CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

020781Orig1s017

Trade Name: Zofran ODT

Generic Name: Ondansetron

Sponsor: Novartis Pharmaceuticals Corporation

Approval Date: September 28, 2016

Indication(s):

- Nausea and vomiting associated with highly emetogenic cancer chemotherapy including cisplatin
- Nausea and vomiting associated with initial and repeat courses of moderately emetogenic cancer chemotherapy
- Nausea and vomiting associated with radiotherapy in patients receiving either total body irradiation, single high-dose fraction to the abdomen or daily fractions to the abdomen
- Postoperative nausea and/or vomiting

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APPLICATION NUMBER:

020781Orig1s017

CONTENTS

Reviews / Information Included in this NDA Review.

Approval Letter	**X**
Other Action Letters	
Labeling	**X**
Summary Review	
Officer/Employee List	
Office Director Memo	
Cross Discipline Team Leader Review	
Medical Review(s)	
Chemistry Review(s)	
Environmental Assessment	
Pharmacology Review(s)	**X**
Statistical Review(s)	
Microbiology Review(s)	
Clinical Pharmacology/Biopharmaceutics Review(s)	**X**
Risk Assessment and Risk Mitigation Review(s)	
Proprietary Name Review(s)	
Other Review(s)	**X**
Administrative/Correspondence Document(s)	**X**

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APPLICATION NUMBER:

020781Orig1s017

APPROVAL LETTER

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 020103/S-033
NDA 020605/S-017
NDA 020781/S-017

SUPPLEMENT APPROVAL

Novartis Pharmaceuticals Corporation
Attention: Luz Patricia Lee
Associate Director, Drug Regulatory Affairs
One Health Plaza
East Hanover, NJ 07936

Dear Ms. Lee:

Please refer to your Supplemental New Drug Application (sNDAs) dated and received March 19, 2014, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for the following:

NDA	Supplement	Drug Product
20103	S-033	Zofran (ondansetron hydrochloride) Tablets
20605	S-017	Zofran (ondansetron hydrochloride) Oral Solution
20781	S-017	Zofran ODT (ondansetron) Orally Disintegrating Tablets

These Prior Approval supplemental new drug applications provide for the conversion of the Prescribing Information to Physician's Labeling Rule (PLR) format as well alignment with current labeling regulations, guidances and best practices. The Use in Specific Populations section was also updated to reflect the Pregnancy and Lactation Labeling Final Rule (PLLR) format.

APPROVAL & LABELING

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

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(l)] 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 that include labeling changes 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).

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}

Joyce Korvick, M.D., M.P.H.
Deputy Director for Safety
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/

JOYCE A KORVICK
09/28/2016

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

020781Orig1s017

LABELING

HIGHLIGHTS OF PRESCRIBING INFORMATION

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

ZOFRAN (ondansetron hydrochloride) tablets, for oral use
ZOFRAN ODT (ondansetron) orally disintegrating tablets
ZOFRAN (ondansetron hydrochloride) oral solution
Initial U.S. Approval: 1991

----------INDICATIONS AND USAGE----------

ZOFRAN is a 5-HT_3 receptor antagonist indicated for the prevention of:

- nausea and vomiting associated with highly emetogenic cancer chemotherapy, including cisplatin ≥50 mg/m^2. (1.1)
- nausea and vomiting associated with initial and repeat courses of moderately emetogenic cancer chemotherapy. (1.2)
- nausea and vomiting associated with radiotherapy in patients receiving either total body irradiation, single high-dose fraction to the abdomen, or daily fractions to the abdomen. (1.3)
- postoperative nausea and/or vomiting. (1.4)

---------- DOSAGE AND ADMINISTRATION ----------

- See full prescribing information for the recommended dosage in adults and pediatrics (2.1)
- Patients with severe hepatic impairment: do not exceed a total daily dose of 8 mg (2.2, 8.6)

---------- DOSAGE FORMS AND STRENGTHS ----------

- Tablets: 4 mg and 8 mg (3)
- Orally Disintegrating Tablets: 4 mg and 8 mg (3)
- Oral Solution: 4 mg/5 mL (3)

----------CONTRAINDICATIONS----------

- Patients known to have hypersensitivity (e.g., anaphylaxis) to ondansetron or any components of the formulation. (4)
- Concomitant use of apomorphine. (4)

---------- WARNINGS and PRECAUTIONS ----------

- Hypersensitivity reactions including anaphylaxis and bronchospasm: Discontinue ZOFRAN if suspected. Monitor and treat promptly per standard of care until signs and symptoms resolve (5.1)
- QT interval prolongation and Torsade de Pointes: Avoid in patients with congenital long QT syndrome; monitor with ECGs if concomitant electrolyte abnormalities, cardiac failure or arrhythmias, or use of other QT prolonging drugs. (5.2)
- Serotonin syndrome: Reported with 5-HT_3 receptor antagonists alone but particularly with concomitant use of serotonergic drugs. If such symptoms occur, discontinue ZOFRAN and initiate supportive treatment. If concomitant use of ZOFRAN with other serotonergic drugs is clinically warranted, patients should be made aware of a potential increased risk for serotonin syndrome. (5.3)
- Masking of progressive ileus and/or gastric distention following abdominal surgery or chemotherapy-induced nausea and vomiting: Monitor for decreased bowel activity, particularly in patients with risk factors for gastrointestinal obstruction. (5.4)

---------- ADVERSE REACTIONS ----------

The most common adverse reactions in adults for the:

- prevention of chemotherapy-induced (>5%) are: headache, malaise/fatigue, constipation, diarrhea. (6 1)
- prevention of radiation-induced nausea and vomiting (≥2%) are: headache, constipation, and diarrhea. (6.1)
- prevention of postoperative nausea and vomiting (≥9%) are: headache and hypoxia. (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.

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 9/2016

FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the full prescribing information are not listed

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

ZOFRAN® is indicated for the prevention of nausea and vomiting associated with:

- highly emetogenic cancer chemotherapy, including cisplatin ≥50 mg/m^2.
- initial and repeat courses of moderately emetogenic cancer chemotherapy.
- radiotherapy in patients receiving either total body irradiation, single high-dose fraction to the abdomen, or daily fractions to the abdomen.

ZOFRAN is also indicated for the prevention of postoperative nausea and/or vomiting.

2 DOSAGE AND ADMINISTRATION

2.1 Dosage

The recommended dosage regimens for adult and pediatric patients are described in Table 1 and Table 2, respectively.

Corresponding doses of ZOFRAN tablets, ZOFRAN ODT® orally disintegrating tablets and ZOFRAN oral solution may be used interchangeably.

Table 1: Adult Recommended Dosage Regimen for Prevention of Nausea and Vomiting

Indication	Dosage Regimen
Highly Emetogenic Cancer Chemotherapy	A single 24-mg dose administered 30 minutes before the start of single-day highly emetogenic chemotherapy, including cisplatin ≥50 mg/m^2
Moderately Emetogenic Cancer Chemotherapy	8 mg administered 30 minutes before the start of chemotherapy, with a subsequent 8-mg dose 8 hours after the first dose. Then administer 8 mg twice a day (every 12 hours) for 1 to 2 days after completion of chemotherapy.
Radiotherapy	For total body irradiation: 8 mg administered 1 to 2 hours before each fraction of radiotherapy each day. For single high-dose fraction radiotherapy to the abdomen: 8 mg administered 1 to 2 hours before radiotherapy, with subsequent 8-mg doses every 8 hours after the first dose for 1 to 2 days after completion of radiotherapy. For daily fractionated radiotherapy to the abdomen: 8 mg administered 1 to 2 hours before radiotherapy, with subsequent 8-mg doses every 8 hours after the first dose for each day radiotherapy is given.
Postoperative	16 mg administered 1 hour before induction of anesthesia.

Table 2: Pediatric Recommended Dosage Regimen for Prevention of Nausea and Vomiting

Indication	Dosage Regimen
Moderately Emetogenic Cancer Chemotherapy	12 to 17 years of age: 8 mg administered 30 minutes before the start of chemotherapy, with a subsequent 8-mg dose 4 and 8 hours after the first dose. Then administer 8 mg three times a day for 1 to 2 days after completion of chemotherapy. 4 to 11 years of age: 4 mg administered 30 minutes before the start of chemotherapy, with a subsequent 4-mg dose 4 and 8 hours after the first dose. Then administer 4 mg three times a day for 1 to 2 days after completion of chemotherapy.

2.2 Dosage in Hepatic Impairment

In patients with severe hepatic impairment (Child-Pugh score of 10 or greater), do not exceed a total daily dose of 8 mg *[see Use in Specific Populations (8.6), Clinical Pharmacology (12.3)]*.

2.3 Administration Instructions for ZOFRAN ODT Orally Disintegrating Tablets

Do not attempt to push ZOFRAN ODT tablets through the foil backing. With dry hands, PEEL BACK the foil backing of 1 blister and GENTLY remove the tablet. IMMEDIATELY place the ZOFRAN ODT tablet on top of the tongue where it will dissolve in seconds, then swallow with saliva. Administration with liquid is not necessary.

3 DOSAGE FORMS AND STRENGTHS

ZOFRAN tablets are oval, film-coated tablets engraved with “Zofran” on one side and are available in the following strengths:

- 4 mg – white tablet with “4” engraved on the other side.
- 8 mg – yellow tablet with “8” engraved on the other side.

ZOFRAN ODT orally disintegrating tablets are white, round, and plano-convex tablets available in the following strengths:

- 4 mg – debossed with “Z4” on one side.
- 8 mg – debossed with “Z8” on one side.

ZOFRAN oral solution, 4 mg/5 mL, is a clear, colorless to light yellow liquid with a characteristic strawberry odor available in a 50-mL bottle.

4 CONTRAINDICATIONS

ZOFRAN is contraindicated in patients:

- known to have hypersensitivity (e.g., anaphylaxis) to ondansetron or any of the components of the formulation *[see Adverse Reactions (6.2)]*.

- receiving concomitant apomorphine due to the risk of profound hypotension and loss of consciousness.

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-HT_3 receptor antagonists. If hypersensitivity reactions occur, discontinue use of ZOFRAN; treat promptly per standard of care and monitor until signs and symptoms resolve *[see Contraindications (4)]*.

5.2 QT Prolongation

ECG changes including QT interval prolongation have been seen in patients receiving ondansetron. In addition, postmarketing cases of Torsade de Pointes have been reported in patients using ZOFRAN. Avoid ZOFRAN in patients with congenital long QT syndrome. ECG monitoring is recommended in patients with electrolyte abnormalities (e.g., hypokalemia or hypomagnesemia), congestive heart failure, bradyarrhythmias, or patients taking other medicinal products that lead to QT prolongation *[see Clinical Pharmacology (12.2)]*.

5.3 Serotonin Syndrome

The development of serotonin syndrome has been reported with 5-HT_3 receptor antagonists alone. Most reports have been associated with concomitant use of serotonergic drugs (e.g., selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors (SNRIs), monoamine oxidase inhibitors, mirtazapine, fentanyl, lithium, tramadol, and intravenous methylene blue). Some of the reported cases were fatal. Serotonin syndrome occurring with overdose of ZOFRAN alone has also been reported. The majority of reports of serotonin syndrome related to 5-HT_3 receptor antagonist use occurred in a post-anesthesia care unit or an infusion center.

Symptoms associated with serotonin syndrome may include the following combination of signs and symptoms: mental status changes (e.g., agitation, hallucinations, delirium, and coma), autonomic instability (e.g., tachycardia, labile blood pressure, dizziness, diaphoresis, flushing, hyperthermia), neuromuscular symptoms (e.g., tremor, rigidity, myoclonus, hyperreflexia, incoordination), seizures, with or without gastrointestinal symptoms (e.g., nausea, vomiting, diarrhea). Patients should be monitored for the emergence of serotonin syndrome, especially with concomitant use of ZOFRAN and other serotonergic drugs. If symptoms of serotonin syndrome occur, discontinue ZOFRAN and initiate supportive treatment. Patients should be informed of the increased risk of serotonin syndrome, especially if ZOFRAN is used concomitantly with other serotonergic drugs *[see Drug Interactions (7.1), Overdosage (10)]*.

5.4 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/or gastric distension. Monitor for decreased bowel activity, particularly in patients with risk factors for gastrointestinal obstruction.

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

5.5 Phenylketonuria

Phenylketonuric patients should be informed that ZOFRAN ODT orally disintegrating tablets contain phenylalanine (a component of aspartame). Each 4-mg and 8-mg orally disintegrating tablet contains less than 0.03 mg phenylalanine.

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 with rates in the clinical trials of another drug and may not reflect the rates observed in practice.

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

Prevention of Chemotherapy-induced Nausea and Vomiting

The most common adverse reactions reported in ≥4% of 300 adults receiving a single 24-mg dose of ZOFRAN orally in 2 trials for the prevention of nausea and vomiting associated with highly emetogenic chemotherapy (cisplatin ≥50 mg/m^2) were: headache (11%) and diarrhea (4%).

The most common adverse reactions reported in 4 trials in adults for the prevention of nausea and vomiting associated with moderately emetogenic chemotherapy (primarily cyclophosphamide-based regimens) are shown in Table 3.

Table 3. Most Common Adverse Reactions in Adults[a] for the Prevention of Nausea and Vomiting Associated with Moderately Emetogenic Chemotherapy [Primarily Cyclophosphamide-based Regimens]

Adverse Reaction	ZOFRAN 8 mg Twice Daily (n = 242)	Placebo (n = 262)
Headache	58 (24%)	34 (13%)
Malaise/fatigue	32 (13%)	6 (2%)
Constipation	22 (9%)	1 (<1%)
Diarrhea	15 (6%)	10 (4%)

[a] Reported in ≥5% of patients treated with ZOFRAN and at a rate that exceeded placebo.

Less Common Adverse Reactions

Central Nervous System: Extrapyramidal reactions (less than 1% of patients).

Hepatic: Aspartate transaminase (AST) and/or alanine transaminase (ALT) values exceeded twice the upper limit of normal in approximately 1% to 2% of 723 patients receiving ZOFRAN and cyclophosphamide-based chemotherapy in US clinical trials. The increases were transient and did not appear to be related to dose or duration of therapy. On repeat exposure, similar transient elevations in transaminase values occurred in some courses, but symptomatic hepatic disease did not occur. The role of cancer chemotherapy in these biochemical changes is unclear.

Liver failure and death has been reported in cancer patients receiving concurrent medications, including potentially hepatotoxic cytotoxic chemotherapy and antibiotics. The etiology of the liver failure is unclear.

Integumentary: Rash (approximately 1% of patients).

Other (less than 2%): Anaphylaxis, bronchospasm, tachycardia, angina, hypokalemia, electrocardiographic alterations, vascular occlusive events, and grand mal seizures. Except for bronchospasm and anaphylaxis, the relationship to ZOFRAN is unclear.

Prevention of Radiation-induced Nausea and Vomiting

The most common adverse reactions (≥2%) reported in patients receiving ZOFRAN and concurrent radiotherapy were similar to those reported in patients receiving ZOFRAN and concurrent chemotherapy and were headache, constipation, and diarrhea.

Prevention of Postoperative Nausea and Vomiting

The most common adverse reactions reported in adults in trial(s) of prevention of postoperative nausea and vomiting are shown in Table 4. In these trial(s) patients were receiving multiple concomitant perioperative and postoperative medications in both treatment groups.

Table 4. Most Common Adverse Reactions in Adults[a] for the Prevention of Postoperative Nausea and Vomiting

Adverse Reaction	ZOFRAN 16 mg as a Single Dose (n = 550)	Placebo (n = 531)
Headache	49 (9%)	27 (5%)
Hypoxia	49 (9%)	35 (7%)
Pyrexia	45 (8%)	34 (6%)
Dizziness	36 (7%)	34 (6%)
Gynecological disorder	36 (7%)	33 (6%)
Anxiety/agitation	33 (6%)	29 (5%)
Urinary retention	28 (5%)	18 (3%)
Pruritus	27 (5%)	20 (4%)

[a] Reported in ≥5% of patients treated with ZOFRAN and at a rate that exceeded placebo.

In a crossover study with 25 subjects, headache was reported in 6 subjects administered ZOFRAN ODT with water (24%) as compared with 2 subjects administered ZOFRAN ODT without water (8%).

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.

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 interval prolongation have been reported.

General

Flushing. Rare cases of hypersensitivity reactions, sometimes severe (e.g., anaphylactic reactions, angioedema, bronchospasm, shortness of breath, hypotension, laryngeal edema, stridor) have also been reported.

Laryngospasm, shock, and cardiopulmonary arrest have occurred during allergic reactions in patients receiving injectable ondansetron.

Hepatobiliary

Liver enzyme abnormalities.

Lower Respiratory

Hiccups.

Neurology

Oculogyric crisis, appearing alone, as well as with other dystonic reactions.

Skin

Urticaria, Stevens-Johnson syndrome, and toxic epidermal necrolysis.

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.

7 DRUG INTERACTIONS

7.1 Serotonergic Drugs

Serotonin syndrome (including altered mental status, autonomic instability, and neuromuscular symptoms) has been described following the concomitant use of 5-HT_3 receptor antagonists and other serotonergic drugs, including selective serotonin reuptake inhibitors (SSRIs) and serotonin and noradrenaline reuptake inhibitors (SNRIs). Monitor for the emergence of serotonin syndrome. If symptoms occur, discontinue ZOFRAN and initiate supportive treatment *[see Warnings and Precautions (5.3)]*.

7.2 Drugs Affecting Cytochrome P-450 Enzymes

Ondansetron does not itself appear to induce or inhibit the cytochrome P-450 drug-metabolizing enzyme system of the liver *[see Clinical Pharmacology (12.3)]*. 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. 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 ZOFRAN is recommended for patients on these drugs *[see Clinical Pharmacology (12.3)]*.

7.3 Tramadol

Although no pharmacokinetic drug interaction between ondansetron and tramadol has been observed, data from 2 small trials indicate that when used together, ZOFRAN may increase patient-controlled administration of tramadol. Monitor patients to ensure adequate pain control when ondansetron is administered with tramadol.

7.4 Chemotherapy

Carmustine, etoposide, and cisplatin do not affect the pharmacokinetics of ondansetron.

In a crossover trial in 76 pediatric patients, intravenous ondansetron did not increase systemic concentrations of high-dose methotrexate.

7.5 Alfentanil and Atracurium

ZOFRAN 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

Risk Summary

Available data do not reliably inform the association of ZOFRAN and adverse fetal outcomes. Published epidemiological studies on the association between ondansetron and fetal outcomes have reported inconsistent findings and have important methodological limitations hindering interpretation [*see Data*]. Reproductive studies in rats and rabbits did not show evidence of harm to the fetus when ondansetron was administered during organogenesis at approximately 6 and 24 times the maximum recommended human oral dose of 24 mg/day, based on body surface area, respectively [*see Data*].

The background risk of major birth defects and miscarriage for the indicated population is unknown. In the US general population, the estimated background risk of major birth defects and miscarriages in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively.

Data

Human Data
Methodological limitations of the epidemiology studies preclude a reliable evaluation of the potential risk of adverse fetal outcomes with the use of ondansetron in pregnancy.

Two large retrospective cohort studies of ondansetron use in pregnancy have been published. In one study with 1,349 infants born to women who reported the use of ondansetron or received an ondansetron prescription in the first trimester, no increased risk for major congenital malformations was seen in aggregate analysis. In this same study, however, a sub-analysis for specific malformations reported an association between ondansetron exposure and cardiovascular defect (odds ratio (OR) 1.62 [95% CI (1.04, 2.14)]) and cardiac septal defect (OR 2.05 [95% CI (1.19, 3.28)]). The second study examined 1970 women who received ondansetron prescription during pregnancy and reported no association between ondansetron exposure and major congenital malformations, miscarriage or stillbirth, and infants of low birth weight or small for gestational age. Important methodological limitations with these studies include the uncertainty of whether women who filled a prescription actually took the medication, the concomitant use of other medications or treatments, and other unadjusted confounders that may account for the study findings.

A case-control study evaluating associations between several common non-cardiac malformations and multiple antiemetic drugs reported an association between maternal use of ondansetron and isolated cleft palate (reported adjusted OR = 2.37 [95% CI (1.18, 4.76)]). However, this association could be a chance finding, given the large number of drugs-birth defect comparisons in this study. It is unknown whether ondansetron exposure in utero in the cases of cleft palate occurred during the time of palate formation (the palate is formed between the 6^{th} and 9^{th} weeks of pregnancy) or whether mothers of infants with cleft palate used other medications or had other risk factors for cleft palate in the offspring. In addition, no cases of isolated cleft palate were identified in

the aforementioned two large retrospective cohort studies. At this time, there is no clear evidence that ondansetron exposure in early pregnancy can cause cleft palate.

Animal Data

In embryo-fetal development studies in rats and rabbits, pregnant animals received oral doses of ondansetron up to 15 mg/kg/day and 30 mg/kg/day, respectively, during the period of organogenesis. With the exception of a slight decrease in maternal body weight gain in the rabbits, there were no significant effects of ondansetron on the maternal animals or the development of the offspring. At doses of 15 mg/kg/day in rats and 30 mg/kg/day in rabbits, the maternal exposure margin was approximately 6 and 24 times the maximum recommended human oral dose of 24 mg/day, respectively, based on body surface area.

In a pre- and postnatal developmental toxicity study, pregnant rats received oral doses of ondansetron up to 15 mg/kg/day from Day 17 of pregnancy to litter Day 21. With the exception of a slight reduction in maternal body weight gain, there were no effects upon the pregnant rats and the pre- and postnatal development of their offspring, including reproductive performance of the mated F1 generation. At a dose of 15 mg/kg/day in rats, the maternal exposure margin was approximately 6 times the maximum recommended human oral dose of 24 mg/day, based on body surface area.

8.2 Lactation

Risk Summary

It is not known whether ondansetron is present in human milk. There are no data on the effects of ZOFRAN on the breastfed infant or the effects on milk production. However, it has been demonstrated that ondansetron is present in the milk of rats.

The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for ZOFRAN and any potential adverse effects on the breast-fed infant from ZOFRAN or from the underlying maternal condition.

8.4 Pediatric Use

The safety and effectiveness of orally administered ZOFRAN have been established in pediatric patients 4 years and older for the prevention of nausea and vomiting associated with moderately emetogenic cancer chemotherapy. Use of ZOFRAN in these age-groups is supported by evidence from adequate and well-controlled studies of ZOFRAN in adults with additional data from 3 open-label, uncontrolled, non-US trials in 182 pediatric patients aged 4 to 18 years with cancer who were given a variety of cisplatin or noncisplatin regimens *[see Dosage and Administration (2.2), Clinical Studies (14.1)]*.

Additional information on the use of ondansetron in pediatric patients may be found in ZOFRAN Injection prescribing information.

The safety and effectiveness of orally administered ZOFRAN have not been established in pediatric patients for:

- prevention of nausea and vomiting associated with highly emetogenic cancer chemotherapy.
- prevention of nausea and vomiting associated with radiotherapy.
- prevention of postoperative nausea and/or vomiting.

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, for which there were subgroup analyses, 938 (19%) were aged 65 years and older.

No overall differences in safety or effectiveness were observed between subjects 65 years of age and older and younger subjects. A reduction in clearance and increase in elimination half-life were seen in patients older than 75 years compared with younger subjects *[see Clinical Pharmacology (12.3)]*. There were an insufficient number of patients older than 75 years of age and older in the clinical trials to permit safety or efficacy conclusions in this age-group. 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. No dosage adjustment is needed in elderly patients.

8.6 Hepatic Impairment

No dosage adjustment is needed in patients with mild or moderate hepatic impairment.

In patients with severe hepatic impairment, clearance is reduced and the apparent volume of distribution is increased, resulting in a significant increase in the half-life of ondansetron. Therefore, do not exceed a total daily dose of 8 mg in patients with severe hepatic impairment (Child-Pugh score of 10 or greater) *[see Dosage and Administration (2.2), Clinical Pharmacology (12.3)]*.

8.7 Renal Impairment

No dosage adjustment is recommended for patients with any degree of renal impairment (mild, moderate, or severe). There is no experience beyond first-day administration of ondansetron *[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

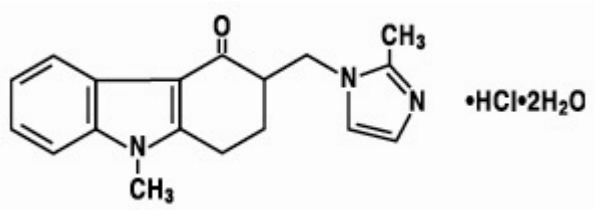
There is no specific antidote for ondansetron overdose. Patients should be managed with appropriate supportive therapy.

In addition to the adverse reactions listed above, the following adverse reactions have been described in the setting of ondansetron overdose: “Sudden blindness” (amaurosis) of 2 to 3 minutes’ duration plus severe constipation occurred in one patient that was administered 72 mg of ondansetron intravenously as a single dose. Hypotension (and faintness) occurred in a patient that took 48 mg of ZOFRAN tablets. Following infusion of 32 mg over only a 4-minute period, a vasovagal episode with transient second-degree heart block was observed. In all instances, the adverse reactions resolved completely.

Pediatric cases consistent with serotonin syndrome have been reported after inadvertent oral overdoses of ondansetron (exceeding estimated ingestion of 5 mg per kg) in young children. Reported symptoms included somnolence, agitation, tachycardia, tachypnea, hypertension, flushing, mydriasis, diaphoresis, myoclonic movements, horizontal nystagmus, hyperreflexia, and seizure. Patients required supportive care, including intubation in some cases, with complete recovery without sequelae within 1 to 2 days.

11 DESCRIPTION

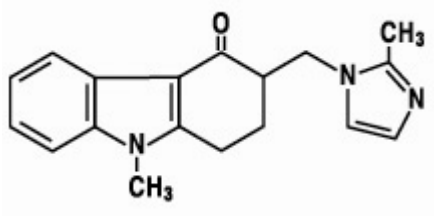
The active ingredient in ZOFRAN tablets and ZOFRAN oral solution is ondansetron hydrochloride as the dihydrate, the racemic form of ondansetron and a selective blocking agent of the serotonin 5-HT_3 receptor type. Chemically it is (±) 1, 2, 3, 9-tetrahydro-9-methyl-3-[(2-methyl-1H-imidazol-1-yl)methyl]-4H-carbazol-4-one,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



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

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

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



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

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

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

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

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Ondansetron is a selective 5-HT_3 receptor antagonist. While its mechanism of action has not been fully characterized, ondansetron is not a dopamine-receptor antagonist. Serotonin receptors of the 5-HT_3 type are present both peripherally on vagal nerve terminals and centrally in the chemoreceptor trigger zone of the area postrema. It is not certain whether ondansetron's antiemetic action is mediated centrally, peripherally, or in both sites. However, cytotoxic chemotherapy appears to be associated with release of serotonin from the enterochromaffin cells of the small intestine. In humans, urinary 5-hydroxyindoleacetic acid (5-HIAA) excretion increases after cisplatin administration in parallel with the onset of emesis. The released serotonin may stimulate the vagal afferents through the 5-HT_3 receptors and initiate the vomiting reflex.

12.2 Pharmacodynamics

In healthy subjects, single intravenous doses of 0.15 mg/kg of ondansetron had no effect on esophageal motility, gastric motility, lower esophageal sphincter pressure, or small intestinal transit time. Multiday administration of ondansetron has been shown to slow colonic transit in healthy subjects. Ondansetron has no effect on plasma prolactin concentrations.

Cardiac Electrophysiology

QTc interval prolongation was studied in a double-blind, single intravenous dose, placebo- and positive-controlled, crossover trial in 58 healthy subjects. The maximum mean (95% upper confidence bound) difference in QTcF from placebo after baseline correction was 19.5 (21.8) milliseconds and 5.6 (7.4) milliseconds after 15-minute intravenous infusions of 32 mg and 8 mg of ondansetron injection, respectively. A significant exposure-response relationship was identified between ondansetron concentration and ΔΔQTcF. Using the established exposure-response relationship, 24 mg infused intravenously over 15 minutes had a mean predicted (95% upper prediction interval) ΔΔQTcF of 14.0 (16.3) milliseconds. In contrast, 16 mg infused intravenously over 15 minutes using the same model had a mean predicted (95% upper prediction interval) ΔΔQTcF of 9.1 (11.2) milliseconds. In this study, the 8-mg dose infused over 15 minutes did not prolong the QT interval to any clinically relevant extent.

12.3 Pharmacokinetics

Absorption

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

Ondansetron systemic exposure does not increase proportionately to dose. The AUC from a 16-mg tablet was 24% greater than predicted from an 8-mg tablet dose. This may reflect some reduction of first-pass metabolism at higher oral doses.

Food Effects: Bioavailability is also slightly enhanced by the presence of food.

Distribution

Plasma protein binding of ondansetron as measured in vitro was 70% to 76% over the concentration range of 10

to 500 ng/mL. Circulating drug also distributes into erythrocytes.

Elimination

Metabolism and Excretion: Ondansetron is extensively metabolized in humans, with approximately 5% of a radiolabeled dose recovered as the parent compound from the urine. The metabolites are observed in the urine. The primary metabolic pathway is hydroxylation on the indole ring followed by subsequent glucuronide or sulfate conjugation.

In vitro metabolism studies have shown that ondansetron is a substrate for human hepatic cytochrome P-450 enzymes, including CYP1A2, CYP2D6, and CYP3A4. In terms of overall ondansetron turnover, CYP3A4 played the predominant role. Because of the multiplicity of metabolic enzymes capable of metabolizing ondansetron, it is likely that inhibition or loss of one enzyme (e.g., CYP2D6 genetic deficiency) will be compensated by others and may result in little change in overall rates of ondansetron elimination.

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.

Specific Populations

Age: Geriatric Population: A reduction in clearance and increase in elimination half-life are seen in patients older than 75 years compared to younger subjects *[see Use in Specific Populations (8.5)]*.

Sex: Gender differences were shown in the disposition of ondansetron given as a single dose. The extent and rate of absorption are greater in women than men. Slower clearance in women, a smaller apparent volume of distribution (adjusted for weight), and higher absolute bioavailability resulted in higher plasma ondansetron concentrations. These higher plasma concentrations may in part be explained by differences in body weight between men and women. It is not known whether these sex-related differences were clinically important. More detailed pharmacokinetic information is contained in Tables 5 and 6.

Table 5. Pharmacokinetics in Male and Female Healthy Subjects after a Single Dose of a ZOFRAN 8-mg Tablet

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

Table 6. Pharmacokinetics in Male and Female Healthy Subjects after a Single Dose of a ZOFRAN 24-mg Tablet

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

Renal Impairment: Renal impairment is not expected to significantly influence the total clearance of ondansetron as renal clearance represents only 5% of the overall clearance. However, the mean plasma clearance of ondansetron was reduced by about 50% in patients with severe renal impairment (creatinine clearance less than 30 mL/min). The reduction in clearance was variable and not consistent with an increase in half-life *[see Use in Specific Populations (8.7)]*.

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 with 5.7 hours in healthy subjects. 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 *[see Dosage and Administration (2.2), Use in Specific Populations (8.6)]*.

Drug Interaction Studies

CYP 3A4 Inducers: Ondansetron elimination may be affected by cytochrome P-450 inducers. In a pharmacokinetic trial of 16 epileptic patients maintained chronically on CYP3A4 inducers, carbamazepine, or phenytoin, a reduction in AUC, C_{max}, and $t_{½}$ of ondansetron was observed. This resulted in a significant increase in the clearance of ondansetron. However, this increase is not thought to be clinically relevant *[see Drug Interactions (7.2)]*.

Chemotherapeutic Agents: Carmustine, etoposide, and cisplatin do not affect the pharmacokinetics of ondansetron *[see Drug Interactions (7.4)]*.

Antacids: Concomitant administration of antacids does not alter the absorption of ondansetron.

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 mg/kg per day and 30 mg/kg per day, respectively (approximately 4 and 6 times the maximum recommended human oral dose of 24 mg per 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 6 times the maximum recommended human oral dose of 24 mg per day, based on body surface area) did not affect fertility or general reproductive performance of male and female rats.

14 CLINICAL STUDIES

14.1 Prevention of Chemotherapy-induced Nausea and Vomiting

Highly Emetogenic Chemotherapy

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

The first trial compared oral doses of ondansetron 24 mg as a single dose, 8 mg every 8 hours for 2 doses, and 32 mg as a single dose in 357 adult cancer patients receiving chemotherapy regimens containing cisplatin ≥50 mg/m^2. The first or single dose was administered 30 minutes prior to chemotherapy. A total of 66% of patients in the ondansetron 24-mg once-a-day group, 55% in the ondansetron 8-mg twice-a-day group, and 55% in the ondansetron 32-mg once-a-day group completed the 24-hour trial period with 0 emetic episodes and no rescue antiemetic medications, the primary endpoint of efficacy. Each of the 3 treatment groups was shown to be statistically significantly superior to a historical placebo control.

In the same trial, 56% of patients receiving a single 24-mg oral dose of ondansetron experienced no nausea during the 24-hour trial period, compared with 36% of patients in the oral ondansetron 8-mg twice-a-day group (P = 0.001) and 50% in the oral ondansetron 32-mg once-a-day group. Dosage regimens of ZOFRAN 8 mg twice daily and 32 mg once daily are not recommended for the prevention of nausea and vomiting associated with highly emetogenic chemotherapy *[see Dosage and Administration (2.1)]*.

In a second trial, efficacy of a single 24-mg oral dose of ZOFRAN for the prevention of nausea and vomiting associated with highly emetogenic cancer chemotherapy, including cisplatin ≥50 mg/m^2, was confirmed.

Moderately Emetogenic Chemotherapy

A randomized, placebo-controlled, double-blind trial was conducted in the US in 67 patients receiving a cyclophosphamide-based chemotherapy regimen containing doxorubicin. The first 8-mg dose of ZOFRAN was administered 30 minutes before the start of chemotherapy, with a subsequent dose 8 hours after the first dose, followed by 8 mg of ZOFRAN twice a day for 2 days after the completion of chemotherapy.

ZOFRAN was significantly more effective than placebo in preventing vomiting. Treatment response was based on the total number of emetic episodes over the 3-day trial period. The results of this trial are summarized in Table 7:

Table 7. Emetic Episodes: Treatment Response in Patients Receiving Moderately Emetogenic Chemotherapy (Cyclophosphamide-based Regimen Containing Doxorubicin)

	ZOFRAN (n = 33)	**Placebo (n = 34)**	***P* Value**
Treatment response 0 Emetic episodes 1 to 2 Emetic episodes More than 2 emetic episodes/withdrawn	 20 (61%) 6 (18%) 7 (21%)	 2 (6%) 8 (24%) 24 (71%)	 <0.001 <0.001
Median number of emetic episodes	0.0	Undefined[a]	
Median time to first emetic episode (hours)	Undefined[b]	6.5	

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

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

In a double-blind US trial in 336 patients receiving a cyclophosphamide-based chemotherapy regimen containing either methotrexate or doxorubicin, ZOFRAN 8 mg administered twice a day was as effective as ZOFRAN 8 mg administered 3 times a day in preventing nausea and vomiting. ZOFRAN 8 mg three times daily is not a recommended regimen for the treatment of moderately emetogenic chemotherapy *[see Dosage and Administration (2.1)]*.

Treatment response was based on the total number of emetic episodes over the 3-day trial period. See Table 8 for the details of the dosage regimens studied and results of this trial.

Table 8. Emetic Episodes: Treatment Response after ZOFRAN Tablets Administered Twice a Day and Three Times a Day

	ZOFRAN Tablets	
	8 mg Twice Daily[a] (n = 165)	**8 mg Three Times a Day[b] (n = 171)**
Treatment response		
0 Emetic episodes	101 (61%)	99 (58%)
1-2 Emetic episodes	16 (10%)	17 (10%)
More than 2 emetic episodes/withdrawn	48 (29%)	55 (32%)
Median number of emetic episodes	0.0	0.0
Median time to first emetic episode (h)	Undefined[c]	Undefined[c]
Median nausea scores (0-100)[d]	6	6

[a] The first 8-mg dose was administered 30 minutes before the start of emetogenic chemotherapy, with a subsequent 8-mg dose 8 hours after the first dose, followed by 8 mg administered twice a day for 2 days after the completion of chemotherapy.

[b] The first 8-mg dose was administered 30 minutes before the start of emetogenic chemotherapy, with subsequent 8-mg doses at 4 hours and 8 hours after the first dose, followed by 8 mg administered 3 times a day for 2 days after the completion of chemotherapy.

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

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

Re-treatment

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

Pediatric Trials

Three open-label, single-arm, non-US trials have been performed with 182 pediatric patients aged 4 to 18 years with cancer who were given a variety of cisplatin or noncisplatin regimens. The initial dose of ZOFRAN injection ranged from 0.04 to 0.87 mg per kg (total dose of 2.16 mg to 12 mg) followed by the administration of oral doses of ZOFRAN ranging from 4 to 24 mg daily for 3 days. In these trials, 58% of the 170 evaluable patients had a complete response (no emetic episodes) on Day 1. In two trials the response rates to ZOFRAN 4 mg three times a day in patients younger than 12 years was similar to ZOFRAN 8 mg three times daily in patients 12 to 18 years. Prevention of emesis in these pediatric patients was essentially the same as for adults.

14.2 Radiation-induced Nausea and Vomiting

Total Body Irradiation

In a randomized, placebo-controlled, double-blind trial in 20 patients, 8 mg of ZOFRAN administered 1.5 hours before each fraction of radiotherapy for 4 days was significantly more effective than placebo in preventing vomiting induced by total body irradiation. Total body irradiation consisted of 11 fractions (120 cGy per fraction) over 4 days for a total of 1,320 cGy. Patients received 3 fractions for 3 days, then 2 fractions on Day 4.

Single High-dose Fraction Radiotherapy

In an active-controlled, double-blind trial in 105 patients receiving single high-dose radiotherapy (800 to 1,000 cGy) over an anterior or posterior field size of $\geq$80 cm^2 to the abdomen, ZOFRAN was significantly more effective than metoclopramide with respect to complete control of emesis (0 emetic episodes). Patients received the first dose of ZOFRAN (8 mg) or metoclopramide (10 mg) 1 to 2 hours before radiotherapy. If radiotherapy was given in the morning, 8 mg of ZOFRAN or 10 mg of metoclopramide was administered in the late afternoon and repeated again before bedtime. If radiotherapy was given in the afternoon, patients took 8 mg of ZOFRAN or 10 mg of metoclopramide only once before bedtime. Patients continued the doses of oral medication three times daily for 3 days.

Daily Fractionated Radiotherapy

In an active-controlled, double-blind trial in 135 patients receiving a 1- to 4-week course of fractionated radiotherapy (180 cGy doses) over a field size of $\geq$100 cm^2 to the abdomen, ZOFRAN was significantly more effective than prochlorperazine with respect to complete control of emesis (0 emetic episodes). Patients received the first dose of ZOFRAN (8 mg) or prochlorperazine (10 mg) 1 to 2 hours before the first daily radiotherapy fraction, with subsequent 8-mg doses approximately every 8 hours on each day of radiotherapy.

14.3 Postoperative Nausea and Vomiting

In two placebo-controlled, double-blind trials (one conducted in the US and the other outside the US) in 865 females undergoing inpatient surgical procedures, ZOFRAN 16 mg as a single dose or placebo was administered one hour before the induction of general balanced anesthesia (barbiturate, opioid, nitrous oxide, neuromuscular blockade, and supplemental isoflurane or enflurane), ZOFRAN tablets was significantly more effective than placebo in preventing postoperative nausea and vomiting.

No trials have been performed in males.

16 HOW SUPPLIED/STORAGE AND HANDLING

ZOFRAN Tablets

- 4 mg (ondansetron hydrochloride dihydrate equivalent to 4 mg of ondansetron), are white, oval, film-coated tablets engraved with “Zofran” on one side and “4” on the other in bottles of 30 tablets (NDC 0173-0446-00).

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

- 8 mg (ondansetron hydrochloride dihydrate equivalent to 8 mg of ondansetron), are yellow, oval, film-coated tablets engraved with “Zofran” on one side and “8” on the other in bottles of 30 tablets (NDC 0173-0447-00).

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

ZOFRAN ODT Orally Disintegrating Tablets

- 4 mg (as 4 mg ondansetron base) are white, round and plano-convex tablets debossed with a “Z4” on one side in unit dose packs of 30 tablets (NDC 0173-0569-00).
- 8 mg (as 8 mg ondansetron base) are white, round and plano-convex tablets debossed with a “Z8” on one side in unit dose packs of 30 tablets (NDC 0173-0570-00).

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

ZOFRAN Oral Solution

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

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

17 PATIENT COUNSELING INFORMATION

QT Prolongation

Inform patients that ZOFRAN may cause serious cardiac arrhythmias such as QT prolongation. Instruct patients to tell their healthcare provider right away if they perceive a change in their heart rate, if they feel lightheaded, or if they have a syncopal episode.

Hypersensitivity Reactions

Inform patients that ZOFRAN may cause hypersensitivity reactions, some as severe as anaphylaxis and bronchospasm. Instruct patients to immediately report any signs and symptoms of hypersensitivity reactions, including fever, chills, rash, or breathing problems to their healthcare provider.

Masking of Progressive Ileus and Gastric Distension

Inform patients following abdominal surgery or those with chemotherapy-induced nausea and vomiting that ZOFRAN may mask signs and symptoms of bowel obstruction. Instruct patients to immediately report any signs or symptoms consistent with a potential bowel obstruction to their healthcare provider.

Drug Interactions

- Instruct the patient to report the use of all medications, especially apomorphine, to their healthcare provider. Concomitant use of apomorphine and ZOFRAN may cause a significant drop in blood pressure and loss of consciousness.
- Advise patients of the possibility of serotonin syndrome with concomitant use of ZOFRAN and another serotonergic agent such as medications to treat depression and migraines. Advise patients to seek immediate medical attention if the following symptoms occur: changes in mental status, autonomic instability, neuromuscular symptoms with or without gastrointestinal symptoms.

Administration of ZOFRAN ODT Orally Disintegrating Tablets

Instruct patients not to remove ZOFRAN ODT tablets from the blister until just prior to dosing.

- Do not attempt to push ZOFRAN ODT tablets through the foil backing.
- With dry hands, peel back the foil backing of 1 blister and gently remove the tablet.
- Immediately place the ZOFRAN ODT tablet on top of the tongue where it will dissolve in seconds, then swallow with saliva.
- Administration with liquid is not necessary.
- Peelable illustrated stickers are affixed to the product carton that can be provided with the prescription to ensure proper use and handling of the product.

GlaxoSmithKline
Research Triangle Park, NC 27709

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

ZOFRAN ODT Orally Disintegrating Tablets:
Manufactured for
GlaxoSmithKline
Research Triangle Park, NC 27709

ZFT:XPI

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

020781Orig1s017

PHARMACOLOGY REVIEW(S)

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

PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION

Application number/Supporting documents:	NDA 20103/S-033, NDA 20605/S-017, and NDA 20781/S-017
Applicant's letter date:	September 22, 2015 (NDA 20103/SDN#594, NDA 20605/SDN#253, NDA 20781/SDN#285)
CDER stamp date:	September 22, 2015
Product:	Zofran (ondansetron hydrochloride) tablets, Zofran (ondansetron hydrochloride) oral solution, and Zofran (ondansetron) orally disintegrating tablets (ODT)
Indication:	Prevention of nausea and vomiting
Applicant:	Novartis Pharmaceuticals corporation
Review Division:	Division of Gastroenterology and Inborn Errors Products (DGIEP)
Reviewer:	Tracy Behrsing, Ph.D.
Supervisor/Team Leader:	Sushanta Chakder, Ph.D.
Division Director:	Donna Griebel, M.D.
Project Manager:	Heather Buck, MS, MBA

SUMMARY AND EVALUATION

GlaxoSmithKline submitted NDA 20103, Supplement 033; NDA 20605, Supplement 017; and NDA 20781, Supplement 017 for the conversion of the labeling of Zofran tablets, oral solution, and oral disintegrating tablets (ODT), respectively, in the Physician Labeling Rule (PLR) format. While the originally proposed text for sections 8.1 (b) (4) was revised in a submission dated March 3, 2015, it was determined that the label would be converted according to the Pregnancy and Lactation Labeling Rule (PLLR) format at a later date. Recommended changes to the labeling were provided in a nonclinical review dated May 6, 2015.

As of March 23, 2015, NDA 201013, NDA 20605, and NDA 20781 have been transferred from GlaxoSmithKline to Novartis Pharmaceuticals Corporation. In the current September 22, 2015 amendment submission, the Applicant has proposed language to convert the labeling according to PLLR format. Nonclinical information in the Applicant's proposed labeling is reviewed below, and the following changes are recommended.

Applicant's Version (dated September 22, 2015):

8.1 Pregnancy

Risk Summary

(b) (4)

Data

Human Data

(b) (4)

Animal Data

In embryo-fetal development studies in rats and rabbits, pregnant animals received oral doses of ZOFRAN up to 15 mg/kg/day and 30 mg/kg/day, respectively, during the period of organogenesis. With the exception of a slight decrease in maternal body weight gain in the rabbits, there were no significant effects of ZOFRAN on the maternal animals or the development of the offspring. At doses of 15 mg/kg/day in rats and 30 mg/kg/day in rabbits, the maternal exposure margin was approximately 6 and 24 times the maximum human oral dose of 24 mg/day, respectively, based on body surface area.

In a pre- and postnatal developmental toxicity study, pregnant rats received oral doses of ZOFRAN up to 15 mg/kg/day from Day 17 of pregnancy to litter Day 21. With the exception of a slight reduction in maternal body weight gain, there were no effects upon the pregnant rats and the pre- and postnatal development of their offspring, including reproductive performance of the mated F1 generation. At a dose of 15 mg/kg/day in rats, the maternal exposure margin was approximately 6 times the maximum human oral dose of 24 mg/day, based on body surface area.

Evaluation: In the Animal Data section, the drug should be referred to as ondansetron rather than ZOFRAN.

Recommended Version:

8.1 Pregnancy

Risk Summary

(b) (4)

(b) (4)

Data

Human Data

(b) (4)

Animal Data

In embryo-fetal development studies in rats and rabbits, pregnant animals received oral doses of ondansetron up to 15 mg/kg/day and 30 mg/kg/day, respectively, during the period of organogenesis. With the exception of a slight decrease in maternal body weight gain in the rabbits, there were no significant effects of ondansetron on the maternal animals or the development of the offspring. At doses of 15 mg/kg/day in rats and 30 mg/kg/day in rabbits, the maternal exposure margin was approximately 6 and 24 times the maximum human oral dose of 24 mg/day, respectively, based on body surface area.

In a pre- and postnatal developmental toxicity study, pregnant rats received oral doses of ondansetron up to 15 mg/kg/day from Day 17 of pregnancy to litter Day 21. With the exception of a slight reduction in maternal body weight gain, there were no effects upon the pregnant rats and the pre- and postnatal development of their offspring, including reproductive performance of the mated F1 generation. At a dose of 15 mg/kg/day in

rats, the maternal exposure margin was approximately 6 times the maximum human oral dose of 24 mg/day, based on body surface area.

Applicant's Version (dated September 22, 2015):

8.2 Lactation

Risk Summary

(b) (4)

Evaluation: In the sentence regarding excretion of the drug in breast milk of rats, the drug should be referred to as ondansetron rather than ZOFRAN.

Recommended Version:

8.2 Lactation

Risk Summary

(b) (4)

Applicant's Version (dated September 22, 2015):

(b) (4)

(b) (4)

Evaluation: This section does not contain nonclinical information; and therefore, was not reviewed.

Applicant's Version (dated September 22, 2015):

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 mg/kg per day and 30 mg/kg per day, respectively (approximately 4 and 6 times the maximum human oral dose of 24 mg per 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 6 times the maximum human oral dose of 24 mg per day, based on body surface area) did not affect fertility or general reproductive performance of male and female rats.

Evaluation: No changes are recommended in this section.

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

/s/

TRACY L BEHRSING
09/24/2015

SUSHANTA K CHAKDER
09/24/2015

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

PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION

Application number/Supporting documents:	NDA 20103/S-033, NDA 20605/S-017, and NDA 20781/S-017
Applicant's letter date:	March 19, 2014 (NDA 20103/S-033/SDN#573, NDA 20605/S-017/SDN#231, NDA 20781/S-017/SDN#264); October 10, 2014 (NDA 20103/S-033/SDN#581, NDA 20605/S-017/SDN#239, NDA 20781/S-017/SDN#272); March 3, 2015 (NDA 20103/S-033/SDN#583, NDA 20605/S-017/SDN#242, NDA 20781/S-017/SDN#275)
CDER stamp date:	March 19, 2014; October 10, 2014; March 3, 2015
Product:	Zofran (ondansetron hydrochloride) tablets, Zofran (ondansetron hydrochloride) oral solution, and Zofran (ondansetron) orally disintegrating tablets (ODT)
Indication:	Prevention of nausea and vomiting
Applicant:	Glaxo Group Limited, England d/b/a GlaxoSmithKline
Review Division:	Division of Gastroenterology and Inborn Errors Products (DGIEP)
Reviewer:	Tracy Behrsing, Ph.D.

Supervisor/Team Leader:	Sushanta Chakder, Ph.D.
Division Director:	Donna Griebel, M.D.
Project Manager:	Heather Buck, MS, MBA

SUMMARY AND EVALUATION

GlaxoSmithKline submitted NDA 20103, Supplement 033; NDA 20605, Supplement 017; and NDA 20781, Supplement 017 for the conversion of the labeling of Zofran tablets, oral solution, and oral disintegrating tablets (ODT), respectively, in the Physician Labeling Rule (PLR) format.

Although the proposed labeling conforms to the PLR format, the following recommended changes should be incorporated into the labeling. While the Applicant revised the originally proposed text for sections 8.1 (b) (4) in the most recent submission dated March 3, 2015, it has been determined that the label will be converted according to the Pregnancy and Lactation Rule (PLLR) format at a later date. Thus, the following recommended changes were developed in collaboration with the Maternal Health team.

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Evaluation: The label will be converted according to the PLLR format at a later date.

Recommended Version:

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Evaluation: No changes are recommended in this section.

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/s/

TRACY L BEHRSING
05/06/2015

SUSHANTA K CHAKDER
05/06/2015

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

020781Orig1s017

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

CLINICAL PHARMACOLOGY REVIEW

NDA: 20103 S-033	Zofran tablets
20781 S-017	Zofran ODT
20605 S-017	Zofran oral solution
Brand Name	Zofran
Generic Name	Ondansetron
Reviewer	Elizabeth Y. Shang, Ph.D., R.Ph
Team Leader	Sue-Chih Lee, Ph.D.
OCP Division	DCP3
OND division	DGIEP
Sponsor	Novartis
Submission Type	NDA (PAS PLR Conversions)
Review Priority	Standard

Table of Contents

1 Executive Summary

1.1 Recommendation

The Office of Clinical Pharmacology/Division of Clinical Pharmacology 3 (OCP/DCP3) has reviewed the PLR conversion labeling supplement submitted on March 19, 2014. We found this supplement acceptable from an OCP standpoint. Labeling comments were conveyed to the sponsor.

1.2 Phase IV Commitments

None

1.3 Current Submission

The clinical pharmacology related labeling changes in this submission are editorial in nature to comply with the Clinical Pharmacology guidance on labeling[1] and best labeling practices. The

[1] Guidance for Industry (Draft, 2014): Clinical Pharmacology Labeling for Human Prescription Drug and Biological Products — Considerations, Content, and Format

sponsor's initial proposed PLR conversion language also included relevant information presented in Zofran IV label (rev. 2014) which was already in PLR format.

Labeling negotiation is ongoing. Please refer to the final approved labeling when available. The following captures the key clinical pharmacology related labeling changes.

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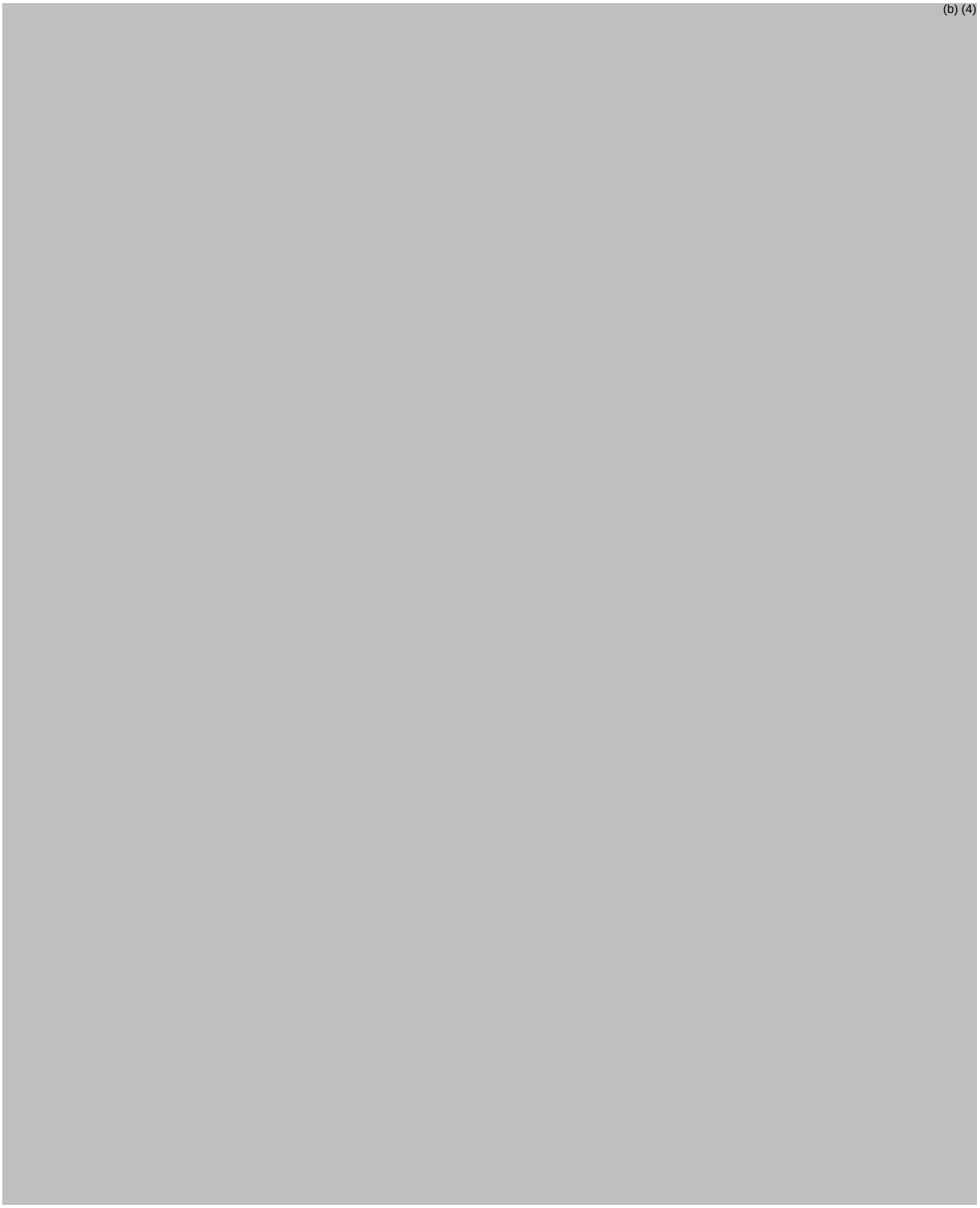

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/s/

ELIZABETH Y SHANG
09/22/2016

SUE CHIH H LEE
09/22/2016

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

020781Orig1s017

OTHER REVIEW(S)

DIVISION OF GASTROENTEROLOGY AND INBORN ERRORS PRODUCTS
Clinical Labeling Review – PLR Conversion

Trade Name (Established Name): ZOFRAN® (ondansetron hydrochloride) Tablets; ZOFRAN ODT® (ondansetron) Orally Disintegrating Tablets, ZOFRAN® (ondansetron hydrochloride) Oral Solution

Submissions:
NDA 20103/S-033: Zofran (ondansetron) tablets (approved 1992)
NDA 20781/S-017: Zofran ODT (approved 1999)
NDA 20605/S-017: Zofran oral solution (approved 1997)

Submission Dates: March 19, 2014; October 10, 2014; March 3, 2015; July 21, 2105; September 22, 2015; May 10, 2016; and August 2, 2016

Date of Last Approved Labeling: December 10, 2013

Indications:
1. Prevention of nausea and vomiting associated with highly emetogenic cancer chemotherapy, including cisplatin ≥ 50 mg/m^2.
2. Prevention of nausea and vomiting associated with initial and repeat courses of moderately emetogenic cancer chemotherapy.
3. Prevention of nausea and vomiting associated with radiotherapy in patients receiving either total body irradiation, single high-dose fraction to the abdomen, or daily fractions to the abdomen.
4. Prevention of postoperative nausea and/or vomiting. As with other antiemetics, routine prophylaxis is not recommended for patients in whom there is little expectation that nausea and/or vomiting will occur postoperatively. In patients where nausea and/or vomiting must be avoided postoperatively, ZOFRAN Tablets, ZOFRAN ODT Orally Disintegrating Tablets, and ZOFRAN Oral Solution are recommended even where the incidence of postoperative nausea and/or vomiting is low.

Sponsor: GlaxoSmithKline

Reviewer: Joette M. Meyer, PharmD, Associate Director for Labeling

The sponsor submitted revised labeling on March 19, 2014 that complies with the January 24, 2006 Final Rule on Requirements on Content and Format of Labeling for Human Prescription Drug and Biological Products, commonly referred to as the Physician's Labeling Rule (PLR). This submission was a voluntary PLR conversion by the sponsor.

The division undertook the processes of revising the Zofran® Prescribing Information (PI) in order to ensure that it was aligned with current labeling regulations (21 CFR 201.57), PLR labeling guidances, the Selected Requirements for Prescribing Information (SRPI), and best labeling practices.

The following is a summary of the substantive revisions made to the PI by section.

HIGHLIGHTS

In general, revisions to this section were made in alignment with the revisions in the Full Prescribing Information and will not be described here, see below.

The following information is of note:

Highlights Limitation Statement: The statement was expanded to include all 3 formulations (i.e., from "ZOFRAN" to "ZOFRAN TABLETS, ZOFRAN ODT, and ZOFRAN ORAL SOLUTION"

Product Title: The three oral formulations are represented as follows, consistent with "model product labeling" recommendations provided by the Labeling Development Team in the Office of New Drugs:

ZOFRAN (ondansetron hydrochloride) tablets, for oral use

ZOFRAN ODT (ondansetron) orally disintegrating tablets

ZOFRAN (ondansetron hydrochloride) oral solution

Initial U.S. Approval: 1991 is the date that ondansetron as an active moiety was first FDA-approved and reflects the approval date of the intravenous formulation.

The Established Pharmacology Class is "5-HT_3 receptor antagonist", consistent with the EPC Text Phase listing found on the FDA website.[1]

FULL PRESCRIBING INFORMATION

1. INDICATIONS AND USAGE

The wording of the indications was retained:

> ZOFRAN® is indicated for the prevention of nausea and vomiting associated with:
>
> - highly emetogenic cancer chemotherapy, including cisplatin ≥50 mg/m^2.
> - initial and repeat courses of moderately emetogenic cancer chemotherapy.
> - radiotherapy in patients receiving either total body irradiation, single high-dose fraction to the abdomen, or daily fractions to the abdomen.
>
> ZOFRAN is also indicated for the prevention of postoperative nausea and/or vomiting.

For the fourth indication, prevention of postoperative nausea and vomiting, the following descriptive wording was removed, as it was not felt to add useful information:

> ~~As with other antiemetics, routine prophylaxis is not recommended for patients in whom there is little expectation that nausea and/or vomiting will occur postoperatively. In patients where nausea and/or vomiting must be avoided postoperatively, ZOFRAN Tablets, ZOFRAN ODT Orally Disintegrating Tablets, and ZOFRAN Oral Solution are recommended even where the incidence of postoperative nausea and/or vomiting is low.~~

[1] http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/UCM428333.pdf

2. DOSAGE AND ADMINISTRATION

Information was reorganized into 3 subsections:

2.1 Dosage

2.2 Dosage in Hepatic Impairment

2.3 Administration Instructions for ZOFRAN ODT Orally Disintegrating Tablets

In Section 2.1, dosing information was reorganized into two tables: one for adult dosing by indication and the other for pediatric dosing information by indication, for ease of use. Of note, the only indication in pediatric patients (4 to 17 years of age) is for prevention of nausea and vomiting associated with moderately emetogenic cancer chemotherapy.

Information on dosage forms and strengths was removed from this section. For example, for the indication of prevention of nausea and vomiting associated with highly emetogenic cancer chemotherapy, the currently approved label says:

> The recommended adult oral dosage of ZOFRAN is 24 mg given as three 8-mg tablets administered 30 minutes before the start of single-day highly emetogenic chemotherapy, including cisplatin ≥ 50 mg/m^2

The revised dosage information is written as:

Indication	Dosage Regimen
Highly Emetogenic Cancer Chemotherapy	A single 24-mg dose administered 30 minutes before the start of single-day highly emetogenic chemotherapy, including cisplatin ≥50 mg/m^2

The reason to remove the dosage forms and strengths (e.g., three 8-mg tablets) from Dosage and Administration is that in the CLINCIAL PHARMACOLOGY, Pharmacokinetics subsection of the currently approved label it states:

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

This information was relocated to the beginning of the Dosage and Administration section, to precede the dosing tables, and was rewritten, as follows, to remove the word "bioequivalent", since this term generally should not be included in labeling.[2]

> Corresponding doses of ZOFRAN tablets, ZOFRAN ODT® orally disintegrating tablets and ZOFRAN oral solution may be used interchangeably.

Statements with regard to "geriatric" dosing and "dosage adjustment for patients with impaired renal function" were removed, as there were no recommended dosage adjustments provided and the recommended dosage for these subpopulations is the same as for the general population.

In Section 2.2, information on dosage in hepatic impairment was simplified to remove discussion of changes in PK parameters (i.e., clearance is reduced and apparent volume of distribution is

[2] http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM109739.pdf

increased with a resultant increase in plasma half-life) and cross-references were added to other sections where additional information can be obtained.

> **2.2 Dosage in Hepatic Impairment**
>
> In patients with severe hepatic impairment (Child-Pugh score of 10 or greater), do not exceed a total daily dose of 8 mg *[see Use in Specific Populations (8.6), Clinical Pharmacology (12.3)]*.

Administration instructions for the ODT formulation were moved from the beginning of the Dosage and Administration section to the end, and numbered as Section 2.3, since the other information on dosage and dosage adjustments are considered to be more important for appropriate use of the drug.

3. DOSAGE FORMS AND STRENGHTS

This section was created using information in the HOW SUPPLIED section of the currently approved label, i.e., available dosage forms, strengths of the dosage forms, and information about imprinting, shape, color, and flavor.

4. CONTRAINDICATIONS

No substantive changes.

5. WARNINGS AND PRECAUTIONS

Information from the currently approved label in the WARNINGS and PRECAUTIONS sections were organized into the following subsections based upon relative public health significance:

> **5.1 Hypersensitivity Reactions**
>
> **5.2 QT Prolongation**
>
> **5.3 Serotonin Syndrome**
>
> **5.4 Masking of Progressive Ileus and Gastric Distension**
>
> **5.5 Phenylketonuria**

No substantive changes were made to the content.

6. ADVERSE REACTIONS

In Section 6.1 Clinical Trials Experience the introductory sentence was revised to be consistent with the Adverse Reactions labeling guidance[3]:

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

The term “adverse events” was replaced with adverse reactions.

[3] http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075057.pdf

Information on the dosage form and strength was removed in this section. For example, for the prevention of chemotherapy-induced nausea and vomiting the current label states (italics added for emphasis):

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

Since the 24-mg tablet strength is no longer marketed, "tablet" was changed to "dose" (italics added for emphasis).

> The most common adverse reactions reported in ≥4% of 300 adults *receiving a single 24-mg dose of ZOFRAN orally* in 2 trials for the prevention of nausea and vomiting associated with highly emetogenic chemotherapy (cisplatin ≥50 mg/m^2) were: headache (11%) and diarrhea (4%).

Also, Table 5 presented adverse reactions for the three treatment groups studied in the two trials: ondansetron 24 mg once daily, ondansetron 8 mg twice daily, and ondansetron 32 mg once daily. However, only the 24 mg once daily regimen is recommended in the Dosage and Administration section. Therefore, the information on the two other dosage regimens were removed and the table was replaced with descriptive information since only two adverse reactions were reported (headache 11% and diarrhea 4%).

Similarly, for the indication of prevention of nausea and vomiting associated with moderately emetogenic chemotherapy, safety information on an unapproved ondansetron 8 mg three times daily regimen was removed from the adverse reactions table for that indication, leaving only the data from the ondansetron 8 mg twice daily group compared to placebo. Also, since the adverse event of dizziness was the same in both the drug and placebo groups, it was removed from the table, as not meeting the definition of an adverse reaction.

Section 6.2 Postmarketing Experience was created using the information found in subsection of Adverse Reactions in the currently approved label "Observed During Clinical Practice". The sponsor was asked to expand scope of the postmarketing section from adverse reactions reported during post-approval use with "oral formulations of ZOFRAN" to include other formulations of Zofran and specifically more information on postmarketing cardiac adverse reactions reported with Zofran IV. The information added is similar to what is found in the Zofran IV label:

> 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 interval prolongation have been reported.

7. DRUG INTERACTIONS

This section was created using information from PRECAUTIONS, Drug Interactions in the currently approved label. The information was organized in decreasing order of clinical importance:

7.1 Serotonergic Drugs

7.2 Drugs Affecting Cytochrome P-450 Enzymes

7.3 Tramadol

7.4 Chemotherapy

7.5 Alfentanil and Atracurim

In vitro information on the potential for ondansetron to induce/inhibit CYP isoenzymes and for other drugs to interact with the metabolism of ondansetron was moved to Section 12.3.

No other substantive changes were made.

8. USE IN SPECIFIC POPULATIONS

The sponsor revised the information on Pregnancy and Nursing Mothers in the PRECAUTIONS section of the currently approved label, into the new Pregnancy and Lactation Labeling Final Rule (PLLR) format (8.1 Pregnancy and 8.2 Lactation) and provided literature data to support changes to the content. For this submission, compliance with PLLR for oral Zofran is voluntary

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The review team consulted the Division of Bone, Reproductive and Urologic Products (DBRUP) in January 2016 for additional input, given the recently completed Citizen Petition review on Zofran.[4] *On January 4, 2013, a Citizen's Petition (CP) was submitted to FDA requesting the FDA:*

1. Reclassify the drug ondansetron from a pregnancy category B to C, D, or X,

2. Notify OB/GYNS that no scientifically acceptable evidence has been published demonstrating efficacy, safety, or superiority of ondansetron over conventional treatments for nausea and vomiting of pregnancy (NVP) and that its use may lead to adverse maternal and/or fetal outcomes, and

3. Notify OB/GYNs that continuous subcutaneous ondansetron pump may not be marketed or promoted in any way in the absence of FDA approval for the indication of treatment of NVP.

In response to the CP, DBRUP, the Office of Surveillance and Epidemiology's Division of Epidemiology (DEPI) and Division of Pharmacovigilance (DPV), and DPMH) reviewed the preclinical data and available safety evidence from the published literature, which included a case-control study, four cohort studies, and a retrospective case series. DBRUP served as the clinical lead on the response for the Zofran citizen petition. On Oct. 27, 2015, FDA issued a response to the CP, denying all three of the petitioner's requests. The FDA concluded the following:[5]

All studies reviewed had various methodological limitations that precluded reliable conclusions about fetal outcomes with ondansetron use in pregnancy.

Of all the studies reviewed, only two studies provided information to suggest adverse fetal outcomes with ondansetron. Anderka et al.[6] *and Danielsson et al.*[7] *reported a modest association between ondansetron exposure and cleft palate and cardiovascular malformations, respectively.*

[4] Citizen Petition (Docket No. FDA-2013-P-0048).

[5] https://www.regulations.gov/document?D=FDA-2013-P-0048-0009

[6] Anderka M, Mitchell AA, Louik C, Werler MM, Hernandez-Diaz S, Rasmussen SA, et al. Medications used to treat nausea and vomiting of pregnancy and the risk of birth defects. *Birth Defects Res A Clin Mol Terata/.* 2012;94(1):22-30. Epub 20 – 11 Nov 19.

[7] Danielsson B, Wikner B, Kallen B. Use of ondansetron during pregnancy and congenital malformations in the infant. Repro Tox 2014; 50:134-137.

A large observation study from Denmark (Pasternak et al)[8], however, did not find a positive association between antenatal ondansetron exposure and cleft palate or a panel of major birth defects, including cardiovascular malformations.

In summary, the totality of evidence, albeit limited, does not suggest an increased risk of fetal adverse outcomes, including birth defects such as cleft palate and cardiac defects, among fetuses exposed to ondansetron.

Both DPMH and DBRUP reviewed the sponsor's December 2015 submission and concluded that no new additional concerns about Zofran use in pregnant or lactating women were identified in the literature.

In a review dated August 30, 2016 in DARRTs, Barbara Wesley of DBRUP concluded:

"Based on the available evidence, DBRUP recommends that only Section 8.1 be revised in PLLR format to convey the limited and inconsistent evidence about fetal outcomes with ondansetron exposure."

In a review dated September 1, 2016 in DARRTS Christos Mastroyannis of DPMH concluded:

"Findings from the observational studies vary and all studies are subject to limitations. Associations between exposure to ondansetron and congenital malformations were detected in some observational studies but not in others. Study limitations preclude conclusive interpretations of the observational data. These findings suggest, but do not conclusively establish, that ondansetron may increase the risk for cardiovascular malformations (atrial and/or ventricular septal defects).

The totality of the data do not support a conclusion that there is an increased risk of fetal adverse outcomes, including birth defects such as cleft palate and cardiac ventricular and/or antral septal defects, among fetuses exposed to ondansetron during the first trimester. Ondansetron is not approved for use to treat NVP. The benefits of controlling NVP versus unknown risks for congenital malformations with Zofran should be considered in these patients taking into account that today there is an FDA approved treatment for NVP (Diclegis)."

Revised labeling was sent to the sponsor on June 14, 2016 with comments from the review team and consultants explaining the rationale for the changes. (b) (4) [redacted]

On August 3, 2016 the sponsor responded by accepting all recommendations and revisions. Final wording in Sections 8.1, 8.2 are shown below.

8.1 Pregnancy

Risk Summary

Available data do not reliably inform the association of ZOFRAN and adverse fetal outcomes. Published epidemiological studies on the association between ondansetron and fetal outcomes have reported inconsistent findings and have important methodological limitations hindering interpretation [*see Data*]. Reproductive studies in rats and rabbits did not show evidence of harm to the fetus when ondansetron was administered during organogenesis at approximately 6 and 24 times the maximum recommended human oral dose of 24 mg/day, based on body surface area, respectively [*see Data*].

[8] Pasternak B, Svanstrom H, and Hviid A. Ondansetron in Pregnancy and Risk of Adverse Fetal Outcomes. N Engl J Med 2013;368:814-23.

The background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the US general population, the estimated background risk of major birth defects and miscarriages in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively.

Data

Human Data

Methodological limitations of the epidemiology studies preclude a reliable evaluation of the potential risk of adverse fetal outcomes with the use of ondansetron in pregnancy.

Two large retrospective cohort studies of ondansetron use in pregnancy have been published. In one study with 1,349 infants born to women who reported the use of ondansetron or received an ondansetron prescription in the first trimester, no increased risk for major congenital malformations was seen in aggregate analysis. In this same study, however, a sub-analysis for specific malformations reported an association between ondansetron exposure and cardiovascular defect (odds ratio (OR) 1.62 [95% CI (1.04, 2.14)]) and cardiac septal defect (OR 2.05 [95% CI (1.19, 3.28)]). The second study examined 1970 women who received ondansetron prescription during pregnancy and reported no association between ondansetron exposure and major congenital malformations, miscarriage or stillbirth, and infants of low birth weight or small for gestational age. Important methodological limitations with these studies include the uncertainty of whether women who filled a prescription actually took the medication, the concomitant use of other medications or treatments, and other unadjusted confounders that may account for the study findings.

A case-control study evaluating associations between several common non-cardiac malformations and multiple antiemetic drugs reported an association between maternal use of ondansetron and isolated cleft palate (reported adjusted OR = 2.37 [95% CI (1.18, 4.76)]). However, this association could be a chance finding, given the large number of drugs-birth defect comparisons in this study. It is unknown whether ondansetron exposure in utero in the cases of cleft palate occurred during the time of palate formation (the palate is formed between the 6th and 9th weeks of pregnancy) or whether mothers of infants with cleft palate used other medications or had other risk factors for cleft palate in the offspring. In addition, no cases of isolated cleft palate were identified in the aforementioned two large retrospective cohort studies. At this time, there is no clear evidence that ondansetron exposure in early pregnancy can cause cleft palate.

Animal Data

In embryo-fetal development studies in rats and rabbits, pregnant animals received oral doses of ondansetron up to 15 mg/kg/day and 30 mg/kg/day, respectively, during the period of organogenesis. With the exception of a slight decrease in maternal body weight gain in the rabbits, there were no significant effects of ondansetron on the maternal animals or the development of the offspring. At doses of 15 mg/kg/day in rats and 30 mg/kg/day in rabbits, the maternal exposure margin was approximately 6 and 24 times the maximum recommended human oral dose of 24 mg/day, respectively, based on body surface area.

In a pre- and postnatal developmental toxicity study, pregnant rats received oral doses of ondansetron up to 15 mg/kg/day from Day 17 of pregnancy to litter Day 21. With the exception of a slight reduction in maternal body weight gain, there were no effects upon the pregnant rats and the pre- and postnatal development of their offspring, including reproductive performance of the mated F1 generation. At a dose of 15 mg/kg/day in rats, the maternal exposure margin was approximately 6 times the maximum recommended human oral dose of 24 mg/day, based on body surface area.

8.2 Lactation

Risk Summary

It is not known whether ondansetron is present in human milk. There are no data on the effects of ZOFRAN on the breastfed infant or the effects on milk production. However, it has been demonstrated that ondansetron is present in the milk of rats.

The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for ZOFRAN and any potential adverse effects on the breast-fed infant from ZOFRAN or from the underlying maternal condition.

The existing PRECAUTIONS, Pediatric Use information was expanded upon to create Section 8.4 Pediatric Use and to state the indication that is approved in pediatrics (prevention of nausea and vomiting associated with moderately emetogenic cancer chemotherapy in patients 4 years of age and older) and the data that supported that indication. The section also states the indications for which safety and effectiveness have not been established in pediatric patients.

8.4 Pediatric Use

The safety and effectiveness of orally administered ZOFRAN have been established in pediatric patients 4 years and older for the prevention of nausea and vomiting associated with moderately emetogenic cancer chemotherapy. Use of ZOFRAN in these age-groups is supported by evidence from adequate and well-controlled studies of ZOFRAN in adults with additional data from 3 open-label, uncontrolled, non-US trials in 182 pediatric patients aged 4 to 18 years with cancer who were given a variety of cisplatin or noncisplatin regimens *[see Dosage and Administration (2.2), Clinical Studies (14.1)]*.

Additional information on the use of ondansetron in pediatric patients may be found in ZOFRAN Injection prescribing information.

The safety and effectiveness of orally administered ZOFRAN have not been established in pediatric patients for:

- prevention of nausea and vomiting associated with highly emetogenic cancer chemotherapy.
- prevention of nausea and vomiting associated with radiotherapy.
- prevention of postoperative nausea and/or vomiting.

Input on this section was provided by Jeanine Best, Division of Pediatric and Maternal Health.

The existing PRECAUTIONS, Geriatric Use information was expanded upon to create Section 8.5 Geriatric Use and include a statement that although changes in the pharmacokinetic (PK) parameters of ondansetron were seen in a PK study comparing elderly to younger healthy subjects, no overall differences in safety or effectiveness were observed in clinical trials between elderly and younger patients or other clinical experience and that dosage adjustment is needed in the elderly.

Sections 8.6 Hepatic Impairment and 8.7 Renal Impairment were created. The hepatic subsection expands upon the information in Section 2.2 and cross-references both that subsection, as well as 12.3 for the PK results

8.6 Hepatic Impairment

No dosage adjustment is needed in patients with mild or moderate hepatic impairment.

In patients with severe hepatic impairment, clearance is reduced and the apparent volume of distribution is increased, resulting in a significant increase in the half-life of ondansetron. Therefore, do not exceed a total daily dose of 8 mg in patients with severe hepatic impairment (Child-Pugh score of 10 or greater) *[see Dosage and Administration (2.2), Clinical Pharmacology (12.3)]*.

As noted previously, no dosage adjustment is recommended for patients with renal impairment. However, there is also no information is available beyond the first-day administration, so that information was included in 8.7 with a cross-reference to Section 12.3.

9. DRUG ABUSE AND DEPENDENCE

No changes.

10. OVERDOSAGE

No changes.

11. DESCRIPTION

No substantive changes.

12. CLINICAL PHARMACOLOGY

The information was reorganized into 3 subsections.

The following paragraph found under CLINICAL PHARMACOLOGY, Pharmacodynamics in the approved label was retained as the basis the subsection on Mechanism of Action

12.1 Mechanism of Action

Ondansetron is a selective 5-HT_3 receptor antagonist. While its mechanism of action has not been fully characterized, ondansetron is not a dopamine-receptor antagonist. Serotonin receptors of the 5-HT_3 type are present both peripherally on vagal nerve terminals and centrally in the chemoreceptor trigger zone of the area postrema. It is not certain whether ondansetron's antiemetic action is mediated centrally, peripherally, or in both sites. However, cytotoxic chemotherapy appears to be associated with release of serotonin from the enterochromaffin cells of the small intestine. In humans, urinary 5-hydroxyindoleacetic acid (5-HIAA) excretion increases after cisplatin administration in parallel with the onset of emesis. The released serotonin may stimulate the vagal afferents through the 5-HT_3 receptors and initiate the vomiting reflex.

The following paragraph in the currently labeling was removed from labeling, as it pertains to animals and was not felt to provide additional information beyond the paragraph above.

~~In animals, the emetic response to cisplatin can be prevented by pretreatment with an inhibitor of serotonin synthesis, bilateral abdominal vagotomy and greater splanchnic nerve section, or pretreatment with a serotonin 5-HT3 receptor antagonist.~~

The following paragraph found under CLINICAL PHARMACOLOGY, Pharmacodynamics in the approved label was retained for use in the subsection on Pharmacodynamics

12.2 Pharmacodynamics

In healthy subjects, single intravenous doses of 0.15 mg/kg of ondansetron had no effect on esophageal motility, gastric motility, lower esophageal sphincter pressure, or small intestinal transit time. Multiday administration of ondansetron has been shown to slow colonic transit in healthy subjects. Ondansetron has no effect on plasma prolactin concentrations….

In addition, the sponsor was asked to include results of a QTc study conducted with intravenous ondansetron to this subsection (language currently found in the Zofran IV label):

> Cardiac Electrophysiology
>
> QTc interval prolongation was studied in a double-blind, single intravenous dose, placebo- and positive-controlled, crossover trial in 58 healthy subjects. The maximum mean (95% upper confidence bound) difference in QTcF from placebo after baseline correction was 19.5 (21.8) milliseconds and 5.6 (7.4) milliseconds after 15-minute intravenous infusions of 32 mg and 8 mg of ondansetron injection, respectively. A significant exposure-response relationship was identified between ondansetron concentration and ΔΔQTcF. Using the established exposure-response relationship, 24 mg infused intravenously over 15 minutes had a mean predicted (95% upper prediction interval) ΔΔQTcF of 14.0 (16.3) milliseconds. In contrast, 16 mg infused intravenously over 15 minutes using the same model had a mean predicted (95% upper prediction interval) ΔΔQTcF of 9.1 (11.2) milliseconds. In this study, the 8-mg dose infused over 15 minutes did not prolong the QT interval to any clinically relevant extent.

The information found in the currently approved label in the CLINICAL PHARMACOLOGY, Pharmacokinetics was reorganized and reformatted under headings and subheadings in Section 12.3 Pharmacokinetics, as recommended in the draft Clinical Pharmacology labeling guidance (e.g., Absorption, Distribution, Elimination, etc.). [9]

As noted above, an "interchangeability" statement was added to the beginning of the Dosage and Administration section preceding the dosing tables to serve as a replacement for the following statement, which has been deleted:

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

No other substantive changes were made.

13. NONCLINICAL TOXICOLOGY

Information in the currently approved label in the PRECAUTIONS, Carcinogenesis, Mutagenesis, Impairment of Fertility was retained in Section 13.2 under the same subheading. Body surface area multiples were added to relate the animal dosing to the recommended human dose (e.g., 15 mg/kg/day is approximately 6 times the maximum recommended human oral dose of 24 mg per day, based on body surface area).

See Pharmacology/Toxicology review from Tracy Behrsing dated May 6, 2015 in DAARTS.

14. CLINCIAL STUDIES

Information in the currently approved label in the CLINICAL TRIALS section was reorganized into three subsections

14.1 Prevention of Chemotherapy-induced Nausea and Vomiting

14.2 Radiation-induced Nausea and Vomiting

14.3 Postoperative Nausea and Vomiting

[9] http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM109739.pdf

Descriptions of the design of the clinical trials were revised for clarity and to describe studied dosing regimens in more details and in a similar way to how they are described in the Dosage and Administration section.

As noted above in other sections, information on the formulation was removed (i.e., "a single 24-mg ZOFRAN Tablet" was changed to "a single 24-mg oral dose of ZOFRAN").

No other substantive changes were made.

16. HOW SUPPLIED/STORAGE AND HANDLING

Information in the HOW SUPPLIED section of the currently approved label was reformatted under headings for each of the three formulations. The presentation of information is consistent with Section 3 Dosage Forms and Strengths and with additional information on NDC numbers and storage conditions retained.

15. REFERENCES

The three literature publications cited in the currently approved label were deleted, as they are not consistent with the regulations (i.e., they did not represent information "by an authoritative scientific body, or on a standardized methodology, scale, or technique, because the information is important to prescribing decisions"). Therefore, Section 15 is not needed.

17. PATIENT COUNSELING

This section was created as described in the Patient Counseling labeling guidance,[10] and describes all the important information needed for a prescriber-patient counseling discussion. Information is organized under the following headings:

QT Prolongation

Hypersensitivity Reactions

Masking of Progressive Ileus and Gastric Distention

Drug Interactions

Administration of ZOFRAN ODT Orally Disintegrating Tablets

[10] http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM368602.pdf

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/s/

JOETTE M MEYER
09/06/2016

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

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Division of Pediatric and Maternal Health Review

Date: December 22, 2015

From: Christos Mastroyannis, M.D.
Medical Officer, Maternal Health Team (MHT)
Division of Pediatric and Maternal Health (DPMH)

Through: Tamara Johnson, M.D., M.S.
Team Leader, Maternal Health Team
Division of Pediatric and Maternal Health

Lynne P. Yao, M.D., Division Director,
Division of Pediatric and Maternal Health

To: The Division of Gastroenterology and Inborn Errors Products (DGIEP)

Drug products: Zofran (ondansetron hydrochloride) oral tablets, disintegrating tablets and oral solution

NDAs: 20103/S-033; 20605/S-017; 20781/S-017

Subject: Maternal Health Labeling Recommendations

Applicant Novartis Pharmaceuticals Co.

Materials Reviewed:

- September 16, 2014, DGIEP's request to DPMH-MHT for labeling review
- September 22, 2015, Submission by applicant on Zofran (ondansetron) package insert. Initial U.S. approval: 1991
- June 16 and September 22, 2015, Annotated Draft Labeling Text

- September 22, 2015, Clinical Overview: Rationale for changes to US Prescribing Information –Pregnancy section and alignment with PLLR format
- September 24, 2015 review in DARRTS by Pharmacology/Toxicology reviewer Tracy Behrsing Ph.D. Reference ID: 3824350
- October 21, 2015, OSE/DPV1/DEPI1 and DEPI2 review for the Citizen Petition on Zofran
- Literature Review
- ACOG's Practice Bulletin Number 153, September 2015, on Nausea and Vomiting of Pregnancy

Consult Question: DGIEP requests assistance with labeling review regarding the new Pregnancy and Lactation Labeling Rule (PLLR) requirements to the Zofran labeling, initially approved in 1991 and lastly revised on September 18, 2014.

INTRODUCTION

Novartis has submitted the supplements 20103/S-033; 20605/S-017; 20781/S-017 for Zofran (ondansetron hydrochloride) oral tablets, disintegrating tablets and oral solution, respectively. The latest submission was on September 22, 2015. It includes the revised package insert to comply with PLLR requirements and a clinical overview with literature references to provide a rationale and summary of data to support updating the pregnancy section of the USPI for Zofran.

Ondansetron was first approved in the U.S. in 1991. It is a selective 5-hydroxy-tryptamine type 3 (5HT3) receptor antagonist indicated for the management of nausea and vomiting induced by emetogenic cancer chemotherapy and radiotherapy and for the prevention of postoperative nausea and vomiting. Zofran does not have an approved indication for nausea and vomiting of pregnancy (NVP) nor for hyperemesis gravidarum (HG). Estimated cumulative post-marketing exposure for Zofran, as per applicant, is approximately 1,021,123 patient-years as of December 2014.

DGIEP consulted the Division of Pediatric and Maternal Health (DPMH) to review the proposed Pregnancy, Lactation, and Females and Males of Reproductive Potential subsections in the Zofran product labeling.

On June 30, 2015, the "*Content and Format of Labeling for Human Prescription Drug and Biological Products; Requirements for Pregnancy and Lactation Labeling"* also known as the Pregnancy and Lactation Labeling Rule (PLLR[1] went into effect. The PLLR requirements include a change to the structure and content of labeling for human prescription drug and biologic products with regard to pregnancy and lactation, and create a new subsection for information with regard to females and males of reproductive potential. Specifically, the pregnancy categories (A, B, C, D and X) are removed from all prescription drug and biological product labeling and a new format will be required for all products that are subject to the 2006 Physician Labeling Rule (PLR)[2] format to include information about the risks and benefits of using these products during pregnancy and lactation.

[1] Content and Format of Labeling for Human Prescription Drug and Biological Products, Requirements for Pregnancy and Lactation Labeling (79 FR 72063, December 4, 2014).

This review provides recommended revisions and structuring of information related to the Pregnancy, Lactation, and Females and Males of Reproductive Potential subsections in labeling in order to provide clinically relevant information for prescribing decisions and to comply with PLLR regulatory requirements.

BACKGROUND

Product Background

Ondansetron is a selective 5-hydroxy-tryptamine 3 ($5\text{-}HT_3$) receptor antagonist. It is not certain whether ondansetron's antiemetic action is mediated centrally, peripherally, or in both sites.

The active ingredient in Zofran tablets is ondansetron hydrochloride as the dihydrate, the racemic form of ondansetron. It has a molecular weight of 365.9. Each Zofran tablet also contains the inactive ingredients hypromellose, iron oxide (8-mg tablet only), lactose, magnesium stearate, microcrystalline cellulose, pregelatinized starch, triacetin, and titanium dioxide.

The active ingredient in Zofran oral solution is the racemic form of ondansetron. It has a molecular weight of 365.9. Zofran oral solution also contains the inactive ingredients citric acid anhydrous, purified water, sodium benzoate, sodium citrate, sorbitol, and strawberry flavor.

Zofran oral tablets and oral solution products contain the same active pharmaceutical ingredient (API), which is the salt form of ondansetron hydrochloride dihydrate.

The active ingredient in Zofran ODT (orally disintegrating tablets) is the racemic form of ondansetron. It has a molecular weight of 293.4. Zofran ODT tablets contain the inactive ingredients aspartame, gelatin, mannitol, methylparaben sodium, propylparaben sodium, and strawberry flavor. The API in the Zofran ODT is the base form of ondansetron hydrochloride.

Zofran and Pregnancy

NVP is a common condition affecting many pregnant women. NVP has a prevalence rate for nausea of 50-80% and for vomiting and retching of 50%[3]. An estimated 50% of pregnant women have nausea and vomiting, 25% have nausea only, and 25% are unaffected[4]. NVP may diminish the woman's quality of life and contribute to time loss from work. Mild cases of NVP may be resolved with lifestyle and dietary changes. Safe and effective treatments are available

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[2] Requirements on Content and Format of Labeling for Human Prescription Drug and Biological Products, published in the Federal Register (71 FR 3922; January 24, 2006).

[3] Matthews A, Haas DM, O'Mathuna DP, Dowswell T, Doyle M. Interventions for nausea and vomiting in early pregnancy. Cochrane Database of Systemic Reviews 2014, Issue 3.Art. No.:CD007575

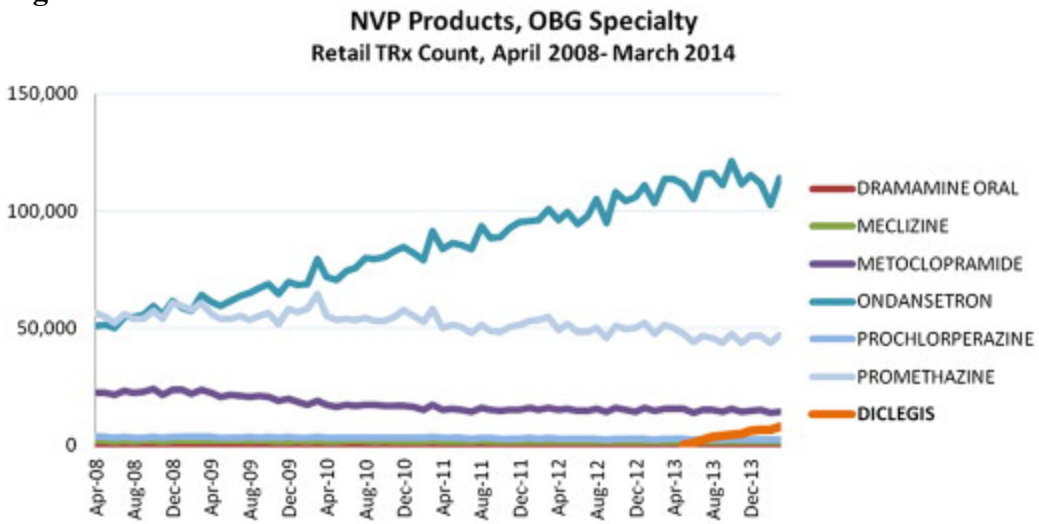
[4] Gadsby R, Barnie-Adshead AM, Jagger C. A prospective study of nausea and vomiting during pregnancy. Br J Gen Pract 1993;43:245-8

for more severe cases. HG represents the extreme end of the spectrum of nausea and vomiting of pregnancy (NVP) with an incidence of 0.3-3%[5].

Diclegis (doxylamine succinate, an antihistamine, and pyridoxine hydrochloride, a vitamin B_6 analog) was approved by FDA on April 8, 2013, for the treatment of nausea and vomiting of pregnancy in women who do not respond to conservative management. It is recommended by the American College of Obstetricians and Gynecologists (ACOG) as first line pharmacotherapy[6]. In the same practice Bulletin, ACOG states that "evidence is limited on the safety or efficacy of ondansetron for NVP. Studies have shown that the absolute risk to the fetus is low. Further studies are warranted" to demonstrate the efficacy and safety of Zofran for treatment of NVP.

Presently, 97.7% of prescriptions for the treatment of nausea and vomiting in pregnancy in the United States are with medications not labeled for use in pregnancy. The use of ondansetron for NVP has increased from 50,000 monthly prescriptions in 2008 to 110,000 at the end of 2013, despite unresolved issues regarding fetal safety and Food and Drug Administration (FDA) warnings about serious dysrhythmias (See Figure 1)[7]. This means that around 1 million pregnant American women are exposed to ondansetron out of 4 million pregnancies a year.

Figure 1.



From Koren. Am J Obstet Gynecol 2014

[5] Klebanoff MA, Koslowe PA, Kaslow R, Rhoads GG. Epidemiology of vomiting in early pregnancy. Obstet Gynecol 1985;66:612-6

[6] The American College of Obstetricians and Gynecologists. Practice Bulletin: Nausea and Vomiting of Pregnancy. Number 153, September 2015

[7] Koren G. Clinical Opinion:Treating morning sickness in the United States—changes in prescribing are needed. AJOG. December 2014;602-6

In a small published double-blind, randomized controlled trial of 36 pregnant women [mean gestational age 8 (7.1-8.9) weeks], Zofran was found to be more effective than the combination of doxylamine and pyridoxine in controlling NVP symptoms.[8]

REVIEW OF DATA

Animal Data on Ondansetron and Pregnancy

As per Pharmacology–Toxicology reviewer, Tracy L. Behrsing, PhD, in her review entered in DARRTS on September 24, 2015, she states "In embryo-fetal development studies in rats and rabbits, pregnant animals received oral doses of Zofran up to 15 mg/kg/day and 30 mg/kg/day, respectively, during the period of organogenesis. With the exception of a slight decrease in maternal body weight gain in the rabbits, there were no significant effects of Zofran on the maternal animals or the development of the offspring. At doses of 15 mg/kg/day in rats and 30 mg/kg/day in rabbits, the maternal exposure margin was approximately 6 and 24 times the maximum human oral dose of 24 mg/day, respectively, based on body surface area. In a pre- and postnatal developmental toxicity study, pregnant rats received oral doses of Zofran up to 15 mg/kg/day from Day 17 of pregnancy to litter Day 21. With the exception of a slight reduction in maternal body weight gain, there were no effects upon the pregnant rats and the pre- and postnatal development of their offspring, including reproductive performance. At a dose of 15 mg/kg/day in rats, the maternal exposure margin was approximately 6 times the maximum human oral dose of 24 mg/day, based on body surface area."

Reviewer comment:

The findings from the animal data are reassuring. However, human epidemiologic data even though not conclusive, provide a safety signal that should not be discarded. See discussion below.

Post-marketing Database Review

Review of post marketing data produced a total of 1028 reports corresponding to 997 pregnancies, that were retrieved from the applicant's safety database. The search was conducted using the MedDRA 17.1 Standardized MedDRA Query (SMQ) "Pregnancy and neonatal topics (narrow)" with cut off of March 8, 2015.

[8] Oliveira LG, Capp SM, You WB, Riffenburgh RH, Carstairs SD. Ondansetron compared with doxylamine and pyridoxine for treatment of nausea in pregnancy: a randomized controlled trial. Obstet Gynecol 2014;124:735-42

Table 1: Pregnancy Outcomes

Outcomes	Number of reports (n=1028)[1]	Number of pregnancies (n=997)[2]
Duplicate reports and non- pregnancy reports[3]	71	N/A
No outcome reported	578	608
Live birth, no congenital anomalies	234	236
Abortion, miscarriage or stillbirth	65	65
Live births or unspecified birth outcome with congenital anomalies	91	92

1. The number of reports adds up to 1039, because there were 7 reports describing two separate pregnancies in the same report with different infant outcomes and 4 reports of twin pregnancies with different infant outcomes that are therefore counted twice in the table.
2. The number of pregnancies adds up to 1001, because there were 4 reports of twin pregnancies with different infant outcomes that are therefore counted twice in the table.
3. There were 30 reports which were duplicates of other reports in the database and 41 reports containing an event within the Pregnancy and Neonatal Topics SMQ that were identified following review as not occurring in the setting of ondansetron use during pregnancy.

From applicant's submission of September 22, 2015. 2.5 Clinical Overview: Rationale for changes to US Prescribing Information – Pregnancy section and alignment with PLLR format. Table 4-4 Pregnancy outcome table, pp 19-20

There were 578 reports corresponding to 608 pregnancies, in which the infant outcome was not reported (see Table 2). In 48% (290) pregnancies of the unknown outcome pregnancies, ondansetron was started during the first trimester (i.e., adjudicated as either definitely or likely). For 6% (39) pregnancies, ondansetron started after the first trimester. For the remaining 46% (279) pregnancies, the timing of first use in reference to trimester could not be determined.

In 234 reports referring to 236 pregnancies, no congenital anomaly was described (see Table 2). Of those, in 47% (111) pregnancies, ondansetron definitely or likely started during the first trimester. In 23% (54) of the pregnancies, ondansetron started after the first trimester. For the remaining 30% (71) of the pregnancies, the timing of the first use could not be determined.

There were 65 reports (65 pregnancies) in which pregnancy ended in an abortion (elective or spontaneous) or stillbirth (see Table 2). Ondansetron was definitely or likely started during the first trimester (defined as the first 98 days following the last menstrual period) in 69% (45) of the abortion/miscarriage/stillbirth reports. Ondansetron was definitely or likely started after the first trimester in 9% (6) of the ending in abortion/miscarriage/stillbirth outcome of pregnancies. The timing of first use with regard to trimester could not be estimated or determined from the reported data for the remaining 22% (14) of pregnancies.

Table 2: Pregnancy outcome, by time of exposure, with no congential anomalies

	# **Reports**	# **Pregnancies**	**Initiation time of ondansetron**
No outcome reported	578	608	
		290 (48%)	First trimester
		39 (6%)	After first trimester
		279 (46%)	Undetermined
No congenital anomalies	234	236	
		111 (47%)	First trimester
		54 (23%)	After first trimester
		71 (30%)	Undetermined
Abortion (AB) (elective or spontaneous)	65	65	
		45 (69%)	First trimester
		6 (9%)	After first trimester
		14 (22%)	Undetermined

Of the 41 pregnancies that ended with spontaneous pregnancy loss, 13 ended during the first trimester, 14 during the second trimester, five during late first or early second trimester, 2 during the third trimester and one described death of a neonate of unreported gestational age. The remaining 6 reports did not specify the timing of the end of the pregnancy (see Table 3).

Table 3: Pregnancy loss with no congenital anomalies

Pregnancy loss	#	**Timing**
	41	
	13	First trimester
	14	Second trimester
	5	Late first/early second trimester
	2	Third trimester
	6	Undetermined
	1	Unknown gestational age

From applicant's submission of September 22, 2015. 2.5 Clinical Overview: Rationale for changes to US Prescribing Information –Pregnancy section and alignment with PLLR format.

There were 35 reports (35 pregnancies, 37 infants) in which there were adverse events described for infants, but none of them was consistent with congenital anomalies. The length of time between first exposure to ondansetron and the timing of the spontaneous pregnancy loss ranged between 0 days and 25-26 weeks. In none of these pregnancies, a fetal anomaly was reported.

There were an additional 9 pregnancies that ended before birth and reported a documented fetal congenital anomaly (7 reports referred to one of each specific congenital anomaly and 2 were Dandy-Walker syndrome. See Table 4.

Table 4: Congenital anomalies reported in abortions/miscarriages/stillbirth

Maternal age	**Timing of ondansetron exposure**	**Concurrent medications**	**Anomalies**	**Outcome**
27 years	Started approximately 38-42 days after LMP and continued for 2	None reported	Anencephaly	Elective abortion
33 years	Pregnancy weeks 13-15	None reported	Dandy-Walker syndrome (described as Dandy- Walker	Elective abortion
29 years	10 week duration ending "sometime past first trimester"	None reported	Dandy-Walker syndrome including hydrocephalus and Tetralogy of Fallot	Elective abortion at 21 weeks
Unknown	Unknown	Cyclizine, Promethazine, Metoclopramide, Folic acid and Thiamine	Large gastroschisis, absent hemidiaphragm, hydronephrosis, scoliosis and pulmonary hypoplasia	Elective abortion at 20 weeks

29 years	Single dose during surgery between 3 1/7 and 4 4/7 weeks)	Amoxicillin-clavulanate, Droperidol, Ephedrine, Ketoprofen, Lidocaine, Methylprednisolone, Metoclopramide, Morphine, Nefopam, Propofol, Pneumococcal vaccine	Meningomyelocele and unspecified abdominal wall anomaly (gastroschisis versus omphalocele based on information in narrative)	Miscarriage at 14 6/7 weeks following single dose approximately 10-11 weeks before
Unknown	Started at 11 weeks gestation, continued for at least 3-4 weeks	Promethazine, Prochlorperazine, Metoclopramide	Fetal akinesia deformation sequence (Pena-Shokeir syndrome) with hydrocephalus, pterygia of both elbows, limited extension of knees, small mandible, clenched fist, and normal XY karyotype	Elective abortion at 23 weeks following as much as 8 weeks since last exposure
Unknown	2nd month of pregnancy	None reported	Caudal regression syndrome with crossed renal ectopia, imperforate vagina and anus, two hemi-uteri, genital tubercle and lumbar hemivertebrae	Elective abortion
30 years	Between 2nd and 3rd month of pregnancy	None reported	Unspecified kidney, genital and skeletal malformations	Elective abortion

19 years; previous second trimester miscarriag	15 weeks gestation	None reported	Two vessel cord but no apparent fetal anomalies	Miscarriage at 15 weeks

[1]: Estimated using start date of ondansetron and date of "11 week" ultrasound.

From applicant's submission of September 22, 2015. 2.5 Clinical Overview: Rationale for changes to US Prescribing Information –Pregnancy section and alignment with PLLR format. Table 4-5 Congenital anomalies reported in abortion/miscarriage/stillbirth, pp 22-23

In all, there were 91 reports corresponding to 92 pregnancies with possible congenital anomalies. The exposure to ondansetron in these 92 pregnancies was as follows: 51 pregnancies with first trimester exposure, 15 with exposure post first trimester and in 26 pregnancies the exposure time could not be estimated or determined. There was no cluster or increased frequency of a specific congenital anomaly with ondansetron use.

Reports of isolated anomalies in live births after maternal use of ondansetron in the first trimester (n=51) :

- Nine cardiovascular anomalies: One of each; hypoplastic left heart syndrome, tricuspid atresia, pulmonary atresia with hypoplastic right ventricle, pulmonary stenosis, ventricular septal defect, unspecified septal defect, and unspecified fetal arrhythmia and 2 unspecified congenital heart defect. (See Table 6.)
- Four facial anomalies: Two cleft lip and palate, and one of each Cleft 7 defect with associated jaw malformation and facial nerve and fat defects, ankyloglossia and acrochordon.
- Ten musculoskeletal anomalies: one of each; possible congenital scoliosis, absence of left hand and short hand bones, congenital dislocation of hip, as well as undefined finger, toe and foot anomalies and 3 Talipes (bilateral club foot).
- Six renal anomalies: one of each; duplication of the collecting system, extrarenal pelvis and hydronephrosis, and events most consistent with posterior urethral valves.
- Four gastrointestinal anomalies: two pyloric stenosis, and one of each; duodenal atresia, and anal atresia.
- Two genitourinary anomalies: Two hypospadias.
- Four respiratory tract anomalies: Two tracheomalacia, and one of each; laryngomalacia and congenital diaphragmatic hernia.
- Twelve neurologic anomalies: Three hypertonia, and one of each; hypotonia, seizures and hemiplegia, as well as potential structural anomalies such as intracranial hemorrhage and anencephaly.

Table 5: Reports with isolated cardiovascular anomalies

Maternal age	Timing of ondansetron exposure	Concurrent medications	Anomalies	Outcome
Unknown	Started at 6 weeks gestation	Promethazine, Pyridoxine, Doxylamine, Vitamins	Hypoplastic left heart syndrome	Live birth; died from unreported cause
23 yo	Unknown	Paracetamol, Vitamins	Tricuspid atresia	Live birth
Unknown	One dose at 6 5/7 weeks, then intermittently	Vitamins	Pulmonary atresia with right ventricular	Live birth
35 yo	8-12 weeks gestation	Meclizine, Metoclopramide, Dimenhydrinate, Prochlorperazine	Pulmonary stenosis	Live birth
Unknown	Started "approximately the second trimester" (3-4 months gestation) and continued into third trimester	None reported	Ventricular septal defect	Live birth
Unknown	12-20 weeks gestation	Paracetamol	Unspecified septal defect	Live birth
Unknown	Started at 8 weeks gestation, continued through at least 28 weeks	Cetirizine, Metoclopramide, Pyridoxine	Fetal arrhythmia	No birth outcome reported
Unknown	Unknown	None reported	Unspecified congenital heart defect	Live birth

Unknown	Unknown	None reported	Unspecified congenital heart defect	Live birth

From applicant's submission of September 22, 2015. 2.5 Clinical Overview: Rationale for changes to US Prescribing Information –Pregnancy section and alignment with PLLR format. Table 4-5 Congenital anomalies reported in abortion/miscarriage/stillbirth, pp 23-24

Reviewer Comments

This reviewer considers that the applicant's report of the post marketing data from safety database regarding use of ondansetron during pregnancy has identified a broad range of congenital anomalies. No particular pattern of anomalies was apparent. In several of the reports, ondansetron use occurred after the susceptible period for reported anomaly and these reports were excluded from consideration. Confounding factors included concomitant medications and underlying medical conditions (e.g. NVP, age, concurrent infection), which by themselves may have contributed to the congenital anomaly.

Applicant's Published Literature Review on Fetal safety concerns regarding Zofran

The applicant evaluated the safety of Zofran during pregnancy by reviewing published literature case series and epidemiologic studies as well as post marketing data.[9,10] The applicant is referring to studies by Einarson et al, 2004, Asker et al, 2005, Colvin et al, 2013, Andersen et al, 2013, Pasternak et al, 2013 and Danielsson et al, 2014 that are reviewed below. Table 6 shows a summary of the epidemiologic studies referenced by the applicant in support for the PLLR labeling conversion.

Table 6: Summary of epidemiological studies with birth outcome data

[9] The post marketing data is retrieved and analyzed from GlaxoSmithKline (GSK) safety database as GSK currently holds the safety database for Zofran (ondansetron). Novartis has recently acquired Zofran from GSK.

[10] Dincer Z, Gao R, Kapoor S, Mali Y. Clinical Overview – Labelling Change. Submission to the NDA Section 2.5 Clinical Overview 2015;1-47

Reference Study Details	Stated Objective	Study population, Methods	Results
(Einarson et al., 2004) Prospective comparative observational cohort study / Motherisk (Canada) and Mothersafe (Australia) supported by an unrestricted grant from GSK Canada	Determine whether ondansetron increases the baseline rate of major malformations	Enrolled women who called Motherisk or Mothersafe in 1st trimester and fell into one of 3 groups: (1) had NVP and were taking ondansetron (n=176) (2) had NVP and were taking other antiemetics (n=176) (3) were taking other drugs considered safe in pregnancy (non-teratogen) or no drugs (n=176) Contacted each caller 4-6 mo after delivery, followed by verification letter to caller's physician.	Major malformation: Ondansetron 6 (3.5%), Other antiemetics 3 (1.8%), Non-teratogen 3 (1.8%); p=0.52 Hypospadias: 3/169 live births in ondansetron group compared to 1/322 live births in other 2 groups combined; p=0.25 Live births, miscarriages, stillbirths, therapeutic abortions, birthweight, gestational age: No statistically significant differences between the 3 groups
(Asker et al., 2005) Cohort study / Swedish Medical Birth Registry (1995-2002)	Describe antiemetic use during pregnancy in Sweden and study delivery outcome after such therapy	Women who reported use of antiemetics during 1st trimester were compared with all women who had given birth during the study period; infants of mothers of the first group were compared with all infants born.	29,807 pregnant women with 31,130 infants reported the use of antiemetic drugs. No congenital malformations observed among infants born to 65 women reporting use of ondansetron (21 in 1st trimester, 12 in 2nd to 3rd trimester, 12 in 1st to 3rd trimester).

(Anderka et al., 2012) Multi-site, population-based, case-control / National Birth Defects Prevention Study /US (1997-2004)	Investigate whether NVP itself or use of NVP medications in the 1st trimester of pregnancy was associated with selected birth defects: orofacial clefts, NTD, and hypospadias.	4524 birth defect cases vs 5859 controls (no major birth defects). Medication exposure during 1st trimester of pregnancy was collected by maternal interviews. Potential confounders for adjusted analyses were selected *a priori*: maternal age, race or ethnicity, education, parity, smoking in month before conception or during 1st trimester, plurality, previous miscarriage, infant sex, use of multivitamin with folic	Adjusted odds ratios (95% CI) for association of birth defects and exposure to ondansetron during 1st trimester of pregnancy: CL/P: 0.88 (0.38-2.00) CP: 2.37 (1.18–4.76) NTD: 0.60 (0.21-1.68) Hypospadias: 0.57 (0.20-1.60) Adjusted odds ratios (95% CI) for association of birth defects and NVP: CL/P: 0.87 (0.76–0.98) CP: 0.93(0.8-1.09) NTD: 1.00 (0.86-1.16) Hypospadias: 0.84 (0.72–0.98)
		acid before conception or during 1st trimester, BMI, study site, year of expected date of delivery.	

(Andersen et al. 2013) (conference abstract) Registry-based cohort study / Danish Medical Birth Register plus National Hospital Register and National Prescription Register (1997-2010)	Test if use of ondansetron during the 1st trimester is associated with a higher prevalence of congenital malformations.	All women giving birth during the study period. Major congenital malformations were defined according to the EUROCAT classification system. Adjustments made in computing adjusted odds ratios are not described in the abstract.	Conference abstract - 897,018 births 1248 women with prescription for ondansetron Major malformations (exposed): 58 (4.7%) Major malformations (unexposed): 31357 (3.5%) aOR (95% CI) for major malformation: 1.3 (1.0-1.7) aOR (95% CI) for heart defects: 2.0 (0.3-3.1) *Note: the lower bound of 0.3 is suspected to be incorrect (actually 1.3) based on updated data below and other publications citing the lower bound as 1.3.* (Updated abstract)- 903,207 births (accessed March 9, 2015) 1368 women with prescription for ondansetron Major malformations (exposed): 61 (4.7%) Major malformations (unexposed): 32241 (3.5%) aOR (95% CI) for major malformation: 1.2 (0.9-1.5) aOR (95% CI) for heart defects: 1.6 (1.1-3.1) OR (95% CI): for ASD: 2.1 (1.3-3.6) OR (95% CI) for VSD: 2.3 (1.2-4.2) OR (95% CI) for AVSD: 4.8 (1.5-15.1)

(Colvin et al., 2013) Cohort study / Linkable health administrative data from the Western Australia Data Linkage System and the national Australian Pharmaceutical Benefits Scheme (2002-2005)	Compare women (and children) who were dispensed ondansetron under the Australian PBS during pregnancy with those who were not dispensed ondansetron with respect to maternal and child characteristics, birth defects, and pregnancy and delivery characteristics.	251 pregnancies in women dispensed ondansetron (263 children) 96,447 pregnancies in women not dispensed ondansetron (98,062 children)	Ondansetron dispensed (%) vs not dispensed (%); OR (95% CI) Any birth defect: 6.1% vs 4.8%; 1.3 (0.8-2.1) Any major birth defect: 4.6% vs 4.1%; 1.1 (0.6-2.0) Major birth defect with first trimester exposure: 4.7% vs 4.1%; 1.2 (0.6–2.2) Obstructive defects of renal pelvis and ureter: not reported; 6.2 (2.0–19.5)* Stillbirth: 1.1% vs 0.6%; 1.8 (0.6-5.5)* APGAR 5min <6: 1.1% vs 0.6%; 2.0 (0.6-6.1)* Ondansetron dispensed vs not dispensed; aOR (95% CI) Birth length ≤50cm: 67.3% vs 57.2%; 1.4 (1.0-1.8) Birth weight <2500g: 11.4% vs 7.2%; 1.3 (0.8-2.2) * number of cases <5

(Pasternak et al., 2013) Registry-based cohort/ Danish Medical Birth Registry (2004-2011)	Investigate the risk of adverse fetal outcomes associated with ondansetron administered during pregnancy	From a historical cohort of 608,385 pregnancies, women exposed to ondansetron and those not exposed were included in propensity-score-matched analyses (1:4) of spontaneous abortion, stillbirth, any major birth defect, preterm delivery, and birth of infants at low birth weight and small for gestational age.	Spontaneous abortion (1849 exposed and 7396 unexposed): - during weeks 7-12: 1.1% and 3.7% (HR 0.49; 95% CI 0.27-0.91) - during weeks 13-22: 1.0% and 2.1% (HR 0.60; 95% CI 0.29-1.21). Stillbirth (1915 exposed and 7660 unexposed): 0.3% and 0.4% (HR 0.42; 95% CI 0.10-1.73) Any major birth defect (1233 exposed and 4932 unexposed): 2.9% and 2.9% (aOR 1.12; 95% CI 0.69-1.82) Cardiovascular defect (calculated by Danielsson et al., 2014 using Supplementary Table S9): crude OR 1.04, 95% CI 0.52-1.95 Septal defect (calculated by using Supplementary Table S9): crude OR 1.22, 95% CI 0.56-2.47 Preterm delivery (1792 exposed and 7168 unexposed): 6.2% and 5.2% (aOR 0.90; 95% CI 0.66-1.25) Low-birth-weight infant (1784 exposed and 7136 unexposed): 4.1% and 3.7% (aOR 0.76; 95% CI 0.51-1.13) Small-for-gestational-age infant (1784 exposed and 7136 unexposed): 10.4% and 9.2% (aOR 1.13; 95% CI 0.89-1.44)

(Danielsson et al., 2014) Registry-based cohort study / Swedish Medical Birth Register combined with the Swedish Register of Prescribed Drugs (1998–2012)	Study the presence of congenital malformations in offspring of women who had taken ondansetron in early pregnancy. Women using meclozine, the most commonly used drug for NVP in Sweden, also were studied to evaluate possible confounding by indication (NVP).	1,501,434 infants; 1349 infants born of women who had taken ondansetron in early pregnancy; 41,388 infants born of women who had taken meclozine during pregnancy (trimester not specified). Odds ratios were adjusted for year of birth, maternal age, parity, maternal smoking in early pregnancy, and body mass index (BMI).	Ondansetron: Any malformation: aOR 0.95, 95% CI 0.72-1.26 Relatively severe malformation (broadly corresponds to major malformation): aOR 1.11, 95% CI 0.81-1.53 Cardiovascular defect: aOR 1.62, 95% CI 1.04-2.14 Septum defect: RR 2.05, 95% CI 1.19-3.28 Meclozine: Any malformation: aOR 0.96, 95% CI 0.90-1.02 Relatively severe malformation: aOR 0.95, 95% CI 0.90-1.00 Cardiovascular defect: aOR 1.02, 95% CI 0.92-1.12 Septum defect: RR 1.03, 95% CI 0.92-1.15
(Werler et al., 2014) Population-based case–control study/ Birth defect registries in Massachusetts, New York, and North Carolina (US, 2007-2011)	Identify whether medications commonly used in early gestation are associated with the risk of isolated clubfoot	Cases: 646 mothers of children with isolated clubfoot Controls: 2037 mothers of children born without major malformations Assessed medication use during lunar months 2-4 (29-112 days after first day of last menstrual period)	Cases vs Controls; aOR (95% CI) Ondansetron use: 5.3% vs 4.5%; 1.33 (0.87, 2.03) Ondansetron use ≤14 days: 1.1% vs 1.1%; 1.02 (0.43, 2.45) Ondansetron use >14 days: 3.1% vs 3.0%; 1.27 (0.74, 2.18) In 570 cases and 2022 controls without 1st-degree relatives affected with clubfoot: Ondansetron use: 5.6% vs 4.4%; 1.47 (0.95, 2.27)

(Larrimer et al., 2014) Observational, longitudinal study (US)	Examine the impact of antiemetic medications in pregnancy on neurobehavioral and obstetric outcomes	Compared 143 children whose mothers received promethazine or ondansetron during pregnancy to 407 unexposed children.	No significant differences between the 2 groups of children using Neonatal Behavioral Assessment Scale and Child Behavior Checklist.

From applicant's submission of September 22, 2015. Dincer Z, Gao R, Kapoor S, Mali Y. Clinical Overview – Labelling change. PP 8-12, Table 4-1.

Agency Review of Published Epidemiology Studies

The Office of Epidemiology (OSE)/ Division of Epidemiology 1(DEPI) evaluated the published epidemiological studies of pregnancy outcomes following ondansetron exposure during the first trimester (see detailed review in DARRTS).[11] They concluded that epidemiologic and animal evidence for an association between ondansetron use in early pregnancy and risk of cleft palate is limited and weak as well as human data on the association between ondansetron use and oral clefts are limited. Chance alone might explain the significant odds ratio observed by Anderka et al. No published evidence exists to suggest an association between ondansetron use in pregnancy and increased risks of adverse pregnancy and birth outcomes. For the study by Danielsson et al. DEPI, in reference to cardiovascular malformations (OR=1.62, 95% CI=1.04-2.14), and septal malformations (a type of cardiovascular malformation) (OR=2.05, 95% CI=1.19-3.28) among women exposed to ondansetron in early pregnancy, concludes that of the 1349 infants exposed to ondansetron in early pregnancy, the only malformations occurring more than once in the study were ventricular septum malformations (n=12), ventricular and atrium septum defects (n=3), and hypospadias (n=3). These findings "are noteworthy but difficult to interpret". The authors note that 17 of the 19 cardiovascular malformations observed in the study were ventricular and/or antral septal defects which as per the study authors are usually not very severe and sometimes the diagnosis is uncertain. The increase observed for overall cardiac malformations is driven by the increase in atrial and/or ventricular septal defects and should therefore not be considered a separate association. So DEPI concludes that because previous published studies have not reported increased associations between ondansetron use in early pregnancy and atrial and/or ventricular septal cardiac malformations, the analysis by Danielsson et al is a new signal that may or may not be causal and as such does not require any further action at this time.

The fetal safety of the ondansetron was first investigated by Einarson et al[12] in 2004 through a prospective comparative observational study. In the trial, three groups of women: 1. Women who were exposed to ondansetron, 2. Women exposed to other anti-emetics, and 3. Women exposed to non-teratogen, reported completed pregnancy outcomes in 176 pregnancies in each of the groups. All of the women called either the NVP Helpline or teratogen information services (TIS) at The Motherisk Program in Toronto, Canada, or The Mothersafe Program in Sydney, Australia. In the ondansetron group, out of 176 pregnancy outcomes, they observed 169 live births, 5 miscarriages, and 2 therapeutic abortions. There were 6 (3.6%) major malformations (3 cases of hypospadias, and a double urinary collecting system in kidney, a mild pulmonary stenosis and a duodenal atresia). In the comparison group (2), there were 3 major malformations (a hydrocephalus, a kidney anomaly and an aortic stenosis), and in the comparison group (3), there were also 3 malformations (one case of hypospadias and two congenital heart defects). The authors did not detect an increased risk of major congenital malformations above baseline in women who used ondansetron versus those women who were

[11] Taylor LG, Shih D., Wang C. Epidemiology Review for Zofran Citizen Petition. DARRTS. October 21,2015

[12] Einarson A, Maltepe C, Navioz Y, Kennedy D, Tan MP, Koren G. The safety of ondansetron for nausea and vomiting of pregnancy: a prospective comparative study. BJOG 2004;111: 940-3

exposed to other anti-emetics or those who had no-exposure to any teratogen. The rate of hypospadias (3/169) live births in the ondansetron group was not statistically significant from the combined controls (1/322, P=0.25). For the combined number of major malformations, again there was not a statistically significant difference 6 (3.5%) in the ondansetron group versus 3 (1.8%) in the other antiemetics group and 3 (1.8%) in the non-teratogen group, P=0.52. Limitation of this study is the sample size. It only had the statistical power to rule out a 5-fold increased risk of major malformations, and not any specific malformation suggesting that the possibility of not detecting any major congenital malformations by the authors may be due to the fact that the study was not powered accordingly.

In 2013, Pasternak et al[13] reported that ondansetron was not associated with increased congenital malformation rates when used for NVP. This was based on a retrospective analysis of data from the Danish Birth Registry and National Patient Registry, collected between 2004 and 2011 and linked to the National Prescription Register. Each of the 1970 pregnant women exposed to ondansetron was matched to 4 unexposed pregnant controls. The authors categorized major congenital malformations based on the European Surveillance of Congenital Anomalies (EUROCAT)[14] classification. The authors excluded women with ondansetron prescriptions filled one month before pregnancy, infants with chromosomal abnormalities and infants whose defects were of known etiology. Analyses of the congenital malformations were limited to pregnancies ending in live birth.

The first ten weeks of gestation are critical to the pregnancy outcome because embryogenesis/ organogenesis occur during this period. In this study, the median age of exposure to ondansetron was 10 gestational weeks (70 days from last menstrual period). Therefore, half of the cases were exposed to ondansetron at later than 10 gestational weeks. Exposure to ondansetron after the 10th week of gestation does not cause the morphologic malformations sought in this study. Exposure to ondansetron when the first prescription was filled at a time later than first trimester can cause a bias toward the null, diluting an existing risk because of inclusion of cases that were not exposed during embryogenesis. In sensitivity analyses, the authors narrowed the exposure to ondansetron from any first trimester exposure to exposure only in gestational weeks 4-10. The authors also reanalyzed the outcome originally limited to live births to include pregnancies ending in stillbirths and induced abortions. Among 1233 women exposed in the first trimester and 4932 unexposed women, the authors observed zero and two cases (0.04%) of cleft palate, respectively. The authors report 3 cases of cleft lip with or without cleft palate in the exposed cohort (0.24%) and 11 cases in the unexposed cohort (0.22%). Receipt of ondansetron was not associated with a significantly increased risk of spontaneous abortion, which occurred in 1.1% of exposed women and 3.7% of unexposed women during gestational weeks 7 to 12 (hazard ratio, 0.49; 95% confidence interval [CI], 0.27

[13] Pasternak B, Svanström H, Hviid A. Ondansetron in pregnancy and risk of adverse fetal outcomes. N Engl J Med 2013;368:814-23

[14] Coding of Eurocat subgroups of congenital anomalies (Version 2012). In: European Surveillance of Congenital Anomalies (Eurocat) guide 1.3 and reference documents - instructions for the registration and surveillance of congenital anomalies. 2013

to 0.91). Ondansetron also conferred no significantly increased risk of stillbirth (0.3% for exposed women and 0.4% for unexposed women; hazard ratio, 0.42; 95% CI, 0.10 to 1.73), and any major birth defect (2.9% and 2.9%, respectively; prevalence odds ratio, 1.12; 95% CI, 0.69 to 1.82). Given the absence of cleft palate cases and the small number of cleft lip (with or without cleft palate) cases, no measures of association were calculated for either defect. The authors state that there was insufficient statistical power to assess associations between ondansetron and specific malformations and concluded that ondansetron is not significantly associated with any major congenital anomaly or other adverse fetal outcome.

In 2013, Andersen *et al*.[15] from Denmark, presented a second study using the same Danish registries reported by Pasternak et al, covering a longer period (1997-2010) and more pregnant women (897,018 vs. 608, 835). In contrast to Pasternak *et al*.[13], Andersen *et al*. detected a 2-fold increased risk of cardiac malformations with ondansetron (odds ratio [OR], 2.0; 95% confidence interval [CI], 1.3-3.1). Use of prescription database linkage to birth registries in the study was not designed specifically to address fetal drug safety. To rule out confounding by indication, Andersen *et al*. also examined metoclopramide taken for "morning sickness" (NVP), and detected no increase in teratogenic risk due to exposure during pregnancy.

A recent large case control study by the Sloan epidemiology unit and the Centers of Disease Control and Prevention, using data from the National Birth Defects Prevention Study (NBDPS)[16]- a multi-site, population-based, case-control study, examined whether NVP or its treatment [including proton pump inhibitors (PPI), steroids and ondansetron] was associated with the most common non-cardiac defects in the NBDPS (non-syndromic cleft lip with or without cleft palate [CL/P], cleft palate alone [CP], neural tube defects, and hypospadias) compared with randomly selected non-malformed live births. The main comparison was between women with NVP who used NVP medications in the first trimester versus those who did not. The women with no NVP permitted comparison of the effect of the condition itself regardless of medication use. Potential confounders for the adjusted analyses were selected a priori and included maternal age, race-ethnicity, education, parity, smoking in the month before conception through the first trimester, previous miscarriage, infant sex, use of multivitamin with folic acid anytime between the month before conception through the first trimester, body mass index (BMI), study site, and year of expected date of delivery. Adjusted odds ratios (aOR) and their corresponding 95 % CI were estimated using unconditional logistic regression. Subjects with a parent, sibling or half sibling with the same birth defect were excluded because their birth defects may be etiologically different from subjects without such a family history.

Where an association was observed between first trimester medication use and a birth defect, medication exposure was further examined according to month of pregnancy and the intensity

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[15] Andersen JT, Jimmenez-Solem E, Andersen NL. Ondansetron use in early pregnancy and the risk of congenital malformations. Int Soc Pharmacoepidemiol 2013. Abstract 25, Pregnancy session

[16] Anderka M, Mitchell AA, Louik C, Werler MM, Hernandez-Diaz S, Rasmussen SA, and the National Birth Defects Prevention Study. Medications Used to Treat Nausea and Vomiting of Pregnancy and the Risk of Selected Birth Defects. Clinical and molecular teratology 2012;94(1):22-30

of nausea and vomiting (average frequency of NVP in months 1, 2 and 3 of pregnancy). These analyses were repeated excluding women with pre-existing diabetes and excluding infants with more than one major congenital anomaly.

The authors determined that NVP was not associated with CP or neural tube defects (NTDs), but, in fact, modest risk reductions were observed for CL/P (aOR=0.87, 0.77–0.98), and hypospadias (OR=0.84, 0.72–0.98). In regard to NVP treatment with ondansetron, they identified a 2-fold increased risk for CP when ondansetron was taken for NVP in the first trimester of pregnancy (OR, 2.37; 95% CI, 1.28e4.76)[17].

Reviewer comment:
This finding of an increased incidence of CP is in contrast with the Danish study by Pasternak et al.

The authors obtained information on both, the NVP diagnosis and severity and the NVP treatment, via a maternal interview conducted between six weeks and 24 months after the estimated date of delivery. On average, control mothers [18]were interviewed three months sooner than cases which may predispose to a recall bias. If cases more often underreported their use of medication, the observed risk might be underestimated. The publication has a number of limitations including the potential for exposure misclassification due to incomplete recall or recall/reporting bias and selection bias.

In 2014, Danielsson *et al.*[19] investigated potential teratogenic risks with ondansetron use in pregnancy. Data from the Swedish Medical Birth Register combined with the Swedish Register ~~of Prescribed Drugs were used~~ to identify 1349 infants born of women who had taken

[17] Anderka M, Mitchell AA, Louik C, Werler MM, Hernández-Diaz S, Rasmussen SA. National Birth Defects Prevention Study. Medications used to treat nausea and vomiting of pregnancy and the risk of selected birth defects. Birth Defects Res A Clin Mol Teratol 2012;94:22-30.

[18] Controls were live born infants without major birth defects identified from the same geographical regions and periods as cases by means of either vital records or birth hospitals. Control infants were randomly selected using a stratified random sampling design; the monthly number of controls selected was proportionate to the number of births in the same month in the previous year.

[19] Danielsson B, Norstedt WiknerB, Källén B. Use of ondansetron during pregnancy and congenital malformations in the infant. Reprod Toxicol.2014;50:134-7

[20] As per Danielson *et al* major malformations include two groups: some relatively common, clinically less significant malformations like preauricular tags, tongue tie, patent ductus in preterm infants, single umbilical artery, undescended testis, hip (sub)luxation, and nevus. The remaining malformations were called "relatively severe" but may contain a few minor or poorly specified conditions. See Appendix A for the described list of malformations observed.

[21] The children's heart foundation and CDC. www.cdc.gov/heart defects. July 31, 2015

[22] Confounding by indication is a term used when a variable is a risk factor for a disease among nonexposed persons and is associated with the exposure of interest in the population from which the cases derive, without being an intermediate step in the causal pathway between the exposure and the disease. Salas M, Hofman A, Stricker BH. Confounding by indication: an example of variation in the use of epidemiologic terminology. Am J Epidemiol.1999;149(11):981-3

ondansetron in early pregnancy, 1998–2012. The authors found no statistically significant increased risk for a major congenital malformation and reported the odds of associations for any malformation at OR=0.95, 95% CI=0.72-1.26, and for "relatively severe malformations"[20] at OR=1.11, 95% CI= 0.81-1.53. They also identified that the risks for a cardio-vascular defect were increased and statistically significant (OR=1.62, 95% CI 1.04–2.14, while the cardiac septal defects showed an RR 2.05, 95% CI 1.19-3.28 among women exposed to ondansetron in early pregnancy. The incidence of congenital heart defects (CHD) in the general population is about 1% of birth per year in the US.[21] The authors concluded that the teratogenic risk with ondansetron is low but an increased risk for a cardiac septum defect is likely. The authors further consider a potential biological mechanism that could "hypothetically" explain the association with septal defects. They specifically suggest that ondansetron's potential to cause QT prolongation and arrhythmia may affect fetal cardiac development.

The authors state that it is not known if the women who filled a prescription actually took the drug during the organogenesis period, which may bias of the risk estimate towards null. The authors made comparisons with other anti-emetics (metoclopramide and meclozine) and found no effect of these drugs. Confounding by indication[22] could explain the increased finding for ondansetron and atrial septal malformations. However, the authors state that the lack of increased associations observed for meclozine, a drug with similar indications, do not suggest that confounding by indication affected the results. They further note that NVP "is associated with a well-functioning placenta and actually a slightly better-than-expected pregnancy outcome." The authors note that 17 of the19 cardiac malformations were atrial and/or ventricular septal defects, while in the Pasternak et al. study there were 10 atrial and/or ventricular septal defects out of 13 cardiac malformations. The increase observed for overall cardiac malformations is due to the increase in atrial and/or ventricular septal defects (ASD) and (VSD) respectively and should therefore not be considered a separate association.

Women with severe NVP may have other complications that could lead to enhanced surveillance of the developing fetus (and newborn). In this case, surveillance bias might explain the increased associations for atrial and septal defects. There are more female infants born of women with NVP than males. In the Danielsson study maternal use of ondansetron in the 17 observed septum defects, 8 occurred in males and 9 in females. Previous published studies have not reported increased associations between ondansetron use in early pregnancy and atrial and/or ventricular septal cardiac malformations.

Reviewer comment:
This reviewer considers that the findings in the Danielsson study constitute a new signal that may or may not be causal and warrant further investigation.

There are insufficient data on fetal safety with ondansetron use and further studies are warranted. Some studies have shown an increased risk for birth defects with early (first trimester) ondansetron use, while others have not. Nonetheless, prescribing ondansetron as a

first line option is not consistent with American Professors in Gynecology and Obstetrics and ACOG evidence-based recommendations for the management of NVP.,[23].

This reviewer having reviewed the data presented above concludes that there is no sufficient data to definitively declare the use of Zofran during the first trimester of pregnancy is contraindicated because it may cause major congenital anomalies. In addition, this reviewer recommends a PMR that the applicant conducts a controlled, prospective study with Zofran use in pregnancy for the NVP indication in order to resolve the aforementioned potential safety signals.

(b) (4)

[redacted]

Zofran and Lactation

The Drugs and Lactation Database (LactMed)[24] was searched for available lactation data on with the use of Zofran. No entries were found. It is not known whether Zofran is excreted in human milk. There are no data on the effects of Zofran on the breastfed child or the effects of Zofran on milk production. However, it has been demonstrated that ondansetron is present in the breast milk of rats.

In conclusion, there is no clinical data to draw meaningful safety inferences about the effects of Zofran during lactation. Further studies may provide a better understanding of use of Zofran during lactation.

Females and Males of Reproductive Potential

[23] American Professors in Gynecology and Obstetrics (APGO) Educational Series on Women's Health. Nausea and vomiting of pregnancy. Crofton, MD: APGO. 2013

[24] United States National Library of Medicine. TOXNET Toxicology Data Network. *Drugs and Lactation Database (LactMed)*. http://toxnet nlm.nih.gov/cgi-bin/sis/htmlgen?LACT
The LactMed database is a National Library of Medicine (NLM) database with information on drugs and lactation geared toward healthcare practitioners and nursing women. The LactMed database provides any available information on maternal levels in breast milk, infant blood levels, any potential effects in the breastfed infants, if known, as well as alternative drugs that can be considered. The database also includes the American Academy of Pediatrics category indicating the level of compatibility of the drug with breastfeeding.

(b) (4)

CONCLUSION

The Pregnancy, Lactation, and Females and Males of Reproductive Potential subsections of labeling were structured to be consistent with the PLLR.

Review of the literature revealed no new additional concerns about Zofran use in pregnant or lactating women. Findings from the observational studies vary and all studies are subject to limitations. Associations between exposure to ondansetron and congenital malformations were detected in some observational studies but not in others. Study limitations preclude conclusive interpretations of the observational data. These findings suggest, but do not conclusively establish, that ondansetron may increase the risk for cardiovascular (atrial and/or ventricular septal defects) malformations.

Taking into consideration both the data available at the time ondansetron was approved and subsequent human data gathered in the post approval setting, at this time the totality of the data do not support a conclusion that there is an increased risk of fetal adverse outcomes, including birth defects such as cleft palate and cardiac ventricular and/or antral septal defects, among fetuses exposed to ondansetron during the first trimester. Ondansetron is not approved for use to treat NVP. The benefits of controlling NVP versus unknown risks for congenital malformations with Zofran should be considered in these patients taking into account that today there is an FDA approved treatment for NVP (Diclegis).

Absent a compelling legal or public health concern, FDA generally does not comment on the number or quality of studies regarding the efficacy of a drug product for an unapproved use or provide relative efficacy as compared to other drug products for such unapproved use (for more detailed discussion, see Citizen Petition in DARRTS).

The Pregnancy and Lactation sections of Zofran labeling were structured to be consistent with the PLLR as follows:

- Pregnancy, Section 8.1
  - The "Pregnancy" section of Zofran labeling was formatted in the PLLR format to include: "Risk Summary," and "Data" subsections.
- Lactation, Section 8.2
  - The "Lactation" section of Zofran labeling was formatted in the PLLR format to include the "Risk Summary" subsection.
- Patient Counseling Information, Section 17

- The "Patient Counseling Information" section of labeling was updated to correspond with sections 8.1 and 8.2 of the labeling.

LABELING RECOMMENDATIONS

DPMH revised sections 8.1, 8.2 and 17 of Zofran labeling for compliance with the PLLR (see below). DPMH discussed our labeling recommendations with DGIEP. On June 14, 2016, after internal discussions among DGIEP, DPMH, DBRUP and OSE/DEPI-1 on previous applicant's comments, a revised labeling was sent to the applicant. The applicant responded on August 3, 2016, accepting all the recommendations by the Division. DPMH refers to the final NDA action for final labeling.

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Methodological limitations of the epidemiology studies preclude a reliable evaluation of the potential risk of adverse fetal outcomes with the use of ondansetron in pregnancy.
Two large retrospective cohort studies of ondansetron use in pregnancy have been published. In one study with 1,349 infants born to women who reported the use of ondansetron or received an ondansetron prescription in the first trimester, no increased risk for major congenital malformations was seen in aggregate analysis. In this same study, however, a sub-analysis for specific malformations reported an association between ondansetron exposure and cardiovascular defect (odds ratio (OR) 1.62 [95% CI (1.04, 2.14)]) and cardiac septal defect (OR 2.05 [95% CI (1.19, 3.28)]). The second study examined 1970 women who received ondansetron prescription during pregnancy and reported no association between ondansetron exposure and major congenital malformations, miscarriage or stillbirth, and infants of low birth weight or small for gestational age. Important methodological limitations with these studies include the uncertainty of whether women who filled a prescription actually took the medication, the concomitant use of other medications or treatments, and other unadjusted confounders that may account for the study findings.
A case-control study evaluating associations between several common non-cardiac malformations and multiple antiemetic drugs reported an association between maternal use of ondansetron and isolated cleft palate (reported adjusted OR = 2.37 [95% CI (1.18, 4.76)]). However, this association could be a chance finding, given the large number of drugs-birth defect comparisons in this study. It is unknown whether ondansetron exposure in utero in the cases of cleft palate occurred during the time of palate formation (the palate is formed between the 6th and 9th weeks of pregnancy) or whether mothers of infants with cleft palate used other medications or had other risk factors for cleft palate in the offspring. In addition, no cases of isolated cleft palate were identified in the aforementioned two large retrospective cohort studies. At this time, there is no clear evidence that ondansetron exposure in early pregnancy can cause cleft palate.

Animal Data
In embryo-fetal development studies in rats and rabbits, pregnant animals received oral doses of ondansetron up to 15 mg/kg/day and 30 mg/kg/day, respectively, during the period of organogenesis. With the exception of a slight decrease in maternal body weight gain in the rabbits, there were no significant effects of ondansetron on the maternal animals or the development of the offspring. At doses of 15 mg/kg/day in rats and 30 mg/kg/day in rabbits, the maternal exposure margin was approximately 6 and 24 times the maximum recommended human oral dose of 24 mg/day, respectively, based on body surface area.
In a pre- and postnatal developmental toxicity study, pregnant rats received oral doses of ondansetron up to 15 mg/kg/day from Day 17 of pregnancy to litter Day 21. With the exception of a slight reduction in maternal body weight gain, there were no effects upon the pregnant rats and the pre- and postnatal development of their offspring, including reproductive performance of the mated F1 generation. At a dose of 15 mg/kg/day in rats, the maternal exposure margin was approximately 6 times the maximum recommended human oral dose of 24 mg/day, based on body surface area.

8.2 Lactation

Risk Summary

It is not known whether ondansetron is present in human milk. There are no data on the effects of ZOFRAN on the breastfed infant or the effects on milk production. However, it has been demonstrated that ondansetron is present in the milk of rats.

The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for ZOFRAN and any potential adverse effects on the breast-fed infant from ZOFRAN or from the underlying maternal condition.

(b) (4)

FDA's Rationale: *Based on the labeling revisions, this information is unnecessary.*

DPMH clean labeling recommendations

FULL PRESCRIBING INFORMATION: CONTENTS

FULL PRESCRIBING INFORMATION

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Available data do not reliably inform the association of ZOFRAN and adverse fetal outcomes. Published epidemiological studies on the association between ondansetron and fetal outcomes have reported inconsistent findings and have important methodological limitations hindering interpretation [see Data]. Reproductive studies in rats and rabbits did not show evidence of harm to the fetus when ondansetron was administered during organogenesis at approximately 6 and 24 times the maximum recommended human oral dose of 24 mg/day, based on body surface area, respectively [see Data].

The background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the US general population, the estimated background risk of major birth defects and miscarriages in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively.

Data

Human Data

Methodological limitations of the epidemiology studies preclude a reliable evaluation of the potential risk of adverse fetal outcomes with the use of ondansetron in pregnancy.

Two large retrospective cohort studies of ondansetron use in pregnancy have been published. In one study with 1,349 infants born to women who reported the use of ondansetron or received an ondansetron prescription in the first trimester, no increased risk for major congenital malformations was seen in aggregate analysis. In this same study, however, a sub-analysis for specific malformations reported an association between ondansetron exposure and cardiovascular

defect (odds ratio (OR) 1.62 [95% CI (1.04, 2.14)]) and cardiac septal defect (OR 2.05 [95% CI (1.19, 3.28)]). The second study examined 1970 women who received ondansetron prescription during pregnancy and reported no association between ondansetron exposure and major congenital malformations, miscarriage or stillbirth, and infants of low birth weight or small for gestational age. Important methodological limitations with these studies include the uncertainty of whether women who filled a prescription actually took the medication, the concomitant use of other medications or treatments, and other unadjusted confounders that may account for the study findings.

A case-control study evaluating associations between several common non-cardiac malformations and multiple antiemetic drugs reported an association between maternal use of ondansetron and isolated cleft palate (reported adjusted OR = 2.37 [95% CI (1.18, 4.76)]). However, this association could be a chance finding, given the large number of drugs-birth defect comparisons in this study. It is unknown whether ondansetron exposure in utero in the cases of cleft palate occurred during the time of palate formation (the palate is formed between the 6th and 9th weeks of pregnancy) or whether mothers of infants with cleft palate used other medications or had other risk factors for cleft palate in the offspring. In addition, no cases of isolated cleft palate were identified in the aforementioned two large retrospective cohort studies. At this time, there is no clear evidence that ondansetron exposure in early pregnancy can cause cleft palate.*Animal Data*

In embryo-fetal development studies in rats and rabbits, pregnant animals received oral doses of ondansetron up to 15 mg/kg/day and 30 mg/kg/day, respectively, during the period of organogenesis. With the exception of a slight decrease in maternal body weight gain in the rabbits, there were no significant effects of ondansetron on the maternal animals or the development of the offspring. At doses of 15 mg/kg/day in rats and 30 mg/kg/day in rabbits, the maternal exposure margin was approximately 6 and 24 times the maximum recommended human oral dose of 24 mg/day, respectively, based on body surface area.

In a pre- and postnatal developmental toxicity study, pregnant rats received oral doses of ondansetron up to 15 mg/kg/day from Day 17 of pregnancy to litter Day 21. With the exception of a slight reduction in maternal body weight gain, there were no effects upon the pregnant rats and the pre- and postnatal development of their offspring, including reproductive performance of the mated F1 generation. At a dose of 15 mg/kg/day in rats, the maternal exposure margin was approximately 6 times the maximum recommended human oral dose of 24 mg/day, based on body surface area.

8.2 Lactation

Risk Summary

It is not known whether ondansetron is present in human milk. There are no data on the effects of ZOFRAN on the breastfed infant or the effects on milk production. However, it has been demonstrated that ondansetron is present in the milk of rats.

The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for ZOFRAN and any potential adverse effects on the breast-fed infant from ZOFRAN or from the underlying maternal condition.

Appendix A

"Relatively severe" congenital malformations in infants exposed during early pregnancy for ondansetron as per Danielsson *et al*

ICD-code	Malformation	Number
Q063	Cauda equina malformation	1
Q210	Ventricular septum defect	12
Q211	Atrium septum defect	1
Q210 + Q211	Ventricular and atrium septum defect	3
Q210 + Q221	Ventricular septum defect + pulmonary valve stenosis	1
Q213	Tetralogy of Fallot	1
Q251	Coarctation of aorta	1
Q320	Tracheomalacia	1
Q375	Cleft lip/palate, unilateral	1
Q391	Esophageal atresia	1
Q400	Pyloric stenosis	1
Q412 + Q429	Ileum and colon atresia	1
Q423	Anal atresia	1
Q432	Colon dilatation	1
Q438	Unspecified intestinal malformation	1
Q540	Hypospadias	3
Q649 + Q669	Urinary tract malformation+ foot deformity	1
Q688	Musculoskeletal malformation, unspec.	1

ICD-code	Malformation	Number
Q690	Polydactyly fingers	1
Q714	Radius reduction	1
Q829	Unspecified skin malformation	1
Q848	Nail malformation	1
Q909	Down syndrome	1

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/s/

CHRISTOS MASTROYANNIS
08/30/2016

TAMARA N JOHNSON
08/30/2016

LYNNE P YAO
09/01/2016

CONSULT MEMORANDUM

Date: August 25, 2016

To: Joyce Korvick, M.D.
Deputy Director for Safety
Division of Gastroenterology and Inborn Errors Products (DGIEP)

From Barbara Wesley, M.D., M.P.H., Medical Officer
Division of Bone, Reproductive and Urologic Products (DBRUP)

Through: Christine P. Nguyen, M.D., Deputy Director for Safety
Division of Bone, Reproductive and Urologic Products (DBRUP)

Subject: Zofran® Pregnancy and Lactation Labeling Rule (PLLR) Consult Review

Products:
NDA 020103
Zofran® (ondansetron hydrochloride)
Tablets 4 mg, 8 mg
Sequence No. 0062
NDA 020605
Zofran® (ondansetron hydrochloride)
Oral Solution 4mg/5mL
Sequence No. 0063
NDA 020781
Zofran® (ondansetron hydrochloride)
Orally Disintegrating Tablets 4 mg, 8 mg
Sequence No. 0062

Background:

Ondansetron, a serotonin selective type three 5-hydrozytryptanine receptor antagonist, is FDA-approved for the prevention of nausea and vomiting associated with chemotherapy, radiotherapy or surgical anesthesia. Due to its well-established antiemetic effects, ondansetron is often used off-label to treat nausea and vomiting in pregnancy.

On January 4, 2013, a citizen's petition was submitted to the FDA, requesting that the FDA:

1. reclassify the drug ondansetron from a pregnancy category B to C, D, or X,
2. notify OB/GYNS that no scientifically acceptable evidence has been published demonstrating efficacy, safety, or superiority of ondansetron over conventional treatments for nausea and vomiting or pregnancy (NVP) and that its use may lead to adverse maternal and/or fetal outcomes, and

3. notify OB/GYNs that continuous subcutaneous ondansetron pump may not be marketed or promoted in any way in the absence of FDA approval for the indication of treatment of NVP.

On Oct. 27, 2015, FDA issued a response to the citizen petition, denying all three of the petitioner's requests.

In response to the above referenced citizen's petition, DBRUP, the Office of Surveillance and Epidemiology's Division of Epidemiology (DEPI) and Division of Pharmacovigilance (DPV), and Pediatric and Maternal Health Staff (now the Division of Pediatric and Maternal Health (DPMH)) reviewed the preclinical data and available safety evidence from the published literature, which included a case-control study, four cohort studies, and a retrospective case series. DBRUP served as the clinical lead on the response for the Zofran citizen petition. Please refer to FDA's October 2015 response to the ondansetron citizen petition and the discipline-specific consult reviews for further details. After a comprehensive assessment, the FDA concluded the following:

- All studies reviewed had various methodological limitations that precluded reliable conclusions about fetal outcomes with ondansetron use in pregnancy.
- Of all the studies reviewed, only two studies provided information to suggest adverse fetal outcomes with ondansetron. Anderka et al.[1] and Danielsson et al.[2] reported a modest association between ondansetron exposure and cleft palate and cardiovascular malformations, respectively.
- A large observation study from Denmark (Pasternak et al)[3], however, did not find a positive association between antenatal ondansetron exposure and cleft palate or a panel of major birth defects, including cardiovascular malformations.

In summary, the totality of evidence, albeit limited, does not suggest an increased risk of fetal adverse outcomes, including birth defects such as cleft palate and cardiac defects, among fetuses exposed to ondansetron.

DBRUP Pregnancy and Lactation Labeling Rule (PLLR) Labeling Review:

On March 19, 2014, the Sponsor, Novartis, submitted supplements to the NDAs for Zofran Tablets (S-033), Zofran Oral Solution (S-017) and Zofran Orally Disintegrating Tablets (S-017). These supplements updated the labeling to comply with the requirements of the January 24, 2006, Final Rule for Requirements on Content and Format of Labeling for Human Prescription Drug and Biological Products. The Sponsor also voluntarily added language to comply with the PLLR.

---

[1] Anderka M, Mitchell AA, Louik C, Werler MM, Hernandez-Diaz S, Rasmussen SA, et al. Medications used to treat nausea and vomiting of pregnancy and the risk of birth defects. *Birth Defects Res A Clin Mol Terata/.* 2012;94(1):22-30. Epub 20 – 11 Nov 19

[2] Danielsson B, Wikner B, Kallen B. Use of ondansetron during pregnancy and congenital malformations in the infant. Repro Tox 2014; 50:134-137.

[3] Pasternak B, Svanstrom H, and Hviid A. Ondansetron in Pregnancy and Risk of Adverse Fetal Outcomes. N Engl J Med 2013;368:814-23

The Division of Gastrointestinal and Inborn Errors of Metabolism (DGIEP) consulted DBRUP to provide input on the Sponsor's proposed pregnancy-related revisions in several sections of the prescribing information. At the time of DGIEP's consult to DBRUP in January 2016, these pregnancy-related labeling revisions included the following:

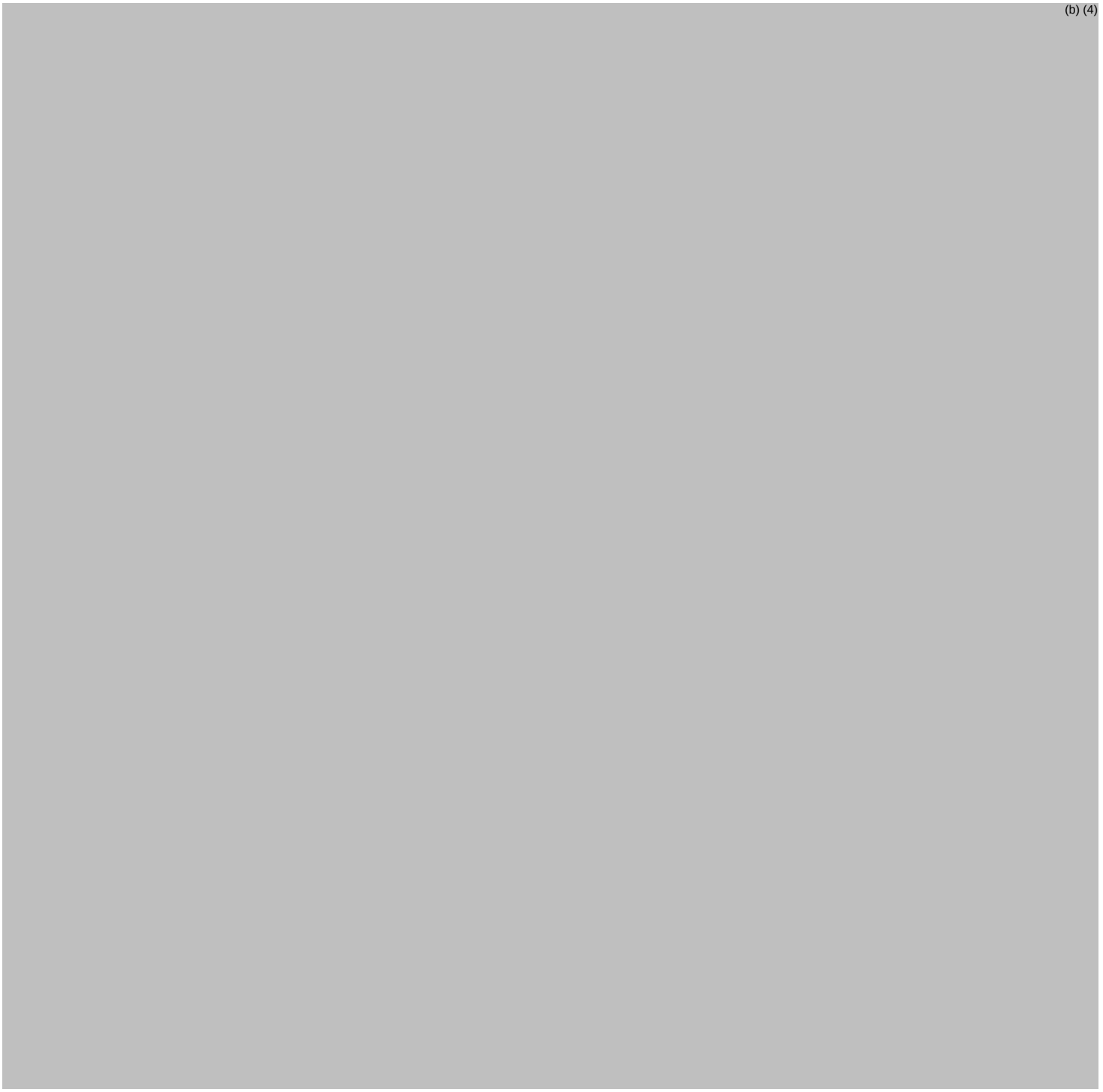
- (b) (4)
- (b) (4)
- **Section 8.1 (Pregnancy)**: Data on adverse fetal outcomes with the use of ondansetron in pregnancy
- (b) (4)

Based on the available evidence, DBRUP recommends that only **section 8.1** be revised in PLLR format convey the limited and inconsistent evidence about fetal outcomes with ondansetron exposure. Our rationale follows:

Section 1 (Indications and Usage)

(b) (4)

(b) (4)



Conclusion/Recommendation: Based on the available evidence, DBRUP believes that only section 8.1 be updated to include pertinent human data on pregnancy/fetal outcomes associated with antenatal ondansetron exposure. After several labeling negotiations, the Sponsor and FDA reached agreement on the PLLR labeling revisions, and we recommend approval of the

pregnancy-related labeling changes submitted on August 2, 2016, to NDAs 20103 (S-033), 20605 (S-017), and 20781(S-017).

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/s/

BARBARA D WESLEY
08/30/2016

CHRISTINE P NGUYEN
08/30/2016

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Division of Pediatric and Maternal Health
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Silver Spring, MD 20993
Tel 301-796-2200
FAX 301-796-9744

Division of Pediatric and Maternal Health Memo

Date: May 5, 2015

From: Carrie Ceresa, Pharm D, MPH, Clinical Analyst
Division of Pediatric and Maternal Health

Through: Tamara Johnson, M.D., M.S, Acting Team Lead
Division of Pediatric and Maternal Health

Lynne P. Yao, M.D., Acting Division Director
Division of Pediatric and Maternal Health

To: The Division of Gastroenterology and Inborn Errors Products (DGIEP)

Products: Zofran (ondansetron) oral tablets, disintegrating tablets & oral solution

NDAs: 20103/S-033; 20605/S-017; 20781/S-017

Subject: PLR conversion labeling review of Pregnancy and Nursing Mothers

Materials Reviewed: Zofran (ondansetron) package insert

The Division of Pediatric and Maternal Health (DPMH) was consulted on the Physicians Labeling Rule (PLR) conversion supplement for the Zofran oral formulation package insert in order to reformat the pregnancy and nursing mothers subsections in labeling.

DPMH's (formerly PMHS) review dated July 26, 2011, reviewed the then available published literature to determine any need for labeling changes. At that time, DPMH concluded that there was insufficient evidence to support a change in the package insert regarding pregnancy and lactation due to limited available data. DPMH recommended labeling continue to state that there is currently no available human data with regard to pregnancy.

Since July 2011, more data on Zofran use in pregnant women has become available in the literature. DPMH recommends that this literature is reviewed to assess whether or not there is any valid human data to add to the Zofran labeling.

Additionally, on December 4, 2014, the Food and Drug Administration (FDA) announced the publication of the "*Content and Format of Labeling for Human Prescription Drug and Biological Products; Requirements for Pregnancy and Lactation Labeling*,"[1] also known as the Pregnancy and Lactation Labeling Rule (PLLR). The PLLR requirements include a change to the structure and content of labeling for human prescription drug and biologic products with regard to pregnancy and lactation, and create a new subsection for information with regard to females and males of reproductive potential. Specifically, the pregnancy categories (A, B, C, D and X) will be removed from all prescription drug and biological product labeling and a new format will be required for all products that are subject to the 2006 Physicians Labeling Rule[2] format to include information about the risks and benefits of using these products during pregnancy and lactation.

The PLLR will officially take effect on June 30, 2015. In the meantime, conversion to the PLLR format is voluntary.

In December 2014, DPMH recommended the following information request for the sponsor:

> "Please review relevant pregnancy and lactation published literature (case reports, case series and epidemiology data) and submit those documents along with a summary of the data. Incorporate the relevant data in revised Zofran pregnancy and lactation labeling that adheres to the *Content and Format of Labeling for Human Prescription Drug and* December 4, 2014)."

The sponsor has responded and they are currently working on fulfilling the information request however they will be delayed a few months as they are currently going through a change in ownership of the product. In the meantime, DGIEP is continuing with the PLR conversion and the pregnancy and nursing information will remain in the old labeling format. DPMH recommends that the Zofran labeling is converted to the PLLR format in the future once the information request is submitted and reviewed.

[1] *Content and Format of Labeling for Human Prescription Drug and Biological Products, Requirements for Pregnancy and Lactation Labeling* (79 FR 72063, December 4, 2014).
[2] *Requirements on Content and Format of Labeling for Human Prescription Drug and Biological Products*, published in the Federal Register (71 FR 3922; January 24, 2006).

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/s/

CARRIE M CERESA
05/05/2015

TAMARA N JOHNSON
05/06/2015

LYNNE P YAO
05/07/2015

REGULATORY PROJECT MANAGER
PHYSICIAN'S LABELING RULE (PLR) FORMAT REVIEW
OF THE PRESCRIBING INFORMATION

Complete for all new NDAs, BLAs, Efficacy Supplements, and PLR Conversion Labeling Supplements

Application Type: PLR Conversion Labeling Supplement

Applicant: GlaxoSmnithKline

NDA 20103/S-033	Zofran (ondansetron hydrochloride)	Tablets
NDA 20605/S-017	Zofran (ondansetron hydrochloride)	Oral Solution
NDA 20781/S-017	Zofran ODT (ondansetron)	Orally Disintegrating Tablets

Receipt Date: March 19, 2014

Goal Date: March 19, 2014

1. Regulatory History and Applicant's Main Proposals

The package inserts (PIs) for the above NDAs were last approved on December 10, 2013. The Zofran Injection product's PIs were converted to PLR on July 7, 2011.

2. Review of the Prescribing Information

This review is based on the applicant's submitted Word format of the prescribing information (PI). The applicant's proposed PI was reviewed in accordance with the labeling format requirements listed in the "Selected Requirements for Prescribing Information (SRPI)" checklist (see the Appendix).

3. Conclusions/Recommendations

SRPI format deficiencies were identified in the review of this PI. For a list of these deficiencies see the Appendix.

Appendix

The Selected Requirement of Prescribing Information (SRPI) is a 42-item, drop-down checklist of important format elements of the prescribing information (PI) based on labeling regulations (21 CFR 201.56 and 201.57) and guidances.

Highlights

See Appendix A for a sample tool illustrating the format for the Highlights.

HIGHLIGHTS GENERAL FORMAT

NO 1. Highlights (HL) must be in a minimum of 8-point font and should be in two-column format, with ½ inch margins on all sides and between columns.

Comment: *The right margin should be 1/2 inch.*

YES 2. The length of HL must be one-half page or less unless a waiver has been granted in a previous submission. The HL Boxed Warning does not count against the one-half page requirement. Instructions to complete this item: If the length of the HL is one-half page or less, select "YES" in the drop-down menu because this item meets the requirement. However, if HL is longer than one-half page, select "NO" unless a waiver has been granted.

Comment:

YES 3. A horizontal line must separate HL from the Table of Contents (TOC). A horizontal line must separate the TOC from the FPI.

Comment:

YES 4. All headings in HL must be **bolded** and presented in the center of a horizontal line (each horizontal line should extend over the entire width of the column as shown in Appendix A). The headings should be in UPPER CASE letters.

Comment:

YES 5. White space should be present before each major heading in HL. There must be no white space between the HL Heading and HL Limitation Statement. There must be no white space between the product title and Initial U.S. Approval. See Appendix A for a sample tool illustrating white space in HL.

Comment:

YES 6. Each summarized statement or topic in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contain more detailed information. The preferred format is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each summarized statement or topic.

Comment:

YES 7. Section headings must be presented in the following order in HL:

Section	Required/Optional
• **Highlights Heading**	Required
• **Highlights Limitation Statement**	Required
• **Product Title**	Required
• **Initial U.S. Approval**	Required

Selected Requirements of Prescribing Information

• **Boxed Warning**	Required if a BOXED WARNING is in the FPI
• **Recent Major Changes**	Required for only certain changes to PI*
• **Indications and Usage**	Required
• **Dosage and Administration**	Required
• **Dosage Forms and Strengths**	Required
• **Contraindications**	Required (if no contraindications must state "None.")
• **Warnings and Precautions**	Not required by regulation, but should be present
• **Adverse Reactions**	Required
• **Drug Interactions**	Optional
• **Use in Specific Populations**	Optional
• **Patient Counseling Information Statement**	Required
• **Revision Date**	Required

* RMC only applies to the BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS sections.

Comment:

HIGHLIGHTS DETAILS

Highlights Heading

YES 8. At the beginning of HL, the following heading must be **bolded** and should appear in all UPPER CASE letters: **"HIGHLIGHTS OF PRESCRIBING INFORMATION"**.

Comment:

Highlights Limitation Statement

YES 9. The **bolded** HL Limitation Statement must include the following verbatim statement: "**These highlights do not include all the information needed to use (insert name of drug product) safely and effectively. See full prescribing information for (insert name of drug product).**" The name of drug product should appear in UPPER CASE letters.

Comment:

Product Title in Highlights

YES 10. Product title must be **bolded**.

Comment:

Initial U.S. Approval in Highlights

YES 11. Initial U.S. Approval in HL must be **bolded**, and include the verbatim statement "**Initial U.S. Approval:**" followed by the **4-digit year**.

Comment:

Boxed Warning (BW) in Highlights

N/A 12. All text in the BW must be **bolded**.

Comment:

N/A 13. The BW must have a heading in UPPER CASE, containing the word "**WARNING**" (even if more than one warning, the term, "**WARNING**" and not "**WARNINGS**" should be used) and other words to identify the subject of the warning (e.g., "**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**"). The BW heading should be centered.

Comment:

N/A 14. The BW must always have the verbatim statement "***See full prescribing information for complete boxed warning***." This statement should be centered immediately beneath the heading and appear in *italics*.

Comment:

N/A 15. The BW must be limited in length to 20 lines (this includes white space but does not include the BW heading and the statement "***See full prescribing information for complete boxed warning.***").

Comment:

Recent Major Changes (RMC) in Highlights

N/A 16. RMC pertains to only the following five sections of the FPI: BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS. RMC must be listed in the same order in HL as the modified text appears in FPI.

Comment:

N/A 17. The RMC must include the section heading(s) and, if appropriate, subsection heading(s) affected by the recent major change, together with each section's identifying number and date (month/year format) on which the change was incorporated in the PI (supplement approval date). For example, "Warnings and Precautions, Acute Liver Failure (5.1) --- 9/2013".

Comment:

N/A 18. The RMC must list changes for at least one year after the supplement is approved and must be removed at the first printing subsequent to one year (e.g., no listing should be one year older than revision date).

Comment:

Indications and Usage in Highlights

YES 19. If a product belongs to an established pharmacologic class, the following statement is required under the Indications and Usage heading in HL: "(Product) is a (name of established pharmacologic class) indicated for (indication)".

Comment:

Dosage Forms and Strengths in Highlights

YES 20. For a product that has several dosage forms (e.g., capsules, tablets, and injection), bulleted subheadings or tabular presentations of information should be used under the Dosage Forms and Strengths heading.

Comment:

Contraindications in Highlights

YES

21. All contraindications listed in the FPI must also be listed in HL or must include the statement "None" if no contraindications are known. Each contraindication should be bulleted when there is more than one contraindication.

Comment:

Adverse Reactions in Highlights

YES 22. For drug products other than vaccines, the verbatim **bolded** statement must be present: "**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer's U.S. phone number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch**".

Comment:

Patient Counseling Information Statement in Highlights

YES 23. The Patient Counseling Information statement must include one of the following three **bolded** verbatim statements that is most applicable:

If a product **does not** have FDA-approved patient labeling:

- **"See 17 for PATIENT COUNSELING INFORMATION"**

If a product **has** FDA-approved patient labeling:

- **"See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling"**
- **"See 17 for PATIENT COUNSELING INFORMATION and Medication Guide"**

Comment:

Revision Date in Highlights

YES 24. The revision date must be at the end of HL, and should be **bolded** and right justified (e.g., "**Revised: 9/2013**").

Comment:

Contents: Table of Contents (TOC)

See Appendix A for a sample tool illustrating the format for the Table of Contents.

YES 25. The TOC should be in a two-column format.

Comment:

YES 26. The following heading must appear at the beginning of the TOC: **"FULL PRESCRIBING INFORMATION: CONTENTS"**. This heading should be in all UPPER CASE letters and **bolded**.

Comment:

N/A 27. The same heading for the BW that appears in HL and the FPI must also appear at the beginning of the TOC in UPPER CASE letters and **bolded**.

Comment:

YES 28. In the TOC, all section headings must be **bolded** and should be in UPPER CASE.

Comment:

YES 29. In the TOC, all subsection headings must be indented and not bolded. The headings should be in title case [first letter of all words are capitalized except first letter of prepositions (through), articles (a, an, and the), or conjunctions (for, and)].

Comment:

NO 30. The section and subsection headings in the TOC must match the section and subsection headings in the FPI.

Comment: *The TOC is missing 5.4 Effect on Peristalsis and 5.5 Phenylketonuria*

YES 31. In the TOC, when a section or subsection is omitted, the numbering must not change. If a section or subsection from 201.56(d)(1) 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."

Comment:

Full Prescribing Information (FPI)

FULL PRESCRIBING INFORMATION: GENERAL FORMAT

YES 32. The **bolded** section and subsection headings in the FPI must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below (section and subsection headings should be in UPPER CASE and title case, respectively). If a section/subsection required by regulation is omitted, the numbering must not change. Additional subsection headings (i.e., those not named by regulation) must also be **bolded** and numbered.

BOXED WARNING
1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
6 ADVERSE REACTIONS
7 DRUG INTERACTIONS
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Labor and Delivery
8.3 Nursing Mothers
8.4 Pediatric Use
8.5 Geriatric Use
9 DRUG ABUSE AND DEPENDENCE
9.1 Controlled Substance
9.2 Abuse
9.3 Dependence
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
12.4 Microbiology (by guidance)
12.5 Pharmacogenomics (by guidance)
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology
14 CLINICAL STUDIES
15 REFERENCES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

Comment:

YES 33. The preferred presentation for cross-references in the FPI is the section (not subsection) heading followed by the numerical identifier. The entire cross-reference should be in *italics* and enclosed within brackets. For example, *"[see Warnings and Precautions (5.2)]"* or *"*[*see Warnings and Precautions (5.2)*]".

Comment:

N/A 34. If RMCs are listed in HL, the corresponding new or modified text in the FPI sections or

subsections must be marked with a vertical line on the left edge.

Comment:

FULL PRESCRIBING INFORMATION DETAILS

FPI Heading

YES 35. The following heading must be **bolded** and appear at the beginning of the FPI: "**FULL PRESCRIBING INFORMATION".** This heading should be in UPPER CASE.

Comment:

BOXED WARNING Section in the FPI

N/A 36. In the BW, all text should be **bolded**.

Comment:

N/A 37. The BW must have a heading in UPPER CASE, containing the word "**WARNING**" (even if more than one Warning, the term, "**WARNING**" and not "**WARNINGS**" should be used) and other words to identify the subject of the Warning (e.g., "**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**").

Comment:

CONTRAINDICATIONS Section in the FPI

N/A 38. If no Contraindications are known, this section must state "None."

Comment:

ADVERSE REACTIONS Section in the FPI

YES 39. When clinical trials adverse reactions data are included (typically in the "Clinical Trials Experience" subsection of ADVERSE REACTIONS), 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 practice."

Comment:

YES 40. When postmarketing adverse reaction data are included (typically in the "Postmarketing Experience" subsection of ADVERSE REACTIONS), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

"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."

Comment:

PATIENT COUNSELING INFORMATION Section in the FPI

N/A 41. Must reference any FDA-approved patient labeling in Section 17 (PATIENT COUNSELING INFORMATION section). The reference should appear at the beginning of Section 17 and

include the type(s) of FDA-approved patient labeling (e.g., Patient Information, Medication Guide, Instructions for Use).

Comment:

N/A 42. FDA-approved patient labeling (e.g., Medication Guide, Patient Information, or Instructions for Use) must not be included as a subsection under section 17 (PATIENT COUNSELING INFORMATION). All FDA-approved patient labeling must appear at the end of the PI upon approval.

Comment:

Appendix A: Format of the Highlights and Table of Contents

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use [DRUG NAME] safely and effectively. See full prescribing information for [DRUG NAME].

[DRUG NAME (nonproprietary name) dosage form, route of administration, controlled substance symbol]
Initial U.S. Approval: [year]

WARNING: [SUBJECT OF WARNING]
See full prescribing information for complete boxed warning.

- [text]
- [text]

----------RECENT MAJOR CHANGES----------
[section (X.X)] [m/year]
[section (X.X)] [m/year]

----------INDICATIONS AND USAGE----------
[DRUG NAME] is a [name of pharmacologic class] indicated for [text]

----------DOSAGE AND ADMINISTRATION----------
- [text]
- [text]

----------DOSAGE FORMS AND STRENGTHS----------
[text]

----------CONTRAINDICATIONS----------
- [text]
- [text]

----------WARNINGS AND PRECAUTIONS----------
- [text]
- [text]

----------ADVERSE REACTIONS----------
Most common adverse reactions (incidence > x%) are [text].

To report SUSPECTED ADVERSE REACTIONS, contact [name of manufacturer] at [phone #] or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

----------DRUG INTERACTIONS----------
- [text]
- [text]

----------USE IN SPECIFIC POPULATIONS----------
- [text]
- [text]

See 17 for PATIENT COUNSELING INFORMATION [and FDA-approved patient labeling OR and Medication Guide].

Revised: [m/year]

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

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/s/

HEATHER G BUCK
03/02/2015

RICHARD W ISHIHARA
03/02/2015

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

020781Orig1s017

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

From: Lee, Luz
To: Buck, Heather
Subject: Zofran (oral formulation) Labeling - FDA Revisions
Date: Friday, September 23, 2016 12:06:25 PM
Sensitivity: Confidential

Dear Heather,

The team has reviewed the additional changes and find them acceptable. Should I re-submit the USPI with these additional changes?

Best regards,

Luz Patricia Lee
Global Program Regulatory Manager (GPRM)
DRA Established Products, Oncology
Novartis Pharmaceuticals Corporation
One Health Plaza
East Hanover, NJ 07936-1080
USA

Phone +1 862 778 4622
(b) (6)
luz.lee@novartis.com

From: Buck, Heather [mailto:Heather.Buck@fda.hhs.gov]
Sent: Thursday, September 22, 2016 2:21 PM
To: Lee, Luz
Subject: RE: Zofran Labeling - FDA Revisions
Sensitivity: Confidential

Ok, so it sounds like you are clear. Just contact me if future questions arise.
-Heather

Heather Buck, RPM
DGIEP | CDER
(301) 796-1413 | Heather.Buck@fda.hhs.gov

From: Lee, Luz [mailto:luz.lee@novartis.com]
Sent: Wednesday, September 21, 2016 2:34 PM
To: Buck, Heather
Subject: RE: Zofran Labeling - FDA Revisions
Sensitivity: Confidential

Dear Heather,

No need for a phone call. It was confusing to see (b) (4) in the first comment
(b) (4)

(b) (4)

Best regards,

Luz Patricia Lee
Global Program Regulatory Manager (GPRM)
DRA Established Products, Oncology
Novartis Pharmaceuticals Corporation
One Health Plaza
East Hanover, NJ 07936-1080
USA

Phone +1 862 778 4622
(b) (6)
luz.lee@novartis.com

From: Lee, Luz
Sent: Wednesday, September 21, 2016 2:20 PM
To: 'Heather.Buck@fda.hhs.gov'
Subject: RE: Zofran Labeling - FDA Revisions
Sensitivity: Confidential

Dear Heather,

I will look into it. May I give you a call regarding the changes requested for the oral dosage USPI? The first comment is not clear.

Best regards,

Luz Patricia Lee
Global Program Regulatory Manager (GPRM)
DRA Established Products, Oncology
Novartis Pharmaceuticals Corporation
One Health Plaza
East Hanover, NJ 07936-1080
USA

Phone +1 862 778 4622
(b) (6)
luz.lee@novartis.com

From: Buck, Heather [mailto:Heather.Buck@fda.hhs.gov]
Sent: Wednesday, September 21, 2016 2:14 PM
To: Lee, Luz
Subject: RE: Zofran Labeling - FDA Revisions
Sensitivity: Confidential

Great – thanks.
(b) (4)

Thanks,
Heather

Heather Buck, RPM
DGIEP | CDER
(301) 796-1413 | Heather.Buck@fda.hhs.gov

From: Lee, Luz [mailto:luz.lee@novartis.com]
Sent: Wednesday, September 21, 2016 2:01 PM
To: Buck, Heather
Subject: RE: Zofran Labeling - FDA Revisions
Sensitivity: Confidential

Dear Heather,

I will route the changes internally for review.

Best regards,

Luz Patricia Lee
Global Program Regulatory Manager (GPRM)
DRA Established Products, Oncology
Novartis Pharmaceuticals Corporation
One Health Plaza
East Hanover, NJ 07936-1080
USA

Phone +1 862 778 4622
(b) (6)
luz.lee@novartis.com

From: Buck, Heather [mailto:Heather.Buck@fda.hhs.gov]
Sent: Wednesday, September 21, 2016 10:39 AM
To: Lee, Luz
Subject: Zofran Labeling - FDA Revisions
Sensitivity: Confidential

Hello Luz,
We are close to getting this approval out, but the Clin Pharm reviewer has (b) (4) (b) (4). Please circulate the attached and let me know whether you agree via email.
Thanks for your patience.

Regards,
Heather

Heather Buck, MS, MBA

Regulatory Project Manager
Division of Gastroenterology and Inborn Errors Products
Office of Drug Evaluation III | CDER | FDA
(301) 796-1413 | Fax (301) 796-9904 | heather.buck@fda.hhs.gov
10903 New Hampshire Ave, WO22-RM 5128, Silver Spring, MD 20903

3 Page(s) has been withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

HEATHER G BUCK
09/26/2016

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

REQUEST FOR CONSULTATION

TO *(Office/Division)*: ODEIII/DBRUP

FROM (*Name, Office/Division, and Phone Number of Requestor)*: Heather Buck, DGIEP x.61413

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
1/13/16		20103/S-033, 20605/S-017, 20781/S-017		3/19/14

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Zofran (ondansetron) tablets			2/9/16

NAME OF FIRM: Novartis

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE / ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE-NDA MEETING
- ☐ END-OF-PHASE 2a MEETING
- ☐ END-OF-PHASE 2 MEETING
- ☐ RESUBMISSION
- ☐ SAFETY / EFFICACY
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☒ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☐ OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

- ☐ PRIORITY P NDA REVIEW
- ☐ END-OF-PHASE 2 MEETING
- ☐ CONTROLLED STUDIES
- ☐ PROTOCOL REVIEW
- ☐ OTHER (SPECIFY BELOW):
- ☐ CHEMISTRY REVIEW
- ☐ PHARMACOLOGY
- ☐ BIOPHARMACEUTICS
- ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE 4 STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL - BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG SAFETY

- ☐ PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ NONCLINICAL

COMMENTS / SPECIAL INSTRUCTIONS: The Package Insert for oral formulations is being converted to PLR format. The sponsor is also voluntarily adding language to comply with PLLR (see submission from 12/14/15). These changes somewhat conflict with the recent Citizen's Petition response (see sharepoint for 10/27/15 response).
DGIEP would appreciate DBRUP's assessment of the appropriateness of the sponsor's proposed labeling changes, based on available data of ondensetron exposure in pregnancy. Christine Nguyen is currently involved and requested that Barbara Wesley also be added.

NDA 20103 Zofran (ondansetron) tablets: \\CDSESUB1\evsprod\NDA020103\020103.enx
NDA 20605 Zofran oral solution: \\CDSESUB1\evsprod\NDA020605\020605.enx
NDA 20781 Zofran ODT: \\CDSESUB1\evsprod\NDA020781\020781.enx
Sharepoint: http://sharepoint.fda.gov/orgs/CDER-ODEIII-DGIEP/applications/Label/Shared%20Documents/Forms/AllItems.aspx?RootFolder=%2Forgs%2FCDER%2DODEIII%2DDGIEP%2Fapplications%2FLabel%2FShared%20Documents%2FZofran%20PLR%2020103%2D33%2C%2020605%2D17%2C%2020781%2D17&FolderCTID=0x012000A3BA284EABAB1D48A87F951850D5E5B2&View={C93BEB63-A30D-45ED-9007-4BEA2644AAE7}&InitialTabId=Ribbon%2EListItem&VisibilityContext=WSSTabPersistence

The next team meeting is 2/9/16 hence the requested complete date. However, a formal write up (if done) won't be needed until closer to action. Note that these supplements are overdue.

SIGNATURE OF REQUESTOR

METHOD OF DELIVERY (Check all that apply)
☒ DARRTS ☐ EMAIL ☐ MAIL ☐ HAND

HGB 1/13/16	
PRINTED NAME AND SIGNATURE OF RECEIVER	PRINTED NAME AND SIGNATURE OF DELIVERER

06/18/2013

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/s/

HEATHER G BUCK
01/13/2016

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION			**PEDIATRIC AND MATERNAL HEALTH STAFF REQUEST FOR CONSULTATION**	
TO: CDER Pediatric and Maternal Health Staff *(please check)* Pediatrics ☐ Maternal Health ☒ Both ☐			FROM *(Name, Office/Division, and Phone Number of Requestor)*: Heather Buck, OND/DGIEP, x.61413	
DATE 9/16/2014	IND NO.	NDA/BLA NO. 20103/S-033 20605/S-017 20781/S-017	TYPE OF DOCUMENT PAS labeling supplement	DATE OF DOCUMENT 3/19/2014
NAME OF DRUG Zofran (ondansetron) oral	NAME OF FIRM GSK		CLASSIFICATION OF DRUG	PDUFA Goal Date Goal date=9/19/14 (won't make)
Requested Consult Completion Date: 10/3/14 if possible	☐ Urgent* (< 14 days)		☐ Priority (14-29 days)	☒ Routine ≥ 30 days

*Note: Any consult requests with a desired completion date of < 14 days from receipt must receive prior approval from PMHS team leaders. Also, please check one of the three boxes above and also put in a due date.

REASON FOR REQUEST

Pediatrics:	Maternal Health Team:
☐ Labeling Review ☐ Written Request/PPSR ☐ PREA PMR/General Regulatory Question ☐ SPA ☐ Action Letter Review ☐ 30-day IND Review ☐ Other Protocol Review ☐ Meeting Attendance ☐ PeRC Preparation Assistance ☐ Other (please explain):	☒ Labeling Review ☐ Pregnancy Exposure Registry (protocol or report) ☐ Clinical Lactation Study (protocol or report) ☐ Pregnancy PK (protocol or report) ☐ 30-day IND Review ☐ Risk Management – Pregnancy Prevention and Planning ☐ Evaluation of possible safety signal ☐ Guidance development ☐ Other (please explain):
Link to electronic submission (if available): NDA 20103 Zofran (ondansetron) tablets: \\CDSESUB1\evsprod\NDA020103\020103.enx NDA 20605 Zofran oral solution: \\CDSESUB1\evsprod\NDA020605\020605.enx NDA 20781 Zofran ODT: \\CDSESUB1\evsprod\NDA020781\020781.enx	Materials to be reviewed: You will find in Sharepoint (**Zofran PLR SharePoint**) (contact Heather Buck for full link): - Approved labeling (for oral, injection PLR, zuplenz) - Clean label to review/revise - Annotated label as reference

1. Please briefly describe the submission including drug's indication(s):
ZOFRAN is a 5-HT_3 receptor antagonist indicated for:

- Prevention of nausea and vomiting associated with highly emetogenic cancer chemotherapy.
- Prevention of nausea and vomiting associated with initial and repeat courses of moderately emetogenic cancer chemotherapy.
- Prevention of nausea and vomiting associated with radiotherapy.
- Prevention of postoperative nausea and/or vomiting.

2. Describe in detail the reason for your consult. Include specific questions:
The PI for oral formulations is being converted to PLR format. We had a kick-off meeting on 9/15/14 in which it was determined that PMHS/Maternal should review section 8 to ensure that the required and standard language is included. At the conclusion of the team and Maternal's review and revisions, it will be determined whether another meeting is necessary before sending the first round of labeling recommendations to the sponsor. DMPP will be involved after that point.

It would be ideal if labeling revisions can be made by 10/3 but this is flexible. A review won't be necessary until approximately early November.

3. Meeting dates:
9/15/14, next TBD

4. DARRTS Reference ID # for Prior Peds or Maternal Health consults for this product (within the last 3 years):

Review team: Project Manager: Heather Buck Clinical reviewer & Team Leader: Karyn Berry/Ruyi He Pharmacology/Toxicology reviewer & Team Leader: Tracy Behrsing/Sushanta Chakder Clinical Pharmacology reviewer & Team Leader: Elizabeth Shang/Sue Chih Lee Other: Joette Meyer – Associate Director Labeling	
PRINTED NAME or SIGNATURE OF REQUESTOR: HGB 9/16/14	METHOD OF DELIVERY (Please check) ☒ DARRTS ☐ EMAIL ☐ HAND ☐ OTHER

Version: DARRTS 06/01/2011

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/s/

HEATHER G BUCK
09/16/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADM NISTRATION

REQUEST FOR OPDP (previously DDMAC) LABELING REVIEW CONSULTATION

****Please send immediately following the Filing/Planning meeting****

TO: **CDER-OPDP-RPM**	FROM: (Name/Title, Office/Division/Phone number of requestor) Heather Buck/RPM

REQUEST DATE	IND NO.	NDA/BLA NO.	TYPE OF DOCUMENTS
8/26/14		20103/S-033 20605/S-017 20781/S-017	(PLEASE CHECK OFF BELOW)

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE (Generally 1 week before the wrap-up meeting)
Zofran (ondansetron HCL) tablets and oral solution			Early October 2014 (negotiable)

NAME OF FIRM:	
Glaxosmithkline	PDUFA Date: goal date = 9/19/14

TYPE OF LABEL TO REVIEW

TYPE OF LABELING:
(Check all that apply)
- ☒ PACKAGE INSERT (PI)
- ☐ PATIENT PACKAGE INSERT (PPI)
- ☐ CARTON/CONTAINER LABELING
- ☐ MEDICATION GUIDE
- ☐ INSTRUCTIONS FOR USE(IFU)

TYPE OF APPLICATION/SUBMISSION
- ☐ ORIGINAL NDA/BLA
- ☐ IND
- ☐ EFFICACY SUPPLEMENT
- ☐ SAFETY SUPPLEMENT
- ☐ LABELING SUPPLEMENT
- ☒ PLR CONVERSION

REASON FOR LABELING CONSULT
- ☐ INITIAL PROPOSED LABELING
- ☐ LABELING REVISION

For OSE USE ONLY
- ☐ REMS

EDR link to submission:
SharePoint: Zofran PLR SharePoint
NDA 20103 Zofran (ondansetron) tablets: \\CDSESUB1\evsprod\NDA020103\020103.enx
NDA 20605 Zofran oral solution: \\CDSESUB1\evsprod\NDA020605\020605.enx
NDA 20781 Zofran ODT: \\CDSESUB1\evsprod\NDA020781\020781.enx

Please Note: There is no need to send labeling at this time. OPDP reviews substantially complete labeling, which has already been marked up by the CDER Review Team. After the disciplines have completed their sections of the labeling, a full review team labeling meeting can be held to go over all of the revisions. Within a week after this meeting, "substantially complete" labeling should be sent to OPDP. Once the substantially complete labeling is received, OPDP will complete its review within 14 calendar days.
OSE/DRISK ONLY: For REMS consults to OPDP, send a word copy of all REMS materials and the most recent labeling to CDER DDMAC RPM. List out all materials included in the consult, broken down by audience (consumer vs provider), in the comments section below.

COMMENTS/SPECIAL INSTRUCTIONS:
1st labeling meeting is 9/15/14. We should have labeling after the 2nd mtg (TBD sometime late Sept). See supporting docs, approved labeling (injection is in PLR), and annotated labeling in Sharepoint (above).

SIGNATURE OF REQUESTER
HGB 8/26/14

SIGNATURE OF RECEIVER	METHOD OF DELIVERY (Check one) ☐ eMAIL ☐ HAND

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/s/

HEATHER G BUCK
08/26/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

NDA 020103/S-033
NDA 020605/S-017
NDA 020781/S-017

ACKNOWLEDGEMENT --
PRIOR APPROVAL SUPPLEMENT

GlaxoSmithKline
Attention: Amita Chaudhari, M.Sc.
Manager, Global Regulatory Affairs
1250 South Collegeville Rd.
UP4400
Collegeville, PA 19426

Dear Ms. Amita:

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

NDA	Supplement	Drug Product
020103	S-033	Zofran (ondansetron hydrochloride) Tablets
020605	S-017	Zofran (ondansetron hydrochloride) Oral Solution
020781	S-017	Zofran ODT (ondansetron) Orally Disintegrating Tablets

DATE OF SUBMISSION: March 19, 2014

DATE OF RECEIPT: March 19, 2014

These supplemental applications propose labeling changes according to the Physician Labeling Rule (PLR) format.

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on May 16, 2014, in accordance with 21 CFR 314.101(a).

If the application is filed, the goal date will be September 19, 2014.

SUBMISSION REQUIREMENTS

Cite the application number listed above at the top of the first page of all submissions to this application. 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 and Inborn Errors Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size. Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, see http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFilesDMFs/ucm073080.htm.

If you have questions, call me at (301) 796-0260.

Sincerely,

{See appended electronic signature page}

Mary Chung, Pharm.D.
Regulatory Project Manager
Division of Gastroenterology and Inborn Errors Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

MARY H CHUNG
04/02/2014