention; it should not be used in place of nasogastric suction. Use with caution in patients with hepatic dysfunction, as absorption may be increased because of reduced first-pass metabolism, and half-life may be prolonged; dosage adjustment may be warranted in severe hepatic impairment.

In humans, ondansetron is pumped by P-glycoprotein (the protein encoded by the MDR1 gene), but there is currently no data stating whether it is pumped by canine P-glycoprotein. It is suggested to use caution when administering ondansetron to dogs with the MDR1 mutation.[7]

Dose-related prolongation of the QT interval and cases of torsades de pointes have been reported in humans, and patients with electrolyte abnormalities, underlying cardiac conditions, or those taking other QT prolonging drugs are at greater risk. A study in dogs identified QTc prolongation in sick dogs before ondansetron administration compared to healthy controls, and identified ondansetron QTc prolongation by only 1 of the 2 methods used to calculate the QTc interval.[8]

Serotonin syndrome has occurred in humans receiving ondansetron.

Adverse Effects

Ondansetron appears to be well tolerated. Constipation, sedation, extrapyramidal clinical signs (head shaking), arrhythmias, and hypotension are possible (incidence in humans <10%).

Reproductive / Nursing Safety

Safety in pregnancy not clearly established, but high dose studies in rodents did not demonstrate overt fetal toxicity or teratogenicity. In humans, the FDA categorizes this drug as category ***B*** for use during pregnancy (*Animal studies have not yet demonstrated risk to the fetus, but there are no adequate studies in pregnant women; or animal studies have shown an adverse effect, but adequate studies in pregnant women have not demonstrated a risk to the fetus in the first trimester of pregnancy, and there is no evidence of risk in later trimesters*).

Ondansetron is excreted in the maternal milk of rats. Exercise caution when 5-HT_3 antagonists are administered to nursing patients.

Overdose / Acute Toxicity

Overdoses of up to 10 times the label dose did not cause significant morbidity in human subjects. If an overdose occurs, treat supportively.

Drug Interactions

- **APOMORPHINE**: A human patient that received ondansetron and apomorphine developed severe hypotension and loss of consciousness. In humans, use together is contraindicated.
- **CISPLATIN**: Plasma cisplatin concentrations may be decreased.

- **CYCLOPHOSPHAMIDE**: Plasma cyclophosphamide concentrations may be decreased.
- **DRUGS AFFECTING QTc INTERVAL** (eg, **amiodarone**, **ciprofloxacin**, **cisapride**, **isoflurane**, **ketoconazole**, **sotalol**): Theoretically, ondansetron may have additive effects on QTc interval; possible serious arrhythmias may result.
- **SEROTONERGIC DRUGS** (eg, clomipramine, fluoxetine, trazodone): Increased risk for serotonin syndrome has been reported in humans.
- **TRAMADOL**: In humans, use together may reduce the efficacy of both drugs. Veterinary significance is not known.

Laboratory Considerations

- See **Drug Interactions.**

Dosages

- **DOGS:**

  Antiemetic (extra-label): Most recommend ondansetron 0.5 – 1 mg/kg PO or IV (slowly over 2-15 minutes) every 12 hours. However, IV dosages of 0.1 – 0.2 mg/kg have been noted and are closer to human pediatric recommendations. If being used before chemotherapy, give IV (slowly) 30 minutes before; may repeat every 8-12 hours.

- **CATS:**

  Acute vomiting (extra-label): Dosage recommendations vary somewhat; 0.1 – 1 mg/kg IV (slowly), SC, IM, or PO every 6-12 hours. Based upon a recent pharmacokinetic study,[3] oral doses may need to be towards the high end and given more frequently than IV or SC. If being used before chemotherapy, give IV (slowly) 30 minutes before chemotherapy; may repeat every 6-12 hours.

  Vomiting associated with chronic kidney disease (extra-label): IRIS Stage 1 or 2: 0.1 – 0.2 mg/kg IV, SC, PO every 6-12 hours. IRIS Stage 3: 0.05 – 0.1 mg/kg IV, SC, PO every 6-12 hours. IRIS Stage 4: 0.025 – 0.05 mg/kg IV, SC, or PO every 6-12 hours.[9]

  Reducing the incidence and severity of vomiting associated with dexmedetomidine/buprenorphine premedication (extra-label): Ondansetron 0.22 mg/kg IM administered with dexmedetomidine and buprenorphine (in the same syringe).[2]

Monitoring

- Clinical efficacy.

Client Information

- Used to treat or prevent severe vomiting. May give oral products with or without food.
- Usually tolerated very well.
- If using compounded topical gel, wear gloves when applying.
- If using orally disintegrating tablets, protect the tablets from moisture, and be sure hands are dry whenever handling them. Place tablet on top of the animal's tongue once removed from package.

Chemistry / Synonyms

A selective inhibitor of 5-HT_3, ondansetron HCl dihydrate occurs as a white to off-white powder that is sparingly soluble in water and alcohol.

Ondansetron HCl may also be known as GR-38032F or ondansetroni hydrochloridum, and *Zofran*®.

Storage / Stability

Unless otherwise labeled, store oral products in tight, light-resistant containers between 2°C and 30°C (36°F-86°F). The injection should be stored between 2°C and 25°C (36°F-77°F) and protected from light.

Compatibility / Compounding Considerations

Drugs reported to be **compatible** with ondansetron when combined in a syringe and administered via a Y-site include alfentanil, atropine, fentanyl, glycopyrrolate, metoclopramide, midazolam, morphine, naloxone, neostigmine, and propofol.

Ondansetron is reported **compatible** with dextrose, saline and lactated Ringer's solutions, and the following drugs when administered via a **Y-site**: amikacin, azithromycin, bleomycin, carboplatin, carmustine, cefazolin, cefotaxime, cefuroxime, cisplatin, clindamycin, cyclophosphamide, cytarabine, dacarbazine, dactinomycin, daunorubicin, dexamethasone sodium phosphate, dexmedetomidine, dexrazoxane, diphenhydramine, dopamine, doxorubicin HCL (also liposome form), doxycycline, famotidine, filgrastim, fluconazole, gemcitabine, gentamicin, heparin, hydromorphone, hydroxyzine, ifosfamide, imipenem-cilastatin, mannitol, mesna, methotrexate, metoclopramide, mitoxantrone, morphine, naloxone, pamidronate, piperacillin-tazobactam, potassium chloride, prochlorperazine, promethazine, ranitidine, vancomycin, vinblastine, vincristine, zidovudine, and zoledronic acid.

Ondansetron is not compatible with ampicillin-sulbactam injection and should not be mixed with this agent.

Compatibility is dependent upon factors such as pH, concentration, temperature, and diluent used; consult specialized references or a hospital pharmacist for more specific information.

Dosage Forms / Regulatory Status

VETERINARY-LABELED PRODUCTS: None.

HUMAN-LABELED PRODUCTS:

Ondansetron HCl Tablets: 4 mg & 8 mg; *Zofran*®, generic; (Rx).

Ondansetron Orally Disintegrating Tablets or Oral Film: 4 mg & 8 mg (as base); *Zofran*® *ODT*, *Zuplenz*®, generic; (Rx).

Ondansetron HCl Oral Solution: 0.8 mg/ml (4 mg/5 mL) in 50 mL; *Zofran*®, generic; (Rx).

Ondansetron HCl Injection: 2 mg/mL in 2-mL single-dose & 20-mL multidose vials; *Zofran*®, generic; (Rx).

References / Revisions

Reviewed and updated by James A. Budde, PharmD, FSVHP, DICVP, and Michele Barletta, DVM, MS, PhD, DACVAA. Last update September 2017.

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