

CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

20-007/S037

20-403/S014

Trade Name: Zofran Injection
 Zofran Injection Premixed

Generic Name: odanesetron hydrochloride

Sponsor: GlaxoSmithKline

Approval Date: December 27, 2005

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APPLICATION NUMBER:

20-007/S037

20-403/S014

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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20-403/S014

APPROVAL LETTER



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-007/S-037

NDA 20-403/S-014

GlaxoSmithKline

Attention: Ellen S. Cutler, Senior Director, Regulatory Affairs

2301 Renaissance Boulevard

Building 510, P.O. Box 61540

King of Prussia, PA 19406-2772

Dear Ms. Cutler:

Please refer to your supplemental new drug applications as follow:

NDA Number	Name of Drug Product	Supplement Number	Date of Supplement	Date of Receipt
20-007	Zofran [®] (ondansetron hydrochloride) Injection	037	June 29, 2005	June 30, 2005
20-403	Zofran [®] (ondansetron hydrochloride) Injection Premixed	014	June 29, 2005	June 30, 2005

submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act.

We acknowledge receipt of your faxed submission dated December 22, 2005 agreeing to our labeling revision.

These "Changes Being Effected" supplemental new drug applications provide to update the ADVERSE REACTIONS section of each label, respectively, by adding a subsection *Special Senses: Eye Disorders*.

We completed our review of these applications, as amended. These applications are approved, effective on the date of this letter, for use as recommended in the agreed-upon labeling text.

The final printed labeling (FPL) must be identical to the enclosed labeling (text for the package insert), and submitted labeling (package insert submitted December 22, 2005).

Please submit an electronic version of the FPL according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDA*. Alternatively, you may submit 20 paper copies of the FPL as soon as it is available but no more than 30 days after it is printed. Individually mount 15 of the copies on heavy-weight paper or similar material. For administrative purposes, designate these submissions **"FPL for approved supplement NDA 20-007/S-037 and NDA 20-403/S-014."** Approval of these submissions by FDA are not required before the labeling is used.

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Betsy Scroggs, Pharm.D, Regulatory Project Manager, at (301) 796-0991.

Sincerely,

{See appended electronic signature page}

Brian E. Harvey, M.D., Ph.D.
Director
Division of Gastroenterology Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Brian Harvey
12/27/2005 01:55:30 PM

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

20-007/S037

20-403/S014

LABELING

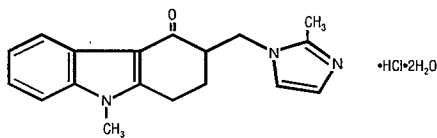
PRESCRIBING INFORMATION

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-HT₃ 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 C₁₈H₁₉N₃O·HCl·2H₂O, 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-HT₃ 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-HT₃ 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 nausea and vomiting 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 vomiting. The released serotonin may stimulate the vagal afferents through the 5-HT₃ 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-HT₃ 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 nausea and vomiting using the ipecacuanha model of emesis.

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_{1/2} 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 adult volunteers, the following mean pharmacokinetic data have been determined following a single 0.15-mg/kg I.V. dose.

Table 1. Pharmacokinetics in Normal Adult Volunteers

Age-group (years)	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 2-fold and mean half-life is increased to 11.6 hours compared to 5.7 hours in normals. In patients with severe hepatic impairment (Child-Pugh² 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. 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 (4 to 18 years of age) 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 4 to 12 years of age 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).

Pharmacokinetic samples were collected from 74 cancer patients 6 to 48 months of age, who received a dose of 0.15 mg/kg of I.V. ondansetron every 4 hours for 3 doses during a safety and efficacy trial. These data were combined with sequential pharmacokinetics data from 41 surgery patients 1 month to 24 months of age, who received a single dose of 0.1 mg/kg of I.V. ondansetron prior to surgery with general anesthesia, and a population pharmacokinetic analysis was performed on the combined data set. The results of this analysis are included in Table 2 and are compared to the pharmacokinetic results in cancer patients 4 to 18 years of age.

Table 2. Pharmacokinetics in Pediatric Cancer Patients 1 Month to 18 Years of Age

Subjects and Age Group	N	CL (L/h/kg)	Vd _{ss} (L/kg)	T _{1/2} (h)
		Geometric Mean		Mean
Pediatric Cancer Patients 4 to 18 years of age	N = 21	0.599	1.9	2.8
Population PK Patients* 1 month to 48 months of age	N = 115	0.582	3.65	4.9

* Population PK (Pharmacokinetic) Patients: 64% cancer patients and 36% surgery patients.

Based on the population pharmacokinetic analysis, cancer patients 6 to 48 months of age who receive a dose of 0.15 mg/kg of I.V. ondansetron every 4 hours for 3 doses would be expected to achieve a systemic exposure (AUC) consistent with the exposure achieved in previous pediatric studies in cancer patients (4 to 18 years of age) at similar doses.

In a study of 21 pediatric patients (3 to 12 years of age) 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 a study of 51 pediatric patients (1 month to 24 months of age) who were undergoing surgery requiring general anesthesia, a single I.V. dose of ondansetron, 0.1 or 0.2 mg/kg, was administered prior to surgery. As shown in Table 3, the 41 patients with pharmacokinetic data were divided into 2 groups, patients 1 month to 4 months of age and patients 5 to 24 months of age, and are compared to pediatric patients 3 to 12 years of age.

Table 3. Pharmacokinetics in Pediatric Surgery Patients 1 Month to 12 Years of Age

Subjects and Age Group	N	CL (L/h/kg)	Vd _{ss} (L/kg)	T _{1/2} (h)
		Geometric Mean		Mean
Pediatric Surgery Patients 3 to 12 years of age	N = 21	0.439	1.65	2.9
Pediatric Surgery Patients 5 to 24 months of age	N = 22	0.581	2.3	2.9
Pediatric Surgery Patients 1 month to 4 months of age	N = 19	0.401	3.5	6.7

In general, surgical and cancer pediatric patients younger than 18 years tend to have a higher ondansetron clearance compared to adults leading to a shorter half-life in most pediatric patients. In patients 1 month to 4 months of age, a longer half-life was observed due to the higher volume of distribution in this age group.

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:

Adult Studies: In a double-blind study of three different dosing regimens of ZOFTRAN 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, ZOFTRAN 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 4.

Table 4. Prevention of Chemotherapy-Induced Nausea and Vomiting in Single-Day Cisplatin Therapy* in Adults

	ZOFRAN Injection	Placebo	<i>P</i> 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)	96	10.5	0.009

* Chemotherapy was high dose (100 and 120 mg/m²; ZOFRAN Injection n = 6, placebo n = 5) or moderate dose (50 and 80 mg/m²; 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.

^{||} 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/m² 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 5.

Table 5. Prevention of Vomiting Induced by Cisplatin (≥ 100 mg/m²) Single-Day Therapy* in Adults

	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/m² or ≥ 100 mg/m². 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 6. Prevention of Chemotherapy-Induced Nausea and Vomiting in Single-Dose Therapy in Adults

	0.15 mg/kg x 3	Ondansetron Dose 32 mg x 1	P Value
High-dose cisplatin (≥ 100 mg/m²)			
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/m²)			
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 ZOFTRAN Injection (three 0.15-mg/kg doses) in 20 patients receiving cyclophosphamide (500 to 600 mg/m²) chemotherapy, ZOFTRAN Injection was significantly more effective than placebo in preventing nausea and vomiting. The results are summarized in Table 7.

Table 7. Prevention of Chemotherapy-Induced Nausea and Vomiting in Single-Day Cyclophosphamide Therapy* in Adults

	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)	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.

^{||} 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/m²) 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 4 to 18 years of age 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 vomiting in these pediatric patients was essentially the same as for patients older than 18 years of age.

An open-label, multicenter, noncomparative trial has been performed in 75 pediatric cancer patients 6 to 48 months of age receiving at least one moderately or highly emetogenic chemotherapeutic agent. Fifty-seven percent (57%) were females; 67% were white, 18% were American Hispanic, and 15% were black patients. ZOFRAN was administered intravenously over 15 minutes in three doses of 0.15 mg/kg. The first dose was administered 30 minutes before the start of

chemotherapy, the second and third doses were administered 4 and 8 hours after the first dose, respectively. Eighteen patients (25%) received routine prophylactic dexamethasone (i.e., not given as rescue). Of the 75 evaluable patients, 56% had a complete response (no emetic episodes) on day 1. Thus, prevention of vomiting in these pediatric patients was comparable to the prevention of vomiting in patients 4 years of age and older.

Postoperative Nausea and Vomiting: *Prevention of Postoperative Nausea and Vomiting:*

Adult Studies: 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 8.

Table 8. 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	136	139	
0 Emetic episodes	103 (76%)	64 (46%)	<0.001
1 Emetic episode	13 (10%)	17 (12%)	
More than 1 emetic episode/rescued	20 (15%)	58 (42%)	
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	136	143	
0 Emetic episodes	85 (63%)	63 (44%)	0.002
1 Emetic episode	16 (12%)	29 (20%)	
More than 1 emetic episode/rescued	35 (26%)	51 (36%)	
Nausea assessments: Number of patients No nausea over 24-h postoperative period	125 48 (38%)	133 42 (32%)	

The study populations in Table 8 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 9.

Table 9. Prevention of Postoperative Nausea and Vomiting in Pediatric Patients 2 to 12 Years of Age

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.

A double-blind, multicenter, placebo-controlled study was conducted in 670 pediatric patients 1 month to 24 months of age who were undergoing routine surgery under general anesthesia. Seventy-five percent (75%) were males; 64% were white, 15% were black, 13% were American Hispanic, 2% were Asian, and 6% were "other race" patients. A single 0.1-mg/kg I.V. dose of ondansetron administered within 5 minutes following induction of anesthesia was statistically significantly more effective than placebo in preventing vomiting. In the placebo group, 28% of patients experienced vomiting compared to 11% of subjects who received ondansetron ($P \leq 0.01$). Overall, 32 (10%) of placebo patients and 18 (5%) of patients who received ondansetron received antiemetic rescue medication(s) or prematurely withdrew from the study.

Prevention of Further Postoperative Nausea and Vomiting:

Adult Studies: 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 ZOFTRAN 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 10.

Table 10. 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 10 consisted mainly of women undergoing laparoscopic procedures.

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.

Pediatric Study: 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 11.

Table 11. Prevention of Further Postoperative Nausea and Vomiting in Pediatric Patients 2 to 12 Years of Age

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

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

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, ZOFTRAN Injection is recommended even where the incidence of postoperative nausea and/or vomiting is low. For patients who do not receive prophylactic ZOFTRAN Injection and experience nausea and/or vomiting postoperatively, ZOFTRAN Injection may be given to prevent further episodes (see CLINICAL TRIALS).

CONTRAINDICATIONS

ZOFTRAN Injection and ZOFTRAN 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-HT₃ 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 the use of ondansetron in pediatric surgical patients younger than 1 month of age. (See CLINICAL TRIALS section for studies of ondansetron in prevention of postoperative nausea and vomiting in patients 1 month of age and older.) Little information is available about the use of ondansetron in pediatric cancer patients younger than 6 months of age. (See CLINICAL TRIALS section for studies of ondansetron in chemotherapy-induced nausea and vomiting in pediatric patients 6 months of age and older.) (See DOSAGE AND ADMINISTRATION.)

The clearance of ondansetron in pediatric patients 1 month to 4 months of age is slower and the half-life is ~2.5 fold longer than patients who are >4 to 24 months of age. As a precaution, it is recommended that patients less than 4 months of age receiving this drug be closely monitored. (See CLINICAL PHARMACOLOGY: Pharmacokinetics).

The frequency and type of adverse events reported in pediatric patients receiving ondansetron were similar to those in patients receiving placebo. (See ADVERSE EVENTS.)

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 12 have been reported in adults 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 12. Principal Adverse Events in Comparative Trials in Adults

	Number of Adult 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 13 have been reported in $\geq 2\%$ 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 13. Adverse Events in $\geq 2\%$ 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 14 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 14. Frequency of Adverse Events From Controlled Studies in Pediatric Patients 2 to 12 Years of Age

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%)

The adverse events in Table 15 were the most commonly reported adverse events in pediatric patients, 1 month to 24 months of age, receiving a single 0.1-mg/kg I.V. dose of ondansetron. The incidence and type of adverse events were similar in both the ondansetron and placebo groups. These patients were receiving multiple concomitant perioperative and postoperative medications.

Table 15. Frequency of Adverse Events (Greater Than or Equal to 2% in Either Treatment Group) in Pediatric Patients 1 Month to 24 Months of Age

Adverse Event	Ondansetron n = 336 Patients	Placebo n = 334 Patients
Pyrexia	14 (4%)	14 (4%)
Bronchospasm	2 (<1%)	6 (2%)
Post-procedural pain	4 (1%)	6 (2%)
Diarrhea	6 (2%)	3 (<1%)

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 dizziness during or shortly after I.V. infusion.

Eye Disorders: Transient blurred vision, in some cases associated with abnormalities of accommodation. 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.

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:

Adult Dosing: The recommended I.V. dosage of ZOFRAN for adults 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 FOR PREVENTION OF CHEMOTHERAPY-INDUCED NAUSEA AND VOMITING. ZOFRAN Injection should be diluted in 50 mL of 5% Dextrose Injection or 0.9% Sodium Chloride Injection before administration.

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

Pediatric Dosing: On the basis of the available information (see CLINICAL TRIALS: Pediatric Studies and CLINICAL PHARMACOLOGY: Pharmacokinetics), the dosage in pediatric cancer patients 6 months to 18 years of age should be three 0.15-mg/kg doses. The first dose is to be administered 30 minutes before the start of moderately to highly emetogenic chemotherapy, subsequent doses (0.15 mg/kg) are administered 4 and 8 hours after the first dose of ZOFRAN. The drug should be infused intravenously over 15 minutes. Little information is available about dosage in pediatric cancer patients younger than 6 months of age.

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

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

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

Prevention of Postoperative Nausea and Vomiting:

Adult Dosing: The recommended I.V. dosage of ZOFTRAN 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: REQUIRES NO DILUTION FOR ADMINISTRATION FOR POSTOPERATIVE NAUSEA AND VOMITING.

Pediatric Dosing: The recommended I.V. dosage of ZOFTRAN for pediatric surgical patients (1 month to 12 years of age) is a single 0.1-mg/kg dose for patients weighing 40 kg or less, or a single 4-mg dose for patients weighing more than 40 kg. The rate of administration should not be less than 30 seconds, preferably over 2 to 5 minutes immediately prior to or following anesthesia induction, or postoperatively if the patient experiences nausea and/or vomiting occurring shortly after surgery. Prevention of further nausea and vomiting was only studied in patients who had not received prophylactic Zofran.

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

Geriatric Dosing: 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-Pugh² 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.

ZOFTRAN 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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GlaxoSmithKline

Research Triangle Park, NC 27709

ZOFRAN® Injection Premixed:

Manufactured for GlaxoSmithKline

Research Triangle Park, NC 27709

by Hospira, Inc., Lake Forest, IL 60045

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June 2005

RL-2197

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

20-007/S037

20-403/S014

MEDICAL REVIEW(S)

DIVISION OF GASTROENTEROLOGY DRUG PRODUCTS

MEDICAL OFFICER'S REVIEW OF LABELING CHANGES

NDA:	20-403/S-014 (Zofran Injection Premixed) 20-605/S-008 (Zofran Oral Solution) 20-103/S-025 (Zofran Tablets) 20-007/S-037 (Zofran Injection) 20-781/S-008 (Zofran ODT)
Sponsor:	GlaxoSmithKline (GSK) 2301 Renaissance Blvd. P.O. Box 61540 King of Prussia, PA 19406-2772
Date Submitted:	June 30, 2005
Drug Name:	Zofran® (Ondansetron)
Drug Class:	5HT ₃ - Antagonist
Documents Reviewed:	Electronic Submission for Changes Being Effectuated in the Label
Division Director:	Brian E. Harvey, M.D., Ph.D.
Deputy Director:	Joyce Korvick, M.D., M.P.H.
Team Leader:	Ruyi He, M.D.
Medical Officer:	Lolita A. Lopez, M.D.

I. INTRODUCTION AND BACKGROUND

On June 30, 2005, the sponsor, GlaxoSmithKline submitted a "Special Supplement – Changes Being Effectuated" to NDAs 20-403/S-037, 20-605/S-008, 20-103/S-025, 20-007/S-014, and 20-781/S-008 for the oral and injection formulations of Zofran®. The supplement provides for revisions to the "ADVERSE REACTIONS" section of the label to add wording to increase the safe use of the product.

This labeling change followed a review of GlaxoSmithKline's (GSK) database by the Medicines and Healthcare Products Regulatory Agency (MHRA) wherein six reports of

transient blindness associated with ondansetron were noted. GSK was therefore requested to provide a cumulative review of all cases of transient blindness associated with ondansetron held in their safety database plus details of any relevant literature reports. The core safety information (CSI) for ondansetron already contains information in the adverse reactions section regarding visual disturbances. However, this does not appear to be sufficient to encompass the visual disturbances that have been reported to occur.

A comprehensive review of the GSK safety database (up to a cut off date of 22 October 2004) and published literature was carried out. A total of 24 reports of transient blindness were identified in patients who had received treatment with ondansetron, of these, 2 reports were considered as unassessable. Of the 22 evaluable cases, 10 were excluded (3 did not meet the definition of transient blindness such as blurred vision or lazy eye), and 7 because of other diagnoses (stroke, CVA, intracerebral haemorrhage, seizure and near arrest) were a more likely explanation for the event.

The 12 key cases were reviewed for both therapy and patient related risk factors: 8 patients received ondansetron for chemotherapy related nausea and vomiting, 3 for post-operative nausea and vomiting, and one patient had unknown treatment indication. Transient blindness onset interval ranged from immediate up to one hour, and in all cases the event resolved within a couple of minutes up to a maximum of 48 hours. Three of these 12 cases were considered as pivotal by GSK since in each case a positive rechallenge was reported and the event of transient blindness was reported to have resolved from a couple minutes to 20 minutes.

There is no known mechanism by which ondansetron could mediate transient blindness. However, given the serious nature of the event and the three positive rechallenges reported, GSK approved the addition of transient blindness to the ondansetron core safety information (CSI) and is revising the "ADVERSE REACTIONS" section of ondansetron's label to add wording to strengthen this section of the label.

II. PROPOSED LABELING CHANGES

Below are the proposed sponsor's proposed changes to the label. Additions in the text are indicated by underlining and deletions are indicated by double strikethrough.

In the **ADVERSE REACTIONS** section, under **Observed During Clinical Practice** subsection:

Special Senses.

Transient dizziness during or shortly after I.V. infusion.

Eye Disorders: Transient blurred vision, in some cases associated with abnormalities of accommodation. cases of transient blindness, predominantly during intravenous administration, have been reported. These cases of transient blindness within

b(4)

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b(4)

Medical Officer Comments: The sponsor's proposal to add the subsection "Eye Disorders" under *Special Senses* in the ADVERSE EVENTS section of the label and the addition of information on reports of rare cases of transient blindness is acceptable. This provides specific adverse event information pertaining to this specific sense organ (eye) and therefore adding clarity and ease in reading this subsection of the label.

However, reports of transient blindness in the 12 key cases reviewed had the event resolved within a couple of minutes up to a maximum of 48 hours. The sponsor

b(4) In this Medical Officer's opinion, it is not appropriate to make a generalized statement based on only on these b(4) It is more appropriate to inform clinicians that transient b(4) blindness have been reported to resolve anytime within a few minutes for up to 48 hours as reported in the 12 key cases reviewed. The word X should also be b(4) deleted. The proposed labeling change should read:

b(4) *Special Senses:* transient dizziness during or shortly after I.V. infusion. b(4)

Eye Disorders: Transient blurred vision, in some cases associated with abnormalities of accommodation. Cases of transient blindness, predominantly during intravenous administration, have been reported. These cases of transient blindness b(4) were reported to resolve within a few minutes up to a maximum of 48 hours. b(4)

III. MEDICAL OFFICER RECOMMENDATIONS

This Medical Officer recommends the following changes to the label to read:

Special Senses: *Transient dizziness during or shortly after I.V. infusion.*

Eye Disorders: *Transient blurred vision, in some cases associated with abnormalities of accommodation. 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 a maximum of 48 hours.*

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/s/

Lolita Lopez
12/21/2005 07:30:47 AM
MEDICAL OFFICER

Ruyi He
12/21/2005 11:35:10 AM
MEDICAL OFFICER

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

20-007/S037

20-403/S014

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**

Division of Gastroenterology Products

PROJECT MANAGER'S REVIEW

Application Number	Name of Drug
NDA 20-103/SLR-025	ZOFRAN [®] (ondansetron hydrochloride) Tablets
NDA 20-605/SLR-008	ZOFRAN [®] (ondansetron hydrochloride) Oral Solution
NDA 20-781/SLR-008	ZOFRAN ODT [®] (ondansetron hydrochloride) Orally Disintegrating Tablets
NDA 20-007/SLR-037	ZOFRAN [®] (ondansetron hydrochloride) Injection
NDA 20-403/SLR-014	ZOFRAN [®] (ondansetron hydrochloride) Injection Premixed

Sponsor: GlaxoSmithKline

Material Reviewed:

Electronic final printed label (FPL) Package Inserts

Submission Date: June 29, 2005

Receipt Date: June 30, 2005

Background and Summary

ZOFRAN[®] (ondansetron hydrochloride), an antiemetic, is approved for oral and parenteral use. GlaxoSmithKline utilizes two package inserts; one for the ZOFRAN[®] oral formulations (NDA 20-103, NDA 20-605, and NDA 20-781) and the other for the ZOFRAN[®] injectable formulations (NDA 20-007 and NDA 20-403).

The approval history for all five NDAs noted above is as follows:

Oral Formulations:

ZOFRAN[®] Tablets (NDA 20-103), approved December 31, 1992)

ZOFRAN[®] Oral Solution (NDA 20-605), approved January 24, 1997)

ZOFRAN ODT[®] Orally Disintegrating Tablets (NDA 20-781, approved January 27, 1999)

and

Injectable Formulations:

ZOFRAN[®] Injection (NDA 20-007, approved January 4, 1991)

ZOFRAN[®] Injection, Premixed (NDA 20-403, approved January 31, 1995).

NDA 20-103/S-025, NDA 20-605/S-008, NDA 20-781/S-008, NDA 20-007/S-037, NDA 20-403/S-014

All of the above NDAs share the following indications:

1. prevention of nausea and vomiting associated with highly emetogenic cancer chemotherapy;
2. prevention of nausea and vomiting associated with initial and repeat courses of moderately emetogenic cancer chemotherapy;
3. prevention of 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; and
4. prevention of postoperative nausea and/or vomiting.

NDA 20-103/SCP-024 for ZOFRAN® Tablets submitted October 19, 2004 and approved February 18, 2005 provided to delete the “protect from light” and related statements from label (package insert), cartons, and blisters for the 8 mg tablet. This supplement updated the shared package insert for NDA 20-103, NDA 20-605, and 20-781.

NDA 20-007/SLR-035 for ZOFRAN® Injection submitted September 28, 2004 and approved March 25, 2005 provided to add additional pediatric information to the package insert. This supplement updated the shared package insert for NDA 20-007 and 20-403.

NDA 20-103/SLR-025, NDA 20-605/SLR-008, NDA 20-781/SLR-008, NDA 20-007/SLR-037, and NDA 20-403/SLR-014 submitted as “Changes Being Effected” labeling supplements June 29, 2005 and provide for revisions to the prescribing information (PI) by proposing to add a subsection under *Special Senses* in the ADVERSE REACTIONS section.

Review

Package Insert

- A. Oral Formulations: NDA 20-103/SLR-025, NDA 20-605/SLR-008, and NDA 20-781/SLR-008

The submitted electronic FPL package insert, submitted June 29, 2005, identified as “RL-2198 June 2005” was compared to the approved package insert, identified as “RL 2183 March 2005), approved February 18, 2005 for ZOFRAN® Orally Disintegrating Tablets (NDA 20-103/SCP-024) and served to update the shared label for NDA 20-103, NDA 20-605, and NDA 20-781.

The following revisions were noted:

1. The identifier has been updated to read "RL 2198 June 2005."

Comment: This is an acceptable revision.

2. In the ADVERSE REACTIONS section, the sponsor has proposed to add the following new subsection:

~~_____~~ b(4) ~~_____~~

Comment: Acceptability of this addition is pending completion of the medical officer's review.

B. Injectable Formulations: NDA 20-007/SLR-037 and NDA 20-403/SLR-014

The submitted electronic FPL package insert, submitted June 29, 2005, identified as "RL-2197 June 2005" was compared to the package insert identified as "Month Year XXXX," approved March 25, 2005 for ZOFRAN® Injection (NDA 20-007/S-035) and served to update the shared label for NDA 20-007 and NDA 20-403.

The following changes were noted:

1. The identifier has been updated to read "RL-2197 June 2005."

Comment: This is an acceptable revision.

2. Minor editorial revisions have been made to revise the formatting and correct grammar.

Comment: These are acceptable revisions.

3. In the ADVERSE REACTIONS section, the sponsor has revised the Special Senses subsection and proposes to add the following new subsection titled: "Eye Disorders:"

Special Senses: _____ b(4)
b(4) _____ Transient dizziness during or shortly after
I.V. infusion.
Eye Disorders: _____ predominantly during b(4)
intravenous administration, have been reported. These cases of transient
blindness _____ within _____ b(4)

Comment: Acceptability of these revisions is pending completion of the medical officer's review.

4. The manufacturer's section has been revised as follows:



GlaxoSmithKline
Research Triangle Park, NC 27709

ZOFRAN® Injection Premixed:
Manufactured for GlaxoSmithKline
Research Triangle Park, NC 27709
~~Abbott Laboratories, North Chicago, IL 60064~~
by Hospira, Inc., Lake Forest, IL 60045

©~~YEAR~~, ©2005, GlaxoSmithKline. All rights reserved.

~~Month~~ YEAR June 2005

~~RL-XXXX~~
RL-2197

Comment: The name and address change noted from Abbott to Hospira reflects the name change that the hospital division of Abbott underwent in May 2004 as an Abbott corporate "spin-off" and is acceptable as an annual reportable.

Conclusions

The changes noted are acceptable except for the revisions to the ADVERSE REACTIONS section which are pending completion of the medical officer's review.

NDA 20-103/S-025, NDA 20-605/S-008, NDA 20-781/S-008, NDA 20-007/S-037, NDA 20-403/S-014

Betsy Scroggs, PharmD
Regulatory Health Project Manager

Julieann DuBeau, MSN, RN
Chief, Project Management Staff

Drafted: BHS 12-05-2005

Revised/Initialed: BS/12-20-2005

Finalized: BHS/12-20-2005

Filename: C:\data\My Documents\NDA\Zofran SLRs\Final PM LR Inj & Oral.doc

PM LABELING REVIEW

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/s/

Betsy Scroggs
12/20/2005 11:09:45 AM
CSO

Brian Strongin
12/20/2005 11:24:18 AM
CSO



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation ODE III

FACSIMILE TRANSMITTAL SHEET

DATE: December 21, 2005

To: Ellen Cutler or Bob Watson	Betsy Scroggs
Company GSK	From: Division of Gastroenterology Products
Fax number: (610) 787-7062	Fax number: (301) 796-9905
Phone number: (610) 787-3733	Phone number: (301) 796-2120
Subject: NDA 20-103/S-025, NDA 20-605/S-008, NDA 20-781/S-008, NDA 20-007/S-037, NDA 20-403/S-014	
Total no. of pages including cover: 2	

DOCUMENT TO BE MAILED? NO

Please refer to your submissions for the above referenced NDAs submitted as CBE labeling supplements on June 29, 2005 which provide to add a new Special Senses subsection in the ADVERSE REACTIONS section of the respective package inserts. We have completed review of your submissions and have the following request for revision as follows:

Eye Disorders: Transient blurred vision, ~~_____~~ ^{b(4)}
~~_____~~ ^{b(4)} Cases of transient blindness, predominantly during intravenous
administration, have been reported. These cases of transient blindness ~~_____~~ ^{b(4)}
~~_____~~ ^{b(4)} were reported to resolve within a few minutes up to 48 hours. ^{b(4)}

If you agree to the above revision, please fax your response to (301) 796-9905 followed by submission to these NDAs on December 22, 2005.

Please contact me to discuss the requested change if needed. We remind you that the PDUFA goal date is December 31, 2005.

Betsy Scroggs, Pharm.D., RHPM

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Betsy Scroggs
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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-007/S-037

NDA 20-403/S-014

CBE-0 SUPPLEMENT

GlaxoSmithKline

Attention: Ellen S. Cutler, Senior Director, Regulatory Affairs

2301 Renaissance Boulevard

Building 510, P.O. Box 61540

King of Prussia, PA 19406-2772

Dear Ms. Cutler:

We have received your supplemental drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

NDA Number	Name of Drug Product	Supplement Number	Date of Supplement	Date of Receipt
20-007	Zofran [®] (ondansetron hydrochloride) Injection	037	June 29, 2005	June 30, 2005
20-403	Zofran [®] (ondansetron hydrochloride) Injection Premixed	014	June 29, 2005	June 30, 2005

These supplemental applications, submitted as "Supplement - Changes Being Effected" propose to update the ADVERSE REACTIONS section of each label, respectively, by adding a subsection *Special Senses: Eye Disorders*.

We filed the applications on August 29, 2005, in accordance with 21 CFR 314.101(a). The application user fee goal dates will be December 30, 2005.

Please cite the application numbers listed above at the top of the first page of all submissions to these applications, respectively. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Gastroenterology Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

If you have any question, call me, at (301) 796-0991.

Sincerely,

{See appended electronic signature page}

Betsy Scroggs, Pharm. D.
Regulatory Health Project Manager
Division of Gastroenterology Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

Betsy Scroggs
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