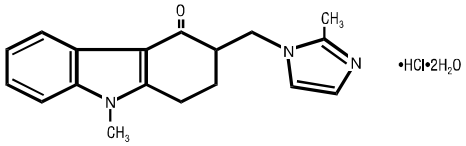
PRESCRIBING INFORMATION

ZOFRAN®
(ondansetron hydrochloride)
Injection

ZOFRAN®
(ondansetron hydrochloride)
Injection Premixed

DESCRIPTION

The active ingredient in ZOFRAN Injection and ZOFRAN Injection Premixed is ondansetron hydrochloride (HCl), 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 HCl is a white to off-white powder that is soluble in water and normal saline.

Sterile Injection for Intravenous (I.V.) or Intramuscular (I.M.) Administration: Each 1 mL of aqueous solution in the 2-mL single-dose vial contains 2 mg of ondansetron as the hydrochloride dihydrate; 9.0 mg of sodium chloride, USP; and 0.5 mg of citric acid monohydrate, USP and 0.25 mg of sodium citrate dihydrate, USP as buffers in Water for Injection, USP.

Each 1 mL of aqueous solution in the 20-mL multidose vial contains 2 mg of ondansetron as the hydrochloride dihydrate; 8.3 mg of sodium chloride, USP; 0.5 mg of citric acid monohydrate, USP and 0.25 mg of sodium citrate dihydrate, USP as buffers; and 1.2 mg of methylparaben, NF and 0.15 mg of propylparaben, NF as preservatives in Water for Injection, USP.

ZOFRAN Injection is a clear, colorless, nonpyrogenic, sterile solution. The pH of the injection solution is 3.3 to 4.0.

Sterile, Premixed Solution for Intravenous Administration in Single-Dose, Flexible Plastic Containers: Each 50 mL contains ondansetron 32 mg (as the hydrochloride dihydrate); dextrose 2,500 mg; and citric acid 26 mg and sodium citrate 11.5 mg as buffers in Water for Injection, USP. It contains no preservatives. The osmolarity of this solution is 270 mOsm/L (approx.), and the pH is 3.0 to 4.0.

The flexible plastic container is fabricated from a specially formulated, nonplasticized, thermoplastic co-polyester (CR3). Water can permeate from inside the container into the overwrap but not in amounts sufficient to affect the solution significantly. Solutions inside the plastic container also can leach out certain of the chemical components in very small amounts before the expiration period is attained. However, the safety of the plastic has been confirmed by tests in animals according to USP biological standards for plastic containers.

CLINICAL PHARMACOLOGY

Pharmacodynamics: Ondansetron is a selective 5-HT_3 receptor antagonist. While ondansetron's mechanism of action has not been fully characterized, it is not a dopamine-receptor antagonist. 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 in chemotherapy-induced emesis 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-HIAA (5-hydroxyindoleacetic acid) 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.

In animals, the emetic response to cisplatin can be prevented by pretreatment with an inhibitor of serotonin synthesis, bilateral abdominal vagotomy and greater splanchnic nerve section, or pretreatment with a serotonin 5-HT_3 receptor antagonist.

In normal volunteers, single I.V. doses of 0.15 mg/kg of ondansetron had no effect on esophageal motility, gastric motility, lower esophageal sphincter pressure, or small intestinal transit time. In another study in six normal male volunteers, a 16-mg dose infused over 5 minutes showed no effect of the drug on cardiac output, heart rate, stroke volume, blood pressure, or electrocardiogram (ECG). Multiday administration of ondansetron has been shown to slow colonic transit in normal volunteers. Ondansetron has no effect on plasma prolactin concentrations.

In a gender-balanced pharmacodynamic study (n = 56), ondansetron 4 mg administered intravenously or intramuscularly was dynamically similar in the prevention of emesis and nausea using the ipecacuanha model of emesis. Both treatments were well tolerated.

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.

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

Although some nonconjugated metabolites have pharmacologic activity, these are not found in plasma at concentrations likely to significantly contribute to the biological activity of ondansetron.

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. Ondansetron elimination may be affected by cytochrome P-450 inducers. In a pharmacokinetic study of 16 epileptic patients maintained chronically on CYP3A4 inducers, carbamazepine, or phenytoin, reduction in AUC, C_{max}, and $T_{½}$ of ondansetron was observed.[1] This resulted in a significant increase in clearance. However, on the basis of available data, no dosage adjustment for ondansetron is recommended (see PRECAUTIONS: Drug Interactions).

In humans, carmustine, etoposide, and cisplatin do not affect the pharmacokinetics of ondansetron.

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

Table 1. Pharmacokinetics in Normal Volunteers

Age-group	n	Peak Plasma Concentration (ng/mL)	Mean Elimination Half-life (h)	Plasma Clearance (L/h/kg)
19-40	11	102	3.5	0.381
61-74	12	106	4.7	0.319
≥75	11	170	5.5	0.262

A reduction in clearance and increase in elimination half-life are seen in patients over 75 years of age. In clinical trials with cancer patients, safety and efficacy were similar in patients over 65 years of age and those under 65 years of age; there was an insufficient number of patients over 75 years of age to permit conclusions in that age-group. No dosage adjustment is recommended in the elderly.

In patients with mild-to-moderate hepatic impairment, clearance is reduced twofold and mean half-life is increased to 11.6 hours compared to 5.7 hours in normals. In patients with severe hepatic impairment (Child-Pugh score[2] of 10 or greater), clearance is reduced twofold to threefold and apparent volume of distribution is increased with a resultant increase in half-life to 20 hours. In patients with severe hepatic impairment, a total daily dose of 8 mg should not be exceeded.

Due to the very small contribution (5%) of renal clearance to the overall clearance, renal impairment was not expected to significantly influence the total clearance of ondansetron.

However, ondansetron mean plasma clearance was reduced by about 41% in patients with severe renal impairment (creatinine clearance <30 mL/min). This reduction in clearance is variable and was not consistent with an increase in half-life. No reduction in dose or dosing frequency in these patients is warranted.

In adult cancer patients, the mean elimination half-life was 4.0 hours, and there was no difference in the multidose pharmacokinetics over a 4-day period. In a study of 21 pediatric cancer patients (aged 4 to 18 years) who received three I.V. doses of 0.15 mg/kg of ondansetron at 4-hour intervals, patients older than 15 years of age exhibited ondansetron pharmacokinetic parameters similar to those of adults. Patients aged 4 to 12 years generally showed higher clearance and somewhat larger volume of distribution than adults. Most pediatric patients younger than 15 years of age with cancer had a shorter (2.4 hours) ondansetron plasma half-life than patients older than 15 years of age. It is not known whether these differences in ondansetron plasma half-life may result in differences in efficacy between adults and some young pediatric patients (see CLINICAL TRIALS: Pediatric Studies).

In a study of 21 pediatric patients (aged 3 to 12 years) who were undergoing surgery requiring anesthesia for a duration of 45 minutes to 2 hours, a single I.V. dose of ondansetron, 2 mg (3 to 7 years) or 4 mg (8 to 12 years), was administered immediately prior to anesthesia induction. Mean weight-normalized clearance and volume of distribution values in these pediatric surgical patients were similar to those previously reported for young adults. Mean terminal half-life was slightly reduced in pediatric patients (range, 2.5 to 3 hours) in comparison with adults (range, 3 to 3.5 hours).

In normal volunteers (19 to 39 years old, n = 23), the peak plasma concentration was 264 ng/mL following a single 32-mg dose administered as a 15-minute I.V. infusion. The mean elimination half-life was 4.1 hours. Systemic exposure to 32 mg of ondansetron was not proportional to dose as measured by comparing dose-normalized AUC values to an 8-mg dose. This is consistent with a small decrease in systemic clearance with increasing plasma concentrations.

A study was performed in normal volunteers (n = 56) to evaluate the pharmacokinetics of a single 4-mg dose administered as a 5-minute infusion compared to a single intramuscular injection. Systemic exposure as measured by mean AUC was equivalent, with values of 156 [95% CI 136, 180] and 161 [95% CI 137, 190] ng•h/mL for I.V. and I.M. groups, respectively. Mean peak plasma concentrations were 42.9 [95% CI 33.8, 54.4] ng/mL at 10 minutes after I.V. infusion and 31.9 [95% CI 26.3, 38.6] ng/mL at 41 minutes after I.M. injection. The mean elimination half-life was not affected by route of administration.

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

A positive lymphoblast transformation test to ondansetron has been reported, which suggests immunologic sensitivity to ondansetron.

CLINICAL TRIALS

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

Cisplatin-Based Chemotherapy: In a double-blind study in 28 patients, ZOFRAN Injection (three 0.15-mg/kg doses) was significantly more effective than placebo in preventing nausea and vomiting induced by cisplatin-based chemotherapy. Treatment response was as shown in Table 2.

Table 2. Prevention of Chemotherapy-Induced Nausea and Emesis in Single-Day Cisplatin Therapy*

	ZOFRAN Injection	Placebo	*P* Value†
Number of patients	14	14	
Treatment response			
0 Emetic episodes	2 (14%)	0 (0%)	
1-2 Emetic episodes	8 (57%)	0 (0%)	
3-5 Emetic episodes	2 (14%)	1 (7%)	
More than 5 emetic episodes/rescued	2 (14%)	13 (93%)	0.001
Median number of emetic episodes	1.5	Undefined‡	
Median time to first emetic episode (h)	11.6	2.8	0.001
Median nausea scores (0-100)§	3	59	0.034
Global satisfaction with control of nausea and vomiting (0-100)II	96	10.5	0.009

* Chemotherapy was high dose (100 and 120 mg/m^2; ZOFRAN Injection n = 6, placebo n = 5) or moderate dose (50 and 80 mg/m^2; ZOFRAN Injection n = 8, placebo n = 9). Other chemotherapeutic agents included fluorouracil, doxorubicin, and cyclophosphamide. There was no difference between treatments in the types of chemotherapy that would account for differences in response.

† Efficacy based on "all patients treated" analysis.

‡ Median undefined since at least 50% of the patients were rescued or had more than five emetic episodes.

§ Visual analog scale assessment of nausea: 0 = no nausea, 100 = nausea as bad as it can be.

II Visual analog scale assessment of satisfaction: 0 = not at all satisfied, 100 = totally satisfied.

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

Table 3. Prevention of Emesis Induced by Cisplatin (≥100 mg/m^2) Single-Day Therapy*

	ZOFRAN Injection	Metoclopramide	*P* Value
Dose	0.15 mg/kg x 3	2 mg/kg x 6	
Number of patients in efficacy population	136	138	
Treatment response			
0 Emetic episodes	54 (40%)	41 (30%)	
1-2 Emetic episodes	34 (25%)	30 (22%)	
3-5 Emetic episodes	19 (14%)	18 (13%)	
More than 5 emetic episodes/rescued	29 (21%)	49 (36%)	
Comparison of treatments with respect to			
0 Emetic episodes	54/136	41/138	0.083
More than 5 emetic episodes/rescued	29/136	49/138	0.009
Median number of emetic episodes	1	2	0.005
Median time to first emetic episode (h)	20.5	4.3	<0.001
Global satisfaction with control of nausea and vomiting (0-100)†	85	63	0.001
Acute dystonic reactions	0	8	0.005
Akathisia	0	10	0.002

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

† Visual analog scale assessment: 0 = not at all satisfied, 100 = totally satisfied.

In a stratified, randomized, double-blind, parallel-group, multicenter study, a single 32-mg dose of ondansetron was compared with three 0.15-mg/kg doses in patients receiving cisplatin doses of either 50 to 70 mg/m^2 or ≥100 mg/m^2. Patients received the first ondansetron dose 30 minutes before cisplatin. Two additional ondansetron doses were administered 4 and 8 hours

later to the group receiving three 0.15-mg/kg doses. In both strata, significantly fewer patients on the single 32-mg dose than those receiving the three-dose regimen failed.

Table 4. Prevention of Chemotherapy-Induced Nausea and Emesis in Single-Dose Therapy

	Ondansetron Dose		
	0.15 mg/kg x 3	32 mg x 1	*P* Value
High-dose cisplatin (≥100 mg/m^2)			
Number of patients	100	102	
Treatment response			
0 Emetic episodes	41 (41%)	49 (48%)	0.315
1-2 Emetic episodes	19 (19%)	25 (25%)	
3-5 Emetic episodes	4 (4%)	8 (8%)	
More than 5 emetic episodes/rescued	36 (36%)	20 (20%)	0.009
Median time to first emetic episode (h)	21.7	23	0.173
Median nausea scores (0-100)*	28	13	0.004
Medium-dose cisplatin (50-70 mg/m^2)			
Number of patients	101	93	
Treatment response			
0 Emetic episodes	62 (61%)	68 (73%)	0.083
1-2 Emetic episodes	11 (11%)	14 (15%)	
3-5 Emetic episodes	6 (6%)	3 (3%)	
More than 5 emetic episodes/rescued	22 (22%)	8 (9%)	0.011
Median time to first emetic episode (h)	Undefined†	Undefined	
Median nausea scores (0-100)*	9	3	0.131

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

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

Cyclophosphamide-Based Chemotherapy: In a double-blind, placebo-controlled study of ZOFRAN Injection (three 0.15-mg/kg doses) in 20 patients receiving cyclophosphamide (500 to 600 mg/m^2) chemotherapy, ZOFRAN Injection was significantly more effective than placebo in preventing nausea and vomiting. The results are summarized in Table 5.

Table 5. Prevention of Chemotherapy-Induced Nausea and Emesis in Single-Day Cyclophosphamide Therapy*

	ZOFRAN Injection	Placebo	*P* Value[†]
Number of patients	10	10	
Treatment response			
0 Emetic episodes	7 (70%)	0 (0%)	0.001
1-2 Emetic episodes	0 (0%)	2 (20%)	
3-5 Emetic episodes	2 (20%)	4 (40%)	
More than 5 emetic episodes/rescued	1 (10%)	4 (40%)	0.131
Median number of emetic episodes	0	4	0.008
Median time to first emetic episode (h)	Undefined[‡]	8.79	
Median nausea scores (0-100)[§]	0	60	0.001
Global satisfaction with control of nausea and vomiting (0-100)[II]	100	52	0.008

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

† Efficacy based on "all patients treated" analysis.

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

§ Visual analog scale assessment of nausea: 0 = no nausea, 100 = nausea as bad as it can be.

II Visual analog scale assessment of satisfaction: 0 = not at all satisfied, 100 = totally satisfied.

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

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

was essentially the same as for patients older than 18 years of age. Overall, ZOFRAN Injection was well tolerated in these pediatric patients.

Postoperative Nausea and Vomiting: ***Prevention of Postoperative Nausea and Vomiting:*** Adult surgical patients who received ondansetron immediately before the induction of general balanced anesthesia (barbiturate: thiopental, methohexital, or thiamylal; opioid: alfentanil or fentanyl; nitrous oxide; neuromuscular blockade: succinylcholine/curare and/or vecuronium or atracurium; and supplemental isoflurane) were evaluated in two double-blind US studies involving 554 patients. ZOFRAN Injection (4 mg) I.V. given over 2 to 5 minutes was significantly more effective than placebo. The results of these studies are summarized in Table 6.

Table 6. Prevention of Postoperative Nausea and Vomiting in Adult Patients

	Ondansetron 4 mg I.V.	Placebo	*P* Value
Study 1			
Emetic episodes: Number of patients Treatment response over 24-h postoperative period 0 Emetic episodes 1 Emetic episode More than 1 emetic episode/rescued	136 103 (76%) 13 (10%) 20 (15%)	139 64 (46%) 17 (12%) 58 (42%)	<0.001
Nausea assessments: Number of patients No nausea over 24-h postoperative period	134 56 (42%)	136 39 (29%)	
Study 2			
Emetic episodes: Number of patients Treatment response over 24-h postoperative period 0 Emetic episodes 1 Emetic episode More than 1 emetic episode/rescued	136 85 (63%) 16 (12%) 35 (26%)	143 63 (44%) 29 (20%) 51 (36%)	0.002
Nausea assessments: Number of patients No nausea over 24-h postoperative period	125 48 (38%)	133 42 (32%)	

The study populations in Table 6 consisted mainly of females undergoing laparoscopic procedures.

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

Two other placebo-controlled studies were conducted in 2,792 patients undergoing major abdominal or gynecological surgeries to evaluate a single 4-mg or 8-mg I.V. ondansetron dose for prevention of postoperative nausea and vomiting over a 24-hour study period. At the 4-mg dosage, 59% of patients receiving ondansetron versus 45% receiving placebo in the first study

(*P*<0.001) and 41% of patients receiving ondansetron versus 30% receiving placebo in the second study (*P*=0.001) experienced no emetic episodes. No additional benefit was observed in patients who received I.V. ondansetron 8 mg compared to patients who received I.V. ondansetron 4 mg.

Pediatric Studies: Three double-blind, placebo-controlled studies have been performed (one US, two foreign) in 1,049 male and female patients (2 to 12 years of age) undergoing general anesthesia with nitrous oxide. The surgical procedures included tonsillectomy with or without adenoidectomy, strabismus surgery, herniorrhaphy, and orchidopexy. Patients were randomized to either single I.V. doses of ondansetron (0.1 mg/kg for pediatric patients weighing 40 kg or less, 4 mg for pediatric patients weighing more than 40 kg) or placebo. Study drug was administered over at least 30 seconds, immediately prior to or following anesthesia induction. Ondansetron was significantly more effective than placebo in preventing nausea and vomiting. The results of these studies are summarized in Table 7.

Table 7. Prevention of Postoperative Nausea and Vomiting in Pediatric Patients

Treatment Response Over 24 Hours	Ondansetron n (%)	Placebo n (%)	*P* Value
Study 1			
Number of patients	205	210	
0 Emetic episodes	140 (68%)	82 (39%)	≤0.001
Failure*	65 (32%)	128 (61%)	
Study 2			
Number of patients	112	110	
0 Emetic episodes	68 (61%)	38 (35%)	≤0.001
Failure*	44 (39%)	72 (65%)	
Study 3			
Number of patients	206	206	
0 Emetic episodes	123 (60%)	96 (47%)	≤0.01
Failure*	83 (40%)	110 (53%)	
Nausea assessments†:			
Number of patients	185	191	
None	119 (64%)	99 (52%)	≤0.01

* Failure was one or more emetic episodes, rescued, or withdrawn.

† Nausea measured as none, mild, or severe.

Prevention of Further Postoperative Nausea and Vomiting: Adult surgical patients receiving general balanced anesthesia (barbiturate: thiopental, methohexital, or thiamylal; opioid: alfentanil or fentanyl; nitrous oxide; neuromuscular blockade: succinylcholine/curare and/or

vecuronium or atracurium; and supplemental isoflurane) who received no prophylactic antiemetics and who experienced nausea and/or vomiting within 2 hours postoperatively were evaluated in two double-blind US studies involving 441 patients. Patients who experienced an episode of postoperative nausea and/or vomiting were given ZOFRAN Injection (4 mg) I.V. over 2 to 5 minutes, and this was significantly more effective than placebo. The results of these studies are summarized in Table 8.

Table 8. Prevention of Further Postoperative Nausea and Vomiting in Adult Patients

	Ondansetron 4 mg I.V.	Placebo	*P* Value
Study 1			
Emetic episodes:			
Number of patients	104	117	
Treatment response 24 h after study drug			
0 Emetic episodes	49 (47%)	19 (16%)	<0.001
1 Emetic episode	12 (12%)	9 (8%)	
More than 1 emetic episode/rescued	43 (41%)	89 (76%)	
Median time to first emetic episode (min)*	55.0	43.0	
Nausea assessments:			
Number of patients	98	102	
Mean nausea score over 24-h postoperative period†	1.7	3.1	
Study 2			
Emetic episodes:			
Number of patients	112	108	
Treatment response 24 h after study drug			
0 Emetic episodes	49 (44%)	28 (26%)	0.006
1 Emetic episode	14 (13%)	3 (3%)	
More than 1 emetic episode/rescued	49 (44%)	77 (71%)	
Median time to first emetic episode (min)*	60.5	34.0	
Nausea assessments:			
Number of patients	105	85	
Mean nausea score over 24-h postoperative period†	1.9	2.9	

* After administration of study drug.

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

The study populations in Table 8 consisted mainly of women undergoing laparoscopic procedures.

Pediatric Studies: One double-blind, placebo-controlled, US study was performed in 351 male and female outpatients (2 to 12 years of age) who received general anesthesia with nitrous oxide and no prophylactic antiemetics. Surgical procedures were unrestricted. Patients who experienced two or more emetic episodes within 2 hours following discontinuation of nitrous oxide were randomized to either single I.V. doses of ondansetron (0.1 mg/kg for pediatric patients weighing 40 kg or less, 4 mg for pediatric patients weighing more than 40 kg) or placebo administered over at least 30 seconds. Ondansetron was significantly more effective than placebo in preventing further episodes of nausea and vomiting. The results of the study are summarized in Table 9.

Table 9. Prevention of Further Postoperative Nausea and Vomiting in Pediatric Patients

Treatment Response Over 24 Hours	Ondansetron n (%)	Placebo n (%)	*P* Value
Number of patients	180	171	
0 Emetic episodes	96 (53%)	29 (17%)	≤0.001
Failure*	84 (47%)	142 (83%)	

* Failure was one or more emetic episodes, rescued, or withdrawn.

Repeat Dosing in Adults: In patients who do not achieve adequate control of postoperative nausea and vomiting following a single, prophylactic, preinduction, I.V. dose of ondansetron 4 mg, administration of a second I.V. dose of ondansetron 4 mg postoperatively does not provide additional control of nausea and vomiting.

INDICATIONS AND USAGE

1. Prevention of nausea and vomiting associated with initial and repeat courses of emetogenic cancer chemotherapy, including high-dose cisplatin. Efficacy of the 32-mg single dose beyond 24 hours in these patients has not been established.
2. Prevention of postoperative nausea and/or vomiting. As with other antiemetics, routine prophylaxis is not recommended for patients in whom there is little expectation that nausea and/or vomiting will occur postoperatively. In patients where nausea and/or vomiting must be avoided postoperatively, ZOFRAN Injection is recommended even where the incidence of postoperative nausea and/or vomiting is low. For patients who do not receive prophylactic ZOFRAN Injection and experience nausea and/or vomiting postoperatively, ZOFRAN Injection may be given to prevent further episodes (see CLINICAL TRIALS).

CONTRAINDICATIONS

ZOFRAN Injection and ZOFRAN Injection Premixed are contraindicated for patients known to have hypersensitivity to the drug.

WARNINGS

Hypersensitivity reactions have been reported in patients who have exhibited hypersensitivity to other selective 5-HT_3 receptor antagonists.

PRECAUTIONS

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

Drug Interactions: Ondansetron does not itself appear to induce or inhibit the cytochrome P-450 drug-metabolizing enzyme system of the liver (see CLINICAL PHARMACOLOGY, Pharmacokinetics). 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. On the basis of limited available data, no dosage adjustment is recommended for patients on these drugs.

Phenytoin, Carbamazepine, and Rifampicin: In patients treated with potent inducers of CYP3A4 (i.e., phenytoin, carbamazepine, and rifampicin), 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.[1,3]

Tramadol: Although no pharmacokinetic drug interaction between ondansetron and tramadol has been observed, data from 2 small studies indicate that ondansetron may be associated with an increase in patient controlled administration of tramadol.[4,5]

Chemotherapy: Tumor response to chemotherapy in the P 388 mouse leukemia model is not affected by ondansetron. In humans, carmustine, etoposide, and cisplatin do not affect the pharmacokinetics of ondansetron.

In a crossover study in 76 pediatric patients, I.V. ondansetron did not increase blood levels of high-dose methotrexate.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Carcinogenic effects were not seen in 2-year studies in rats and mice with oral ondansetron doses up to 10 and 30 mg/kg per day, respectively. Ondansetron was not mutagenic in standard tests for mutagenicity. Oral administration of ondansetron up to 15 mg/kg per day did not affect fertility or general reproductive performance of male and female rats.

Pregnancy: *Teratogenic Effects:* Pregnancy Category B. Reproduction studies have been performed in pregnant rats and rabbits at I.V. doses up to 4 mg/kg per day and have revealed no evidence of impaired fertility or harm to the fetus due to ondansetron. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies

are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers: Ondansetron is excreted in the breast milk of rats. It is not known whether ondansetron is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when ondansetron is administered to a nursing woman.

Pediatric Use: Little information is available about dosage in pediatric patients under 2 years of age (see DOSAGE AND ADMINISTRATION section for use in pediatric patients 4 to 18 years of age receiving cancer chemotherapy or for use in pediatric patients 2 to 12 years of age receiving general anesthesia).

Geriatric Use: Of the total number of subjects enrolled in cancer chemotherapy-induced and postoperative nausea and vomiting in US- and foreign-controlled clinical trials, 862 were 65 years of age and over. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out. Dosage adjustment is not needed in patients over the age of 65 (see CLINICAL PHARMACOLOGY).

ADVERSE REACTIONS

Chemotherapy-Induced Nausea and Vomiting: The adverse events in Table 10 have been reported in individuals receiving ondansetron at a dosage of three 0.15-mg/kg doses or as a single 32-mg dose in clinical trials. These patients were receiving concomitant chemotherapy, primarily cisplatin, and I.V. fluids. Most were receiving a diuretic.

Table 10. Principal Adverse Events in Comparative Trials

	Number of Patients With Event			
	ZOFRAN Injection 0.15 mg/kg x 3 n = 419	ZOFRAN Injection 32 mg x 1 n = 220	Metoclopramide n = 156	Placebo n = 34
Diarrhea	16%	8%	44%	18%
Headache	17%	25%	7%	15%
Fever	8%	7%	5%	3%
Akathisia	0%	0%	6%	0%
Acute dystonic reactions*	0%	0%	5%	0%

* See Neurological.

The following have been reported during controlled clinical trials:

Cardiovascular: Rare cases of angina (chest pain), electrocardiographic alterations, hypotension, and tachycardia have been reported. In many cases, the relationship to ZOFRAN Injection was unclear.

Gastrointestinal: Constipation has been reported in 11% of chemotherapy patients receiving multiday ondansetron.

Hepatic: In comparative trials in cisplatin chemotherapy patients with normal baseline values of aspartate transaminase (AST) and alanine transaminase (ALT), these enzymes have been reported to exceed twice the upper limit of normal in approximately 5% of patients. The increases were transient and did not appear to be related to dose or duration of therapy. On repeat exposure, similar transient elevations in transaminase values occurred in some courses, but symptomatic hepatic disease did not occur.

Integumentary: Rash has occurred in approximately 1% of patients receiving ondansetron.

Neurological: There have been rare reports consistent with, but not diagnostic of, extrapyramidal reactions in patients receiving ZOFRAN Injection, and rare cases of grand mal seizure. The relationship to ZOFRAN was unclear.

Other: Rare cases of hypokalemia have been reported. The relationship to ZOFRAN Injection was unclear.

Postoperative Nausea and Vomiting: The adverse events in Table 11 have been reported in ≥2% of adults receiving ondansetron at a dosage of 4 mg I.V. over 2 to 5 minutes in clinical trials. Rates of these events were not significantly different in the ondansetron and placebo groups. These patients were receiving multiple concomitant perioperative and postoperative medications.

Table 11. Adverse Events in ≥2% of Adults Receiving Ondansetron at a Dosage of 4 mg I.V. over 2 to 5 Minutes in Clinical Trials

	ZOFRAN Injection 4 mg I.V. n = 547 patients	Placebo n = 547 patients
Headache	92 (17%)	77 (14%)
Dizziness	67 (12%)	88 (16%)
Musculoskeletal pain	57 (10%)	59 (11%)
Drowsiness/sedation	44 (8%)	37 (7%)
Shivers	38 (7%)	39 (7%)
Malaise/fatigue	25 (5%)	30 (5%)
Injection site reaction	21 (4%)	18 (3%)
Urinary retention	17 (3%)	15 (3%)
Postoperative CO_2-related pain*	12 (2%)	16 (3%)
Chest pain (unspecified)	12 (2%)	15 (3%)
Anxiety/agitation	11 (2%)	16 (3%)
Dysuria	11 (2%)	9 (2%)
Hypotension	10 (2%)	12 (2%)
Fever	10 (2%)	6 (1%)
Cold sensation	9 (2%)	8 (1%)
Pruritus	9 (2%)	3 (<1%)
Paresthesia	9 (2%)	2 (<1%)

* Sites of pain included abdomen, stomach, joints, rib cage, shoulder.

Pediatric Use: The adverse events in Table 12 were the most commonly reported adverse events in pediatric patients receiving ondansetron (a single 0.1-mg/kg dose for pediatric patients weighing 40 kg or less, or 4 mg for pediatric patients weighing more than 40 kg) administered intravenously over at least 30 seconds. Rates of these events were not significantly different in the ondansetron and placebo groups. These patients were receiving multiple concomitant perioperative and postoperative medications.

Table 12. Frequency of Adverse Events From Controlled Studies in Pediatric Patients

Adverse Event	Ondansetron n = 755 Patients	Placebo n = 731 Patients
Wound problem	80 (11%)	86 (12%)
Anxiety/agitation	49 (6%)	47 (6%)
Headache	44 (6%)	43 (6%)
Drowsiness/sedation	41 (5%)	56 (8%)
Pyrexia	32 (4%)	41 (6%)

Observed During Clinical Practice: In addition to adverse events reported from clinical trials, the following events have been identified during post-approval use of intravenous formulations of ZOFRAN. Because they are reported voluntarily from a population of unknown size, estimates of frequency cannot be made. The events have been chosen for inclusion due to a combination of their seriousness, frequency of reporting, or potential causal connection to ZOFRAN.

Cardiovascular: Arrhythmias (including ventricular and supraventricular tachycardia, premature ventricular contractions, and atrial fibrillation), bradycardia, electrocardiographic alterations (including second-degree heart block and ST segment depression), palpitations**,** and syncope.

General: Flushing. Rare cases of hypersensitivity reactions, sometimes severe (e.g., anaphylaxis/anaphylactoid reactions, angioedema, bronchospasm, cardiopulmonary arrest, hypotension, laryngeal edema, laryngospasm, shock, shortness of breath, stridor) have also been reported.

Hepatobiliary: Liver enzyme abnormalities have been reported. Liver failure and death have been reported in patients with cancer receiving concurrent medications including potentially hepatotoxic cytotoxic chemotherapy and antibiotics. The etiology of the liver failure is unclear.

Local Reactions: Pain, redness, and burning at site of injection.

Lower Respiratory: Hiccups

Neurological: Oculogyric crisis, appearing alone, as well as with other dystonic reactions**.**

Skin: Urticaria

Special Senses: Transient blurred vision, in some cases associated with abnormalities of accommodation, and transient dizziness during or shortly after I.V. infusion.

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.

OVERDOSAGE

There is no specific antidote for ondansetron overdose. Patients should be managed with appropriate supportive therapy. Individual doses as large as 150 mg and total daily dosages

(three doses) as large as 252 mg have been administered intravenously without significant adverse events. These doses are more than 10 times the recommended daily dose.

In addition to the adverse events listed above, the following events have been described in the setting of ondansetron overdose: "Sudden blindness" (amaurosis) of 2 to 3 minutes' duration plus severe constipation occurred in one patient that was administered 72 mg of ondansetron intravenously as a single dose. Hypotension (and faintness) occurred in another patient that took 48 mg of oral ondansetron. Following infusion of 32 mg over only a 4-minute period, a vasovagal episode with transient second-degree heart block was observed. In all instances, the events resolved completely.

DOSAGE AND ADMINISTRATION

Prevention of Chemotherapy-Induced Nausea and Vomiting: The recommended I.V. dosage of ZOFRAN is a single 32-mg dose or three 0.15-mg/kg doses. A single 32-mg dose is infused over 15 minutes beginning 30 minutes before the start of emetogenic chemotherapy. The recommended infusion rate should not be exceeded (see OVERDOSAGE). With the three-dose (0.15-mg/kg) regimen, the first dose is infused over 15 minutes beginning 30 minutes before the start of emetogenic chemotherapy. Subsequent doses (0.15 mg/kg) are administered 4 and 8 hours after the first dose of ZOFRAN.

ZOFRAN Injection should not be mixed with solutions for which physical and chemical compatibility have not been established. In particular, this applies to alkaline solutions as a precipitate may form.

Vial: **DILUTE BEFORE USE**. ZOFRAN Injection should be diluted in 50 mL of 5% Dextrose Injection or 0.9% Sodium Chloride Injection before administration.

Flexible Plastic Container: ZOFRAN Injection Premixed, 32 mg in 5% Dextrose, 50 mL, **REQUIRES NO DILUTION**.

Pediatric Use: On the basis of the limited available information (see CLINICAL TRIALS: Pediatric Studies and CLINICAL PHARMACOLOGY: Pharmacokinetics), the dosage in pediatric patients 4 to 18 years of age should be three 0.15-mg/kg doses (see above). Little information is available about dosage in pediatric patients 3 years of age and younger.

Geriatric Use: The dosage recommendation is the same as for the general population.

Prevention of Postoperative Nausea and Vomiting: The recommended I.V. dosage of ZOFRAN for adults is 4 mg **undiluted** administered intravenously in not less than 30 seconds, preferably over 2 to 5 minutes, immediately before induction of anesthesia, or postoperatively if the patient experiences nausea and/or vomiting occurring shortly after surgery. Alternatively, 4 mg **undiluted** may be administered intramuscularly as a single injection for adults. While recommended as a fixed dose for patients weighing more than 40 kg, few patients above 80 kg have been studied. In patients who do not achieve adequate control of postoperative nausea and vomiting following a single, prophylactic, preinduction, I.V. dose of ondansetron 4 mg, administration of a second I.V. dose of 4 mg ondansetron postoperatively does not provide additional control of nausea and vomiting.

Vial: ZOFRAN Injection **REQUIRES NO DILUTION FOR ADMINISTRATION FOR POSTOPERATIVE NAUSEA AND VOMITING**.

Pediatric Use: The recommended I.V. dosage of ZOFRAN for pediatric patients (2 to 12 years of age) is a single 0.1-mg/kg dose for pediatric patients weighing 40 kg or less, or a single 4-mg dose for pediatric patients weighing more than 40 kg. The rate of administration should not be less than 30 seconds, preferably over 2 to 5 minutes. Little information is available about dosage in pediatric patients younger than 2 years of age.

Geriatric Use: The dosage recommendation is the same as for the general population.

Dosage Adjustment for Patients With Impaired Renal Function: The dosage recommendation is the same as for the general population. There is no experience beyond first-day administration of ondansetron.

Dosage Adjustment for Patients With Impaired Hepatic Function: In patients with severe hepatic impairment (Child-Pugh[2] score of 10 or greater), a single maximal daily dose of 8 mg to be infused over 15 minutes beginning 30 minutes before the start of the emetogenic chemotherapy is recommended. There is no experience beyond first-day administration of ondansetron.

ZOFRAN Injection Premixed in Flexible Plastic Containers: Instructions for Use:

To Open: Tear outer wrap at notch and remove solution container. Check for minute leaks by squeezing container firmly. If leaks are found, discard unit as sterility may be impaired.

Preparation for Administration: Use aseptic technique.

1. Close flow control clamp of administration set.
2. Remove cover from outlet port at bottom of container.
3. Insert piercing pin of administration set into port with a twisting motion until the pin is firmly seated. NOTE: See full directions on administration set carton.
4. Suspend container from hanger.
5. Squeeze and release drip chamber to establish proper fluid level in chamber during infusion of ZOFRAN Injection Premixed.
6. Open flow control clamp to expel air from set. Close clamp.
7. Attach set to venipuncture device. If device is not indwelling, prime and make venipuncture.
8. Perform venipuncture.
9. Regulate rate of administration with flow control clamp.

Caution: ZOFRAN Injection Premixed in flexible plastic containers is to be administered by I.V. drip infusion only. ZOFRAN Injection Premixed should not be mixed with solutions for which physical and chemical compatibility have not been established. In particular, this applies to alkaline solutions as a precipitate may form. If used with a primary I.V. fluid system, the primary solution should be discontinued during ZOFRAN Injection Premixed infusion.

Do not administer unless solution is clear and container is undamaged.

Warning: Do not use flexible plastic container in series connections.

Stability: ZOFRAN Injection is stable at room temperature under normal lighting conditions for 48 hours after dilution with the following I.V. fluids: 0.9% Sodium Chloride Injection, 5%

Dextrose Injection, 5% Dextrose and 0.9% Sodium Chloride Injection, 5% Dextrose and 0.45% Sodium Chloride Injection, and 3% Sodium Chloride Injection.

Although ZOFRAN Injection is chemically and physically stable when diluted as recommended, sterile precautions should be observed because diluents generally do not contain preservative. After dilution, do not use beyond 24 hours.

Note: Parenteral drug products should be inspected visually for particulate matter and discoloration before administration whenever solution and container permit.

Precaution: Occasionally, ondansetron precipitates at the stopper/vial interface in vials stored upright. Potency and safety are not affected. If a precipitate is observed, resolubilize by shaking the vial vigorously.

HOW SUPPLIED

ZOFRAN Injection, 2 mg/mL, is supplied as follows:

NDC 0173-0442-02 2-mL single-dose vials (Carton of 5)
NDC 0173-0442-00 20-mL multidose vials (Singles)

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

ZOFRAN Injection Premixed, 32 mg/50 mL, in 5% Dextrose, contains no preservatives and is supplied as a sterile, premixed solution for I.V. administration in single-dose, flexible plastic containers (NDC 0173-0461-00) (case of 6).

Store between 2° and 30°C (36° and 86°F). Protect from light. Avoid excessive heat. Protect from freezing.

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