CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

20-103/S024

Trade Name: Zofran Tablets, 8mg

Generic Name: (ondansetron hydrochloride)

Sponsor: GlaxoSmithKline

Approval Date: February 18, 2005

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-103/S024

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-103/S024

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-103/SCS-024

GlaxoSmithKline
Attention: Kim Hughes
Five Moore Drive
PO Box 13398
Research Triangle Park, NC 27709-3398

Dear Ms. Hughes:

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

Name of Drug Product:	Zofran (ondansetron hydrochloride) Tablets, 8 mg
NDA Number:	20-103
Supplement number:	#S-024
Date of supplement:	October 19, 2004
Date of receipt:	October 20, 2004

This supplemental application provides for the deletion of the "protect from light" and related statements from the label, cartons, and blisters.

Your application was filed on December 18, 2004 in accordance with 21 CFR 314.101(a). The user fee goal date is February 20, 2005.

We completed our review of this application. This application is 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 draft package insert, draft bottle label (30s), display and tablets carton (3s and 100 unit-dose), Blister printmat (3s and 100 unit-dose), foil label (1), and physician sample pack submitted October 19, 2004.

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 this submission **"FPL for approved supplement NDA 20-103/S-024"**. Approval of this submission 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 Dr. Betsy Scroggs, Regulatory Health Project Manager at (301) 827-1250.

Sincerely,

{See appended electronic signature page}

Liang Zhou, Ph.D.
Chemistry Team Leader for the
Division of Gastrointestinal and Coagulation Drug Products
(HFD-180)
DNDC II, Office of New Drug Chemistry
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/

Liang Zhou
2/18/05 11:17:49 AM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-103/S024

LABELING

PRESCRIBING INFORMATION

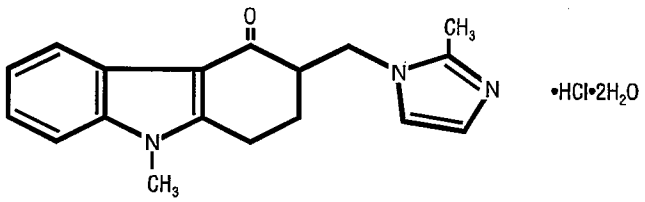
ZOFRAN®
(ondansetron hydrochloride)
Tablets

ZOFRAN ODT®
(ondansetron)
Orally Disintegrating Tablets

ZOFRAN®
(ondansetron hydrochloride)
Oral Solution

DESCRIPTION

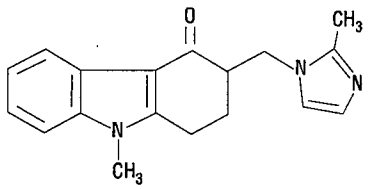
The active ingredient in ZOFRAN Tablets and ZOFRAN Oral Solution is ondansetron hydrochloride (HCl) as the dihydrate, the racemic form of ondansetron and a selective blocking agent of the serotonin 5-HT_3 receptor type. Chemically it is (±) 1, 2, 3, 9-tetrahydro-9-methyl-3-[(2-methyl-1H-imidazol-1-yl)methyl]-4H-carbazol-4-one,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

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

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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Month 2004 RL-XXXX

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
NDA 20-103/S024

CHEMISTRY REVIEW(S)

CHEMIST'S REVIEW # 2	1. Organization: HFD-180	2. NDA number: 20-103	
3. Name and Address of Applicant (City & State): GlaxoSmithKline P. O. Box 13398 Five Moore Drive Research Triangle Park, NC 27709-3398		4. AF Number: 5. Supplement(s)	
6. Name of Drug: ZOFRAN® Tablets	7. Nonproprietary Name: Ondansetron hydrochloride	Numbers	Dates
		SCS-024	10/19/2004
8. Supplement Provides for: Removal of the statement "Protect from light" from packaging components and associated labeling for ZOFRAN® (ondansetron hydrochloride) Tablets 8 mg, packaged in HDPE bottles and blister packs.		9. Amendments & Other (Reports, etc.) Dates: Annual Report Y-011 (2/27/04) CMC Review #1 (2/16/05)	
10. Pharmacological Category: 5-HT_3 Receptor Antagonist	11. How Dispensed: RX _X_ OTC	12. Related IND/NDA/DMF(s):	
13. Dosage Form: Tablet	14. Potency: 4 mg and 8 mg		
15. Chemical Name and Structure: 4*H*-carbazol-4-one, 1,2,3,9-Tetrahydro-9-methyl-3-[(2-methyl-1*H*-imidazol-1-yl)methyl]- , monohydrochloride, (±)-, dihydrate. For structure, see USAN 2000, pg. 518.		16. Records and Reports:	
		Current Yes __ No	
		Reviewed Yes __ No	
17. Comments: From a CMC perspective, adequate information has been provided to support approval of this supplement. Labeling issues associated with this supplement have been resolved (see labeling review, dated February 17, 2005). CC: NDA 20-103 HFD-180/Div File/NDA 20-103 HFD-181/BScroggs HFD-180/RFrankewich R/D init: LZhou			
18. Conclusions and Recommendations: This supplement may be approved.			
19. Reviewer			
Name: Raymond P. Frankewich, Ph.D.	Signature	Date Completed: February 17, 2005	

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

/s/

Ray Frankewich
2/17/05 06:24:20 PM
CHEMIST

Liang Zhou
2/18/05 09:38:42 AM
CHEMIST

Although the labels issues were raised in 1st CMC review, the labels was approved (refer to Reviewer's comments in his 2nd review). In my opinion

b(4)

, b(4) labeling review.

CHEMIST'S REVIEW # 1	1. Organization: HFD-180	2. NDA number: 20-103	
3. Name and Address of Applicant (City & State): GlaxoSmithKline P. O. Box 13398 Five Moore Drive Research Triangle Park, NC 27709-3398		4. AF Number: 5. Supplement(s)	
6. Name of Drug: ZOFRAN® Tablets	7. Nonproprietary Name: Ondansetron hydrochloride	Numbers	Dates
		SCS-024	10/19/2004
8. Supplement Provides for: Removal of the statement "Protect from light" from packaging components and associated labeling for ZOFRAN® (ondansetron hydrochloride) Tablets 8 mg, packaged in HDPE bottles and blister packs.		9. Amendments & Other (Reports, etc.) Dates: Annual Report Y-011 (2/27/04)	
10. Pharmacological Category: 5-HT_3 Receptor Antagonist	11.How Dispensed: RX _X_ OTC	12. Related IND/NDA/DMF(s):	
13.Dosage Form: Tablet	14. Potency: 4 mg and 8 mg		
15. Chemical Name and Structure: 4*H*-carbazol-4-one, 1,2,3,9-Tetrahydro-9-methyl-3-[(2-methyl-1*H*-imidazol-1-yl)methyl]- , monohydrochloride, (±)-, dihydrate. For structure, see USAN 2000, pg. 518.		16. Records and Reports: Current Yes __ No Reviewed Yes __ No	
17. Comments: From a CMC perspective, adequate information has been provided to support approval of this supplement. However, [redacted] b(4) This supplement is Approvable, pending resolution of labeling issues related to these changes. CC: NDA 20-103 HFD-180/Div File/NDA 20-103 HFD-181/BScroggs HFD-180/RFrankewich R/D init: LZhou			
18. Conclusions and Recommendations: This supplement is Approvable.			
19.Reviewer			
Name: Raymond P. Frankewich, Ph.D.	Signature	Date Completed: February 16, 2005	

4 Page(s) Withheld

✓ Trade Secret / Confidential (b4)

_____ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

Withheld Track Number: Chemistry- 20-103
S0261
Chem Draft 1

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/s/

Ray Frankewich
2/16/05 02:42:55 PM
CHEMIST

Liang Zhou
2/16/05 04:06:20 PM
CHEMIST
Pending Labels issues.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-103/S024

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

REGULATORY PROJECT MANAGER REVIEW

Application Number: NDA 20-103/SCS-024
Name of Drug: Zofran® (ondansetron) Tablets, 8 mg
Sponsor: GlaxoSmithKline

Material Reviewed

Submission Date: October 19, 2004

Receipt Date: October 20, 2004

Background and Summary Description: Zofran® was approved December 31, 1992 for the prevention of nausea and vomiting due to highly emetogenic chemotherapy.

Supplement #023, submitted May 19, 2004 to update the PRECAUTIONS and related sections of the label and was approved on November 24, 2004.

Supplement #024, submitted October 19, 2004 provides to remove the "Protect from light" statements from the packaging components and the associated labeling changes for Zofran® Tablets, 8 mg.

This proposed change applies to 8 mg tablets packaged in bottles and blisters.

The proposed labeling changes include removal of the "store blisters in cartons" statement for blisters and removal of the "dispense in light-resistant container" statement for bottles.

Deletions are shown as ~~strikeouts~~ and additions are shown as <u>double underlines</u>. The following revisions were noted.

1. <u>Package insert</u>

   The submitted draft package insert, identified as "Month 2004, RL-XXXX" was compared to the package insert, identified as "May 2004, RL-2082", which was approved with S-023 on November 24, 2004.

The HOW SUPPLIED section has been revised to read as follows:

"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). ~~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).

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). ~~Protect from light. Store blisters in cartons.~~**

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."

Comment: The last approved labeling update for strengthening the precautions section supercedes the label submitted to support this supplement, except for the changes to the HOW SUPPLIED section for which this supplement provides.

This revision is acceptable based CMC review dated February 16, 2005.

This change and the change made in the last approved supplement should be combined to provide for a comprehensive label.

2. Bottle label (30s)

The draft bottle label (30s), identified as "FPL-ZOF-001 Rev. 7/04" was compared to the bottle label, identified as "9137531 Rev. 9/01" submitted in NDA 20-103/Y-011 on February 27, 2004.

Revision made: The protect from light statement has been removed from the bottle label.

Comment: This is an acceptable revision based on the CMC review dated February 16, 2005.

3. Display and tablets carton (3s and 100 unit-dose)

The submitted draft display and tablets carton (3s and 100 unit-dose), identified as "AOO738 Rev. 8/04" and "AOO7506 Rev. 7/04" for the 3s and 100 unit-dose respectively were compared to the display and tablet carton (3s and 100 unit-dose), identified as "4149874 Rev. 902" and "4149847 Rev. 11/02" respectively submitted in NDA 20-103/Y-011 on February 27, 2004.

Revisions made: The protect from light statement has been removed from each carton-size.

Comment: These are acceptable revisions based on the CMC review dated February 16, 2005.

4. Blister printmat (3s and 100 unit-dose)

The submitted draft blister printmat, identified as "AOO7505 Rev. 8/04" and "AOO7703" for the 3s and 100 unit-dose blister printmats respectively were compared to the blister printmat, identified as "4149149 Rev. 4/02" and "4149137 Rev. 12/02" respectively submitted in NDA 20-103/Y-011 on February 27, 2004.

Comment: This is an acceptable revision based on the CMC review dated February 16, 2005.

5. Sample foil (1s)

The submitted draft 8 mg sample foil, identified as "AOO7530 Rev. 9/04" was compared to the 24 mg sample foil, identified as "4135091 Rev. 8/01" submitted in NDA 20-103/Y-011 on February 27, 2004.

Comment: This is an acceptable revision based on the CMC review dated February 27, 2005.

6. Physician sample pack

The submitted draft physician sample pack, identified as "AOO7507 Rev. 8/04" was compared to the physician sample pack, identified as "4149289 Rev. 11/02."

Comment: This is an acceptable revision.

Conclusions and Recommendations

Conclusions:
The submitted labeling is acceptable based on the Chemistry, Manufacturing and Controls review dated February 16, 2005.

Recommendation: An approval letter should be drafted.

Betsy Scroggs, Pharm.D.
Regulatory Health Project Manager

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/s/

Betsy Scroggs
2/17/05 04:57:53 PM
CSO