CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

20-103/S-017
20-605/S-004
20-781/S-001

Trade Name:	Zofran Tablets, Zofran Oral Solution and Zofran Orally Disintegrating Tablets
Generic Name:	(ondansetron)
Sponsor:	Glaxo Wellcome, Inc.
Approval Date:	April 11, 2000

CENTER FOR DRUG EVALUATION AND RESEARCH

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CENTER FOR DRUG EVALUATION AND RESEARCH

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APPROVAL LETTER

NDA 20-103/S-017
NDA 20-605/S-004
NDA 20-781/S-001

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:

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) Tablets, Oral Solution, and Zofran ODT Orally-Disintegrating Tablets, respectively.

These supplemental new drug applications provide for the following revisions to the package insert:

1. A new subsection, entitled "Observed During Clinical Practice," within the ADVERSE REACTIONS section,

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

3. 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 ' ——— 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,

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 20-103, 20-605, 20-781
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 7, 2000
Initialed by: LTalarico 4/10/00
final: April 11, 2000
filename: c:\mydocuments\cso\n\20103004-ap.doc
APPROVAL (AP)

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-103/S-017

20-605/S-004

20-781/S-001

LABELING

PRESCRIBING INFORMATION

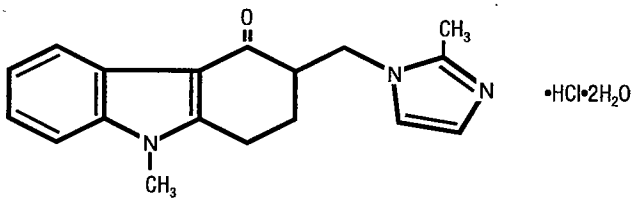
ZOFRAN®
(ondansetron hydrochloride)
Tablets

ZOFRAN ODT®
(ondansetron)
Orally Disintegrating Tablets

ZOFRAN®
(ondansetron hydrochloride)
Oral Solution

DESCRIPTION

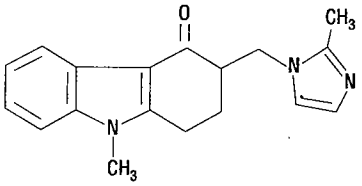
The active ingredient in ZOFRAN Tablets and ZOFRAN Oral Solution is ondansetron hydrochloride (HCl) as the dihydrate, the racemic form of ondansetron and a selective blocking agent of the serotonin 5-HT_3 receptor type. Chemically it is (±) 1, 2, 3, 9-tetrahydro-9-methyl-3-[(2-methyl-1H-imidazol-1-yl)methyl]-4H-carbazol-4-one,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



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

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

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



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

Each 4-mg ZOFRAN Tablet for oral administration contains ondansetron HCl dihydrate equivalent to 4 mg of ondansetron. Each 8-mg ZOFRAN Tablet for oral administration contains ondansetron HCl dihydrate equivalent to 8 mg of ondansetron. Each 24-mg ZOFRAN Tablet for oral administration contains ondansetron HCl dihydrate equivalent to 24 mg of ondansetron. Each tablet also contains the inactive ingredients lactose, microcrystalline cellulose, pregelatinized starch, hypromellose, magnesium stearate, titanium dioxide, triacetin, iron oxide yellow (8-mg tablet only), and iron oxide red (24-mg tablet only).

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

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

CLINICAL PHARMACOLOGY

Pharmacodynamics: Ondansetron is a selective 5-HT_3 receptor antagonist. While its mechanism of action has not been fully characterized, ondansetron is not a dopamine-receptor antagonist. Serotonin receptors of the 5-HT_3 type are present both peripherally on vagal nerve terminals and centrally in the chemoreceptor trigger zone of the area postrema. It is not certain whether ondansetron's antiemetic action is mediated centrally, peripherally, or in both sites. However, cytotoxic chemotherapy appears to be associated with release of serotonin from the enterochromaffin cells of the small intestine. In humans, urinary 5-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 intravenous doses of 0.15 mg/kg of ondansetron had no effect on esophageal motility, gastric motility, lower esophageal sphincter pressure, or small intestinal transit time. Multiday administration of ondansetron has been shown to slow colonic transit in normal volunteers. Ondansetron has no effect on plasma prolactin concentrations.

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

Ondansetron systemic exposure does not increase proportionately to dose. AUC from a 16-mg tablet was 24% greater than predicted from an 8-mg tablet dose. This may reflect some reduction of first-pass metabolism at higher oral doses. Bioavailability is also slightly enhanced by the presence of food but unaffected by antacids.

Ondansetron is extensively metabolized in humans, with approximately 5% of a radiolabeled dose recovered from the urine as the parent compound. The primary metabolic pathway is hydroxylation on the indole ring followed by subsequent glucuronide or sulfate conjugation. Although some nonconjugated metabolites have pharmacologic activity, these are not found in plasma at concentrations likely to significantly contribute to the biological activity of ondansetron.

In vitro metabolism studies have shown that ondansetron is a substrate for human hepatic cytochrome P-450 enzymes, including CYP1A2, CYP2D6, and CYP3A4. In terms of overall ondansetron turnover, CYP3A4 played the predominant role. Because of the multiplicity of metabolic enzymes capable of metabolizing ondansetron, it is likely that inhibition or loss of one enzyme (e.g., CYP2D6 genetic deficiency) will be compensated by others and may result in little change in overall rates of ondansetron elimination. Ondansetron elimination may be affected by cytochrome P-450 inducers. In a pharmacokinetic study of 16 epileptic patients maintained chronically on CYP3A4 inducers, carbamazepine, or phenytoin, reduction in AUC, C_{max}, and $T_{½}$ of ondansetron was observed.[1] This resulted in a significant increase in clearance. However, on the basis of available data, no dosage adjustment for ondansetron is recommended (see PRECAUTIONS: Drug Interactions).

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

Gender differences were shown in the disposition of ondansetron given as a single dose. The extent and rate of ondansetron's absorption is greater in women than men. Slower clearance in women, a smaller apparent volume of distribution (adjusted for weight), and higher absolute bioavailability resulted in higher plasma ondansetron levels. These higher plasma levels may in part be explained by differences in body weight between men and women. It is not known whether these gender-related differences were clinically important. More detailed pharmacokinetic information is contained in Tables 1 and 2 taken from 2 studies.

103 **Table 1. Pharmacokinetics in Normal Volunteers: Single 8-mg ZOFRAN Tablet Dose**

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

104

105 **Table 2. Pharmacokinetics in Normal Volunteers: Single 24-mg ZOFRAN Tablet Dose**

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

106

107 A reduction in clearance and increase in elimination half-life are seen in patients over 75 years
108 of age. In clinical trials with cancer patients, safety and efficacy was similar in patients over
109 65 years of age and those under 65 years of age; there was an insufficient number of patients over
110 75 years of age to permit conclusions in that age-group. No dosage adjustment is recommended
111 in the elderly.

112 In patients with mild-to-moderate hepatic impairment, clearance is reduced 2-fold and mean
113 half-life is increased to 11.6 hours compared to 5.7 hours in normals. In patients with severe
114 hepatic impairment (Child-Pugh[2] score of 10 or greater), clearance is reduced 2-fold to 3-fold and
115 apparent volume of distribution is increased with a resultant increase in half-life to 20 hours. In
116 patients with severe hepatic impairment, a total daily dose of 8 mg should not be exceeded.

117 Due to the very small contribution (5%) of renal clearance to the overall clearance, renal
118 impairment was not expected to significantly influence the total clearance of ondansetron.
119 However, ondansetron oral mean plasma clearance was reduced by about 50% in patients with
120 severe renal impairment (creatinine clearance <30 mL/min). This reduction in clearance is
121 variable and was not consistent with an increase in half-life. No reduction in dose or dosing
122 frequency in these patients is warranted.

123 Plasma protein binding of ondansetron as measured in vitro was 70% to 76% over the
124 concentration range of 10 to 500 ng/mL. Circulating drug also distributes into erythrocytes.

Four- and 8-mg doses of either ZOFRAN Oral Solution or ZOFRAN ODT Orally Disintegrating Tablets are bioequivalent to corresponding doses of ZOFRAN Tablets and may be used interchangeably. One 24-mg ZOFRAN Tablet is bioequivalent to and interchangeable with three 8-mg ZOFRAN Tablets.

CLINICAL TRIALS

Chemotherapy-Induced Nausea and Vomiting: *Highly Emetogenic Chemotherapy:*

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

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

In the same trial, 56% of patients receiving oral ondansetron 24 mg once a day experienced no nausea during the 24-hour study period, compared with 36% of patients in the oral ondansetron 8-mg twice a day group ($p = 0.001$) and 50% in the oral ondansetron 32-mg once a day group.

In a second trial, efficacy of the oral ondansetron 24 mg once a day regimen in the prevention of nausea and vomiting associated with highly emetogenic cancer chemotherapy, including cisplatin $\geq$50 mg/m^2, was confirmed.

Moderately Emetogenic Chemotherapy: In 1 double-blind US study in 67 patients, ZOFRAN Tablets 8 mg administered twice a day were significantly more effective than placebo in preventing vomiting induced by cyclophosphamide-based chemotherapy containing doxorubicin. Treatment response is based on the total number of emetic episodes over the 3-day study period. The results of this study are summarized in Table 3:

156 **Table 3. Emetic Episodes: Treatment Response**

	Ondansetron 8-mg b.i.d. ZOFRAN Tablets*	Placebo	p Value
Number of patients	33	34	
Treatment response			
0 Emetic episodes	20 (61%)	2 (6%)	<0.001
1-2 Emetic episodes	6 (18%)	8 (24%)	
More than 2 emetic episodes/withdrawn	7 (21%)	24 (71%)	<0.001
Median number of emetic episodes	0.0	Undefined†	
Median time to first emetic episode (h)	Undefined‡	6.5	

157 * The first dose was administered 30 minutes before the start of emetogenic chemotherapy, with
158 a subsequent dose 8 hours after the first dose. An 8-mg ZOFRAN Tablet was administered
159 twice a day for 2 days after completion of chemotherapy.
160 † Median undefined since at least 50% of the patients were withdrawn or had more than 2 emetic
161 episodes.
162 ‡ Median undefined since at least 50% of patients did not have any emetic episodes.
163
164 In 1 double-blind US study in 336 patients, ZOFRAN Tablets 8 mg administered twice a day
165 were as effective as ZOFRAN Tablets 8 mg administered 3 times a day in preventing nausea and
166 vomiting induced by cyclophosphamide-based chemotherapy containing either methotrexate or
167 doxorubicin. Treatment response is based on the total number of emetic episodes over the 3-day
168 study period. The results of this study are summarized in Table 4:
169

170 **Table 4. Emetic Episodes: Treatment Response**

	Ondansetron	
	8-mg b.i.d. ZOFRAN Tablets*	8-mg t.i.d. ZOFRAN Tablets†
Number of patients	165	171
Treatment response		
0 Emetic episodes	101 (61%)	99 (58%)
1-2 Emetic episodes	16 (10%)	17 (10%)
More than 2 emetic episodes/withdrawn	48 (29%)	55 (32%)
Median number of emetic episodes	0.0	0.0
Median time to first emetic episode (h)	Undefined‡	Undefined‡
Median nausea scores (0-100)§	6	6

171 * The first dose was administered 30 minutes before the start of emetogenic chemotherapy, with
172 a subsequent dose 8 hours after the first dose. An 8-mg ZOFRAN Tablet was administered
173 twice a day for 2 days after completion of chemotherapy.
174 † The first dose was administered 30 minutes before the start of emetogenic chemotherapy, with
175 subsequent doses 4 and 8 hours after the first dose. An 8-mg ZOFRAN Tablet was
176 administered 3 times a day for 2 days after completion of chemotherapy.
177 ‡ Median undefined since at least 50% of patients did not have any emetic episodes.
178 § Visual analog scale assessment: 0 = no nausea, 100 = nausea as bad as it can be.
179

180 ***Re-treatment:*** In uncontrolled trials, 148 patients receiving cyclophosphamide-based
181 chemotherapy were re-treated with ZOFRAN Tablets 8 mg 3 times daily of oral ondansetron
182 during subsequent chemotherapy for a total of 396 re-treatment courses. No emetic episodes
183 occurred in 314 (79%) of the re-treatment courses, and only 1 to 2 emetic episodes occurred in 43
184 (11%) of the re-treatment courses.
185 ***Pediatric Studies:*** Three open-label, uncontrolled, foreign trials have been performed with
186 182 pediatric patients 4 to 18 years old with cancer who were given a variety of cisplatin or
187 noncisplatin regimens. In these foreign trials, the initial dose of ZOFRAN® (ondansetron HCl)
188 Injection ranged from 0.04 to 0.87 mg/kg for a total dose of 2.16 to 12 mg. This was followed by
189 the administration of ZOFRAN Tablets ranging from 4 to 24 mg daily for 3 days. In these studies,
190 58% of the 170 evaluable patients had a complete response (no emetic episodes) on day 1. Two
191 studies showed the response rates for patients less than 12 years of age who received ZOFRAN
192 Tablets 4 mg 3 times a day to be similar to those in patients 12 to 18 years of age who received
193 ZOFRAN Tablets 8 mg 3 times daily. Thus, prevention of emesis in these pediatric patients was
194 essentially the same as for patients older than 18 years of age. Overall, ZOFRAN Tablets were
195 well tolerated in these pediatric patients.

Radiation-Induced Nausea and Vomiting: ***Total Body Irradiation:*** In a randomized, double-blind study in 20 patients, ZOFRAN Tablets (8 mg given 1.5 hours before each fraction of radiotherapy for 4 days) were significantly more effective than placebo in preventing vomiting induced by total body irradiation. Total body irradiation consisted of 11 fractions (120 cGy per fraction) over 4 days for a total of 1,320 cGy. Patients received 3 fractions for 3 days, then 2 fractions on day 4.

Single High-Dose Fraction Radiotherapy: Ondansetron was significantly more effective than metoclopramide with respect to complete control of emesis (0 emetic episodes) in a double-blind trial in 105 patients receiving single high-dose radiotherapy (800 to 1,000 cGy) over an anterior or posterior field size of $\geq$80 cm^2 to the abdomen. Patients received the first dose of ZOFRAN Tablets (8 mg) or metoclopramide (10 mg) 1 to 2 hours before radiotherapy. If radiotherapy was given in the morning, 2 additional doses of study treatment were given (1 tablet late afternoon and 1 tablet before bedtime). If radiotherapy was given in the afternoon, patients took only 1 further tablet that day before bedtime. Patients continued the oral medication on a 3 times a day basis for 3 days.

Daily Fractionated Radiotherapy: Ondansetron was significantly more effective than prochlorperazine with respect to complete control of emesis (0 emetic episodes) in a double-blind trial in 135 patients receiving a 1- to 4-week course of fractionated radiotherapy (180 cGy doses) over a field size of $\geq$100 cm^2 to the abdomen. Patients received the first dose of ZOFRAN Tablets (8 mg) or prochlorperazine (10 mg) 1 to 2 hours before the patient received the first daily radiotherapy fraction, with 2 subsequent doses on a 3 times a day basis. Patients continued the oral medication on a 3 times a day basis on each day of radiotherapy.

Postoperative Nausea and Vomiting: Surgical patients who received ondansetron 1 hour before the induction of general balanced anesthesia (barbiturate: thiopental, methohexital, or thiamylal; opioid: alfentanil, sufentanil, morphine, or fentanyl; nitrous oxide; neuromuscular blockade: succinylcholine/curare or gallamine and/or vecuronium, pancuronium, or atracurium; and supplemental isoflurane or enflurane) were evaluated in 2 double-blind studies (1 US study, 1 foreign) involving 865 patients. ZOFRAN Tablets (16 mg) were significantly more effective than placebo in preventing postoperative nausea and vomiting.

The study populations in all trials thus far consisted of women undergoing inpatient surgical procedures. No studies have been performed in males. No controlled clinical study comparing ZOFRAN Tablets to ZOFRAN Injection has been performed.

INDICATIONS AND USAGE

1. Prevention of nausea and vomiting associated with highly emetogenic cancer chemotherapy, including cisplatin $\geq$50 mg/m^2.
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.
4. 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 Tablets, ZOFRAN ODT Orally Disintegrating Tablets, and ZOFRAN Oral Solution are recommended even where the incidence of postoperative nausea and/or vomiting is low.

CONTRAINDICATIONS

ZOFRAN Tablets, ZOFRAN ODT Orally Disintegrating Tablets, and ZOFRAN Oral Solution 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 distension.

Information for Patients: ***Phenylketonurics:*** Phenylketonuric patients should be informed that ZOFRAN ODT Orally Disintegrating Tablets contain phenylalanine (a component of aspartame). Each 4-mg and 8-mg orally disintegrating tablet contains <0.03 mg phenylalanine.

Patients should be instructed not to remove ZOFRAN ODT Tablets from the blister until just prior to dosing. The tablet should not be pushed through the foil. With dry hands, the blister backing should be peeled completely off the blister. The tablet should be gently removed and immediately placed on the tongue to dissolve and be swallowed with the saliva. Peelable illustrated stickers are affixed to the product carton that can be provided with the prescription to ensure proper use and handling of the product.

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 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.

Use in Surgical Patients: The coadministration of ondansetron had no effect on the pharmacokinetics and pharmacodynamics of temazepam.

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/day, respectively. Ondansetron was not mutagenic in standard tests for mutagenicity. Oral administration of ondansetron up to 15 mg/kg/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 daily oral doses up to 15 and 30 mg/kg/day, respectively, 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 4 years of age or younger (see CLINICAL PHARMACOLOGY and DOSAGE AND ADMINISTRATION sections for use in pediatric patients 4 to 18 years of age).

Geriatric Use: Of the total number of subjects enrolled in cancer chemotherapy-induced and postoperative nausea and vomiting in US- and foreign-controlled clinical trials, for which there were subgroup analyses, 938 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

The following have been reported as adverse events in clinical trials of patients treated with ondansetron, the active ingredient of ZOFRAN. A causal relationship to therapy with ZOFRAN has been unclear in many cases.

Chemotherapy-Induced Nausea and Vomiting: The adverse events in Table 5 have been reported in ≥5% of adult patients receiving a single 24-mg ZOFRAN Tablet in 2 trials. These patients were receiving concurrent highly emetogenic cisplatin-based chemotherapy regimens (cisplatin dose ≥50 mg/m^2).

Table 5. Principal Adverse Events in US Trials: Single Day Therapy With 24-mg ZOFRAN Tablets (Highly Emetogenic Chemotherapy)

Event	Ondansetron 24 mg q.d. n = 300	Ondansetron 8 mg b.i.d. n = 124	Ondansetron 32 mg q.d. n = 117
Headache	33 (11%)	16 (13%)	17 (15%)
Diarrhea	13 (4%)	9 (7%)	3 (3%)

The adverse events in Table 6 have been reported in ≥5% of adults receiving either 8 mg of ZOFRAN Tablets 2 or 3 times a day for 3 days or placebo in 4 trials. These patients were receiving concurrent moderately emetogenic chemotherapy, primarily cyclophosphamide-based regimens.

Table 6. Principal Adverse Events in US Trials: 3 Days of Therapy With 8-mg ZOFRAN Tablets (Moderately Emetogenic Chemotherapy)

Event	Ondansetron 8 mg b.i.d. n = 242	Ondansetron 8 mg t.i.d. n = 415	Placebo n = 262
Headache	58 (24%)	113 (27%)	34 (13%)
Malaise/fatigue	32 (13%)	37 (9%)	6 (2%)
Constipation	22 (9%)	26 (6%)	1 (<1%)
Diarrhea	15 (6%)	16 (4%)	10 (4%)
Dizziness	13 (5%)	18 (4%)	12 (5%)

Central Nervous System: There have been rare reports consistent with, but not diagnostic of, extrapyramidal reactions in patients receiving ondansetron.

Hepatic: In 723 patients receiving cyclophosphamide-based chemotherapy in US clinical trials, AST and/or ALT values have been reported to exceed twice the upper limit of normal in approximately 1% to 2% of patients receiving ZOFRAN Tablets. The increases were transient and did not appear to be related to dose or duration of therapy. On repeat exposure, similar transient elevations in transaminase values occurred in some courses, but symptomatic hepatic disease did

not occur. The role of cancer chemotherapy in these biochemical changes cannot be clearly determined.

There have been reports of liver failure and death in patients with cancer receiving concurrent medications including potentially hepatotoxic cytotoxic chemotherapy and antibiotics. The etiology of the liver failure is unclear.

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

Other: Rare cases of anaphylaxis, bronchospasm, tachycardia, angina (chest pain), hypokalemia, electrocardiographic alterations, vascular occlusive events, and grand mal seizures have been reported. Except for bronchospasm and anaphylaxis, the relationship to ZOFRAN was unclear.

Radiation-Induced Nausea and Vomiting: The adverse events reported in patients receiving ZOFRAN Tablets and concurrent radiotherapy were similar to those reported in patients receiving ZOFRAN Tablets and concurrent chemotherapy. The most frequently reported adverse events were headache, constipation, and diarrhea.

Postoperative Nausea and Vomiting: The adverse events in Table 7 have been reported in ≥5% of patients receiving ZOFRAN Tablets at a dosage of 16 mg orally in clinical trials. With the exception of headache, 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 7. Frequency of Adverse Events From Controlled Studies With ZOFRAN Tablets (Postoperative Nausea and Vomiting)

Adverse Event	Ondansetron 16 mg (n = 550)	Placebo (n = 531)
Wound problem	152 (28%)	162 (31%)
Drowsiness/sedation	112 (20%)	122 (23%)
Headache	49 (9%)	27 (5%)
Hypoxia	49 (9%)	35 (7%)
Pyrexia	45 (8%)	34 (6%)
Dizziness	36 (7%)	34 (6%)
Gynecological disorder	36 (7%)	33 (6%)
Anxiety/agitation	33 (6%)	29 (5%)
Bradycardia	32 (6%)	30 (6%)
Shiver(s)	28 (5%)	30 (6%)
Urinary retention	28 (5%)	18 (3%)
Hypotension	27 (5%)	32 (6%)
Pruritus	27 (5%)	20 (4%)

357 Preliminary observations in a small number of subjects suggest a higher incidence of
358 headache when ZOFRAN ODT Orally Disintegrating Tablets are taken with water, when
359 compared to without water.
360 **Observed During Clinical Practice:** In addition to adverse events reported from clinical
361 trials, the following events have been identified during post-approval use of oral formulations of
362 ZOFRAN. Because they are reported voluntarily from a population of unknown size, estimates of
363 frequency cannot be made. The events have been chosen for inclusion due to a combination of
364 their seriousness, frequency of reporting, or potential causal connection to ZOFRAN.
365 ***General:*** Flushing. Rare cases of hypersensitivity reactions, sometimes severe (e.g.,
366 anaphylaxis/anaphylactoid reactions, angioedema, bronchospasm, shortness of breath,
367 hypotension, laryngeal edema, stridor) have also been reported. Laryngospasm, shock, and
368 cardiopulmonary arrest have occurred during allergic reactions in patients receiving injectable
369 ondansetron.
370 ***Hepatobiliary:*** Liver enzyme abnormalities
371 ***Lower Respiratory:*** Hiccups
372 ***Neurology:*** Oculogyric crisis, appearing alone, as well as with other dystonic reactions
373 ***Skin:*** Urticaria

374 **DRUG ABUSE AND DEPENDENCE**
375 Animal studies have shown that ondansetron is not discriminated as a benzodiazepine nor does
376 it substitute for benzodiazepines in direct addiction studies.

377 **OVERDOSAGE**
378 There is no specific antidote for ondansetron overdose. Patients should be managed with
379 appropriate supportive therapy. Individual intravenous doses as large as 150 mg and total daily
380 intravenous doses as large as 252 mg have been inadvertently administered without significant
381 adverse events. These doses are more than 10 times the recommended daily dose.
382 In addition to the adverse events listed above, the following events have been described in the
383 setting of ondansetron overdose: "Sudden blindness" (amaurosis) of 2 to 3 minutes' duration plus
384 severe constipation occurred in 1 patient that was administered 72 mg of ondansetron
385 intravenously as a single dose. Hypotension (and faintness) occurred in a patient that took 48 mg
386 of ZOFRAN Tablets. Following infusion of 32 mg over only a 4-minute period, a vasovagal
387 episode with transient second-degree heart block was observed. In all instances, the events
388 resolved completely.

389 **DOSAGE AND ADMINISTRATION**
390 **Instructions for Use/Handling ZOFRAN ODT Orally Disintegrating Tablets:** Do not
391 attempt to push ZOFRAN ODT Tablets through the foil backing. With dry hands, PEEL BACK
392 the foil backing of 1 blister and GENTLY remove the tablet. IMMEDIATELY place the
393 ZOFRAN ODT Tablet on top of the tongue where it will dissolve in seconds, then swallow with
394 saliva. Administration with liquid is not necessary.

395 **Prevention of Nausea and Vomiting Associated With Highly Emetogenic Cancer**
396 **Chemotherapy:** The recommended adult oral dosage of ZOFRAN is a single 24-mg tablet
397 administered 30 minutes before the start of single-day highly emetogenic chemotherapy, including
398 cisplatin ≥50 mg/m^2. Multiday, single-dose administration of ZOFRAN 24-mg Tablets has not
399 been studied.
400 ***Pediatric Use:*** There is no experience with the use of 24-mg ZOFRAN Tablets in pediatric
401 patients.
402 ***Geriatric Use:*** The dosage recommendation is the same as for the general population.
403 **Prevention of Nausea and Vomiting Associated With Moderately Emetogenic**
404 **Cancer Chemotherapy:** The recommended adult oral dosage is one 8-mg ZOFRAN Tablet or
405 one 8-mg ZOFRAN ODT Tablet or 10 mL (2 teaspoonfuls equivalent to 8 mg of ondansetron) of
406 ZOFRAN Oral Solution given twice a day. The first dose should be administered 30 minutes
407 before the start of emetogenic chemotherapy, with a subsequent dose 8 hours after the first dose.
408 One 8-mg ZOFRAN Tablet or one 8-mg ZOFRAN ODT Tablet or 10 mL (2 teaspoonfuls
409 equivalent to 8 mg of ondansetron) of ZOFRAN Oral Solution should be administered twice a day
410 (every 12 hours) for 1 to 2 days after completion of chemotherapy.
411 ***Pediatric Use:*** For pediatric patients 12 years of age and older, the dosage is the same as for
412 adults. For pediatric patients 4 through 11 years of age, the dosage is one 4-mg ZOFRAN Tablet
413 or one 4-mg ZOFRAN ODT Tablet or 5 mL (1 teaspoonful equivalent to 4 mg of ondansetron) of
414 ZOFRAN Oral Solution given 3 times a day. The first dose should be administered 30 minutes
415 before the start of emetogenic chemotherapy, with subsequent doses 4 and 8 hours after the first
416 dose. One 4-mg ZOFRAN Tablet or one 4-mg ZOFRAN ODT Tablet or 5 mL (1 teaspoonful
417 equivalent to 4 mg of ondansetron) of ZOFRAN Oral Solution should be administered 3 times a
418 day (every 8 hours) for 1 to 2 days after completion of chemotherapy.
419 ***Geriatric Use:*** The dosage is the same as for the general population.
420 **Prevention of Nausea and Vomiting Associated With Radiotherapy, Either Total**
421 **Body Irradiation, or Single High-Dose Fraction or Daily Fractions to the Abdomen:**
422 The recommended oral dosage is one 8-mg ZOFRAN Tablet or one 8-mg ZOFRAN ODT
423 Tablet or 10 mL (2 teaspoonfuls equivalent to 8 mg of ondansetron) of ZOFRAN Oral Solution
424 given 3 times a day.
425 *For total body irradiation*, one 8-mg ZOFRAN Tablet or one 8-mg ZOFRAN ODT Tablet or
426 10 mL (2 teaspoonfuls equivalent to 8 mg of ondansetron) of ZOFRAN Oral Solution should be
427 administered 1 to 2 hours before each fraction of radiotherapy administered each day.
428 *For single high-dose fraction radiotherapy to the abdomen*, one 8-mg ZOFRAN Tablet or one
429 8-mg ZOFRAN ODT Tablet or 10 mL (2 teaspoonfuls equivalent to 8 mg of ondansetron) of
430 ZOFRAN Oral Solution should be administered 1 to 2 hours before radiotherapy, with subsequent
431 doses every 8 hours after the first dose for 1 to 2 days after completion of radiotherapy.
432 *For daily fractionated radiotherapy to the abdomen*, one 8-mg ZOFRAN Tablet or one 8-mg
433 ZOFRAN ODT Tablet or 10 mL (2 teaspoonfuls equivalent to 8 mg of ondansetron) of ZOFRAN

434 Oral Solution should be administered 1 to 2 hours before radiotherapy, with subsequent doses
435 every 8 hours after the first dose for each day radiotherapy is given.
436 ***Pediatric Use:*** There is no experience with the use of ZOFRAN Tablets, ZOFRAN ODT
437 Tablets, or ZOFRAN Oral Solution in the prevention of radiation-induced nausea and vomiting
438 in pediatric patients.
439 ***Geriatric Use:*** The dosage recommendation is the same as for the general population.
440 **Postoperative Nausea and Vomiting:** The recommended dosage is 16 mg given as two 8-mg
441 ZOFRAN Tablets or two 8-mg ZOFRAN ODT Tablets or 20 mL (4 teaspoonfuls equivalent to
442 16 mg of ondansetron) of ZOFRAN Oral Solution 1 hour before induction of anesthesia.
443 ***Pediatric Use:*** There is no experience with the use of ZOFRAN Tablets, ZOFRAN ODT
444 Tablets, or ZOFRAN Oral Solution in the prevention of postoperative nausea and vomiting in
445 pediatric patients.
446 ***Geriatric Use:*** The dosage is the same as for the general population.
447 **Dosage Adjustment for Patients With Impaired Renal Function:** The dosage
448 recommendation is the same as for the general population. There is no experience beyond first-day
449 administration of ondansetron.
450 **Dosage Adjustment for Patients With Impaired Hepatic Function:** In patients with
451 severe hepatic impairment (Child-Pugh[2] score of 10 or greater), clearance is reduced and apparent
452 volume of distribution is increased with a resultant increase in plasma half-life. In such patients, a
453 total daily dose of 8 mg should not be exceeded.

454 **HOW SUPPLIED**
455 ZOFRAN Tablets, 4 mg (ondansetron HCl dihydrate equivalent to 4 mg of ondansetron), are
456 white, oval, film-coated tablets engraved with "Zofran" on one side and "4" on the other in daily
457 unit dose packs of 3 tablets (NDC 0173-0446-04), bottles of 30 tablets (NDC 0173-0446-00), and
458 unit dose packs of 100 tablets (NDC 0173-0446-02).
459 ZOFRAN Tablets, 8 mg (ondansetron HCl dihydrate equivalent to 8 mg of ondansetron), are
460 yellow, oval, film-coated tablets engraved with "Zofran" on one side and "8" on the other in daily
461 unit dose packs of 3 tablets (NDC 0173-0447-04), bottles of 30 tablets (NDC 0173-0447-00), and
462 unit dose packs of 100 tablets (NDC 0173-0447-02).
463 **Bottles: Store between 2° and 30°C (36° and 86°F). Protect from light. Dispense in tight,**
464 **light-resistant container as defined in the USP.**
465 **Unit Dose Packs: Store between 2° and 30°C (36° and 86°F). Protect from light. Store**
466 **blisters in cartons.**
467 ZOFRAN Tablets, 24 mg (ondansetron HCl dihydrate equivalent to 24 mg of ondansetron), are
468 pink, oval, film-coated tablets engraved with "GX CF7" on one side and "24" on the other in daily
469 unit dose packs of 1 tablet (NDC 0173-0680-00)
470 **Store between 2° and 30°C (36° and 86°F).**

ZOFRAN ODT Orally Disintegrating Tablets, 4 mg (as 4 mg ondansetron base) are white, round and plano-convex tablets debossed with a"Z4" on one side in unit dose packs of 30 tablets (NDC 0173-0569-00).

ZOFRAN ODT Orally Disintegrating Tablets, 8 mg (as 8 mg ondansetron base) are white, round and plano-convex tablets debossed with a "Z8" on one side in unit dose packs of 10 tablets (NDC 0173-0570-04) and 30 tablets (NDC 0173-0570-00).

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

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

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

REFERENCE

1. Britto MR, Hussey EK, Mydlow P, et al. Effect of enzyme inducers on ondansetron (OND) metabolism in humans. *Clin Pharmacol Ther* 1997;61:228.
2. 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.
3. Villikka K, Kivisto KT, Neuvonen PJ. The effect of rifampin on the pharmacokinetics of oral and intravenous ondansetron. *Clin Pharmacol Ther* 1999;65:377-381.
4. De Witte JL, Schoenmaekers B, Sessler DI, et al. *Anesth Analg* 2001;92:1319-1321.
5. Arcioni R, della Rocca M, Romanò R, et al. *Anesth Analg* 2002;94:1553-1557.

GlaxoSmithKline

GlaxoSmithKline
Research Triangle Park, NC 27709

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

ZOFRAN ODT Orally Disintegrating Tablets:
Manufactured for GlaxoSmithKline
Research Triangle Park, NC 27709
by Cardinal Health
Blagrove, Swindon, Wiltshire, UK SN5 8RU

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-103/S-017

20-605/S-004

20-781/S-001

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

Division of Gastrointestinal & Coagulation Drug Products

CONSUMER SAFETY OFFICER REVIEW

Application Number and Name of Drug:

NDA 20-103/S-017; Zofran (ondansetron) Tablets
NDA 20-605/S-004; Zofran (ondansetron) Oral Solution
NDA 20-781/S-001; Zofran ODT (ondansetron) Orally-Disintegrating Tablets

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 20-103, approved December 31, 1992, provides for Zofran Tablets. NDA 20-605, approved January 24, 1997, provides for Zofran Oral Solution. NDA 20-781, approved [on draft labeling] January 27, 1999 provides for Zofran ODT Orally-Disintegrating Tablets. All three products share a common package insert and are indicated for the following indications:

1. Prevention of nausea and vomiting associated with highly emetogenic cancer chemotherapy, including cisplatin $\geq$ 50 mg/m^2,

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 patents 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.

(Zofran is also approved in injection and injection premixed formulations; these injectable products share a common package insert.)

NDAs 20-103/S-017, 20-605/S-004, and 20-781/S-001 were submitted October 13, 1999 as "Changes Being Effected" and provide for the following revisions to the package insert:

1. A new subsection, entitled "Observed During Clinical Practice," within the ADVERSE REACTIONS section,

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

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

Note: The FPL submitted with this supplement also includes the revisions necessitated by the approval on draft of NDA 20-781 (provides for the Zofran ODT Orally-Disintegrating Tablet) and the approval on draft of NDA 20-103/S-015 (provides for a new indication: prevention of nausea and vomiting due to highly emetogenic cancer chemotherapy).

Review

The submitted insert (**October 1999, RL-755**) was compared to the currently approved insert (**June 1999; approved on draft with NDA 20-103/S-015, August 27, 1999**). In addition to minor editorial and formatting changes which do not affect the meaning of any information being conveyed, the following revisions have been made:

Note: Throughout this review, added text is indicated by a double underline; deletions are indicated by a strikethrough.

1. Overall: The header has been editorially revised to reflect the availability of a new dosage form, the Zofran ODT Orally-Disintegrating Tablets. (There are numerous other minor editorial revisions throughout the insert which reflect the approval of Zofran ODT as well.)

   This is an acceptable revision.

2. DESCRIPTION section:

   a. This section has been modified to include a description of the active ingredient, the chemical structure, and the empirical formula of Zofran ODT.

      This revision was requested in the January 27, 1999 approval letter for NDA 20-781, therefore, it is acceptable.

   b. The following paragraph has been added (next to the last paragraph):

      "Each 4-mg ZOFRAN ODT Orally Disintegrating Tablet for oral administration contains 4 mg ondansetron base. Each 8-mg ZOFRAN ODT Orally Disintegrating Tablet for oral administration contains 8 mg ondansetron base. Each ZOFRAN ODT Tablet also contains

the inactive ingredients aspartame, gelatin, mannitol, methylparaben sodium, propylparaben sodium, and strawberry flavor. ZOFRAN ODT Tablets are a freeze-dried, orally administered formulation of ondansetron which rapidly disintegrates on the tongue and does not require water to aid dissolution or swallowing."

This revision was requested in the January 27, 1999 approval letter for NDA 20-781, therefore, it is acceptable.

3. CLINICAL PHARMACOLOGY section, Pharmacokinetics subsection: The text [illegible] in this subsection has been revised as follows:

[illegible] Four and 8-mg doses of either ZOFRAN Oral Solution or ZOFRAN ODT Orally Disintegrating Tablets are bioequivalent to corresponding doses of ZOFRAN Tablets and may be used interchangeably."

This revision was requested in the January 27, 1999 approval letter for NDA 20-781, therefore, it is acceptable.

4. PRECAUTIONS section:

A new "Information for Patients" subsection has been added. It reads,

"**Information for Patients *Phenylketonurics:*** Phenylketonuric patients should be informed that ZOFRAN ODT Orally Disintegrating Tablets contain phenylalanine (a component of aspartame). Each 4-mg and 8-mg orally disintegrating tablet contains <0.03 mg phenylalanine.

Patients should be instructed not to remove ZOFRAN ODT Tablets from the blister until just prior to dosing. The tablet should not be pushed through the foil. With dry hands, the blister backing should be peeled completely off the blister. The tablet should be gently removed and immediately placed on the tongue to dissolve and be swallowed with the saliva. Peelable illustrated stickers are affixed to the product carton that can be provided with the prescription to ensure proper use and handling of the product."

This revision was requested in the January 27, 1999 approval letter for NDA 20-781, therefore, it is acceptable.

5. ADVERSE REACTIONS section:

a. New text has been added to the beginning of this section as follows: "The following have been reported as adverse events in clinical trials of patients treated with ondansetron, the active ingredient of ZOFRAN. A causal relationship to therapy with ZOFRAN has been unclear in many cases."

   On October 20, 1999 Dr. Hugo Gallo-Torres, Medical Team Leader, indicated that this change is acceptable.

b. The following text has been added immediately after the table in this section:

   "Preliminary observations in a small number of subjects suggest a higher incidence of headache when ZOFRAN ODT Orally Disintegrating Tablets are taken with water, when compared to without water."

   This revision was requested in the January 27, 1999 approval letter for NDA 20-781, therefore, it is acceptable.

c. A new subsection entitled "Observed During Clinical Practice" has been added. It reads, "**Observed During Clinical Practice:** In addition to adverse events reported from clinical trials, the following events have been identified during post-approval use of oral 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.

   General: Flushing. Rare cases of hypersensitivity reactions, sometimes severe (e.g., anaphylaxis/anaphylactoid reactions, angioedema, bronchospasm, shortness of breath, hypotension, laryngeal edema, stridor) have also been reported. Laryngospasm, shock, and cardiopulmonary arrest have occurred during allergic reactions in patients receiving injectable ondansetron.
   Hepatobiliary: Liver enzyme abnormalities
   Lower Respiratory: Hiccups
   Neurology: Oculogyric crisis, appearing alone, as well as with other dystonic reactions
   Skin: Urticaria"

   According to Dr. Gallo-Torres on October 20, 1999, these changes are acceptable.

6. OVERDOSAGE section: This section now reads,

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

daily intravenous doses as large as 252 mg have been inadvertently administered 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 a patient that took 48 mg of ZOFRAN Tablets. Following infusion of 32 mg over only a 4-minute period, a vasovagal episode with transient second degree heart block was observed. In all instances, the events resolved completely."

According to Dr. Gallo-Torres on October 20, 1999, these changes are acceptable.

7. DOSAGE AND ADMINISTRATION section:

   a. The following text has been added to the beginning of this section:

      "**Instructions for Use/Handling ZOFRAN ODT Orally Disintegrating Tablets:** Do not attempt to push ZOFRAN ODT Tablets through the foil backing. With dry hands, PEEL BACK the foil backing of one blister and GENTLY remove the tablet. IMMEDIATELY place the ZOFRAN ODT Tablet on top of the tongue where it will dissolve in seconds, then swallow with saliva. Administration with liquid is not necessary."

      This revision was requested in the January 27, 1999 approval letter for NDA 20-781, therefore, it is acceptable.

   b. In the Prevention of Nausea and Vomiting Associated With Highly Emetogenic Cancer Chemotherapy subsection, Pediatric Use subsection, the applicant has replaced the words "pediatric patients" with the word

      The applicant should be requested to retain the former wording, in accordance with 21 CFR 201.57 (f)(9). (For consistency, the applicant should be requested to replace with "pediatric patients" throughout the insert.)

   c. This section has been editorially revised to reflect the availability of the Zofran 4 and 8 mg ODT Orally Disintegrating Tablets.

      These changes are acceptable.

8. HOW SUPPLIED section:

a. This section has been modified to reflect the availability of the 4 and 8 mg Zofran ODT Orally-Disintegrating Tablets.

   This is an acceptable editorial revision.

b. For the 24 mg tablet, the phrases have been deleted.

   The Division agreed to this revision in a September 7, 1999 teleconference, therefore, it is acceptable.

9. Manufacturer/Distributor Block:

   The following has been added to this section:

   ZOFRAN Tablets and Oral Solution:
   Glaxo Wellcome Inc., Research Triangle Park, NC 27709

   ZOFRAN ODT Orally Disintegrating Tablets:
   Manufactured for Glaxo Wellcome Inc.
   Research Triangle Park, NC 27709
   by Scherer DDS
   Blagrove, Swindon, Wiltshire, UK SN5 8RU

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

   These are acceptable editorial revisions.

Conclusions

The submitted labeling is acceptable and an approval letter should be drafted. However, at the next printing of the package insert, the applicant should replace all instances of the word with the words "pediatric patients." The Division may be notified of this change in the next annual report.

Regulatory Health Project Manager

cc:
Original NDAs
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

GlaxoWellcome

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NDA NO. 20-103 REF. NO. 017

NDA SUPPL FOR

Changes are acceptable 10/20/99 HG-T

October 13, 1999

CENTER FOR DRUG EVALUATION AND RESEARCH
REC'D
OCT 14 1999
HFD-180

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 20-103; ZOFRAN® (ondansetron hydrochloride) Tablets
NDA 20-781; ZOFRAN® ODT™ (ondansetron) Orally Disintegrating Tablets
NDA 20-605; ZOFRAN® (ondansetron hydrochloride) Oral Solution
Special Supplement: Changes Being Effected, Labeling

Dear Dr. Talarico:

Reference is made to our New Drug Applications for Zofran Tablets, ODT Tablets, and Oral Solution.

We have completed an extensive review of all spontaneous reports for the oral and injectable Zofran products. The attached revised labeling for the oral products includes a new subsection "Observed During Clinical Practice" under the ADVERSE REACTIONS section. All adverse reactions reported during postmarketing will be included in this section. This section includes several new adverse reactions for which supporting data is being supplied under ATTACHMENTS 2-8. In addition, changes were made to the OVERDOSAGE section to provide consistency in wording between the oral and injectable package inserts. The revised injectable 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 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.

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

Telephone
919 483 2100

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

Sincerely,

Craig A. Metz

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

NDA 20-103/S-017
NDA 20-781/S-001
NDA 20-605/S-004

Glaxo Wellcome Inc.
Attention: Craig A. Metz, Ph.D.
Director, Regulatory Affairs
Five Moore Drive
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
20-103	S-017	Zofran (ondansetron) Tablets
20-605	S-004	Zofran (ondansetron) Oral Solution
20-781	S-001	Zofran ODT (ondansetron) Orally-Disintegrating Tablets

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) a new subsection, entitled "Observed During Clinical Practice," within the ADVERSE REACTIONS section, 2) addition of several new adverse reactions in the Observed During Clinical Practice subsection, and 3) 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,

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 20-103, 20-781, 20-605
HFD-180/Div. Files
HFD-180/M.McNeil
DISTRICT OFFICE

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SUPPLEMENT ACKNOWLEDGEMENT (AC)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

Form Approved: OMB No. 0910-0297
Expiration Date: 04-30-01

USER FEE COVER SHEET

See Instructions on Reverse Side Before Completing This Form.

1. APPLICANT'S NAME AND ADDRESS

Glaxo Wellcome Inc.
Five Moore Drive
Research Triangle Park, NC 27709

2. TELEPHONE NUMBER *(Include Area Code)*

(919) 483-2100

3. PRODUCT NAME

ZOFRAN (ondansetron hydrochloride) Tablets

4. DOES THIS APPLICATION REQUIRE CLINICAL DATA FOR APPROVAL? No
IF YOUR RESPONSE IS "NO" AND THIS IS FOR A SUPPLEMENT, STOP HERE AND SIGN THIS FORM.

IF RESPONSE IS "YES", CHECK THE APPROPRIATE RESPONSE BELOW:

☐ THE REQUIRED CLINICAL DATA ARE CONTAINED IN THE APPLICATION.

☐ THE REQUIRED CLINICAL DATA ARE SUBMITTED BY REFERENCE TO _____
(APPLICATION NO. CONTAINING THE DATA).

5. USER FEE I.D. NUMBER

6. LICENSE NUMBER / NDA NUMBER

NDA 20-103

7. IS THIS APPLICATION COVERED BY ANY OF THE FOLLOWING USER FEE **EXCLUSIONS**? IF SO, CHECK THE APPLICABLE EXCLUSION.

☐ A LARGE VOLUME PARENTERAL DRUG PRODUCT APPROVED UNDER SECTION 505 OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT BEFORE 9/1/92 *(Self Explanatory)*

☒ A 505(b)(2) APPLICATION THAT DOES NOT REQUIRE A FEE. *(See item 7, reverse side before checking box.)*

☐ THE APPLICATION QUALIFIES FOR THE ORPHAN EXCEPTION UNDER SECTION 736(a)(1)(E) of the Federal Food, Drug, and Cosmetic Act *(See item 7, reverse side before checking box.)*

☐ THE APPLICATION IS A PEDIATRIC SUPPLEMENT THAT QUALIFIES FOR THE EXCEPTION UNDER SECTION 736(a)(1)(F) of the Federal Food, drug, and Cosmetic Act *(See item 7, reverse side before checking box.)*

☐ THE APPLICATION IS SUBMITTED BY A STATE OR FEDERAL GOVERNMENT ENTITY FOR A DRUG THAT IS NOT DISTRIBUTED COMMERCIALLY *(Self Explanatory)*

FOR BIOLOGICAL PRODUCTS ONLY

☐ WHOLE BLOOD OR BLOOD COMPONENT FOR TRANSFUSION

☐ A CRUDE ALLERGENIC EXTRACT PRODUCT

☐ AN APPLICATION FOR A BIOLOGICAL PRODUCT FOR FURTHER MANUFACTURING USE ONLY

☐ AN "IN VITRO" DIAGNOSTIC BIOLOGICAL PRODUCT LICENSED UNDER SECTION 351 OF THE PHS ACT

☐ BOVINE BLOOD PRODUCT FOR TOPICAL APPLICATION LICENSED BEFORE 9/1/92

8. HAS A WAIVER OF AN APPLICATION FEE BEEN GRANTED FOR THIS APPLICATION? ☐ YES ☒ NO
(See reverse side if answered YES)

A completed form must be signed and accompany each new drug or biologic product application and each new supplement. If payment is sent by U.S. mail or courier, please include a copy of this completed form with payment.

Public reporting burden for this collection of information is estimated to average 30 minutes per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

DHHS, Reports Clearance Officer
Paperwork Reduction Project (0910-0297)
Hubert H. Humphrey Building, Room 531-H
200 Independence Avenue, S.W.
Washington, DC 20201

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

Please **DO NOT RETURN** this form to this address.

SIGNATURE OF AUTHORIZED COMPANY REPRESENTATIVE	TITLE	DATE
Craig A. Metz **Craig A. Metz, Ph.D.**	**Director, Regulatory Affairs**	**October 13, 1999**

FORM FDA 3397 (5/98)

NDA 20-103

FINAL PRINTED LABELING
ZOFRAN® Tablets
(ondansetron hydrochloride)

Package Insert

Labeling: ORIG SCR | DM
NDA No: 20-103 Rc'd. 10/99
Reviewed by: M. McNeil
4/11/00

6 Page(s) Withheld

_____ § 552(b)(4) Trade Secret / Confidential

✓ § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

20-103 S017

Withheld Track Number: Administrative- 20-781

S001

20605 S004