CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

20-103/S025
20-781/S008
20-605/S008

Trade Name: Zofran Tablets
Zofran ODT
Zofran Oral Solution

Generic Name: odansetron hydrochloride
odansetron
odansetron hydrochloride

Sponsor: GlaxoSmithKline

Approval Date: December 27, 2005

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-103/S025

20-781/S008

20-605/S008

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APPLICATION NUMBER:

20-103/S025

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20-605/S008

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

NDA 20-103/S-025
NDA 20-781/S-008
NDA 20-605/S-008

GlaxoSmithKline
Attention: Ellen S. Cutler, Senior Director, Regulatory Affairs
2301 Renaissance Boulevard
Building 510, P.O. Box 61540
King of Prussia, PA 19406-2772

Dear Ms. Cutler:

Please refer to your supplemental new drug application as follow:

NDA Number	Name of Drug Product	Supplement Number	Date of Supplement	Date of Receipt
20-103	Zofran® (ondansetron hydrochloride) Tablets	025	June 29, 2005	June 30, 2005
20-781	Zofran ODT® (ondansetron) Orally Disintegrating Tablets	008	June 29, 2005	June 30, 2005
20-605	Zofran® (ondansetron hydrochloride) Oral Solution	008	June 29, 2005	June 30, 2005

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

We acknowledge receipt of your faxed submission dated December 22, 2005.

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

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

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

Please submit an electronic version of the FPL according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDA.* Alternatively, you may submit 20 paper copies of the FPL as soon as it is available but no more than 30 days after it is printed. Individually mount 15

of the copies on heavy-weight paper or similar material. For administrative purposes, designate these submissions "**FPL for approved supplement NDA 20-103/S-025, NDA 20-781/S-008, and NDA 20-605/S-008.**" Approval of these submissions by FDA is not required before the labeling is used.

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

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

Sincerely,

{See appended electronic signature page}

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

Enclosure

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

/s/

Brian Harvey
12/27/2005 01:50:56 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-103/S025

20-781/S008

20-605/S008

LABELING

PRESCRIBING INFORMATION

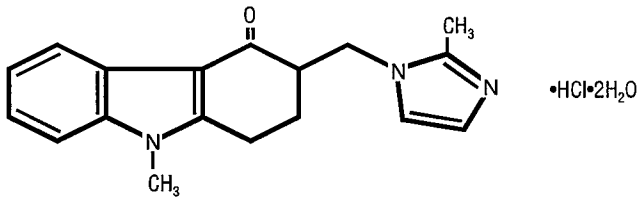
ZOFRAN®
(ondansetron hydrochloride)
Tablets

ZOFRAN ODT®
(ondansetron)
Orally Disintegrating Tablets

ZOFRAN®
(ondansetron hydrochloride)
Oral Solution

DESCRIPTION

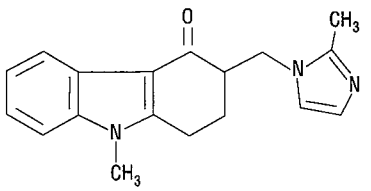
The active ingredient in ZOFRAN Tablets and ZOFRAN Oral Solution is ondansetron hydrochloride (HCl) as the dihydrate, the racemic form of ondansetron and a selective blocking agent of the serotonin 5-HT_3 receptor type. Chemically it is (±) 1, 2, 3, 9-tetrahydro-9-methyl-3-[(2-methyl-1H-imidazol-1-yl)methyl]-4H-carbazol-4-one,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



The empirical formula is $C_{18}H_{19}N_3O•HCl•2H_2O$, 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 as the parent compound from the urine. 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.

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

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

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

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

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

Plasma protein binding of ondansetron as measured in vitro was 70% to 76% over the 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 ≥50 mg/m^2. Steroid administration was excluded from these clinical trials. More than 90% of patients receiving a cisplatin dose ≥50 mg/m^2 in the historical placebo comparator experienced vomiting in the absence of antiemetic therapy.

The first trial compared oral doses of ondansetron 24 mg once a day, 8 mg twice a day, and 32 mg once a day in 357 adult cancer patients receiving chemotherapy regimens containing cisplatin ≥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 ≥ 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:

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 1-2 Emetic episodes More than 2 emetic episodes/withdrawn	 20 (61%) 6 (18%) 7 (21%)	 2 (6%) 8 (24%) 24 (71%)	 <0.001 <0.001
Median number of emetic episodes	0.0	Undefined†	
Median time to first emetic episode (h)	Undefined‡	6.5	

* The first dose was administered 30 minutes before the start of emetogenic chemotherapy, with a subsequent dose 8 hours after the first dose. An 8-mg ZOFRAN Tablet was administered twice a day for 2 days after completion of chemotherapy.

† Median undefined since at least 50% of the patients were withdrawn or had more than 2 emetic episodes.

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

In 1 double-blind US study in 336 patients, ZOFRAN Tablets 8 mg administered twice a day were as effective as ZOFRAN Tablets 8 mg administered 3 times a day in preventing nausea and vomiting induced by cyclophosphamide-based chemotherapy containing either methotrexate or 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 4:

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

* The first dose was administered 30 minutes before the start of emetogenic chemotherapy, with a subsequent dose 8 hours after the first dose. An 8-mg ZOFRAN Tablet was administered twice a day for 2 days after completion of chemotherapy.

† The first dose was administered 30 minutes before the start of emetogenic chemotherapy, with subsequent doses 4 and 8 hours after the first dose. An 8-mg ZOFRAN Tablet was administered 3 times a day for 2 days after completion of chemotherapy.

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

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

Re-treatment: In uncontrolled trials, 148 patients receiving cyclophosphamide-based chemotherapy were re-treated with ZOFRAN Tablets 8 mg 3 times daily of oral ondansetron during subsequent chemotherapy for a total of 396 re-treatment courses. No emetic episodes occurred in 314 (79%) of the re-treatment courses, and only 1 to 2 emetic episodes occurred in 43 (11%) of the re-treatment courses.

Pediatric Studies: Three open-label, uncontrolled, foreign trials have been performed with 182 pediatric patients 4 to 18 years old with cancer who were given a variety of cisplatin or noncisplatin regimens. In these foreign trials, the initial dose of ZOFRAN® (ondansetron HCl) Injection ranged from 0.04 to 0.87 mg/kg for a total dose of 2.16 to 12 mg. This was followed by the administration of ZOFRAN Tablets ranging from 4 to 24 mg daily for 3 days. In these studies, 58% of the 170 evaluable patients had a complete response (no emetic episodes) on day 1. Two studies showed the response rates for patients less than 12 years of age who received ZOFRAN Tablets 4 mg 3 times a day to be similar to those in patients 12 to 18 years of age who received ZOFRAN Tablets 8 mg 3 times daily. Thus, prevention of emesis in these pediatric patients was essentially the same as for patients older than 18 years of age. Overall, ZOFRAN Tablets were 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%)

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.

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

Special Senses: Eye Disorders: Cases of transient blindness, predominantly during intravenous administration, have been reported. These cases of transient blindness were reported to resolve within a few minutes up to 48 hours.

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 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 1 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.

DOSAGE AND ADMINISTRATION

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 1 blister and GENTLY remove the tablet. IMMEDIATELY place the ZOFRAN ODT Tablet on top of the tongue where it will dissolve in seconds, then swallow with saliva. Administration with liquid is not necessary.

Prevention of Nausea and Vomiting Associated With Highly Emetogenic Cancer Chemotherapy: The recommended adult oral dosage of ZOFRAN is a single 24-mg tablet administered 30 minutes before the start of single-day highly emetogenic chemotherapy, including cisplatin ≥50 mg/m^2. Multiday, single-dose administration of ZOFRAN 24-mg Tablets has not been studied.

Pediatric Use: There is no experience with the use of 24-mg ZOFRAN Tablets in pediatric patients.

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

Prevention of Nausea and Vomiting Associated With Moderately Emetogenic Cancer Chemotherapy: The recommended adult oral dosage is one 8-mg ZOFRAN Tablet or one 8-mg ZOFRAN ODT Tablet or 10 mL (2 teaspoonfuls equivalent to 8 mg of ondansetron) of ZOFRAN Oral Solution given twice a day. The first dose should be administered 30 minutes before the start of emetogenic chemotherapy, with a subsequent dose 8 hours after the first dose. One 8-mg ZOFRAN Tablet or one 8-mg ZOFRAN ODT Tablet or 10 mL (2 teaspoonfuls equivalent to 8 mg of ondansetron) of ZOFRAN Oral Solution should be administered twice a day (every 12 hours) for 1 to 2 days after completion of chemotherapy.

Pediatric Use: For pediatric patients 12 years of age and older, the dosage is the same as for adults. For pediatric patients 4 through 11 years of age, the dosage is one 4-mg ZOFRAN Tablet or one 4-mg ZOFRAN ODT Tablet or 5 mL (1 teaspoonful equivalent to 4 mg of ondansetron) of ZOFRAN Oral Solution given 3 times a day. The first dose should be administered 30 minutes before the start of emetogenic chemotherapy, with subsequent doses 4 and 8 hours after the first dose. One 4-mg ZOFRAN Tablet or one 4-mg ZOFRAN ODT Tablet or 5 mL (1 teaspoonful equivalent to 4 mg of ondansetron) of ZOFRAN Oral Solution should be administered 3 times a day (every 8 hours) for 1 to 2 days after completion of chemotherapy.

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

Prevention of Nausea and Vomiting Associated With Radiotherapy, Either Total Body Irradiation, or Single High-Dose Fraction or Daily Fractions to the Abdomen: The recommended oral dosage is one 8-mg ZOFRAN Tablet or one 8-mg ZOFRAN ODT Tablet or 10 mL (2 teaspoonfuls equivalent to 8 mg of ondansetron) of ZOFRAN Oral Solution given 3 times a day.

For total body irradiation, one 8-mg ZOFRAN Tablet or one 8-mg ZOFRAN ODT Tablet or 10 mL (2 teaspoonfuls equivalent to 8 mg of ondansetron) of ZOFRAN Oral Solution should be administered 1 to 2 hours before each fraction of radiotherapy administered each day.

For single high-dose fraction radiotherapy to the abdomen, one 8-mg ZOFRAN Tablet or one 8-mg ZOFRAN ODT Tablet or 10 mL (2 teaspoonfuls equivalent to 8 mg of ondansetron) of ZOFRAN Oral Solution should be administered 1 to 2 hours before radiotherapy, with subsequent doses every 8 hours after the first dose for 1 to 2 days after completion of radiotherapy.

For daily fractionated radiotherapy to the abdomen, one 8-mg ZOFRAN Tablet or one 8-mg ZOFRAN ODT Tablet or 10 mL (2 teaspoonfuls equivalent to 8 mg of ondansetron) of ZOFRAN Oral Solution should be administered 1 to 2 hours before radiotherapy, with subsequent doses every 8 hours after the first dose for each day radiotherapy is given.

Pediatric Use: There is no experience with the use of ZOFRAN Tablets, ZOFRAN ODT Tablets, or ZOFRAN Oral Solution in the prevention of radiation-induced nausea and vomiting in pediatric patients.

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

Postoperative Nausea and Vomiting: The recommended dosage is 16 mg given as two 8-mg ZOFRAN Tablets or two 8-mg ZOFRAN ODT Tablets or 20 mL (4 teaspoonfuls equivalent to 16 mg of ondansetron) of ZOFRAN Oral Solution 1 hour before induction of anesthesia.

Pediatric Use: There is no experience with the use of ZOFRAN Tablets, ZOFRAN ODT Tablets, or ZOFRAN Oral Solution in the prevention of postoperative nausea and vomiting in pediatric patients.

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

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

Dosage Adjustment for Patients With Impaired Hepatic Function: In patients with severe hepatic impairment (Child-Pugh[2] score of 10 or greater), clearance is reduced and apparent volume of distribution is increased with a resultant increase in plasma half-life. In such patients, a total daily dose of 8 mg should not be exceeded.

HOW SUPPLIED

ZOFRAN Tablets, 4 mg (ondansetron HCl dihydrate equivalent to 4 mg of ondansetron), are white, oval, film-coated tablets engraved with "Zofran" on one side and "4" on the other in daily unit dose packs of 3 tablets (NDC 0173-0446-04), bottles of 30 tablets (NDC 0173-0446-00), and unit dose packs of 100 tablets (NDC 0173-0446-02).

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

Unit Dose Packs: Store between 2° and 30°C (36° and 86°F). Protect from light. Store blisters in cartons.

ZOFRAN Tablets, 8 mg (ondansetron HCl dihydrate equivalent to 8 mg of ondansetron), are yellow, oval, film-coated tablets engraved with "Zofran" on one side and "8" on the other in daily

unit dose packs of 3 tablets (NDC 0173-0447-04), bottles of 30 tablets (NDC 0173-0447-00), and unit dose packs of 100 tablets (NDC 0173-0447-02).

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

Unit Dose Packs: Store between 2° and 30°C (36° and 86°F).

ZOFRAN Tablets, 24 mg (ondansetron HCl dihydrate equivalent to 24 mg of ondansetron), are pink, oval, film-coated tablets engraved with "GX CF7" on one side and "24" on the other in daily unit dose packs of 1 tablet (NDC 0173-0680-00)

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.

REFERENCES

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
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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June 2005 RL-2198

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-103/S025

20-781/S008

20-605/S008

MEDICAL REVIEW(S)

DIVISION OF GASTROENTEROLOGY DRUG PRODUCTS

MEDICAL OFFICER'S REVIEW
OF LABELING CHANGES

NDAs:	20-403/S-014 (Zofran Injection Premixed) 20-605/S-008 (Zofran Oral Solution) 20-103/S-025 (Zofran Tablets) 20-007/S-037 (Zofran Injection) 20-781/S-008 (Zofran ODT)
Sponsor:	GlaxoSmithKline (GSK) 2301 Renaissance Blvd. P.O. Box 61540 King of Prussia, PA 19406-2772
Date Submitted:	June 30, 2005
Drug Name:	Zofran® (Ondansetron)
Drug Class:	$5HT_3$ - Antagonist
Documents Reviewed:	Electronic Submission for Changes Being Effected in the Label
Division Director:	Brian E. Harvey, M.D., Ph.D.
Deputy Director:	Joyce Korvick, M.D., M.P.H.
Team Leader:	Ruyi He, M.D.
Medical Officer:	Lolita A. Lopez, M.D.

I. INTRODUCTION AND BACKGROUND

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

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

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

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

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

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

II. PROPOSED LABELING CHANGES

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

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

Special Senses: ~~-~~

Eye Disorders ~~-~~ b(4) b(4)

b(4)

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

However, reports of transient blindness in the 12 key cases reviewed had the event resolved within a couple of minutes up to a maximum of 48 hours. The sponsor based their labeling change on the three cases they considered pivotal (see Background and Introduction section above); therefore, they are proposing the language ' b(4) **. In this Medical Officer's opinion,** b(4) **these three cases** b(4) **transient blindness have been reported to resolve anytime within a few minutes for up to 48 hours as reported in the 12 key cases reviewed. The word** b(4) **should also be deleted. The proposed labeling change should read:**

b(4)

Special Senses: b(4)

b(4)

Eye Disorders b(4)

b(4)

III. MEDICAL OFFICER RECOMMENDATIONS

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

Special Senses: b(4)

Eye Disorders:

b(4)

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

/s/

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

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

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-103/S025

20-781/S008

20-605/S008

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

Division of Gastroenterology Products

PROJECT MANAGER'S REVIEW

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

Sponsor: GlaxoSmithKline

Material Reviewed:

Electronic final printed label (FPL) Package Inserts

Submission Date: June 29, 2005

Receipt Date: June 30, 2005

Background and Summary

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

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

Oral Formulations:
ZOFRAN® Tablets (NDA 20-103), approved December 31, 1992)
ZOFRAN® Oral Solution (NDA 20-605), approved January 24, 1997)
ZOFRAN ODT® Orally Disintegrating Tablets (NDA 20-781, approved January 27, 1999)

and

Injectable Formulations:
ZOFRAN® Injection (NDA 20-007, approved January 4, 1991)
ZOFRAN® Injection, Premixed (NDA 20-403, approved January 31, 1995).

All of the above NDAs share the following indications:

1. prevention of nausea and vomiting associated with highly emetogenic cancer chemotherapy;

2. prevention of nausea and vomiting associated with initial and repeat courses of moderately emetogenic cancer chemotherapy;

3. prevention of nausea and vomiting associated with radiotherapy in patients receiving either total body irradiation, single high-dose fraction to the abdomen, or daily fractions to the abdomen; and

4. prevention of postoperative nausea and/or vomiting.

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

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

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

Review

Package Insert

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

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

The following revisions were noted:

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

Comment: This is an acceptable revision.

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

b(4)

Special Senses: Eye Disorders: cases of transient blindness, predominantly during intravenous administration, have been reported. These cases of transient blindness

b(4)

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

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

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

The following changes were noted:

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

   Comment: This is an acceptable revision.

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

   Comment: These are acceptable revisions.

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

Special Senses: [redacted] b(4)
[redacted] Transient dizziness during or shortly after b(4)
I.V. infusion.
Eye Disorders: [redacted]
b(4)
[redacted]
b(4)

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

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

GlaxoSmithKline
GlaxoSmithKline
Research Triangle Park, NC 27709

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

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~~Month YEAR~~ June 2005 ~~RL-XXXX~~ RL-2197

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

Conclusions

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

Betsy Scroggs, PharmD
Regulatory Health Project Manager

Julieann DuBeau, MSN, RN
Chief, Project Management Staff

Drafted: BHS 12-05-2005
Revised/Initialed: BS/12-20-2005
Finalized: BHS/12-20-2005
Filename: C:\data\My Documents\NDA\Zofran SLRs\Final PM LR Inj & Oral.doc

PM LABELING REVIEW

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/s/

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

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

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

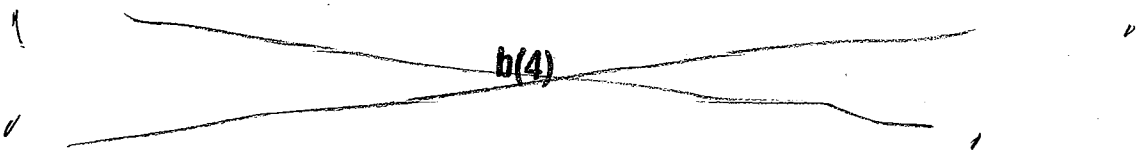
FACSIMILE TRANSMITTAL SHEET

DATE: December 21, 2005

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

DOCUMENT TO BE MAILED? NO

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



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

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

Betsy Scroggs, Pharm.D., RHPM

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Betsy Scroggs
12/21/2005 05:17:56 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

NDA 20-103
NDA 20-781
NDA 20-605

CBE-0 SUPPLEMENT

GlaxoSmithKline
Attention: Ellen S. Cutler, Senior Director, Regulatory Affairs
2301 Renaissance Boulevard
Building 510, P.O. Box 61540
King of Prussia, PA 19406-2772

Dear Ms. Cutler:

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

NDA Number	Name of Drug Product	Supplement Number	Date of Supplement	Date of Receipt
20-103	Zofran® (ondansetron hydrochloride) Tablets	025	June 29, 2005	June 30, 2005
20-781	Zofran ODT® (ondansetron) Orally Disintegrating Tablets	008	June 29, 2005	June 30, 2005
20-605	Zofran® (ondansetron hydrochloride) Oral Solution	008	June 29, 2005	June 30, 2005

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

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

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

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

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

Sincerely,

{See appended electronic signature page}

Betsy Scroggs, Pharm. D.
Regulatory Health Project Manager
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/s/

Betsy Scroggs
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