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HIGHLIGHTS OF PRESCRIBING INFORMATION

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

ZOFRAN (ondansetron hydrochloride) tablets, for oral use
ZOFRAN ODT (ondansetron) orally disintegrating tablets
ZOFRAN (ondansetron hydrochloride) oral solution
Initial U.S. Approval: 1991

INDICATIONS AND USAGE

ZOFRAN is a 5-HT_3 receptor antagonist indicated for the prevention of:

- nausea and vomiting associated with highly emetogenic cancer chemotherapy, including cisplatin ≥50 mg/m^2. (1.1)
- nausea and vomiting associated with initial and repeat courses of moderately emetogenic cancer chemotherapy. (1.2)
- 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. (1.3)
- postoperative nausea and/or vomiting. (1.4)

DOSAGE AND ADMINISTRATION

- See full prescribing information for the recommended dosage in adults and pediatrics (2.1)
- Patients with severe hepatic impairment: do not exceed a total daily dose of 8 mg (2.2, 8.6)

DOSAGE FORMS AND STRENGTHS

- Tablets: 4 mg and 8 mg (3)
- Orally Disintegrating Tablets: 4 mg and 8 mg (3)
- 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)

WARNINGS and PRECAUTIONS

- Hypersensitivity reactions including anaphylaxis and bronchospasm: Discontinue ZOFRAN 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 ECGs if concomitant electrolyte abnormalities, cardiac failure or arrhythmias, or use of other QT prolonging drugs. (5.2)
- Serotonin syndrome: Reported with 5-HT_3 receptor antagonists alone but particularly with concomitant use of serotonergic drugs. If such symptoms occur, discontinue ZOFRAN and initiate supportive treatment. If concomitant use of ZOFRAN 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 (>5%) are: headache, malaise/fatigue, constipation, diarrhea. (6.1)
- prevention of radiation-induced nausea and vomiting (≥2%) are: headache, constipation, and diarrhea. (6.1)
- prevention of postoperative nausea and vomiting (≥9%) are: headache and hypoxia. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact GlaxoSmithKline at 1-888-825-5249 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 9/2016

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

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

- highly emetogenic cancer chemotherapy, including cisplatin ≥50 mg/m^2.
- 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.

ZOFRAN 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 ZOFRAN tablets, ZOFRAN ODT® orally disintegrating tablets and ZOFRAN 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 ≥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	For total body irradiation: 8 mg administered 1 to 2 hours before each fraction of radiotherapy each day. For single high-dose fraction radiotherapy to the abdomen: 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. For daily fractionated radiotherapy to the abdomen: 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.

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

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

2.3 Administration Instructions for ZOFRAN ODT Orally Disintegrating Tablets

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

3 DOSAGE FORMS AND STRENGTHS

ZOFRAN tablets are oval, film-coated tablets engraved with “Zofran” on one side and are available in the following strengths:

- 4 mg – white tablet with “4” engraved on the other side.
- 8 mg – yellow tablet with “8” engraved on the other side.

ZOFRAN ODT orally disintegrating tablets are white, round, and plano-convex tablets available in the following strengths:

- 4 mg – debossed with “Z4” on one side.
- 8 mg – debossed with “Z8” on one side.

ZOFRAN oral solution, 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

ZOFRAN 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)]*.

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- 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-HT_3 receptor antagonists. If hypersensitivity reactions occur, discontinue use of ZOFRAN; treat promptly per standard of care and monitor until signs and symptoms resolve *[see Contraindications (4)]*.

5.2 QT Prolongation

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 ZOFRAN. Avoid ZOFRAN 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-HT_3 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 ZOFRAN alone has also been reported. The majority of reports of serotonin syndrome related to 5-HT_3 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 ZOFRAN and other serotonergic drugs. If symptoms of serotonin syndrome occur, discontinue ZOFRAN and initiate supportive treatment. Patients should be informed of the increased risk of serotonin syndrome, especially if ZOFRAN 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 ZOFRAN 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.

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

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5.5 Phenylketonuria

Phenylketonuric patients should be informed that ZOFRAN ODT orally disintegrating tablets contain phenylalanine (a component of aspartame). Each 4-mg and 8-mg orally disintegrating tablet contains less than 0.03 mg phenylalanine.

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 ZOFRAN. A causal relationship to therapy with ZOFRAN was unclear in many cases.

Prevention of Chemotherapy-induced Nausea and Vomiting

The most common adverse reactions reported in ≥4% of 300 adults receiving a single 24-mg dose of ZOFRAN orally in 2 trials for the prevention of nausea and vomiting associated with highly emetogenic chemotherapy (cisplatin ≥50 mg/m^2) 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[a] for the Prevention of Nausea and Vomiting Associated with Moderately Emetogenic Chemotherapy [Primarily Cyclophosphamide-based Regimens]

Adverse Reaction	ZOFRAN 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%)

[a] Reported in ≥5% of patients treated with ZOFRAN and at a rate that exceeded placebo.

Less Common Adverse Reactions

Central Nervous System: Extrapyramidal 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 ZOFRAN 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).

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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 ZOFRAN is unclear.

Prevention of Radiation-induced Nausea and Vomiting

The most common adverse reactions (≥2%) reported in patients receiving ZOFRAN and concurrent radiotherapy were similar to those reported in patients receiving ZOFRAN and concurrent chemotherapy and were headache, constipation, and diarrhea.

Prevention of Postoperative Nausea and Vomiting

The most common adverse reactions reported in adults in trial(s) of 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[a] for the Prevention of Postoperative Nausea and Vomiting

Adverse Reaction	ZOFRAN 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%)

[a] Reported in ≥5% of patients treated with ZOFRAN and at a rate that exceeded placebo.

In a crossover study with 25 subjects, headache was reported in 6 subjects administered ZOFRAN ODT with water (24%) as compared with 2 subjects administered ZOFRAN ODT without water (8%).

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.

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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-HT_3 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 ZOFRAN 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 ZOFRAN 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, ZOFRAN 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.

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

7.5 Alfentanil and Atracurium

ZOFRAN 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 ZOFRAN 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.

Data

Human Data
Methodological limitations of the epidemiology studies preclude a reliable evaluation of the potential risk of adverse fetal outcomes with the use of ondansetron in pregnancy.

Two large retrospective cohort studies of ondansetron use in pregnancy have been published. In one study with 1,349 infants born to women who reported the use of ondansetron or received an ondansetron prescription in the first trimester, no increased risk for major congenital malformations was seen in aggregate analysis. In this same study, however, a sub-analysis for specific malformations reported an association between ondansetron exposure and cardiovascular defect (odds ratio (OR) 1.62 [95% CI (1.04, 2.14)]) and cardiac septal defect (OR 2.05 [95% CI (1.19, 3.28)]). The second study examined 1970 women who received ondansetron prescription during pregnancy and reported no association between ondansetron exposure and major congenital malformations, miscarriage or stillbirth, and infants of low birth weight or small for gestational age. Important methodological limitations with these studies include the uncertainty of whether women who filled a prescription actually took the medication, the concomitant use of other medications or treatments, and other unadjusted confounders that may account for the study findings.

A case-control study evaluating associations between several common non-cardiac malformations and multiple antiemetic drugs reported an association between maternal use of ondansetron and isolated cleft palate (reported adjusted OR = 2.37 [95% CI (1.18, 4.76)]). However, this association could be a chance finding, given the large number of drugs-birth defect comparisons in this study. It is unknown whether ondansetron exposure in utero in the cases of cleft palate occurred during the time of palate formation (the palate is formed between the 6^{th} and 9^{th} weeks of pregnancy) or whether mothers of infants with cleft palate used other medications or had other risk factors for cleft palate in the offspring. In addition, no cases of isolated cleft palate were identified in

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the aforementioned two large retrospective cohort studies. At this time, there is no clear evidence that ondansetron exposure in early pregnancy can cause cleft palate.

Animal Data

In embryo-fetal development studies in rats and rabbits, pregnant animals received oral doses of ondansetron up to 15 mg/kg/day and 30 mg/kg/day, respectively, during the period of organogenesis. With the exception of a slight decrease in maternal body weight gain in the rabbits, there were no significant effects of ondansetron on the maternal animals or the development of the offspring. At doses of 15 mg/kg/day in rats and 30 mg/kg/day in rabbits, the maternal exposure margin was approximately 6 and 24 times the maximum recommended human oral dose of 24 mg/day, respectively, based on body surface area.

In a pre- and postnatal developmental toxicity study, pregnant rats received oral doses of ondansetron up to 15 mg/kg/day from Day 17 of pregnancy to litter Day 21. With the exception of a slight reduction in maternal body weight gain, there were no effects upon the pregnant rats and the pre- and postnatal development of their offspring, including reproductive performance of the mated F1 generation. At a dose of 15 mg/kg/day in rats, the maternal exposure margin was approximately 6 times the maximum recommended human oral dose of 24 mg/day, based on body surface area.

8.2 Lactation

Risk Summary

It is not known whether ondansetron is present in human milk. There are no data on the effects of ZOFRAN on the breastfed infant or the effects on milk production. However, it has been demonstrated that ondansetron is present in the milk of rats.

The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for ZOFRAN and any potential adverse effects on the breast-fed infant from ZOFRAN or from the underlying maternal condition.

8.4 Pediatric Use

The safety and effectiveness of orally administered ZOFRAN have been established in pediatric patients 4 years and older for the prevention of nausea and vomiting associated with moderately emetogenic cancer chemotherapy. Use of ZOFRAN in these age-groups is supported by evidence from adequate and well-controlled studies of ZOFRAN in adults with additional data from 3 open-label, uncontrolled, non-US trials in 182 pediatric patients aged 4 to 18 years with cancer who were given a variety of cisplatin or noncisplatin regimens *[see Dosage and Administration (2.2), Clinical Studies (14.1)]*.

Additional information on the use of ondansetron in pediatric patients may be found in ZOFRAN Injection prescribing information.

The safety and effectiveness of orally administered ZOFRAN have not been established in pediatric patients for:

- prevention of nausea and vomiting associated with highly emetogenic cancer chemotherapy.
- prevention of nausea and vomiting associated with radiotherapy.
- prevention of postoperative nausea and/or vomiting.

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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, for which there were subgroup analyses, 938 (19%) were aged 65 years and older.

No overall differences in safety or effectiveness were observed between subjects 65 years of age and older and younger subjects. A reduction in clearance and increase in elimination half-life were seen in patients older than 75 years compared with younger subjects *[see Clinical Pharmacology (12.3)]*. There were an insufficient number of patients older than 75 years of age and older in the clinical trials to permit safety or efficacy conclusions in this age-group. 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. No dosage adjustment is needed in elderly patients.

8.6 Hepatic Impairment

No dosage adjustment is needed in patients with mild or moderate hepatic impairment.

In patients with severe hepatic impairment, clearance is reduced and the apparent volume of distribution is increased, resulting in a significant increase in the half-life of ondansetron. Therefore, do not exceed a total daily dose of 8 mg in patients with severe hepatic impairment (Child-Pugh score of 10 or greater) *[see Dosage and Administration (2.2), Clinical Pharmacology (12.3)]*.

8.7 Renal Impairment

No dosage adjustment is recommended for patients with any degree of renal impairment (mild, moderate, or severe). There is no experience beyond first-day administration of ondansetron *[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.

In addition to the adverse reactions listed above, the following adverse reactions 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 a patient that took 48 mg of ZOFRAN 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 adverse reactions resolved completely.

Pediatric cases consistent with serotonin syndrome have been reported after inadvertent oral overdoses of ondansetron (exceeding estimated ingestion of 5 mg per kg) in young children. Reported symptoms included somnolence, agitation, tachycardia, tachypnea, hypertension, flushing, mydriasis, diaphoresis, myoclonic movements, horizontal nystagmus, hyperreflexia, and seizure. Patients required supportive care, including intubation in some cases, with complete recovery without sequelae within 1 to 2 days.

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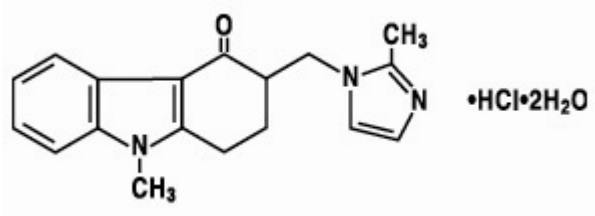
11 DESCRIPTION

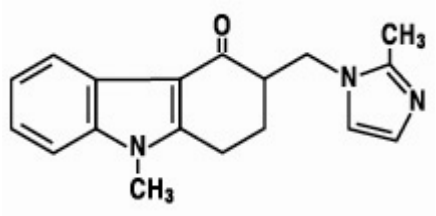
The active ingredient in ZOFRAN tablets and ZOFRAN oral solution is ondansetron hydrochloride as the dihydrate, the racemic form of ondansetron and a selective blocking agent of the serotonin 5-HT_3 receptor type. Chemically it is (±) 1, 2, 3, 9-tetrahydro-9-methyl-3-[(2-methyl-1H-imidazol-1-yl)methyl]-4H-carbazol-4-one,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



The empirical formula is $C_{18}H_{19}N_3O$•HCl•$2H_2O$, representing a molecular weight of 365.9.

Ondansetron hydrochloride dihydrate is a white to off-white powder that is soluble in water and normal saline.

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



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

Each 4-mg ZOFRAN tablet for oral administration contains ondansetron hydrochloride dihydrate equivalent to 4 mg of ondansetron. Each 8-mg ZOFRAN tablet for oral administration contains ondansetron hydrochloride dihydrate equivalent to 8 mg of ondansetron. Each tablet also contains the inactive ingredients hypromellose, iron oxide yellow (8-mg tablet only), lactose, magnesium stearate, microcrystalline cellulose, pregelatinized starch, triacetin, and titanium dioxide.

Each 4-mg ZOFRAN ODT orally disintegrating tablet for oral administration contains 4 mg ondansetron base. Each 8-mg ZOFRAN ODT orally disintegrating tablet for oral administration contains 8 mg ondansetron base. Each ZOFRAN ODT tablet also contains the inactive ingredients aspartame, gelatin, mannitol, methylparaben sodium, propylparaben sodium, and strawberry flavor. ZOFRAN ODT tablets are a freeze-dried, orally administered formulation of ondansetron which disintegrates on the tongue and does not require water to aid dissolution or swallowing.

Each 5 mL of ZOFRAN oral solution contains 5 mg of ondansetron hydrochloride dihydrate equivalent to 4 mg of ondansetron. ZOFRAN oral solution contains the inactive ingredients citric acid anhydrous, purified water, sodium benzoate, sodium citrate, sorbitol, and strawberry flavor.

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12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

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

12.2 Pharmacodynamics

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

Cardiac Electrophysiology

QTc interval prolongation was studied in a double-blind, single intravenous dose, placebo- and positive-controlled, crossover trial in 58 healthy subjects. The maximum mean (95% upper confidence bound) difference in QTcF from placebo after baseline correction was 19.5 (21.8) milliseconds and 5.6 (7.4) milliseconds after 15-minute intravenous infusions of 32 mg and 8 mg of ondansetron injection, 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 minutes had a mean predicted (95% upper prediction interval) ΔΔQTcF of 14.0 (16.3) milliseconds. In contrast, 16 mg infused intravenously over 15 minutes using the same model had a mean predicted (95% upper prediction interval) ΔΔQTcF of 9.1 (11.2) milliseconds. In this study, the 8-mg dose infused over 15 minutes did not prolong the QT interval to any clinically relevant extent.

12.3 Pharmacokinetics

Absorption

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

Ondansetron systemic exposure does not increase proportionately to dose. The AUC from a 16-mg tablet was 24% greater than predicted from an 8-mg tablet dose. This may reflect some reduction of first-pass metabolism at higher oral doses.

Food Effects: Bioavailability is also slightly enhanced by the presence of food.

Distribution

Plasma protein binding of ondansetron as measured in vitro was 70% to 76% over the concentration range of 10

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to 500 ng/mL. Circulating drug also distributes into erythrocytes.

Elimination

Metabolism and Excretion: Ondansetron is extensively metabolized in humans, with approximately 5% of a radiolabeled dose recovered as the parent compound from the urine. The metabolites are observed in the urine. The primary metabolic pathway is hydroxylation on the indole ring followed by subsequent glucuronide or sulfate conjugation.

In vitro metabolism studies have shown that ondansetron is a substrate for human hepatic cytochrome P-450 enzymes, including CYP1A2, CYP2D6, and CYP3A4. In terms of overall ondansetron turnover, CYP3A4 played the predominant role. Because of the multiplicity of metabolic enzymes capable of metabolizing ondansetron, it is likely that inhibition or loss of one enzyme (e.g., CYP2D6 genetic deficiency) will be compensated by others and may result in little change in overall rates of ondansetron elimination.

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.

Specific Populations

Age: Geriatric Population: A reduction in clearance and increase in elimination half-life are seen in patients older than 75 years compared to younger subjects *[see Use in Specific Populations (8.5)]*.

Sex: Gender differences were shown in the disposition of ondansetron given as a single dose. The extent and rate of absorption are greater in women than men. Slower clearance in women, a smaller apparent volume of distribution (adjusted for weight), and higher absolute bioavailability resulted in higher plasma ondansetron concentrations. These higher plasma concentrations may in part be explained by differences in body weight between men and women. It is not known whether these sex-related differences were clinically important. More detailed pharmacokinetic information is contained in Tables 5 and 6.

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Table 5. Pharmacokinetics in Male and Female Healthy Subjects after a Single Dose of a ZOFRAN 8-mg Tablet

Age-group (years) Sex (M/F)	Mean Weight (kg)	N	Peak Plasma Concentration (ng/mL)	Time of Peak Plasma Concentration (h)	Mean Elimination Half-life (h)	Systemic Plasma Clearance L/h/kg	Absolute Bioavailability
18-40 M	69.0	6	26.2	2.0	3.1	0.403	0.483
F	62.7	5	42.7	1.7	3.5	0.354	0.663
61-74 M	77.5	6	24.1	2.1	4.1	0.384	0.585
F	60.2	6	52.4	1.9	4.9	0.255	0.643
≥75 M	78.0	5	37.0	2.2	4.5	0.277	0.619
F	67.6	6	46.1	2.1	6.2	0.249	0.747

Table 6. Pharmacokinetics in Male and Female Healthy Subjects after a Single Dose of a ZOFRAN 24-mg Tablet

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

Renal Impairment: Renal impairment is not expected to significantly influence the total clearance of ondansetron as renal clearance represents only 5% of the overall clearance. However, the mean plasma clearance of ondansetron was reduced by about 50% in patients with severe renal impairment (creatinine clearance less than 30 mL/min). The reduction in clearance was variable and not consistent with an increase in half-life *[see Use in Specific Populations (8.7)]*.

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 with 5.7 hours in healthy subjects. 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 *[see Dosage and Administration (2.2), Use in Specific Populations (8.6)]*.

Drug Interaction Studies

CYP 3A4 Inducers: Ondansetron elimination may be affected by cytochrome P-450 inducers. In a pharmacokinetic trial of 16 epileptic patients maintained chronically on CYP3A4 inducers, carbamazepine, or phenytoin, a reduction in AUC, C_{max}, and $t_{½}$ of ondansetron was observed. This resulted in a significant increase in the clearance of ondansetron. However, this increase is not thought to be clinically relevant *[see Drug Interactions (7.2)]*.

Chemotherapeutic Agents: Carmustine, etoposide, and cisplatin do not affect the pharmacokinetics of ondansetron *[see Drug Interactions (7.4)]*.

Antacids: Concomitant administration of antacids does not alter the absorption of ondansetron.

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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 mg/kg per day and 30 mg/kg per day, respectively (approximately 4 and 6 times the maximum recommended human oral dose of 24 mg per 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 6 times the maximum recommended human oral dose of 24 mg per day, based on body surface area) did not affect fertility or general reproductive performance of male and female rats.

14 CLINICAL STUDIES

14.1 Prevention of Chemotherapy-induced Nausea and Vomiting

Highly Emetogenic Chemotherapy

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

The first trial compared oral doses of ondansetron 24 mg as a single dose, 8 mg every 8 hours for 2 doses, and 32 mg as a single dose in 357 adult cancer patients receiving chemotherapy regimens containing cisplatin ≥50 mg/m^2. The first or single dose was administered 30 minutes prior to chemotherapy. A total of 66% of patients in the ondansetron 24-mg once-a-day group, 55% in the ondansetron 8-mg twice-a-day group, and 55% in the ondansetron 32-mg once-a-day group completed the 24-hour trial period with 0 emetic episodes and no rescue antiemetic medications, the primary endpoint of efficacy. Each of the 3 treatment groups was shown to be statistically significantly superior to a historical placebo control.

In the same trial, 56% of patients receiving a single 24-mg oral dose of ondansetron experienced no nausea during the 24-hour trial period, compared with 36% of patients in the oral ondansetron 8-mg twice-a-day group (P = 0.001) and 50% in the oral ondansetron 32-mg once-a-day group. Dosage regimens of ZOFRAN 8 mg twice daily and 32 mg once daily are not recommended for the prevention of nausea and vomiting associated with highly emetogenic chemotherapy *[see Dosage and Administration (2.1)]*.

In a second trial, efficacy of a single 24-mg oral dose of ZOFRAN for the prevention of nausea and vomiting associated with highly emetogenic cancer chemotherapy, including cisplatin ≥50 mg/m^2, was confirmed.

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Moderately Emetogenic Chemotherapy

A randomized, placebo-controlled, double-blind trial was conducted in the US in 67 patients receiving a cyclophosphamide-based chemotherapy regimen containing doxorubicin. The first 8-mg dose of ZOFRAN was administered 30 minutes before the start of chemotherapy, with a subsequent dose 8 hours after the first dose, followed by 8 mg of ZOFRAN twice a day for 2 days after the completion of chemotherapy.

ZOFRAN was significantly more effective than placebo in preventing vomiting. Treatment response was based on the total number of emetic episodes over the 3-day trial period. The results of this trial are summarized in Table 7:

Table 7. Emetic Episodes: Treatment Response in Patients Receiving Moderately Emetogenic Chemotherapy (Cyclophosphamide-based Regimen Containing Doxorubicin)

	ZOFRAN (n = 33)	**Placebo (n = 34)**	***P* Value**
Treatment response 0 Emetic episodes 1 to 2 Emetic episodes More than 2 emetic episodes/withdrawn	 20 (61%) 6 (18%) 7 (21%)	 2 (6%) 8 (24%) 24 (71%)	 <0.001 <0.001
Median number of emetic episodes	0.0	Undefined[a]	
Median time to first emetic episode (hours)	Undefined[b]	6.5	

[a] Median undefined since at least 50% of the patients were withdrawn or had more than 2 emetic episodes.
[b] Median undefined since at least 50% of patients did not have any emetic episodes.

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In a double-blind US trial in 336 patients receiving a cyclophosphamide-based chemotherapy regimen containing either methotrexate or doxorubicin, ZOFRAN 8 mg administered twice a day was as effective as ZOFRAN 8 mg administered 3 times a day in preventing nausea and vomiting. ZOFRAN 8 mg three times daily is not a recommended regimen for the treatment of moderately emetogenic chemotherapy *[see Dosage and Administration (2.1)]*.

Treatment response was based on the total number of emetic episodes over the 3-day trial period. See Table 8 for the details of the dosage regimens studied and results of this trial.

Table 8. Emetic Episodes: Treatment Response after ZOFRAN Tablets Administered Twice a Day and Three Times a Day

	ZOFRAN Tablets	
	8 mg Twice Daily[a] (n = 165)	**8 mg Three Times a Day[b] (n = 171)**
Treatment response		
0 Emetic episodes	101 (61%)	99 (58%)
1-2 Emetic episodes	16 (10%)	17 (10%)
More than 2 emetic episodes/withdrawn	48 (29%)	55 (32%)
Median number of emetic episodes	0.0	0.0
Median time to first emetic episode (h)	Undefined[c]	Undefined[c]
Median nausea scores (0-100)[d]	6	6

[a] The first 8-mg dose was administered 30 minutes before the start of emetogenic chemotherapy, with a subsequent 8-mg dose 8 hours after the first dose, followed by 8 mg administered twice a day for 2 days after the completion of chemotherapy.

[b] The first 8-mg dose was administered 30 minutes before the start of emetogenic chemotherapy, with subsequent 8-mg doses at 4 hours and 8 hours after the first dose, followed by 8 mg administered 3 times a day for 2 days after the completion of chemotherapy.

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

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

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Re-treatment

In single-arm trials, 148 patients receiving cyclophosphamide-based chemotherapy were re-treated with ZOFRAN 8 mg three times daily during subsequent chemotherapy for a total of 396 re-treatment courses. No emetic episodes occurred in 314 (79%) of the re-treatment courses, and only 1 to 2 emetic episodes occurred in 43 (11%) of the re-treatment courses.

Pediatric Trials

Three open-label, single-arm, non-US trials have been performed with 182 pediatric patients aged 4 to 18 years with cancer who were given a variety of cisplatin or noncisplatin regimens. The initial dose of ZOFRAN injection ranged from 0.04 to 0.87 mg per kg (total dose of 2.16 mg to 12 mg) followed by the administration of oral doses of ZOFRAN ranging from 4 to 24 mg daily for 3 days. In these trials, 58% of the 170 evaluable patients had a complete response (no emetic episodes) on Day 1. In two trials the response rates to ZOFRAN 4 mg three times a day in patients younger than 12 years was similar to ZOFRAN 8 mg three times daily in patients 12 to 18 years. Prevention of emesis in these pediatric patients was essentially the same as for adults.

14.2 Radiation-induced Nausea and Vomiting

Total Body Irradiation

In a randomized, placebo-controlled, double-blind trial in 20 patients, 8 mg of ZOFRAN administered 1.5 hours before each fraction of radiotherapy for 4 days was significantly more effective than placebo in preventing vomiting induced by total body irradiation. Total body irradiation consisted of 11 fractions (120 cGy per fraction) over 4 days for a total of 1,320 cGy. Patients received 3 fractions for 3 days, then 2 fractions on Day 4.

Single High-dose Fraction Radiotherapy

In an active-controlled, double-blind trial in 105 patients receiving single high-dose radiotherapy (800 to 1,000 cGy) over an anterior or posterior field size of $\geq$80 cm^2 to the abdomen, ZOFRAN was significantly more effective than metoclopramide with respect to complete control of emesis (0 emetic episodes). Patients received the first dose of ZOFRAN (8 mg) or metoclopramide (10 mg) 1 to 2 hours before radiotherapy. If radiotherapy was given in the morning, 8 mg of ZOFRAN or 10 mg of metoclopramide was administered in the late afternoon and repeated again before bedtime. If radiotherapy was given in the afternoon, patients took 8 mg of ZOFRAN or 10 mg of metoclopramide only once before bedtime. Patients continued the doses of oral medication three times daily for 3 days.

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Daily Fractionated Radiotherapy

In an active-controlled, double-blind trial in 135 patients receiving a 1- to 4-week course of fractionated radiotherapy (180 cGy doses) over a field size of ≥100 cm^2 to the abdomen, ZOFRAN was significantly more effective than prochlorperazine with respect to complete control of emesis (0 emetic episodes). Patients received the first dose of ZOFRAN (8 mg) or prochlorperazine (10 mg) 1 to 2 hours before the first daily radiotherapy fraction, with subsequent 8-mg doses approximately every 8 hours on each day of radiotherapy.

14.3 Postoperative Nausea and Vomiting

In two placebo-controlled, double-blind trials (one conducted in the US and the other outside the US) in 865 females undergoing inpatient surgical procedures, ZOFRAN 16 mg as a single dose or placebo was administered one hour before the induction of general balanced anesthesia (barbiturate, opioid, nitrous oxide, neuromuscular blockade, and supplemental isoflurane or enflurane), ZOFRAN tablets was significantly more effective than placebo in preventing postoperative nausea and vomiting.

No trials have been performed in males.

16 HOW SUPPLIED/STORAGE AND HANDLING

ZOFRAN Tablets

- 4 mg (ondansetron hydrochloride dihydrate equivalent to 4 mg of ondansetron), are white, oval, film-coated tablets engraved with “Zofran” on one side and “4” on the other in bottles of 30 tablets (NDC 0173-0446-00).

Store between 2°C and 30°C (36°F and 86°F). Protect from light. Dispense in tight, light-resistant container as defined in the USP.

- 8 mg (ondansetron hydrochloride dihydrate equivalent to 8 mg of ondansetron), are yellow, oval, film-coated tablets engraved with “Zofran” on one side and “8” on the other in bottles of 30 tablets (NDC 0173-0447-00).

Store between 2°C and 30°C (36°F and 86°F). Dispense in tight container as defined in the USP.

ZOFRAN ODT Orally Disintegrating Tablets

- 4 mg (as 4 mg ondansetron base) are white, round and plano-convex tablets debossed with a “Z4” on one side in unit dose packs of 30 tablets (NDC 0173-0569-00).
- 8 mg (as 8 mg ondansetron base) are white, round and plano-convex tablets debossed with a “Z8” on one side in unit dose packs of 30 tablets (NDC 0173-0570-00).

Store between 2°C and 30°C (36°F and 86°F).

ZOFRAN Oral Solution

- a clear, colorless to light yellow liquid with a characteristic strawberry odor, contains 5 mg of ondansetron hydrochloride dihydrate equivalent to 4 mg of ondansetron per 5 mL in amber glass bottles of 50 mL with child-resistant closures (NDC 0173-0489-00).

Store upright between 15°C and 30°C (59°F and 86°F). Protect from light. Store bottles upright in cartons.

17 PATIENT COUNSELING INFORMATION

QT Prolongation

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Inform patients that ZOFRAN may cause serious cardiac arrhythmias such as QT prolongation. Instruct patients to tell their healthcare provider right away if they perceive a change in their heart rate, if they feel lightheaded, or if they have a syncopal episode.

Hypersensitivity Reactions

Inform patients that ZOFRAN may cause hypersensitivity reactions, some as severe as anaphylaxis and bronchospasm. Instruct patients to immediately report any signs and symptoms of hypersensitivity reactions, including fever, chills, rash, or breathing problems to their healthcare provider.

Masking of Progressive Ileus and Gastric Distension

Inform patients following abdominal surgery or those with chemotherapy-induced nausea and vomiting that ZOFRAN may mask signs and symptoms of bowel obstruction. Instruct patients to immediately report any signs or symptoms consistent with a potential bowel obstruction to their healthcare provider.

Drug Interactions

- Instruct the patient to report the use of all medications, especially apomorphine, to their healthcare provider. Concomitant use of apomorphine and ZOFRAN may cause a significant drop in blood pressure and loss of consciousness.
- Advise patients of the possibility of serotonin syndrome with concomitant use of ZOFRAN and another serotonergic agent such as medications to treat depression and migraines. Advise patients to seek immediate medical attention if the following symptoms occur: changes in mental status, autonomic instability, neuromuscular symptoms with or without gastrointestinal symptoms.

Administration of ZOFRAN ODT Orally Disintegrating Tablets

Instruct patients not to remove ZOFRAN ODT tablets from the blister until just prior to dosing.

- Do not attempt to push ZOFRAN ODT tablets through the foil backing.
- With dry hands, peel back the foil backing of 1 blister and gently remove the tablet.
- Immediately place the ZOFRAN ODT tablet on top of the tongue where it will dissolve in seconds, then swallow with saliva.
- Administration with liquid is not necessary.
- Peelable illustrated stickers are affixed to the product carton that can be provided with the prescription to ensure proper use and handling of the product.

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GlaxoSmithKline
Research Triangle Park, NC 27709

ZOFRAN Tablets and Oral Solution:
GlaxoSmithKline
Research Triangle Park, NC 27709

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