CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

20-007/S030
20-403/S009

Trade Name: Zofran Injection
Zofran Injection Premixed

Generic Name: (ondansetron)

Sponsor: Glaxo Wellcome Inc.

Approval Date: April 11, 2000

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-007/S030
20-403/S009

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-007/S030

20-403/S009

APPROVAL LETTER

08.81

NDA 20-007/S-030
NDA 20-403/S-009

Glaxo Wellcome, Inc.
Attention: Craig A. Metz, Ph.D.
Director, Regulatory Affairs
Five Moore Drive
P.O. Box 13398
Research Triangle Park, NC 27709

APR 11 2000

Dear Dr. Metz:

Please refer to your supplemental new drug applications dated October 13, 1999, received October 14, 1999, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Zofran (ondansetron) Injection and Zofran Injection Premixed, respectively.

These "Changes Being Effected" supplemental new drug applications provide for revision of the package insert to include 1) addition of several new adverse reactions in the Observed During Clinical Practice subsection of the ADVERSE REACTIONS section and 2) revisions to the OVERDOSAGE section to provide consistency in wording between the oral and injectable product package inserts.

We have completed the review of these supplemental applications and have concluded that adequate information has been presented to demonstrate that the drug products are safe and effective for use as recommended in the submitted final printed labeling (package insert submitted October 13, 1999). Accordingly, these supplemental applications are approved effective on the date of this letter.

At the next printing of the package insert, please revise all instances of the word "children" to "pediatric patients" in accordance with 21 CFR 201.57(f)(9). The Division may be informed of this revision in the subsequent annual reports.

If a letter communicating important information about this drug product (i.e., a "Dear Health Care Practitioner" letter) is issued to physicians and others responsible for patient care, we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HF-2
FDA
5600 Fishers Lane
Rockville, MD 20857

We remind you that you must comply with the requirements for an approved NDA set forth

under 21 CFR 314.80 and 314.81.

If you have any questions, call Melodi McNeil, Regulatory Health Project Manager, at (301) 827-7310.

Sincerely,

LT 4-11-00 mm 4/11/00

Lilia Talarico, M.D.
Director
Division of Gastrointestinal and Coagulation Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

cc:
Archival NDAs 20-007, 20-403
HFD-180/Div. Files
HFD-180/M.McNeil
HF-2/MedWatch (with labeling)
HFD-002/ORM (with labeling)
HFD-103/ADRA (with labeling)
HFD-40/DDMAC (with labeling)
HFI-20/Press Office (with labeling)
HFD-400/OPDRA (with labeling)
HFD-613/OGD (with labeling)
HFD-095/DDMS-IMT (with labeling)
HFD-820/DNDC Division Director
DISTRICT OFFICE

Drafted by: mm/April 10, 2000
Initialed by: LTalarico 4/10/00
final: April 11, 2000
filename: c:\mydocuments\cso\n\20007004-ap.doc

APPROVAL (AP)

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-007/S030

20-403/S009

LABELING

NDA 20-403

FINAL PRINTED LABELING

ZOFRAN® (ondansetron hydrochloride) Injection Premixed
Package Insert

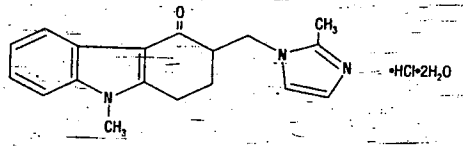
Labeling: OIG sce 0009
NDA No: 20-403 Rc'd. 10/99
Reviewed by: M. McNeil
4/11/00

PRODUCT 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 2500 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.

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

From a single-dose infusion study, patients with severe hepatic impairment showed a fivefold and those with mild-to-moderate liver impairment a twofold reduction in mean plasma clearance, with increases in the mean apparent volume of distribution of less than twofold, as compared to normals. The mean half-life of 3.6 hours in normals increased to 9.2 hours in patients with mild-to-moderate hepatic impairment and was prolonged to 20.6 hours in patients with severe hepatic insufficiency.

A reduction in clearance and increase in elimination half-life are seen in patients over 75 years old. In clinical trials with patients with cancer, there was neither a difference in safety nor efficacy between 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 adjustment in dosage is recommended in the elderly.

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 21.0 [95% CI 16.5, 26.7]

ZOFRAN®
(ondansetron hydrochloride) Injection

ZOFRAN®
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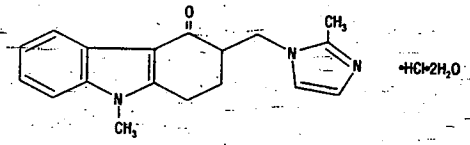

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ZOFRAN® (ondansetron hydrochloride) Injection
ZOFRAN® (ondansetron hydrochloride) Injection Premixed

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 follows:

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)¶	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 below:

Table 3: Prevention of Emesis Induced by Cisplatin (≥100 mg/m²) 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.

Forty-one of the ondansetron patients were over 65 years of age. The complete response rate (zero emetic episodes) was 41% in this group compared with 40% in those 65 years old or younger.

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

	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.

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.

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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 below:

Table 3: Prevention of Emesis Induced by Cisplatin (≥100 mg/m²) 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.

Forty-one of the ondansetron patients were over 65 years of age. The complete response rate (zero emetic episodes) was 41% in this group compared with 40% in those 65 years old or younger.

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 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/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 ZOFRAN Injection (three 0.15-mg/kg doses) in 20 patients receiving cyclophosphamide (500 to 600 mg/m²) chemotherapy, ZOFRAN Injection was significantly more effective than placebo

in preventing nausea and vomiting. The results are summarized below:

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)¶	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 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 below:

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	136	139	
Treatment response over 24-h postoperative period			
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	134	136	
No nausea over 24-h postoperative period	56 (42%)	39 (29%)	
Study 2			
Emetic episodes:			
Number of patients	136	143	
Treatment response over 24-h postoperative period			
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	125	133	
No nausea over 24-h postoperative period	48 (38%)	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 ($P \leq 0.001$).

Two other placebo-controlled studies were conducted in 2792 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 1649 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 below:

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%)	
Failure*			

in preventing nausea and vomiting. The results are summarized below:

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)¶	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.
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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.

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Emetic episodes:			
Number of patients	136	139	
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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	134	136	
No nausea over 24-h postoperative period	56 (42%)	39 (29%)	
Study 2			
Emetic episodes:			
Number of patients	136	143	
Treatment response over 24-h postoperative period			
0 Emetic episodes	85 (63%)	63 (44%)	0.002
1 Emetic episode	16 (12%)	29 (20%)	
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Nausea assessments:			
Number of patients	125	133	
No nausea over 24-h postoperative period	48 (38%)	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 2792 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 ($P\leq0.001$) 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 1049 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 below:

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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.

ZOFRAN® (ondansetron hydrochloride) Injection
ZOFRAN® (ondansetron hydrochloride) Injection Premixed

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 below:

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 below:

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. Because ondansetron is metabolized by hepatic cytochrome P-450 drug-metabolizing enzymes, 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. 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.

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).

Use in Elderly Patients: Dosage adjustment is not needed in patients over the [illegible]

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 below:

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

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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 below:

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).

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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. Because ondansetron is metabolized by hepatic cytochrome P-450 drug-metabolizing enzymes, 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. 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.

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).

Use in Elderly Patients: Dosage adjustment is not needed in patients over the age of 65 (see CLINICAL PHARMACOLOGY). Prevention of nausea and vomiting in elderly patients was no different than in younger age-groups.

ADVERSE REACTIONS:

Chemotherapy-Induced Nausea and Vomiting: The following adverse events 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.

ZOFRAN® (ondansetron hydrochloride) Injection
ZOFRAN® (ondansetron hydrochloride) Injection Premixed

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 following adverse events 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%)	03 (<1%)
Paresthesia	9 (2%)	02 (<1%)

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

Pediatric Use: The following 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), 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

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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.

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

Postoperative Nausea and Vomiting: The following adverse events 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.

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Pruritus	9 (2%)	03 (<1%)
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*Sites of pain included abdomen, stomach, joints, rib cage, shoulder.

Pediatric Use: The following 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.

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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.

Use in the Elderly: 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.

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

Dosage Adjustment for Patients With Impaired Renal Function: No specific studies have been conducted in patients with renal insufficiency.

Dosage Adjustment for Patients With Impaired Hepatic Function: In patients with severe hepatic impairment according to Child-Pugh[1] criteria, 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.

REFERENCE:

1. Pugh RNH, Murray-Lyon IM, Dawson JL, Pietroni MC, Williams R. Transection of the oesophagus for bleeding oesophageal varices. *Brit J Surg.* 1973;60:646-649.

GlaxoWellcome
Glaxo Wellcome Inc.
Research Triangle Park, NC 27709

ZOFRAN® Injection Premixed:
Manufactured for Glaxo Wellcome Inc.
Research Triangle Park, NC 27709
by Abbott Laboratories, North Chicago, IL 60064

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.

Use in the Elderly: 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.**

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Preparation for Administration: Use aseptic technique.

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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.

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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.

REFERENCE:

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US Patent Nos. 4,695,578; 4,753,789; and 5,578,628

October 1999

RL-756

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-007/S030

20-403/S009

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

ORA 8.1

Division of Gastrointestinal & Coagulation Drug Products

CONSUMER SAFETY OFFICER REVIEW

Application Number: NDA 20-007/S-030
NDA 20-403/S-009

APR 11

Name of Drug: Zofran (ondansetron) Injection
Zofran (ondansetron) Injection Premixed

Sponsor: Glaxo Wellcome, Inc.

Material Reviewed

Submission Date(s): October 13, 1999, Final Printed Labeling (FPL)

Receipt Date(s): October 14, 1999

Background and Summary Description: NDA 20-007, approved January 4, 1991, provides for Zofran Injection. NDA 20-403, approved January 31, 1995, provides for Zofran Injection Premixed. Both products share a common package insert and are indicated for 1) the prevention of nausea and vomiting associated with emetogenic cancer chemotherapy and 2) the prevention of post-operative nausea and vomiting.

Zofran is also approved in oral tablet, oral solution, and orally disintegrating tablet formulations. These oral products share a common package insert.

NDAs 20-007/S-030 and 20-403/S-009 were submitted October 13, 1999 and provide for the following revisions to the package insert.

1. Addition of several new adverse reactions in the Observed During Clinical Practice subsection, and

2. Revisions to the OVERDOSAGE section to provide consistency in wording between the oral and injectable product package inserts.

Review

The submitted insert (**October 1999, RL-756**) was compared to the currently approved insert (**March 1999, RL-690, acknowledged and retained April 10, 2000**). In addition to minor editorial and formatting changes that do not affect the meaning of any information conveyed, the following revisions have been made:

Note: Throughout this review new text is represented by a double underline; the firm's deletions

are represented by a strikethrough.

1. ADVERSE REACTIONS section, Observed During Clinical Practice subsection:

   a. The General subsection has been revised as follows:

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

   b. The Hepatic subsection has been renamed the "Hepatobiliary" subsection. The first sentence has been revised as follows:

   Hepatobiliary: Liver enzyme abnormalities have been reported."

   c. A new subsection entitled "Lower Respiratory" has been added. It reads "**Lower Respiratory**: Hiccups"

   d. A new subsection entitled "Skin" has been added. It reads "**Skin**: Urticaria"

   On October 20, 1999 Dr. ~~Hugo~~ Gallo-Torres, Medical Team Leader, indicated that these changes are acceptable.

2. OVERDOSAGE section:

   a. The second sentence now reads, "Individual doses as large as 150 mg and total daily doses (three doses) as large as 252 mg have been administered intravenously without significant adverse events.

   b. The following sentence has been added to the beginning of the second paragraph: "In addition to the adverse events listed above, the following events have been described in the setting of ondansetron overdose:"

   On October 20, 1999 Dr. Gallo-Torres indicated that both changes are acceptable.

c.

Conclusions

The submitted labeling is acceptable and can be considered the currently approved labeling. An approval letter should be drafted.

Melodi McNeil 4/11/00
Regulatory Health Project Manager

Lib Talarico MD 4-11-00

cc:
Original
HFD-180/Div. Files
HFD-180/McNeil

draft: mm/April 7, 2000/c:\mydocuments\cso\reviews\20007004-slr.doc
r/d Initials: LTalarico 4/10/00
final: April 11, 2000

CSO REVIEW

8.1

NDA 20-007/S-030
NDA 20-403/S-009

OCT 25 1999

Glaxo Wellcome Inc.
Attention: Craig A. Metz, Ph.D.
Director, Regulatory Affairs
Five Moore Drive, P.O. Box 13398
Research Triangle Park, NC 27709

Dear Dr. Metz:

We acknowledge receipt of your labeling supplemental applications submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

NDA Number	Supplement Number	Drug Name
20-007	S-030	Zofran (ondansetron) Injection
20-403	S-009	Zofran (ondansetron) Injection Premixed

Date of Supplements: October 13, 1999

Date of Receipt: October 14, 1999

These supplements propose the following change(s): revision of the package insert to include 1) addition of several new adverse reactions in the Observed During Clinical Practice subsection, and 2) revisions to the OVERDOSAGE section to provide consistency in wording between the oral and injectable product package inserts.

Your submission stated that the revised labeling would be implemented at the next printing.

We note that you have submitted these supplements under 21 CFR 314.70(c), 'Special Supplement - Changes Being Effected.'

Unless we notify you within 60 days of our receipt date that the applications are not sufficiently complete to permit a substantive review, these applications will be filed under section 505(b) of the Act on December 13, 1999 in accordance with 21 CFR 314.101(a).

Please cite the application numbers listed above at the top of the first page of any communications concerning these applications. All communications concerning these supplemental applications should be addressed as follows:

U.S. Postal/Courier/Overnight Mail:
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Gastrointestinal and Coagulation Drug Products, HFD-180
Attention: Division Document Room
5600 Fishers Lane
Rockville, Maryland 20857

If you have any questions, contact me at (301) 827-7310.

Sincerely,

mm 10/25/99

Melodi McNeil
Regulatory Health Project Manager
Division of Gastrointestinal and Coagulation Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

cc:
Archival NDAs 20-007, 20-403
HFD-180/Div. Files
HFD-180/M.McNeil
DISTRICT OFFICE

Drafted by: mm/October 25, 1999
final: October 25, 1999
filename: c:\mydocuments\cso\n\20007910-ack.doc

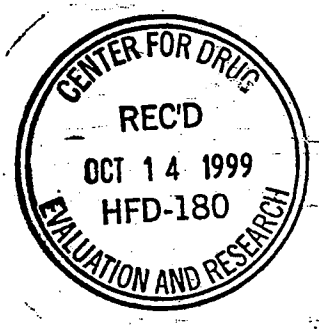
SUPPLEMENT ACKNOWLEDGEMENT (AC)

GlaxoWellcome

ARCHIVAL COPY

NDA NO. 20-403 REF. NO. 009
NDA SUPPL FOR SE

Changes as acceptable
10/20/99
HG-T



October 13, 1999

Lilia Talarico, M.D., Director
Division of Gastrointestinal and Coagulation Drug Products
Center for Drug Evaluation and Research
Attn: Document Control Room
Office of Drug Evaluation III
Food and Drug Administration
HFD-180, PKLN, 6B-45
5600 Fishers Lane
Rockville, MD 20857

Re: NDA 20-007; ZOFRAN® (ondansetron hydrochloride) Injection
NDA 20-403; ZOFRAN® (ondansetron hydrochloride) Injection Premixed
Special Supplement: Changes Being Effected, Labeling

Dear Dr. Talarico:

Reference is made to our New Drug applications for Zofran Injection and Injection Premix.

We have completed an extensive review of all spontaneous reports for the injectable and oral Zofran products. The attached revised labeling for the injectable products includes several new adverse reactions for which supporting data is being supplied under ATTACHMENTS 2-7. In addition, changes were made to the OVERDOSAGE section to provide consistency in wording between the injectable and oral package inserts. The revised oral product labeling is being submitted under separate cover.

In accordance with 21 CFR 314.70 (c)(2)(i) and (ii), we are submitting twelve (12) copies of final printed labeling. The package insert will be used at the next printing.

To facilitate your review, a draft package insert is included under ATTACHMENT 1. The package insert is annotated to the supporting data and is line-revisioned to show the new copy underlined and the deleted copy struck through. A diskette of the clean version of the package insert in Word 97 is also attached.

If you have any questions concerning this submission, please contact me at (919) 483-3640.

Glaxo Wellcome Inc.
Five Moore Drive
PO Box 13398
Research Triangle Park
North Carolina 27709

Telephone
919 483 2100

Sincerely,

Craig A. Metz

Craig A. Metz, Ph.D.
Director
Regulatory Affairs