

CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

20007Orig1s041

Trade Name: ZOFRAN

Generic or Proper Name: Ondansetron Hydrochloride Injection

Sponsor: Glaxo Wellcome Manufacturing Pte Limited d/b/a
GlaxoSmithKline

Approval Date: July 7, 2011

Indication: ZOFRAN Injection is a 5-HT₃ receptor antagonist indicated:

- Prevention of nausea and vomiting associated with initial and repeat

courses of emetogenic cancer chemotherapy. (1.1)

- Prevention of postoperative nausea and/or vomiting. (1.2).

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RESEARCH**

APPLICATION NUMBER:

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APPROVAL LETTER



NDA 20-007/S-041
NDA 20-403/S-019

SUPPLEMENT APPROVAL

Glaxo Wellcome Manufacturing Pte Limited d/b/a GlaxoSmithKline
Attention: Eric Richards
Associated Director
1250 Collegeville Road UP4110
Collegeville, PA 19426

Dear Mr. Richards:

Please refer to your Supplemental New Drug Applications (sNDAs) dated and received June 28, 2010, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for the following:

NDA	Supplement	Drug Product
20-007	S-041	Zofran (ondansetron hydrochloride) Injection
20-403	S-019	Zofran (ondansetron hydrochloride) Injection Premixed

We acknowledge receipt of your amendments dated December 14, 2010, January 26, 2011, May 5, 2011, and July 7, 2011.

These “Prior Approval” supplemental new drug applications provide for the conversion of the package insert to Physician’s Labeling Rule (PLR) format.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(1)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>. Content of labeling must be identical to the enclosed labeling with the addition of any labeling changes in pending “Changes Being Effected” (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling.

Information on submitting SPL files using eLIST may be found in the guidance for industry titled “SPL Standard for Content of Labeling Technical Qs and As” at <http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf>.

The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications for this NDA, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in MS Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes and annotate each change. To facilitate review of your submission, provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit the following, in triplicate, (1) a cover letter requesting advisory comments, (2) the proposed materials in draft or mock-up form with annotated references, and (3) the package insert to:

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

You must submit final promotional materials and package insert(s), accompanied by a Form FDA 2253, at the time of initial dissemination or publication [21 CFR 314.81(b)(3)(i)]. Form FDA 2253 is available at <http://www.fda.gov/opacom/morechoices/fdaforms/cder.html>; instructions are provided on page 2 of the form. For more information about submission of promotional materials to the Division of Drug Marketing, Advertising, and Communications (DDMAC), see <http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm>.

REPORTING REQUIREMENTS

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 Heather Buck, Regulatory Project Manager, at (301) 796-1413.

Sincerely,

{See appended electronic signature page}

Andrew Mulberg, MD, FAAP, CPI
Deputy Directory
Division of Gastroenterology and Inborn Errors Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

ENCLOSURE: Content of Labeling

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

/s/

ANDREW E MULBERG
07/07/2011

**CENTER FOR DRUG EVALUATION AND
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APPLICATION NUMBER:

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LABELING

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use ZOFRAN safely and effectively. See full prescribing information for ZOFRAN.

ZOFRAN® (ondansetron hydrochloride) injection for intravenous use
Initial U.S. Approval: 1991

INDICATIONS AND USAGE

ZOFRAN Injection is a 5-HT₃ receptor antagonist indicated:

- Prevention of nausea and vomiting associated with initial and repeat courses of emetogenic cancer chemotherapy. (1.1)
- Prevention of postoperative nausea and/or vomiting. (1.2)

DOSAGE AND ADMINISTRATION

Prevention of nausea and vomiting associated with initial and repeat courses of emetogenic cancer chemotherapy (2.1):

Population	Age	ZOFRAN Injection Dosage	Intravenous Infusion Rate (30 min before the start of chemotherapy)
Adults	> 18 yrs	32 mg x 1 or 0.15 mg/kg x 3	over 15 min
Pediatrics	6 mos. – 18 yrs	0.15 mg/kg x 3	over 15 min

Prevention of Postoperative Nausea and/or Vomiting (2.2):

Population	Age	ZOFRAN Injection Dosage	Intravenous Infusion Rate
Adults	> 12 yrs	4 mg x 1	over 2 - 5 min
Pediatrics (> 40 kg)	1 mo. – 12 yrs	4 mg x 1	over 2 - 5 min
Pediatrics (≤ 40 kg)	1 mo. – 12 yrs	0.1 mg/kg x 1	over 2 - 5 min

- In patients with severe hepatic impairment, a total daily dose of 8 mg should not be exceeded. (2.4)

DOSAGE FORMS AND STRENGTHS

ZOFRAN Injection (2 mg/mL): 2 mL single dose vial and 20 mL multidose vials. (3)

CONTRAINDICATIONS

- Patients known to have hypersensitivity (e.g., anaphylaxis) to this product or any of its components. (4)
- Concomitant use of apomorphine. (4)

WARNINGS AND PRECAUTIONS

- Hypersensitivity reactions including anaphylaxis and bronchospasm, have been reported in patients who have exhibited hypersensitivity to other selective 5-HT₃ receptor antagonists. (5.1)
- Use in patients following abdominal surgery or in patients with chemotherapy-induced nausea and vomiting may mask a progressive ileus and/or gastric distention. (5.3)(5.4)
- Transient ECG changes including QT interval prolongation have been reported. (5.2)

ADVERSE REACTIONS

Chemotherapy-Induced Nausea and Vomiting –

- The most common adverse reactions (≥ 7%) in adults are diarrhea, headache, and fever. (6.1)

Postoperative Nausea and Vomiting –

- The most common adverse reaction (≥ 10%) which occurs at a higher frequency compared to placebo in adults is headache. (6.1)
- The most common adverse reaction (≥ 2%) which occurs at a higher frequency compared to placebo in pediatric patients 1 to 24 months of age is diarrhea. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact

GlaxoSmithKline at 1-888-825-5249 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- Apomorphine – profound hypotension and loss of consciousness. Concomitant use with ondansetron is contraindicated. (7.2)

See 17 for PATIENT COUNSELING INFORMATION

Revised: July 2011

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Prevention of Nausea and Vomiting Associated with Initial and Repeat Courses of Emetogenic Cancer Chemotherapy

ZOFRAN Injection is indicated for the prevention of nausea and vomiting associated with initial and repeat courses of emetogenic cancer chemotherapy, including high-dose cisplatin [see *Clinical Studies (14.1)*].

ZOFRAN is approved for patients aged 6 months and older.

1.2 Prevention of Postoperative Nausea and/or Vomiting

ZOFRAN Injection is indicated for the 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 in whom nausea and/or vomiting must be avoided postoperatively, ZOFRAN Injection is recommended even when the incidence of postoperative nausea and/or vomiting is low. For patients who do not receive prophylactic ZOFRAN Injection and experience nausea and/or vomiting postoperatively, ZOFRAN Injection may be given to prevent further episodes [see *Clinical Studies (14.3)*].

ZOFRAN is approved for patients aged 1 month and older.

2 DOSAGE AND ADMINISTRATION

2.1 Prevention of Nausea and Vomiting Associated with Initial and Repeat Courses of Emetogenic Chemotherapy

ZOFRAN Injection should be diluted in 50 mL of 5% Dextrose Injection or 0.9% Sodium Chloride Injection before administration.

Adults: The recommended adult intravenous dosage of ZOFRAN is a single 32-mg dose or three 0.15-mg/kg doses. A single 32-mg dose is infused over 15 minutes beginning 30 minutes before the start of emetogenic chemotherapy. Efficacy of the 32-mg single dose beyond 24 hours has not been established. The recommended infusion rate should not be exceeded [see *Overdosage(10)*]. With the three-dose (0.15-mg/kg) regimen, the first dose is infused over 15 minutes beginning 30 minutes before the start of emetogenic chemotherapy. Subsequent doses (0.15 mg/kg) are administered 4 and 8 hours after the first dose of ZOFRAN.

Pediatrics: For pediatric patients 6 months through 18 years of age, the intravenous dosage of ZOFRAN is three 0.15-mg/kg doses [see *Clinical Studies (14.1)* and *Clinical Pharmacology (12.3)*]. The first dose is to be administered 30 minutes before the start of moderately to highly emetogenic chemotherapy. Subsequent doses (0.15 mg/kg) are administered 4 and 8 hours after the first dose of ZOFRAN. The drug should be infused intravenously over 15 minutes.

2.2 Prevention of Postoperative Nausea and Vomiting

ZOFRAN Injection should not be mixed with solutions for which physical and chemical compatibility have not been established. In particular, this applies to alkaline solutions as a precipitate may form.

Adults: The recommended adult intravenous dosage of ZOFRAN is 4 mg *undiluted* administered intravenously in not less than 30 seconds, preferably over 2 to 5 minutes, immediately before induction of anesthesia, or postoperatively if the patient did not receive prophylactic antiemetics and experiences nausea and/or vomiting occurring within 2 hours after surgery. Alternatively, 4 mg *undiluted* may be administered intramuscularly as a single injection for adults. While recommended as a fixed dose for patients weighing more than 40 kg, few patients above 80 kg have been studied. In patients who do not achieve adequate control of postoperative nausea and vomiting following a single, prophylactic, preinduction, intravenous dose of ondansetron 4 mg, administration of a second intravenous dose of 4 mg ondansetron postoperatively does not provide additional control of nausea and vomiting.

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

2.3 Stability and Handling

After dilution, do not use beyond 24 hours. Although ZOFRAN Injection is chemically and physically stable when diluted as recommended, sterile precautions should be observed because diluents generally do not contain preservative.

ZOFRAN Injection is stable at room temperature under normal lighting conditions for 48 hours after dilution with the following intravenous fluids: 0.9% Sodium Chloride Injection, 5% Dextrose Injection, 5% Dextrose and 0.9% Sodium Chloride Injection, 5% Dextrose and 0.45% Sodium Chloride Injection, and 3% Sodium Chloride Injection.

Note: Parenteral drug products should be inspected visually for particulate matter and discoloration before administration whenever solution and container permit.

Precaution: Occasionally, ondansetron precipitates at the stopper/vial interface in vials stored upright. Potency and safety are not affected. If a precipitate is observed, resolubilize by shaking the vial vigorously.

2.4 Dosage Adjustment for Patients with Impaired Hepatic Function

In patients with severe hepatic impairment (Child-Pugh score of 10 or greater), a single maximal daily dose of 8 mg infused over 15 minutes beginning 30 minutes before the start of the emetogenic chemotherapy is recommended. There is no experience beyond first-day administration of ondansetron in these patients [*see Clinical Pharmacology (12.3)*].

3 DOSAGE FORMS AND STRENGTHS

ZOFRAN Injection, 2 mg/mL is a clear, colorless, nonpyrogenic, sterile solution available as a 2 mL single dose vial and 20 mL multidose vial.

4 CONTRAINDICATIONS

ZOFRAN Injection is contraindicated for patients known to have hypersensitivity (e.g., anaphylaxis) to this product or any of its components. Anaphylactic reactions have been reported in patients taking ondansetron. [*See Adverse Reactions (6.2)*].

The concomitant use of apomorphine with ondansetron is contraindicated based on reports of profound hypotension and loss of consciousness when apomorphine was administered with ondansetron.

5 WARNINGS AND PRECAUTIONS

5.1 Hypersensitivity Reactions

Hypersensitivity reactions, including anaphylaxis and bronchospasm, have been reported in patients who have exhibited hypersensitivity to other selective 5-HT₃ receptor antagonists.

5.2 Electrocardiographic Changes

Rarely and predominantly with intravenous ondansetron, transient ECG changes including QT/QTc interval prolongation have been reported.

5.3 Masking of Progressive Ileus and Gastric Distension

The use of ZOFRAN in patients following abdominal surgery or in patients with chemotherapy-induced nausea and vomiting may mask a progressive ileus and gastric distention.

5.4 Effect on Peristalsis

ZOFRAN is not a drug that stimulates gastric or intestinal peristalsis. It should not be used instead of nasogastric suction.

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

The following adverse events have been reported in clinical trials of adult patients treated with ondansetron, the active ingredient of intravenous ZOFRAN at a dosage of three 0.15-mg/kg doses or as a single 32-mg dose. A causal relationship to therapy with ZOFRAN (ondansetron) was unclear in many cases.

Chemotherapy-Induced Nausea and Vomiting:

Table 1. Adverse Reactions Reported in > 5% of Adult Patients Who Received Ondansetron at a Dosage of Three 0.15-mg/kg Doses or as a Single 32-mg Dose

Adverse Reaction	Number of Adult Patients With Reaction			
	ZOFTRAN Injection 0.15 mg/kg x 3 n = 419	ZOFTRAN Injection 32 mg x 1 n = 220	Metoclopramide n = 156	Placebo n = 34
Diarrhea	16%	8%	44%	18%
Headache	17%	25%	7%	15%
Fever	8%	7%	5%	3%

Cardiovascular: Rare cases of angina (chest pain), electrocardiographic alterations, hypotension, and tachycardia have been reported.

Gastrointestinal: Constipation has been reported in 11% of chemotherapy patients receiving multiday ondansetron.

Hepatic: In comparative trials in cisplatin chemotherapy patients with normal baseline values of aspartate transaminase (AST) and alanine transaminase (ALT), these enzymes have been reported to exceed twice the upper limit of normal in approximately 5% of patients. The increases were transient and did not appear to be related to dose or duration of therapy. On repeat exposure, similar transient elevations in transaminase values occurred in some courses, but symptomatic hepatic disease did not occur.

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

Neurological: There have been rare reports consistent with, but not diagnostic of, extrapyramidal reactions in patients receiving ZOFTRAN Injection, and rare cases of grand mal seizure.

Other: Rare cases of hypokalemia have been reported.

Postoperative Nausea and Vomiting: The adverse reactions in Table 2 have been reported in $\geq 2\%$ of adults receiving ondansetron at a dosage of 4 mg intravenous over 2 to 5 minutes in clinical trials.

Table 2. Adverse Reactions Reported in $\geq 2\%$ (and With Greater Frequency than the Placebo Group) of Adult Patients Receiving Ondansetron at a Dosage of 4 mg Intravenous over 2 to 5 Minutes

Adverse Reaction ^{a,b}	ZOFRAN Injection 4 mg Intravenous n = 547 patients	Placebo n = 547 patients
Headache	92 (17%)	77 (14%)
Drowsiness/sedation	44 (8%)	37 (7%)
Injection site reaction	21 (4%)	18 (3%)
Fever	10 (2%)	6 (1%)
Cold sensation	9 (2%)	8 (1%)
Pruritus	9 (2%)	3 (< 1%)
Paresthesia	9 (2%)	2 (< 1%)

^a Adverse Reactions: Rates of these reactions were not significantly different in the ondansetron and placebo groups.

^b Patients were receiving multiple concomitant perioperative and postoperative medications

Pediatric Use: Rates of adverse reactions were similar in both the ondansetron and placebo groups in pediatric patients receiving ondansetron (a single 0.1-mg/kg dose for pediatric patients weighing 40 kg or less, or 4 mg for pediatric patients weighing more than 40 kg) administered intravenously over at least 30 seconds. Diarrhea was seen more frequently in patients taking ZOFRAN (2%) compared to placebo (<1%) in the 1 month to 24 month age group. These patients were receiving multiple concomitant perioperative and postoperative medications.

6.2 Postmarketing Experience

The following adverse reactions have been identified during post-approval use of ondansetron. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. The reactions have been chosen for inclusion due to a combination of their seriousness, frequency of reporting, or potential causal connection to ondansetron.

Cardiovascular: Arrhythmias (including ventricular and supraventricular tachycardia, premature ventricular contractions, and atrial fibrillation), bradycardia, electrocardiographic alterations (including second-degree heart block, QT/QTc interval prolongation, and ST segment depression), palpitations, and syncope. Rarely and predominantly with intravenous ondansetron, transient ECG changes including QT/QTc interval prolongation have been reported [*see Warnings and Precautions (5.2)*].

General: Flushing. Rare cases of hypersensitivity reactions, sometimes severe (e.g., anaphylactic reactions, angioedema, bronchospasm, cardiopulmonary arrest, hypotension, laryngeal edema, laryngospasm, shock, shortness of breath, stridor) have also been reported. A

positive lymphocyte transformation test to ondansetron has been reported, which suggests immunologic sensitivity to ondansetron.

Hepatobiliary: Liver enzyme abnormalities have been reported. Liver failure and death have been reported in patients with cancer receiving concurrent medications including potentially hepatotoxic cytotoxic chemotherapy and antibiotics.

Local Reactions: Pain, redness, and burning at site of injection.

Lower Respiratory: Hiccups

Neurological: Oculogyric crisis, appearing alone, as well as with other dystonic reactions. Transient dizziness during or shortly after intravenous infusion.

Skin: Urticaria

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. Transient blurred vision, in some cases associated with abnormalities of accommodation have also been reported.

7 DRUG INTERACTIONS

7.1 Drugs Affecting Cytochrome P-450 Enzymes

Ondansetron does not appear to induce or inhibit the cytochrome P-450 drug-metabolizing enzyme system of the liver. Because ondansetron is metabolized by hepatic cytochrome P-450 drug-metabolizing enzymes (CYP3A4, CYP2D6, CYP1A2), inducers or inhibitors of these enzymes may change the clearance and, hence, the half-life of ondansetron [see *Clinical Pharmacology (12.3)*]. On the basis of limited available data, no dosage adjustment is recommended for patients on these drugs.

7.2 Apomorphine

Based on reports of profound hypotension and loss of consciousness when apomorphine was administered with ondansetron, the concomitant use of apomorphine with ondansetron is contraindicated [see *Contraindications (4)*].

7.3 Phenytoin, Carbamazepine, and Rifampin

In patients treated with potent inducers of CYP3A4 (i.e., phenytoin, carbamazepine, and rifampin), 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 [see *Clinical Pharmacology (12.3)*].

7.4 Tramadol

Although there are no data on pharmacokinetic drug interactions between ondansetron and tramadol, data from two small studies indicate that concomitant use of ondansetron may result in reduced analgesic activity of tramadol. Patients on concomitant ondansetron self administered tramadol more frequently in these studies, leading to an increased cumulative dose in patient controlled administration (PCA) of tramadol.

7.5 Chemotherapy

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

In a crossover study in 76 pediatric patients, intravenous ondansetron did not increase blood levels of high-dose methotrexate.

7.6 Temazepam

The coadministration of ondansetron had no effect on the pharmacokinetics and pharmacodynamics of temazepam.

7.7 Alfentanil and Atracurium

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.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category B. Reproduction studies have been performed in pregnant rats and rabbits at intravenous doses up to 4 mg/kg per day (approximately 1 and 2 times the recommended human intravenous dose of 32 mg/day, respectively, based on body surface area) 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.

8.3 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.

8.4 Pediatric Use

Little information is available about the use of ondansetron in pediatric surgical patients younger than 1 month of age. [See *Clinical Studies (14.2)*]. Little information is available about the use of ondansetron in pediatric cancer patients younger than 6 months of age. [See *Clinical Studies (14.1) and Dosage and Administration (2)*].

The clearance of ondansetron in pediatric patients 1 month to 4 months of age is slower and the half-life is ~2.5 fold longer than patients who are > 4 to 24 months of age. As a precaution, it is recommended that patients less than 4 months of age receiving this drug be closely monitored. [See *Clinical Pharmacology (12.3)*].

8.5 Geriatric Use

Of the total number of subjects enrolled in cancer chemotherapy-induced and postoperative nausea and vomiting in US- and foreign-controlled clinical trials, 862 were 65 years of age and over. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some

older individuals cannot be ruled out. Dosage adjustment is not needed in patients over the age of 65 [see *Clinical Pharmacology* (12.3)].

8.6 Hepatic Impairment

In patients with severe hepatic impairment (Child-Pugh score of 10 or greater), clearance is reduced and apparent volume of distribution is increased with a resultant increase in plasma half-life [see *Clinical Pharmacology* (12.3)]. In such patients, a total daily dose of 8 mg should not be exceeded [see *Dosage and Administration* (2.3)].

8.7 Renal Impairment

Although plasma clearance is reduced in patients with severe renal impairment (creatinine clearance < 30 mL/min), no dosage adjustment is recommended [see *Clinical Pharmacology* (12.3)].

9 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.

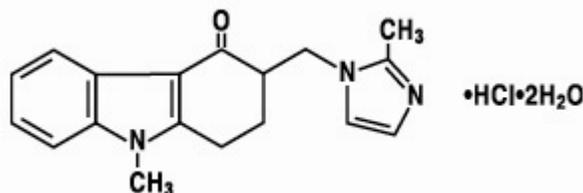
10 OVERDOSAGE

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 one patient that was administered 72 mg of ondansetron intravenously as a single dose. Hypotension (and faintness) occurred in another patient that took 48 mg of ondansetron hydrochloride 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.

11 DESCRIPTION

The active ingredient of ZOFRAN Injection is ondansetron hydrochloride, a selective blocking agent of the serotonin 5-HT₃ receptor type. Its chemical name 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 $C_{18}H_{19}N_3O \cdot HCl \cdot 2H_2O$, representing a molecular weight of 365.9.

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

Each 1 mL of aqueous solution in the 2 mL single-dose vial contains 2 mg of ondansetron as the hydrochloride dihydrate; 9 mg of sodium chloride, USP; and 0.5 mg of citric acid monohydrate, USP and 0.25 mg of sodium citrate dihydrate, USP as buffers in Water for Injection, USP.

Each 1 mL of aqueous solution in the 20 mL multidose vial contains 2 mg of ondansetron as the hydrochloride dihydrate; 8.3 mg of sodium chloride, USP; 0.5 mg of citric acid monohydrate, USP and 0.25 mg of sodium citrate dihydrate, USP as buffers; and 1.2 mg of methylparaben, NF and 0.15 mg of propylparaben, NF as preservatives in Water for Injection, USP.

ZOFRAN Injection is a clear, colorless, nonpyrogenic, sterile solution for intravenous use. The pH of the injection solution is 3.3 to 4.0.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Ondansetron is a selective 5-HT₃ receptor antagonist. While ondansetron's mechanism of action has not been fully characterized, it is not a dopamine-receptor antagonist.

12.2 Pharmacodynamics

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. In another study in six normal male volunteers, a 16-mg dose infused over 5 minutes showed no effect of the drug on cardiac output, heart rate, stroke volume, blood pressure, or electrocardiogram (ECG). However, no thorough QT study has been conducted with ondansetron. Multiday administration of ondansetron has been shown to slow colonic transit in normal volunteers. Ondansetron has no effect on plasma prolactin concentrations.

In a gender-balanced pharmacodynamic study (n = 56), ondansetron 4 mg administered intravenously or intramuscularly was dynamically similar in the prevention of nausea and vomiting using the ipecacuanha model of emesis.

12.3 Pharmacokinetics

In normal adult volunteers, the following mean pharmacokinetic data have been determined following a single 0.15-mg/kg intravenous dose.

Table 3. Pharmacokinetics in Normal Adult Volunteers

Age-group (years)	n	Peak Plasma Concentration (ng/mL)	Mean Elimination Half-life (h)	Plasma Clearance (L/h/kg)
19-40	11	102	3.5	0.381
61-74	12	106	4.7	0.319
≥ 75	11	170	5.5	0.262

Absorption: A study was performed in normal volunteers (n = 56) to evaluate the pharmacokinetics of a single 4-mg dose administered as a 5-minute infusion compared to a single intramuscular injection. Systemic exposure as measured by mean AUC were equivalent, with values of 156 [95% CI 136, 180] and 161 [95% CI 137, 190] ng•h/mL for intravenous and intramuscular groups, respectively. Mean peak plasma concentrations were 42.9 [95% CI 33.8, 54.4] ng/mL at 10 minutes after intravenous infusion and 31.9 [95% CI 26.3, 38.6] ng/mL at 41 minutes after intramuscular injection. In normal volunteers (19 to 39 years old, n = 23), the peak plasma concentration was 264 ng/mL following a single 32-mg dose administered as a 15-minute intravenous infusion.

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

Metabolism: 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. The metabolites are observed in the urine.

In vitro metabolism studies have shown that ondansetron is a substrate for multiple human hepatic cytochrome P-450 enzymes, including CYP1A2, CYP2D6, and CYP3A4. In terms of overall ondansetron turnover, CYP3A4 plays a predominant role while formation of the major in vivo metabolites is apparently mediated by CYP1A2. The role of CYP2D6 in ondansetron in vivo metabolism is relatively minor.

The pharmacokinetics of intravenous ondansetron did not differ between subjects who were poor metabolisers of CYP2D6 and those who were extensive metabolisers of CYP2D6, further supporting the limited role of CYP2D6 in ondansetron disposition in vivo.

Elimination: In normal volunteers (19 to 39 years old, n = 23), following a single 32-mg dose administered as a 15-minute intravenous infusion, the mean elimination half-life was 4.1 hours. Systemic exposure to 32 mg of ondansetron was not proportional to dose as measured by comparing dose-normalized AUC values to an 8-mg dose. This is consistent with a small decrease in systemic clearance with increasing plasma concentrations.

In adult cancer patients, the mean elimination half-life was 4.0 hours, and there was no difference in the multidose pharmacokinetics over a 4-day period.

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

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

Table 4. Pharmacokinetics in Pediatric Cancer Patients 1 Month to 18 Years of Age

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

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

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

In a study of 21 pediatric patients (3 to 12 years of age) who were undergoing surgery requiring anesthesia for a duration of 45 minutes to 2 hours, a single intravenous dose of ondansetron, 2 mg (3 to 7 years) or 4 mg (8 to 12 years), was administered immediately prior to anesthesia induction. Mean weight-normalized clearance and volume of distribution values in these pediatric surgical patients were similar to those previously reported for young adults. Mean terminal half-life was slightly reduced in pediatric patients (range, 2.5 to 3 hours) in comparison with adults (range, 3 to 3.5 hours).

In a study of 51 pediatric patients (1 month to 24 months of age) who were undergoing surgery requiring general anesthesia, a single intravenous dose of ondansetron, 0.1 or 0.2 mg/kg, was administered prior to surgery. As shown in Table 5, the 41 patients with pharmacokinetic

data were divided into 2 groups, patients 1 month to 4 months of age and patients 5 to 24 months of age, and are compared to pediatric patients 3 to 12 years of age.

Table 5. Pharmacokinetics in Pediatric Surgery Patients 1 Month to 12 Years of Age

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

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

In a study of 21 pediatric cancer patients (4 to 18 years of age) who received three intravenous doses of 0.15 mg/kg of ondansetron at 4-hour intervals, patients older than 15 years of age exhibited ondansetron pharmacokinetic parameters similar to those of adults.

Renal Impairment: Due to the very small contribution (5%) of renal clearance to the overall clearance, renal impairment was not expected to significantly influence the total clearance of ondansetron. However, ondansetron mean plasma clearance was reduced by about 41% in patients with severe renal impairment (creatinine clearance < 30 mL/min). This reduction in clearance is variable and was not consistent with an increase in half-life. No reduction in dose or dosing frequency in these patients is warranted.

Hepatic Impairment: 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 those without hepatic impairment. In patients with severe hepatic impairment (Child-Pugh 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.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenic effects were not seen in 2-year studies in rats and mice with oral ondansetron doses up to 10 and 30 mg/kg per day, respectively (approximately 2.5 and 3.8 times the recommended human intravenous dose of 32 mg/day, based on body surface area).

Ondansetron was not mutagenic in standard tests for mutagenicity.

Oral administration of ondansetron up to 15 mg/kg per day (approximately 3.8 times the recommended human intravenous dose, based on body surface area) did not affect fertility or general reproductive performance of male and female rats.

14 CLINICAL STUDIES

The clinical efficacy of ondansetron hydrochloride, the active ingredient of ZOFTRAN, was assessed in clinical trials as described below.

14.1 Chemotherapy-Induced Nausea and Vomiting

Adult Studies: In a double-blind study of three different dosing regimens of ZOFTRAN Injection, 0.015 mg/kg, 0.15 mg/kg, and 0.30 mg/kg, each given three times during the course of cancer chemotherapy, the 0.15-mg/kg dosing regimen was more effective than the 0.015-mg/kg dosing regimen. The 0.30-mg/kg dosing regimen was not shown to be more effective than the 0.15-mg/kg dosing regimen.

Cisplatin-Based Chemotherapy: In a double-blind study in 28 patients, ZOFTRAN Injection (three 0.15-mg/kg doses) was significantly more effective than placebo in preventing nausea and vomiting induced by cisplatin-based chemotherapy. Therapeutic response was as shown in Table 6.

Table 6. Therapeutic Response in Prevention of Chemotherapy-Induced Nausea and Vomiting in Single-Day Cisplatin Therapy^a in Adults

	ZOFTRAN Injection (0.15 mg/kg x 3)	Placebo	<i>P</i> Value ^b
Number of patients	14	14	
Treatment response			
0 Emetic episodes	2 (14%)	0 (0%)	
1-2 Emetic episodes	8 (57%)	0 (0%)	
3-5 Emetic episodes	2 (14%)	1 (7%)	
More than 5 emetic episodes/rescued	2 (14%)	13 (93%)	0.001
Median number of emetic episodes	1.5	Undefined ^c	
Median time to first emetic episode (h)	11.6	2.8	0.001
Median nausea scores (0-100) ^d	3	59	0.034
Global satisfaction with control of nausea and vomiting (0-100) ^e	96	10.5	0.009

^a Chemotherapy was high dose (100 and 120 mg/m²; ZOFTRAN Injection n = 6, placebo n = 5) or moderate dose (50 and 80 mg/m²; ZOFTRAN Injection n = 8, placebo n = 9). Other chemotherapeutic agents included fluorouracil, doxorubicin, and cyclophosphamide. There was no difference between treatments in the types of chemotherapy that would account for differences in response.

- ^b Efficacy based on "all patients treated" analysis.
- ^c Median undefined since at least 50% of the patients were rescued or had more than five emetic episodes.
- ^d Visual analog scale assessment of nausea: 0 = no nausea, 100 = nausea as bad as it can be.
- ^e Visual analog scale assessment of satisfaction: 0 = not at all satisfied, 100 = totally satisfied.

Ondansetron injection (0.15-mg/kg x 3 doses) was compared with metoclopramide (2 mg/kg x 6 doses) in a single-blind trial in 307 patients receiving cisplatin ≥ 100 mg/m² with or without other chemotherapeutic agents. Patients received the first dose of ondansetron or metoclopramide 30 minutes before cisplatin. Two additional ondansetron doses were administered 4 and 8 hours later, or five additional metoclopramide doses were administered 2, 4, 7, 10, and 13 hours later. Cisplatin was administered over a period of 3 hours or less. Episodes of vomiting and retching were tabulated over the period of 24 hours after cisplatin. The results of this study are summarized in Table 7.

Table 7. Therapeutic Response in Prevention of Vomiting Induced by Cisplatin (≥ 100 mg/m²) Single-Day Therapy^a in Adults

	ZOFTRAN Injection	Metoclopramide	P Value
Dose	0.15 mg/kg x 3	2 mg/kg x 6	
Number of patients in efficacy population	136	138	
Treatment response			
0 Emetic episodes	54 (40%)	41 (30%)	
1-2 Emetic episodes	34 (25%)	30 (22%)	
3-5 Emetic episodes	19 (14%)	18 (13%)	
More than 5 emetic episodes/rescued	29 (21%)	49 (36%)	
Comparison of treatments with respect to			
0 Emetic episodes	54/136	41/138	0.083
More than 5 emetic episodes/rescued	29/136	49/138	0.009
Median number of emetic episodes	1	2	0.005
Median time to first emetic episode (h)	20.5	4.3	< 0.001
Global satisfaction with control of nausea and vomiting (0-100) ^b	85	63	0.001
Acute dystonic reactions	0	8	0.005
Akathisia	0	10	0.002

^a In addition to cisplatin, 68% of patients received other chemotherapeutic agents, including cyclophosphamide, etoposide, and fluorouracil. There was no difference between treatments in the types of chemotherapy that would account for differences in response.

^b Visual analog scale assessment: 0 = not at all satisfied, 100 = totally satisfied.

In a stratified, randomized, double-blind, parallel-group, multicenter study, a single 32-mg dose of ondansetron was compared with three 0.15-mg/kg doses in patients receiving cisplatin doses of either 50 to 70 mg/m² or ≥ 100 mg/m². Patients received the first ondansetron dose 30 minutes before cisplatin. Two additional ondansetron doses were administered 4 and 8 hours later to the group receiving three 0.15-mg/kg doses. In both strata, significantly fewer patients on the single 32-mg dose than those receiving the three-dose regimen failed. The results are summarized in Table 8.

Table 8. Therapeutic Response in Prevention of Chemotherapy-Induced Nausea and Vomiting in 32 mg Single-Dose Therapy in Adults

	Ondansetron Dose		P Value
	0.15 mg/kg x 3	32 mg x 1	
High-dose cisplatin (≥ 100 mg/m²)			
Number of patients	100	102	
Treatment response			
0 Emetic episodes	41 (41%)	49 (48%)	0.315
1-2 Emetic episodes	19 (19%)	25 (25%)	
3-5 Emetic episodes	4 (4%)	8 (8%)	
More than 5 emetic episodes/rescued	36 (36%)	20 (20%)	0.009
Median time to first emetic episode (h)	21.7	23	0.173
Median nausea scores (0-100) ^a	28	13	0.004
Medium-dose cisplatin (50-70 mg/m²)			
Number of patients	101	93	
Treatment response			
0 Emetic episodes	62 (61%)	68 (73%)	0.083
1-2 Emetic episodes	11 (11%)	14 (15%)	
3-5 Emetic episodes	6 (6%)	3 (3%)	
More than 5 emetic episodes/rescued	22 (22%)	8 (9%)	0.011
Median time to first emetic episode (h)	Undefined ^b	Undefined	
Median nausea scores (0-100) ^a	9	3	0.131

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

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

Cyclophosphamide-Based Chemotherapy: In a double-blind, placebo-controlled study of ZOFTRAN Injection (three 0.15-mg/kg doses) in 20 patients receiving cyclophosphamide (500 to 600 mg/m²) chemotherapy, ZOFTRAN Injection was significantly more effective than placebo in preventing nausea and vomiting. The results are summarized in Table 9.

Table 9. Therapeutic Response in Prevention of Chemotherapy-Induced Nausea and Vomiting in Single-Day Cyclophosphamide Therapy^a in Adults

	ZOFTRAN Injection (0.15 mg/kg x 3)	Placebo	P Value ^b
Number of patients	10	10	
Treatment response			
0 Emetic episodes	7 (70%)	0 (0%)	0.001
1-2 Emetic episodes	0 (0%)	2 (20%)	
3-5 Emetic episodes	2 (20%)	4 (40%)	
More than 5 emetic episodes/rescued	1 (10%)	4 (40%)	0.131
Median number of emetic episodes	0	4	0.008
Median time to first emetic episode (h)	Undefined ^c	8.79	
Median nausea scores (0-100) ^d	0	60	0.001
Global satisfaction with control of nausea and vomiting (0-100) ^e	100	52	0.008

^a Chemotherapy consisted of cyclophosphamide in all patients, plus other agents, including fluorouracil, doxorubicin, methotrexate, and vincristine. There was no difference between treatments in the type of chemotherapy that would account for differences in response.

^b Efficacy based on "all patients treated" analysis.

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

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

^e Visual analog scale assessment of satisfaction: 0 = not at all satisfied, 100 = totally satisfied.

Re-treatment: In uncontrolled trials, 127 patients receiving cisplatin (median dose, 100 mg/m²) and ondansetron who had two or fewer emetic episodes were re-treated with ondansetron and chemotherapy, mainly cisplatin, for a total of 269 re-treatment courses (median, 2; range, 1 to 10). No emetic episodes occurred in 160 (59%), and two or fewer emetic episodes occurred in 217 (81%) re-treatment courses.

Pediatrics: Four open-label, noncomparative (one US, three foreign) trials have been performed with 209 pediatric cancer patients 4 to 18 years of age given a variety of cisplatin or noncisplatin regimens. In the three foreign trials, the initial ZOFTRAN Injection dose ranged from 0.04 to 0.87 mg/kg for a total dose of 2.16 to 12 mg. This was followed by the oral administration of ondansetron ranging from 4 to 24 mg daily for 3 days. In the US trial, ZOFTRAN was administered intravenously (only) in three doses of 0.15 mg/kg each for a total daily dose of 7.2 to 39 mg. In these studies, 58% of the 196 evaluable patients had a complete response (no emetic

episodes) on day 1. Thus, prevention of vomiting in these pediatric patients was essentially the same as for patients older than 18 years of age.

An open-label, multicenter, noncomparative trial has been performed in 75 pediatric cancer patients 6 to 48 months of age receiving at least one moderately or highly emetogenic chemotherapeutic agent. Fifty-seven percent (57%) were females; 67% were white, 18% were American Hispanic, and 15% were black patients. ZOFRAN was administered intravenously over 15 minutes in three doses of 0.15 mg/kg. The first dose was administered 30 minutes before the start of chemotherapy, the second and third doses were administered 4 and 8 hours after the first dose, respectively. Eighteen patients (25%) received routine prophylactic dexamethasone (i.e., not given as rescue). Of the 75 evaluable patients, 56% had a complete response (no emetic episodes) on day 1. Thus, prevention of vomiting in these pediatric patients was comparable to the prevention of vomiting in patients 4 years of age and older.

14.2 Prevention of Postoperative Nausea and/or Vomiting

Adults: Adult surgical patients who received ondansetron immediately before the induction of general balanced anesthesia (barbiturate: thiopental, methohexital, or thiamylal; opioid: alfentanil or fentanyl; nitrous oxide; neuromuscular blockade: succinylcholine/curare and/or vecuronium or atracurium; and supplemental isoflurane) were evaluated in two double-blind US studies involving 554 patients. ZOFRAN Injection (4 mg) intravenous given over 2 to 5 minutes was significantly more effective than placebo. The results of these studies are summarized in Table 10.

Table 10. Therapeutic Response in Prevention of Postoperative Nausea and Vomiting in Adult Patients

	Ondansetron 4 mg Intravenous	Placebo	<i>P</i> Value
Study 1			
Emetic episodes: Number of patients Treatment response over 24-h postoperative period	136	139	
0 Emetic episodes	103 (76%)	64 (46%)	< 0.001
1 Emetic episode	13 (10%)	17 (12%)	
More than 1 emetic episode/rescued	20 (15%)	58 (42%)	
Nausea assessments: Number of patients No nausea over 24-h postoperative period	134 56 (42%)	136 39 (29%)	
Study 2			
Emetic episodes: Number of patients Treatment response over 24-h postoperative period	136	143	
0 Emetic episodes	85 (63%)	63 (44%)	0.002
1 Emetic episode	16 (12%)	29 (20%)	
More than 1 emetic episode/rescued	35 (26%)	51 (36%)	
Nausea assessments: Number of patients No nausea over 24-h postoperative period	125 48 (38%)	133 42 (32%)	

The study populations in Table 10 consisted mainly of females undergoing laparoscopic procedures.

In a placebo-controlled study conducted in 468 males undergoing outpatient procedures, a single 4-mg intravenous ondansetron dose prevented postoperative vomiting over a 24-hour study period in 79% of males receiving drug compared to 63% of males receiving placebo ($P < 0.001$).

Two other placebo-controlled studies were conducted in 2,792 patients undergoing major abdominal or gynecological surgeries to evaluate a single 4-mg or 8-mg intravenous ondansetron dose for prevention of postoperative nausea and vomiting over a 24-hour study period. At the

4-mg dosage, 59% of patients receiving ondansetron versus 45% receiving placebo in the first study ($P < 0.001$) and 41% of patients receiving ondansetron versus 30% receiving placebo in the second study ($P = 0.001$) experienced no emetic episodes. No additional benefit was observed in patients who received intravenous ondansetron 8 mg compared to patients who received intravenous ondansetron 4 mg.

Pediatrics: Three double-blind, placebo-controlled studies have been performed (one US, two foreign) in 1,049 male and female patients (2 to 12 years of age) undergoing general anesthesia with nitrous oxide. The surgical procedures included tonsillectomy with or without adenoidectomy, strabismus surgery, herniorrhaphy, and orchidopexy. Patients were randomized to either single intravenous doses of ondansetron (0.1 mg/kg for pediatric patients weighing 40 kg or less, 4 mg for pediatric patients weighing more than 40 kg) or placebo. Study drug was administered over at least 30 seconds, immediately prior to or following anesthesia induction. Ondansetron was significantly more effective than placebo in preventing nausea and vomiting. The results of these studies are summarized in Table 11.

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

Treatment Response Over 24 Hours	Ondansetron n (%)	Placebo n (%)	<i>P</i> Value
Study 1			
Number of patients	205	210	
0 Emetic episodes	140 (68%)	82 (39%)	≤ 0.001
Failure ^a	65 (32%)	128 (61%)	
Study 2			
Number of patients	112	110	
0 Emetic episodes	68 (61%)	38 (35%)	≤ 0.001
Failure ^a	44 (39%)	72 (65%)	
Study 3			
Number of patients	206	206	
0 Emetic episodes	123 (60%)	96 (47%)	≤ 0.01
Failure ^a	83 (40%)	110 (53%)	
Nausea assessments ^b :			
Number of patients	185	191	
None	119 (64%)	99 (52%)	≤ 0.01

^a Failure was one or more emetic episodes, rescued, or withdrawn.

^b Nausea measured as none, mild, or severe.

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

14.3 Prevention of Further Postoperative Nausea and Vomiting

Adults: Adult surgical patients receiving general balanced anesthesia (barbiturate: thiopental, methohexital, or thiamylal; opioid: alfentanil or fentanyl; nitrous oxide; neuromuscular blockade: succinylcholine/curare and/or vecuronium or atracurium; and supplemental isoflurane) who received no prophylactic antiemetics and who experienced nausea and/or vomiting within 2 hours postoperatively were evaluated in two double-blind US studies involving 441 patients. Patients who experienced an episode of postoperative nausea and/or vomiting were given ZOFTRAN Injection (4 mg) intravenous over 2 to 5 minutes, and this was significantly more effective than placebo. The results of these studies are summarized in Table 12.

Table 12. Therapeutic Response in Prevention of Further Postoperative Nausea and Vomiting in Adult Patients

	Ondansetron 4 mg Intravenous	Placebo	<i>P</i> Value
Study 1			
Emetic episodes: Number of patients	104	117	
Treatment response 24 h after study drug			
0 Emetic episodes	49 (47%)	19 (16%)	< 0.001
1 Emetic episode	12 (12%)	9 (8%)	
More than 1 emetic episode/rescued	43 (41%)	89 (76%)	
Median time to first emetic episode (min) ^a	55.0	43.0	
Nausea assessments: Number of patients	98	102	
Mean nausea score over 24-h postoperative period ^b	1.7	3.1	
Study 2			
Emetic episodes: Number of patients	112	108	
Treatment response 24 h after study drug			
0 Emetic episodes	49 (44%)	28 (26%)	0.006
1 Emetic episode	14 (13%)	3 (3%)	
More than 1 emetic episode/rescued	49 (44%)	77 (71%)	
Median time to first emetic episode (min) ^a	60.5	34.0	
Nausea assessments: Number of patients	105	85	
Mean nausea score over 24-h postoperative period ^b	1.9	2.9	

^a After administration of study drug.

^b Nausea measured on a scale of 0-10 with 0 = no nausea, 10 = nausea as bad as it can be.

The study populations in Table 12 consisted mainly of women undergoing laparoscopic procedures.

Repeat Dosing in Adults: In patients who do not achieve adequate control of postoperative nausea and vomiting following a single, prophylactic, preinduction, intravenous dose of ondansetron 4 mg, administration of a second intravenous dose of ondansetron 4 mg

postoperatively does not provide additional control of nausea and vomiting.

Pediatrics: One double-blind, placebo-controlled, US study was performed in 351 male and female outpatients (2 to 12 years of age) who received general anesthesia with nitrous oxide and no prophylactic antiemetics. Surgical procedures were unrestricted. Patients who experienced two or more emetic episodes within 2 hours following discontinuation of nitrous oxide were randomized to either single intravenous doses of ondansetron (0.1 mg/kg for pediatric patients weighing 40 kg or less, 4 mg for pediatric patients weighing more than 40 kg) or placebo administered over at least 30 seconds. Ondansetron was significantly more effective than placebo in preventing further episodes of nausea and vomiting. The results of the study are summarized in Table 13.

Table 13. Therapeutic Response in Prevention of Further Postoperative Nausea and Vomiting in Pediatric Patients 2 to 12 Years of Age

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

^a Failure was one or more emetic episodes, rescued, or withdrawn.

16 HOW SUPPLIED/STORAGE AND HANDLING

ZOFRAN Injection, 2 mg/mL, is supplied as follows:

NDC 0173-0442-02 2 mL single-dose vials (Carton of 5)

NDC 0173-0442-00 20 mL multidose vials (Singles)

Storage: Store vials between 2° and 30°C (36° and 86°F). Protect from light.

17 PATIENT COUNSELING INFORMATION

- Inform patients that ZOFRAN may cause hypersensitivity reactions, some as severe as anaphylaxis and bronchospasm. The patient should report any signs and symptoms of hypersensitivity reactions, including fever, chills, rash, or breathing problems.
- The patient should report the use of all medications, especially apomorphine, to their health care provider. Concomitant use of apomorphine and ZOFRAN may cause a significant drop in blood pressure and loss of consciousness.
- Inform patients that ZOFRAN may cause headache, drowsiness/sedation, constipation, fever and diarrhea.



GlaxoSmithKline

Research Triangle Park, NC 27709

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July 2011

ZFJ:XPI

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

20007Orig1s041

MEDICAL REVIEW(S)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DIVISION OF GASTROENTEROLOGY PRODUCTS (DGP)
MEDICAL OFFICER'S SUPPLEMENTAL LABELING REVIEW

Application Number	NDA 20-007
Applicant	GlaxoSmithKline (GSK)
Date	November 8, 2010
Established Name	Ondansetron
Trade Name	Zofran
Therapeutic Class	Anti-emetic
Reviewer	Helen Sile, MD
Formulation(s)	Injection
Dosing Regimen(s)	<p>Adults Chemotherapy induced nausea and vomiting (CINV): single 32 mg IV administered 30 minutes prior to the start of emetogenic chemotherapy OR three 0.15 mg/kg, the first dose administered 30 minutes prior to start of emetogenic chemotherapy and subsequent doses (0.15 mg/kg) administered 4 and 8 hours after the first dose Postoperative nausea and vomiting (PONV): 4 mg IV administered immediately before induction of anesthesia</p> <p>Pediatrics CINV: 6 months to 18 years of age: three 0.15 mg/kg, the first dose administered 30 minutes prior to start of moderately to highly emetogenic chemotherapy and subsequent doses (0.15 mg/kg) administered 4 and 8 hours after the first dose PONV: 1 month to 12 years of age: single 0.1 mg/kg IV for patients weighing \leq 40 kg OR single 4 mg IV for patients weighing > 40 kg</p>

Indication(s)

Adults

- Prevention of nausea and vomiting associated with initial and repeat courses of emetogenic cancer chemotherapy, including high-dose cisplatin
- Prevention of postoperative nausea and/or vomiting

Pediatrics

- Prevention of nausea and vomiting associated with initial and repeat courses of emetogenic cancer chemotherapy, including high-dose cisplatin in children ages 6 months to 18 years of age
- Prevention of postoperative nausea and/or vomiting in children ages 1 month to 12 years of age

1 RECOMMENDATION ON REGULATORY ACTION

The sponsor, GlaxoSmithKline (GSK), submits this labeling supplement for conversion to the Physician's Labeling Rule (PLR) format and the addition of postmarketing adverse event data from a publication in the Annals of Internal Medicine October 15, 1993 (Vol 119, No. 8, page 862). This reviewer provides recommendations that may be considered for implementation once agreement has been reached between team members, the Agency and the Sponsor. The labeling review has yet to be completed from a clinical standpoint and might undergo more revisions once feedback is received from Division of Drug Marketing, Advertising, and Communications (DDMAC), SEALD, and the Sponsor.

2 RATIONALE FOR PROPOSED LABELING CHANGE

The sponsor seeks to revise the drug product insert to meet the reformatting requirements of FDA's Physician's Labeling Rule (PLR) per 21 CFR 201.56(d) and 201.57. GSK has also updated the labeling by making minor editorial clarifications, and removing adverse events listings, which had the same incidence rates in the Zofran treated group compared to placebo (see section 6 Adverse Reactions).

3 RELEVANT REGULATORY BACKGROUND

Ondansetron Injection (ZOFTRAN) was initially approved January 4, 1991 under NDA 20-007.

4 PRODUCT INFORMATION

Ondansetron hydrochloride is a white to off-white powder, which is soluble in water or normal saline. Zofran injection is a clear, colorless, nonpyrogenic sterile solution. The pH of the injection solution is 3.3 to 4.0. Zofran injection, 2 mg/mL is supplied as either 2mL single dose vials or 20 mL multidose vials.

5 REVIEW OF LABELING CHANGE

5.1 Materials Referenced

- Current Label for Zuplenz (NDA 22-524) version dated July 2010
- NDA 22-524, Medical officer (Tamara Johnson, MD, MS) review dated December 22, 2009.
- NDA 22-524, Medical officer (Tamara Johnson, MD, MS) review dated February 4, 2010
- NDA 22-524, Division Director (Donna Griebel, MD) review dated July 2, 2010
- Current Label for ZOFRAN Tablets, Orally Disintegrating Tablets, and Oral Solution version dated May 2010
- Current Label for ZOFRAN Injection version dated May 2010

5.2 Reviewer Comments on Labeling

This reviewer made revisions in concurrence with the required PLR formatting as referenced in 21 CFR §201.56 and 201.57. These changes mainly affected the subheadings for section 1 *Indications and Usage*, section 2 *Dosage and Administration*, section 4 *Contraindications*, section 5 *Warnings and Precautions*, section 6 *Adverse Reactions*, and section 14 *Clinical Studies*. All aforementioned sections were cross-referenced to *Highlights of Prescribing Information*. The currently approved label of Zuplenz version dated July 2010 served as a model for the wording and format of the Zofran injection label.

For exact wording of revisions made, please see Appendix B for labeling with clinical reviewer's tracked changes in red.

This is a list of the changes, which are being considered for implementation and the reasoning behind the proposed changes.

- For section 6 *Adverse Reactions* in PLR labeling, a terminology change is recommended to include adverse "reactions" in the labeling, not "events."
- For section 6.1 *Clinical Trials Experience*, the standard disclaimer was added.
- For section 6.2 *Postmarketing Experience*, the standard disclaimer was added.

- Under section *14 Clinical Studies*, the table titles were revised to remove the word *prevention* so that the titles did not make conclusions about the data. Clarifying edits were made to table header rows and section text to specify ondansetron formulation and dosing regimens.
- In accordance with PLR labeling, subheadings and subheading numberings were added for section *5 Warnings and Precautions*. The adverse reactions were also prioritized based on the relative significance.

5.3 Significant Safety/Efficacy Issues Related to Other Review Disciplines

Additional revisions to the labeling are currently outstanding at the time of this medical officer review completion. Additional revisions might be necessary based on comments from DDMAC and SEALD. See Appendix B for the labeling with tracked changes.

6 LABELING NEGOTIATION

Labeling negotiations with the Sponsor have yet to begin. The Agency proposed revisions to the label have not yet been forwarded to the Sponsor.

7 CONCLUSION

As the Sponsor, GSK, submits this labeling supplement to comply with the required conversion of the product prescribing information to PLR format, this reviewer recommends updating the Zofran (Ondansetron hydrochloride) Injection label. The changes will be negotiated with the Sponsor in the coming weeks.

APPENDIX A

Current Approved Zuplenz label, version dated July 2010

APPENDIX B

Tracked changes version of the Zofran injection label:

- Clinical Reviewer changes noted in *red*

47 Page(s) of Draft Labeling has been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

HELEN SILE
11/08/2010

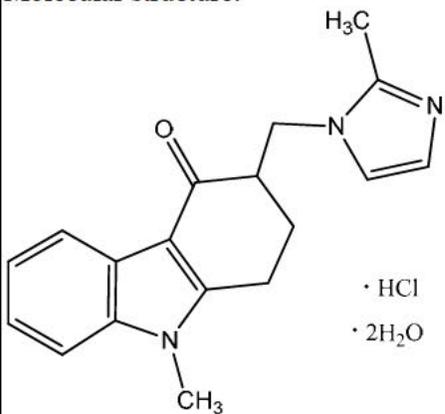
RUYI HE
11/08/2010

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

20007Orig1s041

CHEMISTRY REVIEW(S)

CHEMISTS REVIEW	1. ORGANIZATION	2. NDA NUMBER
	HFD-590	20-007
3. NAME AND ADDRESS OF APPLICANT		4. COMMUNICATION, DATE
Glaxo Wellcome Manufacturing Pte Limited 1 Pioneer Sector 1 Jurong, Singapore, 628413 US Agent: Eric Richards, M.S., 1250 S. Collegeville Rd UP4110, Collegeville, PA 19426		Supplement# 041 Submission: PAS Letter Date: 28-Jun-2010 Stamp Date: 28-Jun-2010 Receipt Date: 06-Jul-2010 PDUFA Date: 28-Dec-2010
5. PROPRIETARY NAME	6. NAME OF THE DRUG	7. AMENDMENTS, REPORT, DATE
Zofran	Ondansetron hydrochloride dihydrate	none
8. COMMUNICATION PROVIDES FOR:		
The conversion of the package insert labeling to physician's labeling rule format.		
9. PHARMACOLOGICAL CATEGORY	10. HOW DISPENSED	11. RELATED IND, NDA, DMF
Antiemetic	Rx	none
12. DOSAGE FORM	13. POTENCY	
iv injection	2 mg/mL	
14. CHEMICAL NAME AND STRUCTURE		
<p>USAN/INN: Ondansetron hydrochloride dihydrate 1,2,3,9-Tetrahydro-9-methyl-3-[(2-methyl-1H-imidazol-1-yl) methyl]-4H-carbazol-4-one, monohydrochloride, dihydrate Molecular formula: C₁₈H₁₉N₃O HCl; Molecular mass: 365.86 g/mol CAS: 99614-02-5 Molecular structure:</p>  <p>· HCl · 2H₂O</p>		
15. COMMENTS		
NDA 20-007/S-041 is a prior approval supplement providing for the conversion of the package insert labeling to physician's rule format. Proposed changes were sent to Sponsor on 16-Dec-2010. The Sponsor sent the Agency two further proposals on 21-Jan-2011 and 05-May-2011 involving only clinical labeling issues. The present draft of the PLR labeling contains several changes, including a re-introduction of the route of administration in the first sentence of the Description. No changes were made to Sections 3 & 16.		
16. CONCLUSION AND RECOMMENDATION		
APPROVAL		

17. NAME	18. REVIEWERS SIGNATURE	19. DATE COMPLETED
Christopher Hough, Ph.D.	See appended electronic signature sheet	21-Jun-2011
DISTRIBUTION: ORIGINAL JACKET CSO REVIEWER DIVISION FILE		

Chemistry Review Notes

This supplement provides for the conversion of the labeling insert to PLR format. A draft of the physician's labeling insert is provided in the supplement. Since the drug product of NDA 20-403 has been discontinued, all references to Zofran Injection Premixed (32 mg/50 mL), its dosage form, preparation/handling and how supplied have been removed from the labeling. The following are the Description sections (11) as amended for the Physicians Rule Labeling on 16-Dec-2010 and as amended in the current draft (21-Jun-2011).

(b) (4)



(b) (4)



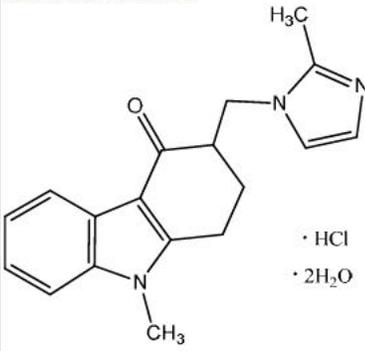
Reviewer's Comment: Other than the changes made to the Description text, no changes have been made to the text or meaning of the labeling in these sections. Sections 3 and 16 are acceptable as they are in both versions.

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/s/

CHRISTOPHER J HOUGH
06/22/2011

THOMAS F OLIVER
06/28/2011

CHEMISTS REVIEW	1. ORGANIZATION	2. NDA NUMBER
	HFD-590	20-007
3. NAME AND ADDRESS OF APPLICANT		4. COMMUNICATION, DATE
Glass Wellcome Manufacturing Pte Limited 1 Pioneer Sector 1 Jurong, Singapore, 628413 US Agent: Eric Richards, M.S., 1250 S. Collegeville Rd UP4110, Collegeville, PA 19426		S-041, dated 28-Jun-2010 Submission: PAS PDUFA Date: 28-Dec-2010
5. PROPRIETARY NAME	6. NAME OF THE DRUG	7. AMENDMENTS, REPORT, DATE
Zofran	Ondansetron hydrochloride	none
8. COMMUNICATION PROVIDES FOR:		
The conversion of the package insert labeling to physician's labeling rule format.		
9. PHARMACOLOGICAL CATEGORY	10. HOW DISPENSED	11. RELATED IND, NDA, DMF
Antiemetic	Rx	none
12. DOSAGE FORM	13. POTENCY	
iv injection	2 mg/mL	
14. CHEMICAL NAME AND STRUCTURE		
<p>USAN/INN: Ondansetron hydrochloride dihydrate 1,2,3,9-Tetrahydro-9-methyl-3-[(2-methyl-1H-imidazol-1-yl) methyl]-4H-carbazol-4-one, monohydrochloride, dihydrate Molecular formula: C₁₈H₁₉N₃O HCl; Molecular mass: 365.86 g/mol CAS: 99614-02-5 Molecular structure:</p>  <p>· HCl · 2H₂O</p>		
15. COMMENTS		
NDA 20-007/S-041 is a prior approval supplement providing for the conversion of the package insert labeling to physician's rule format.		
16. CONCLUSION AND RECOMMENDATION		
APPROVAL		
17. NAME	18. REVIEWERS SIGNATURE	19. DATE COMPLETED
Christopher Hough, Ph.D.	See appended electronic signature sheet	09-Dec-2010
DISTRIBUTION: ORIGINAL JACKET CSO REVIEWER DIVISION FILE		

Chemistry Review Notes

This supplement provides for the conversion of the labeling insert to PLR format. A draft of the physician's labeling insert is provided in the supplement. Since the drug product of NDA 20-403 has been discontinued, all references to Zofran Injection Premixed (32 mg/50 mL), its dosage form, preparation/handling and how supplied have been removed from the labeling. Where the name of the drug product of NDA 20-007, "**ZOFRAN® (ondansetron hydrochloride) Injection,**" is used, "ZOFRAN Injection," or simply "ZOFRAN" is used in the running text. The following are the sections 3,11, and 16, as amended for the Physicians Rule Labeling:

(b) (4)

Reviewer's Comment: Other than the removal of references to the drug product of NDA 20-403 and reformatting according to the Physicians Rule, no changes have been made to the text or

meaning of the labeling in these sections. The immediate packaging label, shown on next page, also remains unchanged:



Reviewer's Evaluation: From the CMC perspective, the labeling changes proposed are acceptable.

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/s/

CHRISTOPHER J HOUGH
12/16/2010

THOMAS F OLIVER
12/16/2010

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

20007Orig1s041

PHARMACOLOGY REVIEW(S)

NDA 20-007

**PHARMACOLOGIST'S REVIEW OF NDA 20-007
(Sequence # 0041 Dated June 28, 2010)**

Sponsor and Address: GlaxoSmithKline
Research Triangle Park, NC 27709

Reviewer: Sushanta Chakder, Ph. D.
Supervisory Pharmacologist, HFD-180

Date of Submission: June 28, 2010

Date of HFD-180 Receipt: June 28, 2010

Date of Review: December 16, 2010

Drug: ZOFRAN (ondansetron) Injection

Category: 5-HT3 receptor antagonist.

Submission Contents: Labeling Supplement (PLR conversion)

SUMMARY AND EVALUATION:

GlaxoSmithKline submitted NDA 20-007, Supplement 0041 for the conversion of the labeling for ZOFRAN Injection in the PLR format. The proposed labeling conforms to the current labeling rule (21 CFR 201.57). However, the following recommended changes should be incorporated in the labeling.

(b) (4)



Recommendations: None

Sushanta Chakder, Ph. D.
Supervisory Pharmacologist

Date

cc:

IND

HFD-180

HFD-180/CSO

HFD-180/Dr. Chakder

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/s/

SUSHANTA K CHAKDER
12/16/2010

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

20007Orig1s041

**CLINICAL PHARMACOLOGY AND
BIOPHARMACEUTICS REVIEW(S)**

OFFICE OF CLINICAL PHARMACOLOGY REVIEW

NDA: 20007 / S-041	Submission Date(s): 06/28/2010
Brand Name	ZOFRAN [®] Injection
Generic Name	Ondansetron hydrochloride
Reviewers	Dilara Jappar, Ph.D.
Team Leader	Sue-Chih Lee, Ph.D.
OCP Division	Division of Clinical Pharmacology 3
OND Division	Division of Gastroenterology Products
Sponsor	GlaxoSmithKline
Submission Type; Code	PLR conversion
Formulation; Strength(s)	IV injection, 2 mL single dose & 20 mL multidose vials <ul style="list-style-type: none">• Prevention of nausea and vomiting associated with initial and repeat courses of emetogenic cancer chemotherapy.• Prevention of postoperative nausea and/or vomiting.
Indication:	Prevention of nausea and vomiting associated with initial and repeat courses of emetogenic cancer chemotherapy: <ul style="list-style-type: none">• Adults: 32 mg infused I.V. over 15 minutes beginning 30 min before the start of chemotherapy, or three 0.15 mg/kg doses infused initially the same with subsequent doses administered 4 and 8 hours after the first dose.• Pediatric patients 6 months to 18 years of age: three 0.15 mg/kg doses infused I.V. over 15 minutes beginning 30 min before the start of chemotherapy with subsequent doses administered 4 and 8 hours after the first dose.
Dosing Regiment:	Prevention of Postoperative Nausea and/or Vomiting: <ul style="list-style-type: none">• Adult Dosing: 4 mg infused I.V. over 2 to 5 minutes (2.2)• Pediatric Dosing (1 month to 12 years of age): A single 0.1 mg/kg dose for patients \leq 40 or a single 4 mg dose for patients $>$ 40 kg, I.V. over 2 to 5 minutes.

Table of Contents

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2 Detailed Labeling Recommendations.....	2

1 Executive Summary

GlaxoSmithKline submitted NDA 20007- supplement 041 for the PLR conversion of Zofran Injection label on 06/28/2010. We recommend several changes in the label language, placement of label statements, or layout to conform to the PLR format as shown in the section below in color font.

2 Detailed Labeling Recommendations

All recommended changes are noted by color font. Specifically, any additions are noted by underlined text in blue and any deletions are identified by ~~strikethrough text in red~~.



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/s/

DILARA JAPPAR
12/06/2010

SUE CHIH H LEE
12/06/2010

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

20007Orig1s041

OTHER REVIEW(S)

SEALD LABELING: PI SIGN-OFF REVIEW

APPLICATION NUMBER	NDA 20-007/041
APPLICANT	GlaxoSmithKline
PRODUCT NAME	ZOFRAN (ondansetron hydrochloride)
SUBMISSION DATE	June 28, 2010
PDUFA DATE	PLR Conversion
SEALD SIGN-OFF DATE	June 29, 2011
OND ASSOCIATE DIRECTOR FOR STUDY ENDPOINTS AND LABELING	Ann Marie Trentacosti for Laurie Burke

This memo confirms that all critical prescribing information (PI) deficiencies noted in the SEALD Labeling Review filed June 20, 2011 have been addressed in the final agreed-upon PI. SEALD has no objection to PI approval at this time.

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/s/

ANN M TRENTACOSTI
06/29/2011
Signing for Laurie Burke

SEALD LABELING REVIEW

This SEALD Labeling Review identifies major aspects of the draft labeling that do not meet the requirements of 21 CFR 201.56 and 201.57 and related CDER labeling policies.

APPLICATION NUMBER	NDA 20-007/041
APPLICANT	GlaxoSmithKline
PRODUCT NAME	ZOFRAN (ondansetron hydrochloride)
RECEIVED DATE	June 28, 2010
PDUFA DATE	December 28, 2011 (PLR Conversion)
SEALD REVIEW DATE	June 20, 2011
SEALD LABELING REVIEWER	Jeanne Marie Delasko, RN, MS Labeling Initiatives Specialist

The following checked Selected Requirements for Prescribing Information items are outstanding labeling issues that must be corrected before the final draft labeling is approved.

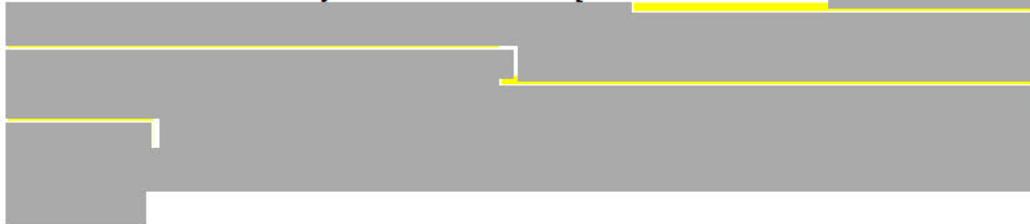
Selected Requirements for Prescribing Information (SRPI)

This document is meant to be used as a checklist in order to identify critical issues during labeling development and review. For additional information concerning the content and format of the prescribing information, see regulatory requirements (21 CFR 201.56 and 201.57) and labeling guidances. When used in reviewing the PI, only identified deficiencies should be checked.

Highlights (HL)

• General comments

- HL must be in two-column format, with ½ inch margins on all sides and between columns, and in a minimum of 8-point font.
- HL is limited in length to one-half page. If it is longer than one-half page, a waiver has been granted or requested by the applicant in this submission.
- There is no redundancy of information. [JMD Comment: (b) (4)



- If a Boxed Warning is present, it must be limited to 20 lines. (Boxed Warning lines do not count against the one-half page requirement.)
- A horizontal line must separate the HL and Table of Contents (TOC).
- All headings must be presented in the center of a horizontal line, in UPPER-CASE letters and **bold** type.
- Each summarized statement must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contains more detailed information.
- Section headings are presented in the following order:

• Highlights Limitation Statement (required statement)
• Drug names, dosage form, route of administration, and controlled substance symbol, if applicable (required information)
• Initial U.S. Approval (required information)
• Boxed Warning (if applicable)
• Recent Major Changes (for a supplement)
• Indications and Usage (required information)
• Dosage and Administration (required information)
• Dosage Forms and Strengths (required information)
• Contraindications (required heading – if no contraindications are known, it must state “None”)

• Warnings and Precautions (required information)
• Adverse Reactions (required AR contact reporting statement)
• Drug Interactions (optional heading)
• Use in Specific Populations (optional heading)
• Patient Counseling Information Statement (required statement)
• Revision Date (required information)

- **Highlights Limitation Statement**
 - Must be placed at the beginning of HL, **bolded**, and read as follows: “**These highlights do not include all the information needed to use (insert name of drug product in UPPER CASE) safely and effectively. See full prescribing information for (insert name of drug product in UPPER CASE).**”

- **Product Title**
 - Must be **bolded** and note the proprietary and established drug names, followed by the dosage form, route of administration (ROA), and, if applicable, controlled substance symbol.

- **Initial U.S. Approval**
 - The verbatim statement “Initial U.S. Approval” followed by the 4-digit year in which the FDA initially approved of the new molecular entity (NME), new biological product, or new combination of active ingredients, must be placed immediately beneath the product title line. If this is an NME, the year must correspond to the current approval action.

- **Boxed Warning**
 - All text in the boxed warning is **bolded**.
 - Summary of the warning must not exceed a length of 20 lines.
 - Requires a heading in UPPER-CASE, **bolded** letters containing the word “**WARNING**” and other words to identify the subject of the warning (e.g., “**WARNING: LIFE-THREATENING ADVERSE REACTIONS**”).
 - Must have the verbatim statement “*See full prescribing information for complete boxed warning.*” If the boxed warning in HL is identical to boxed warning in FPI, this statement is not necessary.

- **Recent Major Changes (RMC)**
 - Applies only to supplements and is limited to substantive changes in five sections: Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions.
 - The heading and, if appropriate, subheading of each section affected by the recent change must be listed with the date (MM/YYYY) of supplement approval. For example, “Dosage and Administration, Coronary Stenting (2.2) --- 2/2010.”
 - For each RMC listed, the corresponding new or modified text in the FPI must be marked with a vertical line (“margin mark”) on the left edge.
 - A changed section must be listed for at least one year after the supplement is approved and must be removed at the first printing subsequent to one year.
 - Removal of a section or subsection should be noted. For example, “Dosage and Administration, Coronary Stenting (2.2) --- removal 2/2010.”

- **Indications and Usage**

- If a product belongs to an established pharmacologic class, the following statement is required in HL: [Drug/Biologic Product) is a (name of class) indicated for (indication(s)).” Identify the established pharmacologic class for the drug at:

<http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/ucm162549.htm>.

- **Contraindications**

- This section must be included in HL and cannot be omitted. If there are no contraindications, state “None.”
- All contraindications listed in the FPI must also be listed in HL.
- List known hazards and not theoretical possibilities (i.e., hypersensitivity to the drug or any inactive ingredient). If the contraindication is not theoretical, describe the type and nature of the adverse reaction.
- For drugs with a pregnancy Category X, state “Pregnancy” and reference Contraindications section (4) in the FPI.

- **Adverse Reactions**

- Only “adverse reactions” as defined in 21 CFR 201.57(a)(11) are included in HL. Other terms, such as “adverse events” or “treatment-emergent adverse events,” should be avoided. Note the criteria used to determine their inclusion (e.g., incidence rate greater than X%).
- For drug products other than vaccines, the verbatim **bolded** statement, “**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer’s phone number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch**” must be present. Only include toll-free numbers.

- **Patient Counseling Information Statement**

- Must include the verbatim statement: “**See 17 for Patient Counseling Information**” or if the product has FDA-approved patient labeling: “**See 17 for Patient Counseling Information and (insert either “FDA-approved patient labeling” or “Medication Guide”)**”.

- **Revision Date**

- A placeholder for the revision date, presented as “Revised: MM/YYYY or Month Year,” must appear at the end of HL. The revision date is the month/year of application or supplement approval. **[JMD Comment: Remember to update upon approval. It should be June 2011, (b) (4)]**

Contents: Table of Contents (TOC)

- The heading **FULL PRESCRIBING INFORMATION: CONTENTS** must appear at the beginning in UPPER CASE and **bold** type.
- The section headings and subheadings (including the title of boxed warning) in the TOC must match the headings and subheadings in the FPI.
- All section headings must be in **bold** type, and subsection headings must be indented and not bolded.
- When a section or subsection is omitted, the numbering does not change. For example, under Use in Specific Populations, if the subsection 8.2 (Labor and Delivery) is omitted, it must read:
 - 8.1 Pregnancy
 - 8.3 Nursing Mothers (not 8.2)
 - 8.4 Pediatric Use (not 8.3)
 - 8.5 Geriatric Use (not 8.4)
- If a section or subsection is omitted from the FPI and TOC, the heading “**Full Prescribing Information: Contents**” must be followed by an asterisk and the following statement must appear at the end of TOC: “*Sections or subsections omitted from the Full Prescribing Information are not listed.”

Full Prescribing Information (FPI)

- **General Format**

- A horizontal line must separate the TOC and FPI.
- The heading – **FULL PRESCRIBING INFORMATION** – must appear at the beginning in UPPER CASE and **bold** type.
- The section and subsection headings must be named and numbered in accordance with 21 CFR 201.56(d)(1).

- **Boxed Warning**

- Must have a heading, in UPPER CASE, **bold** type, containing the word “**WARNING**” and other words to identify the subject of the warning. Use **bold** type and lower-case letters for the text.
- Must include a brief, concise summary of critical information and cross-reference to detailed discussion in other sections (e.g., Contraindications, Warnings and Precautions).

- **Contraindications**

For Pregnancy Category X drugs, list pregnancy as a contraindication.

- **Adverse Reactions**

Only “adverse reactions” as defined in 21 CFR 201.57(c)(7) should be included in labeling. Other terms, such as “adverse events” or “treatment-emergent adverse events,” should be avoided.

For the “Clinical Trials Experience” subsection, the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

“Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.”

For the “Postmarketing Experience” subsection, the listing of post-approval adverse reactions must be separate from the listing of adverse reactions identified in clinical trials. Include the following verbatim statement or appropriate modification:

“The following *adverse reactions* have been identified during post-approval use of (insert drug name). Because these *reactions* are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.” [JMD Comment: The word “event” is used instead of “adverse reactions” and “reactions” in the recommended statement above.]

- **Use in Specific Populations**

Subsections 8.4 Pediatric Use and 8.5 Geriatric Use are required and cannot be omitted.

- **Patient Counseling Information**

This section is required and cannot be omitted.

Must reference any FDA-approved patient labeling, including the type of patient labeling. The statement “See FDA-approved patient labeling (insert type of patient labeling).” should appear at the beginning of Section 17 for prominence. For example:

- “See FDA-approved patient labeling (Medication Guide)”
- “See FDA-approved patient labeling (Medication Guide and Instructions for Use)”
- “See FDA-approved patient labeling (Patient Information)”
- “See FDA-approved patient labeling (Instructions for Use)”
- “See FDA-approved patient labeling (Patient Information and Instructions for Use)”

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/s/

JEANNE M DELASKO
06/20/2011

SEALD LABELING REVIEW

This SEALD Labeling Review identifies major aspects of the draft labeling that do not meet the requirements of 21 CFR 201.56 and 201.57 and related CDER labeling policies.

APPLICATION NUMBER	NDA 20-007/041
APPLICANT	GlaxoSmithKline
PRODUCT NAME	ZOFRAN (ondansetron hydrochloride)
SUBMISSION DATE	June 28, 2010
PDUFA DATE	December 28, 2010 (PLR Conversion)
SEALD REVIEW DATE	January 28, 2011
SEALD LABELING REVIEWER	Jeanne Marie Delasko, RN, MS Label Initiatives Specialist

The following checked Selected Requirements for Prescribing Information items are outstanding labeling issues that must be corrected before the final draft labeling is approved.

Selected Requirements for Prescribing Information (SRPI)

This document is meant to be used as a checklist in order to identify critical issues during labeling development and review. For additional information concerning the content and format of the prescribing information, see regulatory requirements (21 CFR 201.56 and 201.57) and labeling guidances.

Highlights (HL)

- **General comments**

- HL must be in two-column format, with ½ inch margins on all sides and between columns, and in a minimum of 8-point font.
- HL is limited in length to one-half page. If it is longer than one-half page, a waiver has been granted or requested by the applicant in this submission.
- There is no redundancy of information.
- If a Boxed Warning is present, it must be limited to 20 lines. (Boxed Warning lines do not count against the one-half page requirement.)
- A horizontal line must separate the HL and Table of Contents (TOC).
- All headings must be presented in the center of a horizontal line, in UPPER-CASE letters and **bold** type.
- Each summarized statement must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contains more detailed information.
- Section headings are presented in the following order:

• Highlights Limitation Statement (required statement)
• Drug names, dosage form, route of administration, and controlled substance symbol, if applicable (required information)
• Initial U.S. Approval (required information)
• Boxed Warning (if applicable)
• Recent Major Changes (for a supplement)
• Indications and Usage (required information)
• Dosage and Administration (required information)
• Dosage Forms and Strengths (required information)
• Contraindications (required heading – if no contraindications are known, it must state “None”)
• Warnings and Precautions (required information)
• Adverse Reactions (required AR contact reporting statement)
• Drug Interactions (optional heading)
• Use in Specific Populations (optional heading)
• Patient Counseling Information Statement (required statement)
• Revision Date (required information)

- **Highlights Limitation Statement**

- Must be placed at the beginning of HL, **bolded**, and read as follows: “**These highlights do not include all the information needed to use (insert name of drug product in UPPER CASE) safely and effectively. See full prescribing information for (insert name of drug product in UPPER CASE).**”

- **Product Title**

- Must be **bolded** and note the proprietary and established drug names, followed by the dosage form, route of administration (ROA), and, if applicable, controlled substance symbol (b) (4)

- **Initial U.S. Approval**

- The verbatim statement “Initial U.S. Approval” followed by the 4-digit year in which the FDA initially approved of the new molecular entity (NME), new biological product, or new combination of active ingredients, must be placed immediately beneath the product title line. If this is an NME, the year must correspond to the current approval action.

- **Boxed Warning**

- All text in the boxed warning is **bolded**.
- Summary of the warning must not exceed a length of 20 lines.
- Requires a heading in UPPER-CASE, **bolded** letters containing the word “**WARNING**” and other words to identify the subject of the warning (e.g., “**WARNING: LIFE-THREATENING ADVERSE REACTIONS**”).
- Must have the verbatim statement “*See full prescribing information for complete boxed warning.*” If the boxed warning in HL is identical to boxed warning in FPI, this statement is not necessary.

- **Recent Major Changes (RMC)**

- Applies only to supplements and is limited to substantive changes in five sections: Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions.
- The heading and, if appropriate, subheading of each section affected by the recent change must be listed with the date (MM/YYYY) of supplement approval. For example, “Dosage and Administration, Coronary Stenting (2.2) --- 2/2010.”
- For each RMC listed, the corresponding new or modified text in the FPI must be marked with a vertical line (“margin mark”) on the left edge.
- A changed section must be listed for at least one year after the supplement is approved and must be removed at the first printing subsequent to one year.

- Removal of a section or subsection should be noted. For example, “Dosage and Administration, Coronary Stenting (2.2) --- removal 2/2010.”

- **Indications and Usage**

- If a product belongs to an established pharmacologic class, the following statement is required in HL: [Drug/Biologic Product) is a (name of class) indicated for (indication(s)).” Identify the established pharmacologic class for the drug at:
<http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/ucm162549.htm>.

- **Contraindications**

- This section must be included in HL and cannot be omitted. If there are no contraindications, state “None.”
- All contraindications listed in the FPI must also be listed in HL.
- List known hazards and not theoretical possibilities (i.e., hypersensitivity to the drug or any inactive ingredient). If the contraindication is not theoretical, describe the type and nature of the adverse reaction.
- For drugs with a pregnancy Category X, state “Pregnancy” and reference Contraindications section (4) in the FPI.

- **Adverse Reactions**

- Only “adverse reactions” as defined in 21 CFR 201.57(a)(11) are included in HL. Other terms, such as “adverse events” or “treatment-emergent adverse events,” should be avoided. Note the criteria used to determine their inclusion (e.g., incidence rate greater than X%).
- For drug products other than vaccines, the verbatim **bolded** statement, “**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer’s phone number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch**” must be present. Only include toll-free numbers.

- **Patient Counseling Information Statement**

- Must include the verbatim statement: “**See 17 for Patient Counseling Information**” or if the product has FDA-approved patient labeling: “**See 17 for Patient Counseling Information and (insert either “FDA-approved patient labeling” or “Medication Guide”)**”.

- **Revision Date**

- A placeholder for the revision date, presented as “Revised: MM/YYYY or Month Year,” must appear at the end of HL. The revision date is the month/year of application or supplement approval. [**JMD Comment: Remember to update before approval.**]

Contents: Table of Contents (TOC)

- The heading **FULL PRESCRIBING INFORMATION: CONTENTS** must appear at the beginning in UPPER CASE and **bold** type.
- The section headings and subheadings (including the title of boxed warning) in the TOC must match the headings and subheadings in the FPI.
- All section headings must be in **bold** type, and subsection headings must be indented and not bolded.
- When a section or subsection is omitted, the numbering does not change. For example, under Use in Specific Populations, if the subsection 8.2 (Labor and Delivery) is omitted, it must read:
 - 8.1 Pregnancy
 - 8.3 Nursing Mothers (not 8.2)
 - 8.4 Pediatric Use (not 8.3)
 - 8.5 Geriatric Use (not 8.4)
- If a section or subsection is omitted from the FPI and TOC, the heading “**Full Prescribing Information: Contents**” must be followed by an asterisk and the following statement must appear at the end of TOC: “*Sections or subsections omitted from the Full Prescribing Information are not listed.”

Full Prescribing Information (FPI)

- **General Format**

- A horizontal line must separate the TOC and FPI.
- The heading – **FULL PRESCRIBING INFORMATION** – must appear at the beginning in UPPER CASE and **bold** type.
- The section and subsection headings must be named and numbered in accordance with 21 CFR 201.56(d)(1).

- **Boxed Warning**

- Must have a heading, in UPPER CASE, **bold** type, containing the word “**WARNING**” and other words to identify the subject of the warning. Use **bold** type and lower-case letters for the text.
- Must include a brief, concise summary of critical information and cross-reference to detailed discussion in other sections (e.g., Contraindications, Warnings and Precautions).

- **Contraindications**

- For Pregnancy Category X drugs, list pregnancy as a contraindication.

- **Adverse Reactions**

- Only “adverse reactions” as defined in 21 CFR 201.57(c)(7) should be included in labeling. Other terms, such as “adverse events” or “treatment-emergent adverse events,” should be avoided.

- For the “Clinical Trials Experience” subsection, the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

“Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.”

- For the “Postmarketing Experience” subsection, the listing of post-approval adverse reactions must be separate from the listing of adverse reactions identified in clinical trials. Include the following verbatim statement or appropriate modification:

“The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.”

- **Use in Specific Populations**

- Subsections 8.4 Pediatric Use and 8.5 Geriatric Use are required and cannot be omitted.

- **Patient Counseling Information**

- This section is required and cannot be omitted.

- Must reference any FDA-approved patient labeling, including the type of patient labeling. The statement “See FDA-approved patient labeling (insert type of patient labeling).” should appear at the beginning of Section 17 for prominence. For example:

- “See FDA-approved patient labeling (Medication Guide)”
- “See FDA-approved patient labeling (Medication Guide and Instructions for Use)”
- “See FDA-approved patient labeling (Patient Information)”
- “See FDA-approved patient labeling (Instructions for Use)”
- “See FDA-approved patient labeling (Patient Information and Instructions for Use)”

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/s/

JEANNE M DELASKO
01/28/2011

ANN M TRENTACOSTI
01/28/2011

REGULATORY PROJECT MANAGER LABELING REVIEW (PHYSICIAN LABELING RULE)

Division of Gastroenterology Products

NDA	Supplement	Drug Product
20-007	S-041	Zofran (ondansetron hydrochloride) Injection
20-403	S-019	Zofran (ondansetron hydrochloride) Injection Premixed

Applicant: GlaxoSmithKline

Material Reviewed

Submission Date: June 28, 2010

Receipt Date: June 28, 2010

Submission Date of Structure Product Labeling (SPL): June 28, 2010

Type of Labeling Reviewed: Word and SPL

Background and Summary

The Prior Approval Labeling Supplements submitted to the above NDAs provide for the conversion of the package insert (PI) to Physician's Labeling Rule (PLR) format. The Zofran Injection label was last approved on September 22, 2010, with Changes Being Effected labeling supplements that provided for the contraindication of apomorphine with concomitant use with ondansetron. The Zofran Injection Premixed formulation (NDA 20-403) was discontinued as of September 30, 2008, therefore the proposed labeling only references the Injection product.

Review

Proposed SPL versus Proposed Word

The labels are identical except for the following found in the SPL label:

- The drug name at the [REDACTED] (b) (4).
- The following statement appears twice at the beginning of the label:

[REDACTED] (b) (4)

Proposed Word versus last approved label

The sponsor included in the proposed label, the changes approved on September 22, 2010. Since the PI is in the new PLR format, each discipline is responsible for reviewing their respective areas for content purposes. The following issues were found when the format of the proposed PI

in Word format was reviewed according to the regulations cited above.

Highlights

- There should be white space between each major heading in Highlights.
- Dosage and Administration: A tabular format should be used to enhance accessibility of information (e.g., when there are different dosing regimens for different indications).

Full Prescribing Information

- Sections 2.1, 2.2, and 2.3: [REDACTED] (b) (4)
- Section 4: For each contraindication, use numbered subsection headings or bullets.

Recommendations

The proposed labels are recommended for approval pending review by each discipline. Upon approval, the sponsor will be reminded in to submit final SPL identical to the approved PI.

Heather Buck
Regulatory Project Manager

Supervisory Comment/Concurrence:

Richard Ishihara
Chief, Project Management Staff

Drafted: HB 7/26/10
Revised/Initialed:
Finalized:

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/s/

HEATHER G BUCK
11/02/2010

RICHARD W ISHIHARA
11/02/2010

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications

******Pre-decisional Agency Information******

Memorandum

Date: September 13, 2010

To: Heather Buck, Regulatory Project Manager
Division of Gastroenterology Products (DGP)

From: Kathleen Klemm, Regulatory Review Officer
Division of Drug Marketing, Advertising, and Communications (DDMAC)

CC: Lisa Hubbard, Professional Group Leader
Shefali Doshi, Acting DTC Group Leader
Cynthia Collins, Regulatory Review Officer
Wayne Amchin, Regulatory Health Project Manager
DDMAC

Subject: NDA 020007/S-041
NDA 020403/S-019

DDMAC labeling comments for ZOFRAN[®] (ondansetron hydrochloride) Injection

In response to DGP's July 28, 2010, consult request, DDMAC has reviewed the draft product labeling (PI) for ZOFRAN[®] (ondansetron hydrochloride) Injection and offers the following comments.

DDMAC's comments on the PI are based on the proposed draft marked-up labeling titled, "Zofran Inj PLR_Clean.doc" that was accessed via the eRoom and last modified on September 8, 2010, at 6:31pm. DDMAC's comments on the PI are provided directly on the document attached below.

Thank you for the opportunity to comment on this proposed material.

If you have any questions, please contact Kathleen Klemm at 301.796.3946 or Kathleen.Klemm@fda.hhs.gov.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-20403	SUPPL-19	GLAXOSMITHKLIN E	ZOFRAN (ONDANSETRON HCL DIHYDRATE) INJ P
NDA-20007	SUPPL-41	GLAXOSMITHKLIN E	ZOFRAN INJ (ONDANSETRON HCL)

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/s/

KATHLEEN KLEMM

09/13/2010

Comments by other reviewers and track changes were hid for reading clarity.

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

20007Orig1s041

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION		REQUEST FOR DDMAC LABELING REVIEW CONSULTATION **Please send immediately following the Filing/Planning meeting**	
TO: CDER-DDMAC-RPM (attention Katie Klemm, Wayne Amchin)		FROM: (Name/Title, Office/Division/Phone number of requestor) Heather Buck, RPM, OND/ODE III/DGP, (301) 796-1413	
REQUEST DATE 7/28/10	IND NO.	NDA/BLA NO. 20-007 / S-041 20-403 / S-019	TYPE OF DOCUMENTS: PAS Labeling Supplements
NAME OF DRUG Zofran Injection	PRIORITY CONSIDERATION standard	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE 9/13/10
NAME OF FIRM: GlaxoSmithKline		PDUFA Date: 12/28/10	
TYPE OF LABEL TO REVIEW			
TYPE OF LABELING: (Check all that apply) <input checked="" type="checkbox"/> PACKAGE INSERT (PI) <input type="checkbox"/> PATIENT PACKAGE INSERT (PPI) <input type="checkbox"/> CARTON/CONTAINER LABELING <input type="checkbox"/> MEDICATION GUIDE <input type="checkbox"/> INSTRUCTIONS FOR USE(IFU)		TYPE OF APPLICATION/SUBMISSION <input type="checkbox"/> ORIGINAL NDA/BLA <input type="checkbox"/> IND <input type="checkbox"/> EFFICACY SUPPLEMENT <input type="checkbox"/> SAFETY SUPPLEMENT <input checked="" type="checkbox"/> LABELING SUPPLEMENT <input checked="" type="checkbox"/> PLR CONVERSION	
REASON FOR LABELING CONSULT <input type="checkbox"/> INITIAL PROPOSED LABELING <input checked="" type="checkbox"/> LABELING REVISION			
EDR link to submission:		20-403/19 \CDSESUB1\EVSPROD\NDA020403\020403.enx 20-007/41 \CDSESUB1\EVSPROD\NDA020007\020007.enx	
Please Note: There is no need to send labeling at this time. DDMAC reviews substantially complete labeling, which has already been marked up by the CDER Review Team. The DDMAC reviewer will contact you at a later date to obtain the substantially complete labeling for review.			
COMMENTS/SPECIAL INSTRUCTIONS: We received this is PLR conversion of the PI on 6/28/10. We plan to have our revisions made by 9/3/10 (you may access the label after this date). Our team meeting is 9/13/10 to which you are invited. The latest label is in the eRoom: http://eroom.fda.gov/eRoom/CDER3/CDERDivisionofGastroenterologyProducts/0_17c58 Clinical reviewer: Helen Sile. RPM: Heather Buck (contact with questions). Thank you in advance.			
SIGNATURE OF REQUESTER Heather Buck 7/26/10			
SIGNATURE OF RECEIVER		METHOD OF DELIVERY (Check one) <input checked="" type="checkbox"/> eMAIL <input checked="" type="checkbox"/> DARRTS <input type="checkbox"/> HAND	

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-20403	SUPPL-19	GLAXOSMITHKLIN E	ZOFRAN (ONDANSETRON HCL DIHYDRATE) INJ P
NDA-20007	SUPPL-41	GLAXOSMITHKLIN E	ZOFRAN INJ (ONDANSETRON HCL)

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/s/

HEATHER G BUCK
07/28/2010



NDA 20-007/S-041
NDA 20-403/S-019

PRIOR APPROVAL SUPPLEMENT

Glaxo Wellcome Manufacturing Pte Limited d/b/a GlaxoSmithKline
Attention: Eric Richards
Associated Director
1250 Collegeville Rd.
UP4110
Collegeville, PA 19426

Dear Mr. Richards:

We have received your Supplemental New Drug Application (sNDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

NDA	Supplement	Drug Product
20-007	S-041	Zofran (ondansetron hydrochloride) Injection
20-403	S-019	Zofran (ondansetron hydrochloride) Injection Premixed

These applications dated June 28, 2010, were received June 28, 2010.

These supplemental applications propose to convert the package insert to Physician's Labeling Rule (PLR) format.

Unless we notify you within 60 days of the receipt date that the applications are not sufficiently complete to permit a substantive review, we will file the applications on August 27, 2010, in accordance with 21 CFR 314.101(a). If the applications are filed, the user fee goal date will be December 28, 2010.

Please cite the application numbers listed above at the top of the first page of all submissions to these applications. 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

NDA 20-007/S-041

NDA 20-403/S-019

Page 2

If you have questions, please call me at (301) 796-1413.

Sincerely,

{See appended electronic signature page}

Heather Buck, MS, MBA
Regulatory Project Manager
Division of Gastroenterology Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
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NDA-20007	SUPPL-41	GLAXOSMITHKLIN E	ZOFRAN INJ (ONDANSETRON HCL)

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HEATHER G BUCK
07/07/2010