



DEPARTMENT OF HEALTH & HUMAN SERVICES

OCT 27 2015

Food and Drug Administration
10903 New Hampshire Avenue
Building #51
Silver Spring, MD 20993

James P. Reichmann
[REDACTED]

Re: Docket No. FDA-2013-P-0048

Dear Mr. Reichmann:

This letter responds to your citizen petition received on January 7, 2013,¹ and the supplemental information submitted by you and received on January 14, 2013, March 12, 2013, May 14, 2014, June 24, 2015, and September 14, 2015 (collectively, the Petition).²

The Petition states that the use of Zofran (ondansetron) by pregnant women poses risks to the fetus, neonate, and mother and that there is insufficient evidence to support the unapproved use of ondansetron for the treatment of nausea and vomiting during pregnancy.

The Petition requests that the Food and Drug Administration (FDA or Agency) take the following actions (Petition at 2):

- Reclassify the drug ondansetron (Zofran) from pregnancy risk category B to category C, D, or X after evaluation of “new safety information”;
- Notify obstetricians and gynecologists (OB/GYNs) that there is insufficient scientifically acceptable evidence that ondansetron is associated with improved treatment outcomes and may lead to adverse maternal and fetal events or outcomes;
- Notify OB/GYNs that promotion of continuous subcutaneous ondansetron pump for the treatment of nausea and vomiting of pregnancy (NVP) is a violation of FDA regulations.

¹ Although this citizen petition was received on January 7, 2013, it was dated January 4, 2012. We believe that the year of 2012 on the Petition was a typographical error. Also, because the Petition is not page-numbered and includes a cover page, for purposes of this response we consider the cover page to be part of the Petition, and refer to the Petition page numbers accordingly (i.e., the cover page is considered page 1 of the Petition).

² Anonymous submissions in support of the Petition were received on September 3, September 24, and October 29, 2013, and on January 23, April 14, and September 26, 2014. A signed submission opposing the Petition was received on January 27, 2014. Signed submissions in support of the Petition were received on February 2, February 9, March 6, April 20, April 27, and October 5, 2015.

We have carefully considered the Petition and submissions to the docket. The Petition's requests are denied for the reasons described below.

I. BACKGROUND

A. Ondansetron Indications and Unapproved Use

1. *Approved Indications*

Ondansetron is a type three 5-hydroxytryptamine receptor antagonist indicated for use in the prevention of nausea and vomiting associated with chemotherapy and radiotherapy and the prevention of postoperative nausea and vomiting associated with anesthesia.

FDA-approved and currently marketed ondansetron drug products³ include the formulations in Table 1, below. Ondansetron is marketed under the trade name Zofran (all dosage forms except oral film) or Zuplenz (oral film only).

Table 1—Currently Marketed Approved Ondansetron Drug Products

Approval Year	Dosage Form	New Drug Application (NDA) No.	NDA Holder
1991	Injectable; Injection	20007	Novartis
1992	Oral tablet	20103	Novartis
1997	Oral solution	20605	Novartis
1999	Orally disintegrating tablet	20781	Novartis
2010	Oral film	22524	Galena BioPharma

In addition, generic versions of the NDA products are available in all dosage forms, except for oral film.

The approved indications of ondansetron for injectable products are:

1. Prevention of nausea and vomiting in patients aged 6 months and older associated with initial and repeat courses of emetogenic cancer chemotherapy, including high-dose cisplatin.
2. Prevention of postoperative nausea and/or vomiting. As with other antiemetics, routine prophylaxis is not recommended for patients in whom there is little expectation that nausea and/or vomiting will occur postoperatively. In patients in whom nausea and/or vomiting must be avoided postoperatively, [Product Name(s) and Formulation(s) is/are] recommended

³ For the injectable, oral tablet, and oral solution dosage forms, ondansetron hydrochloride is used. For the oral disintegrating tablet and oral film, ondansetron base is used. For purposes of this response, all forms will be referred to as ondansetron.

even when the incidence of postoperative nausea and/or vomiting is low. For patients who do not receive prophylactic [Product Name(s) and Formulation(s) is/are] and experience nausea and/or vomiting postoperatively, [Product Name(s) and Formulation(s) is/are] may be given to prevent further episodes. [Product Name(s) and Formulation(s) is/are] approved for patients aged 1 month and older.

The approved indications of ondansetron for oral products (oral tablets, orally disintegrating tablets, oral solution, and oral film) are:

1. Prevention of nausea and vomiting associated with highly emetogenic cancer chemotherapy, including cisplatin \geq 50 milligrams (mg)/meter (m^2)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, [Product Name(s) and Formulation(s) is/are] recommended even where the incidence of postoperative nausea and/or vomiting is low.

2. *Unapproved Use*

No ondansetron drug product has been approved for the treatment of nausea and vomiting in pregnancy (NVP).

We are aware of the unapproved use of oral and injectable ondansetron for the treatment of NVP. NVP is a common condition affecting 50% - 90% of women during their pregnancies.⁴ The severity of NVP exists on a continuum, and the most severe form is known as hyperemesis gravidarum (HG). HG has been reported in 0.5% to 2% of pregnancies and is characterized by persistent and severe nausea and vomiting that may be accompanied by weight loss, large ketonuria, electrolyte abnormalities, and dehydration. HG can pose a risk to the health of both the mother and the fetus and may result in hospitalization. Between 2004 and 2008, approximately 3% of a sample of 4,300 expectant mothers enrolled in the Slone Epidemiology Center Birth Defects Study reported using ondansetron in the first trimester of pregnancy.⁵

⁴ Piwko C, et al., "Economic burden of nausea and vomiting of pregnancy in the USA." *J. of Population Therapeutics & Clin Pharm* 2013; e149.

⁵ Mitchell AA, Gilboa SM, Werler MM, et al. "Medication use during pregnancy, with particular focus on prescription drugs: 1976-2008." *Am J Obstet Gynecol* 2011;205:51.e1-8.

B. Pregnancy Risk Labeling for Ondansetron

1. Pregnancy Risk Categories in Prescription Drug Labeling

At the time the Petition was submitted in 2013, FDA regulations required the *Pregnancy* subsection of the drug product labeling to address the teratogenic effects of the drug by inclusion of the appropriate pregnancy risk category, as well as the relevant required statements for that category unless a drug was not absorbed systemically and the drug was not known to have a potential for indirect harm to the fetus (21 CFR 201.57(c)(9)(i) and 201.80(f)(6)(i)).

2. Current Ondansetron Labeling Regarding Use during Pregnancy

During the NDA review and approval process for Zofran (the first approved ondansetron drug product), FDA determined that pregnancy risk category B was the appropriate category. Other ondansetron drug product applications (for both NDA and generic products) have likewise been assigned pregnancy category B. The regulations in effect when the Petition was submitted in 2013 specified the following criteria for a pregnancy risk Category B designation:

- “animal reproduction studies have failed to demonstrate a risk to the fetus and there are no adequate and well-controlled studies in pregnant women” or “animal reproduction studies have shown an adverse effect (other than decrease in fertility), but adequate and well-controlled studies in pregnant women have failed to demonstrate a risk to the fetus during the first trimester of pregnancy (and there is no evidence of a risk in later trimesters)” (21 CFR 201.57(c)(9)(i)(A)(2) and 201.80(f)(6)(i)(b)).

The current approved labeling for injectable ondansetron products states the following in the Pregnancy section:

Pregnancy; Pregnancy Category B

Pregnancy Category B. Reproduction studies have been performed in pregnant rats and rabbits at intravenous doses up to 4 mg/kg per day (approximately 1.4 and 2.9 times the recommended human intravenous dose of 0.15 mg/kg given three times a day, respectively, based on body surface area) and have revealed no evidence of impaired fertility or harm to the fetus due to ondansetron. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

The current labeling for oral ondansetron products other than oral film (oral tablets, orally disintegrating tablets, and oral solution), states the following in the Pregnancy section:

Pregnancy: Teratogenic Effects

Pregnancy Category B. Reproduction studies have been performed in pregnant rats and rabbits at daily oral doses up to 15 and 30 mg/kg/day, respectively, and have revealed no evidence of impaired fertility or harm to the fetus due to ondansetron. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

The current labeling for the oral film formulation of ondansetron states the following in the Pregnancy section:

Pregnancy

Pregnancy Category B. Reproduction studies have been performed in pregnant rats and rabbits at daily oral doses up to 15 and 30 mg/kg/day, respectively (approximately 8 and 30 times the human dose of 16 mg/day, based on body surface area), and have revealed no evidence of impaired fertility or harm to the fetus due to ondansetron. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, [Product Name] (ondansetron) oral soluble film should be used during pregnancy only if clearly needed.

However, as discussed below, the requirements for prescription drug product labeling with regard to potential risks during pregnancy and lactation recently changed.

3. Pregnancy and Lactation Labeling Rule (effective June 30, 2015)

On December 4, 2014, FDA issued a final rule amending the regulations concerning the requirements for pregnancy and lactation information in prescription drug and biological product labeling (Pregnancy and Lactation Labeling Rule).⁶ The changes to the regulations took effect on June 30, 2015. The Pregnancy and Lactation Labeling Rule requires the following:

- Labeling for drug products that are the subject of applications (including NDAs, Biologics License Applications (BLAs), and efficacy supplements) approved on or after June 30, 2001, must comply with the content and format requirements in 21 CFR 201.57(c)(9)(i), as revised by the Pregnancy and Lactation Labeling Rule.⁷

⁶ *Federal Register* (FR) notice, “Final Rule: Content and Format of Labeling for Human Prescription Drug and Biological Products; Requirements for Pregnancy and Lactation Labeling,” (79 FR 72064, December 4, 2014).

⁷ See 21 CFR 201.56(b); 21 CFR 201.57(c)(9)(i).

- For all human prescription drug and biological products, including those for which an application was approved before June 30, 2001, the pregnancy letter categories A, B, C, D, and X must be removed.⁸

A holder of an application that is not subject to the new content and format requirements of the final rule (i.e. an application subject to 21 CFR 201.80) must remove the pregnancy risk category from its labeling within 3 years after the effective date of the rule.⁹ A holder of an application that is subject to the new content and format requirements of the rule (i.e., an application subject to 21 CFR 201.56) is required to remove the pregnancy category when it revises the labeling of the product according to the implementation schedule in the Pregnancy and Lactation Labeling Rule.¹⁰ Because of this phased implementation schedule, there may be a window of time during which the pregnancy risk categories continue to appear on some ondansetron drug product labeling, while other ondansetron products have labeling that has been revised consistent with the Pregnancy and Lactation Labeling Rule content and format requirements.

II. DISCUSSION

The Petition states concerns regarding certain potential risks to the fetus and neonate (e.g., cleft palate) and to the pregnant woman (e.g., Torsade de Points and QT prolongation) if she receives ondansetron during pregnancy (Petition at 3-4), particularly during unapproved use of ondansetron to treat NVP. These potential risks are discussed in section II.A (Discussion of Risks) below.

The Petition also requests that FDA take specific actions with regard to such potential risks, including: (i) changing the pregnancy category of ondansetron; (ii) providing certain notifications to OB/GYNs regarding the safety and efficacy of ondansetron use during pregnancy; and (iii) providing certain notifications to OB/GYNs regarding marketing or promotion of a continuous subcutaneous pump to deliver ondansetron for the treatment of NVP. These requests are discussed in section II.B (Petition Requests) below.

A. Discussion of Risks

I. *Risks to the Fetus and Neonate*

The Petition raises a safety concern regarding teratogenic and other risks to the fetus and neonate in support of the request that FDA reclassify ondansetron from pregnancy category B to category C, D, or X, based on new safety information. In particular, the Petition alleges that the use of ondansetron during pregnancy may result in an increased risk of cleft palate or other fetal and neonatal anomalies. The Petition includes citations

⁸ 21 CFR 201.57(c)(9); 21 CFR 201.80; see also 79 FR 72064 at 72095.

⁹ See 79 FR 72064 at 72095.

¹⁰ Id.

to a number of studies and case reports. We discuss these points below. We then describe additional clinical and other information we reviewed, discuss our analysis of this information, and provide our conclusions. For the reasons discussed below, we deny the requests.

a. Studies Cited in the Petition (or separately submitted by the Petitioner)

The Petition references one case-control study, four cohort studies, and one case series in support of the request to reclassify ondansetron into a different pregnancy category. The Petition also references a preclinical risk evaluation that was submitted in support of the initial approval of ondansetron. The Petition expresses a specific concern about the potential for increased risk of cleft palate in neonates exposed to ondansetron in the first trimester of pregnancy, based on the findings of the single case-control study. We discuss each of these studies below.

Case control study (1 study)

A case-control study authored by Anderka et al.¹¹ and based on data from the National Birth Defects Prevention Study (NBDPS) has reported birth defects associated with exposure to ondansetron during pregnancy. The authors analyzed data on the most common non-cardiac defects (non-syndromic cleft lip with or without cleft palate, cleft palate alone, neural tube defects, and hypospadias (an anomaly of the male urethra)) from the NBDPS from 1997 to 2004. During the study period, 22,381 women participated in the NBDPS and 75 different medications and a number of herbal products were reported as treatment for NVP. In all, 4,524 cases of birth defects of interest were compared to 5,859 controls for association with NVP or its treatment in the first trimester. The authors reported that exposure to ondansetron was associated with a statistically significant 2.3-fold increase in the risk of cleft palate alone, but not of cleft lip with or without cleft palate, neural tube defects, or hypospadias.

One limitation to the case-control study by Anderka et al. is the potential for recall bias, which may arise if women who delivered infants with birth defects recall their exposure to ondansetron differently from women who delivered infants without birth defects. However, the limitation of most concern in this study is the possibility of a chance finding. According to the authors, approximately 70 comparisons between mothers with NVP who were and were not exposed to various medications were tested for statistical significance. For that number of comparisons (70), 3 to 4 comparisons are expected to achieve statistical significance by chance alone. The authors reported statistically significant associations between drug exposure and fetal anomalies for just three

¹¹ 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 Selected Birth Defects." *Birth Defects Res A Clin Mol Teratol.* 2012 Jan; 94(1):22-30. Epub 2011 Nov 19.

comparisons, including ondansetron.¹² The authors concluded that these positive associations reported in the study, which “could be chance findings,” warrant further investigation.¹³ Moreover, the authors noted that the medication exposure categories were not mutually exclusive (i.e., pregnant women taking ondansetron might also have been exposed to one or more other anti-NVP treatments).¹⁴ Thus, the association of risk with certain drugs may reflect confounding by other factors for which the authors did not control, including other potentially teratogenic medication use or genetic factors.

Cohort studies (4 studies)

1. Pasternak et al.

Pasternak et al.¹⁵ recently published results of a registry-based retrospective cohort study that evaluated adverse pregnancy and fetal outcomes associated with ondansetron exposure. This study relied on a historical cohort of 608,385 pregnancies from the Medical Birth Registry and the National Patient Register in Denmark between 2004 and 2011 and compared spontaneous abortion (miscarriage) (7 – 22 weeks), stillbirth (week 7 – birth), any major birth defect (first trimester), preterm delivery (< 37 weeks), and infants of low birth weight (< 2,500 grams) and small for gestational age (<10th percentile of gestational-age specific birth weights in cohort) between ondansetron-exposed and unexposed pregnancies. Of the entire cohort, 1,970 women (0.3%) received ondansetron during pregnancy (1,233 during the first trimester). These ondansetron-exposed women were matched in a ratio of 1:4 to unexposed pregnant women. The first prescription was filled at a median of 70 gestational days (approximately 10 weeks gestation) and the median number of doses per pregnancy was 30. Among ondansetron-exposed women, over half were hospitalized for NVP, including HG, and almost half received another antiemetic.

The authors concluded that ondansetron use in pregnancy did not confer an increased risk of adverse pregnancy or fetal outcomes of interest.¹⁶ Among the 1,233 pregnancies exposed to ondansetron in the first trimester, 3% of the infants had a major birth defect

¹² The three positive associations between drug exposure and birth defects reported in the study included exposure to ondansetron, proton pump inhibitors, and corticosteroids. See Anderka et al., supra note 11.

¹³ Anderka et al., supra note 11, at 22, 29.

¹⁴ See e.g., Anderka et al., supra note 11, at 26–27, Tables 3 and 4, note “a” (stating that medication exposure includes medications “[u]sed alone or in combination with other agents; categories are not mutually exclusive”).

¹⁵ Pasternak B, Svanstrom H, and Hviid A. “Ondansetron in Pregnancy and Risk of Adverse Fetal Outcomes.” *N Engl J Med* 2013;368:814–23.

¹⁶ The authors of this large study noted, “... we found that exposure to ondansetron in pregnancy was not associated with a significant increase in the risk of spontaneous abortion, stillbirth, any major birth defect, preterm delivery, or infants born with low birth weight or born small for gestational age.” Id. at 823. We note that the “major birth defects” included, in addition to cleft palate and other conditions, cardiovascular malformations. Id. at Supplemental Appendix, Table S9.

compared to 3% of infants born to unexposed mothers. There were no cases of cleft palate among infants exposed to ondansetron *in utero*. 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%). Given the absence of cases of cleft palate alone and the small number of cleft lip (with or without cleft palate) cases, no measures of association were calculated for either defect.¹⁷

2. Einarson et al.

A prospective cohort study¹⁸ from Canadian and Australian teratology information services examined the safety of ondansetron use in pregnancy among infants born to three groups of pregnant women. Each group enrolled 176 women: the first group was exposed to ondansetron, the second group to other antiemetics (Diclectin,¹⁹ metochlopramide, phenothiazines, and ginger), and the third group consisted of women who were either exposed to no medications or only to drugs the authors considered to “be safe in pregnancy.” All women in the ondansetron exposure group received medication in the first trimester of pregnancy, mostly between 5 and 9 gestational weeks.²⁰ No statistically significant differences were found among the three groups regarding live births, miscarriages, stillbirths, therapeutic abortions, major malformations, birth weight, or gestational age at birth.²¹ We note, however, that the study was of limited size and statistical power (the study had 80% power to detect a 3.5-fold increase in major congenital malformations). Also, study enrollment was voluntary, and the comparability of ondansetron-exposed pregnant women who ultimately decided to enroll to the general population of ondansetron-exposed pregnant women is unknown.

¹⁷ One of the most significant limitations of any observational study is confounding (either by indication or by other data confounders and variables, such as small sample size, recall bias, possibility of a chance finding, and other data and method limitations). For this study, unmeasured or residual confounding may have impacted the overall results from Pasternak et al, but this issue was considered by the researchers with the conclusion that any magnitude change in the risk estimate would be minimal (see, e.g., discussion of modeling the effect of a hypothetical unmeasured confounder that might mask a true risk (Pasternak et al., *supra* note 15, at 822 and Supplementary Appendix Table 12), and discussion of post hoc analyses categorizing women according to whether they filled one prescription or two or more prescriptions for ondansetron (*Id.* at 818). Also, the confounding arises when comparing one cohort to another. Since there were no exposed cases of cleft palate, such a comparison could not be made.

¹⁸ Einarson A, Maltepe C, Navioz Y, et al. “The safety of ondansetron for nausea and vomiting of pregnancy: a prospective comparative study.” *BJOG* 2004;111:940-943.

¹⁹ Diclectin is the pyridoxine/doxylamine drug product available in Canada. At the time of this study Diclegis (NDA 021876, held by Duchesnay), a recently-approved pyridoxine/doxylamine drug product, had not yet been approved by FDA for use in the United States.

²⁰ Einarson et al., *supra* note 18 at 941.

²¹ *Id.* at 942.

3. Asker et al.

A retrospective cohort study by Asker et al.²² examined pregnancy outcomes based on data obtained from the Swedish Medical Birth Register between 1995 and 2002. The study compared outcomes of women using antiemetics during pregnancy, including ondansetron, with all women giving birth during the study period. Of 665,572 pregnant women, 45 pregnant women were treated with ondansetron, with 21 women receiving ondansetron during only the first trimester, 12 during only the second to third trimesters, and another 12 throughout pregnancy (first through third trimesters). There were no reports of any major birth defects among these 45 women. This study was limited in its small sample size of pregnant women exposed to ondansetron and scant data on timing, dose, and duration of exposure to ondansetron.

In summary, the four cohort studies cited in the Petition or submitted separately by the Petitioner did not identify an increased risk of adverse pregnancy or fetal outcomes.²³ The results from the Pasternak et al. study, which is one of the largest to date on ondansetron exposure in pregnant women (1,970 women with ondansetron exposure during early pregnancy), provide some assurance regarding the fetal safety of antenatal ondansetron exposure. Specifically, the study did not identify any cases of cleft palate among the 1,233 neonates exposed to first trimester ondansetron.²⁴ In addition to the large size of the Pasternak study, in general, cohort studies by their design have fewer biases and confounders than case-control studies, and the cohort study by Pasternak et al. likely has fewer biases than the case-control study by Anderka et al. that supports the Petitioner's claims.

4. Danielsson et al.

A recent retrospective cohort study by Danielsson et al.²⁵ used data from the Swedish Medical Birth Register collected between 1998 and 2012 to assess a potential association between ondansetron use during pregnancy and a risk of congenital malformations in the infant. (An earlier analysis of this data that included births from 1995-2002 was published by Asker et al. and is briefly reviewed above (see section II.A.1.a.)). Of approximately 1.5 million births during the study period, there were 1,349 infants

²² Asker C, Norstedt W, Källén B. "Use of antiemetic drugs during pregnancy in Sweden." *Eur J Clin Pharmacol*. 2005 Dec; 61 (12):899-906.

²³ See section II.A.b., below, for a discussion of a cohort study by Danielsson et al., cited in a third party comment to the docket, which the authors state may indicate an association between antenatal ondansetron use and infant cardiovascular malformations.

²⁴ Pasternak et al., supra note 15 at 820.

²⁵ Danielsson B, Wikner BN, Kallen B. "Use of ondansetron during pregnancy and congenital malformations in the infant." *Reprod Toxicol* 2014 50:134-137.

exposed to ondansetron during “early pregnancy.”²⁶ The authors report statistically significant increased associations for ondansetron exposure in early pregnancy and cardiovascular malformations and septal malformations (a type of cardiovascular malformation). The authors do not clearly describe the comparison group.²⁷ Of the 1,349 infants exposed to ondansetron in early pregnancy, the only malformations occurring more than once in the study were ventricular septum malformations, ventricular and atrium septum defects, and hypospadias. The authors note that 17 of the 19 cardiovascular malformations observed in the study were ventricular and/or septal defects. In addition to noting possible confounders and other limitations, the authors note that the clinical significance of the increased reported for atrial/septal defects is unknown, and that “detailed clinical information on these cases is missing.”²⁸ Minor atrial/septal defects are common, are often subclinical, and may resolve without intervention.²⁹

Previous published studies have not reported increased associations between ondansetron use in early pregnancy and atrial and/or septal cardiovascular malformations,³⁰ and the signal for cardiovascular malformations reported by Danielsson et al. may or may not be causal.

²⁶ The term “early pregnancy” was not defined by the authors. For purposes of our review, we assumed that “early pregnancy” was the first 12 weeks from the last menstrual period (based on information in the manuscript’s Table 1). Supra note 25 at Table 1.

²⁷ While data from the Asker et al. study as well as the statistical methods in the current study indirectly suggest the control population consisted of the entire population of births during the study period, because the actual composition of the comparison group is not described, we had to make an assumption regarding the group for purposes of our review of the study methodology and conclusions.

²⁸ Supra note 25 at 137.

²⁹ Hoffman JIE, Kaplan S. The incidence of congenital heart disease. *J Am Coll Cardiol* 2002; 39: 1890-1900.

³⁰ Comments submitted in support of the Petition and the September 14, 2015 supplement to the Petition included copies of or references to two abstracts of unpublished data from a cohort study, which the abstract authors state might indicate an increased risk of cardiac congenital anomalies related to antenatal ondansetron use. Both abstracts used data from the same Danish registry sources as used in the study by Pasternak et al. See Andersen JT, et al., “Ondansetron Use in Early Pregnancy and the Risk of Congenital Malformations – A Register Based Nationwide Cohort Study,” International Society of Pharmacoepidemiology, Montreal, Canada; 2013, Abstract 25, Pregnancy Session 1 and Andersen JT, et al., “Ondansetron Use In Early Pregnancy And The Risk Of Congenital Malformations –A Register Based Nationwide Cohort Study,” http://www.acog.org/~media/Districts/District%20II/PDFs/Ondansetron_Use_031514_eNewsletter.pdf. FDA staff reviewed and considered these abstracts, but determined there was insufficient information to meaningfully interpret the abstract results. As of October 9, 2015, the Petitioner and commenters have not provided, and FDA has not found in the literature, reviewable published study data regarding these abstracts.

Retrospective case series (1 case series)

In a retrospective case series covering 2002 to 2011, Ferreira et al.³¹ described outcomes in 14 pregnant women who were treated with ondansetron for HG. No fetal anomalies attributable to ondansetron use were reported.³²

Preclinical safety evaluation

In 1989, Tucker et al. published the results of a preclinical safety evaluation of ondansetron.³³ This evaluation was submitted in support of the 1991 approval of Zofran, and certain information from it is included in labeling for Zofran drug products.³⁴

The reproduction studies conducted as part of the safety evaluation are relevant to this Petition. Tucker et al. described results from reproduction studies performed in pregnant rats and rabbits given ondansetron IV doses up to 4 mg/kg per day, which is approximately 1.5 to 3 times the recommended human IV dose of 0.15 mg/kg given three times daily. These studies did not show any evidence of impaired fertility or harm to the fetus due to ondansetron. Ondansetron was classified as pregnancy category B based on these negative findings (but was appropriately not classified as pregnancy category A³⁵ because of a lack of adequate and well-controlled studies in pregnant women confirming these findings during human use of the drug product).

b. Additional Information Reviewed by FDA

In addition to reviewing the studies cited in the Petition,³⁶ supplements, and third-party submissions to the docket,³⁷ we also performed an independent search of the published medical and scientific literature. This search did not yield any additional human studies about ondansetron exposure and adverse pregnancy, fetal, or neonatal outcomes.

³¹ Ferreira E, Gillet M, Lelievre J, Bussieres JF. "Ondansetron use during pregnancy: a case series." *J Popul Ther Clin Pharmacol.* 2012; 19(1); e1-e10.

³² Id. at e8.

³³ Tucker ML, Jackson MR, Scales MD, Spurling NW, Tweats DJ, Capel-Edwards K. "Ondansetron: pre-clinical safety evaluation." *Eur J Cancer Clin Oncol.* 1989; Suppl 1: S79-93.

³⁴ See, e.g., labeling approved for Zofran injection on September 18, 2014, at Section 8.1 (Pregnancy), http://www.accessdata.fda.gov/drugsatfda_docs/label/2014/020007s046lbl.pdf.

³⁵ The regulations in effect when the Petition was submitted in 2013 specified the following criteria for a pregnancy risk Category A designation: "adequate and well-controlled studies in pregnant women have failed to demonstrate a risk to the fetus in the first trimester of pregnancy (and there is no evidence of risk in later trimesters)" (21 CFR 201.57(c)(9)(i)(A)(1) and 201.80(f)(6)(i)(a)).

³⁶ While all studies cited in the Petition were reviewed, this response does not include separate discussion of each study. All were considered by FDA and included as part of the totality of the evidence reviewed in connection with the Petition, but not all were considered integral to the discussion in this response.

³⁷ These include 13 submissions, which are listed in note 2, above. The submissions may be viewed online at www.regulations.gov (Docket No. FDA-2013-P-0048).

c. Analysis and Conclusions

In summary, of all the studies, case reports, and other data we reviewed, only two studies (the case-control study by Anderka et al. discussed on pp. 7-8, above, and the retrospective cohort study by Danielsson et al. discussed on pp. 10-11, above) provided information that suggests adverse outcomes for the pregnant woman, fetus, or neonate.³⁸

The Anderka et al. study has methodological limitations; its finding of a modest positive association between cleft palate and ondansetron exposure may be a chance finding; and the association has not been observed in other published studies.³⁹ The Danielsson et al. study also has methodological limitations, a modest positive association between cardiovascular malformations and ondansetron that may be due to non-causal factors, and an association not observed in other published studies.⁴⁰ Indeed, a recent observational cohort study from Denmark (Pasternak et al.), a large study on the safety of ondansetron in pregnancy, contradicts the findings in the Anderka et al. study with regard to an association between ondansetron use during pregnancy and cleft palate, as well as finding no association between ondansetron use and a panel of “major birth defects” including, but not limited to, cardiovascular malformations.⁴¹ While the Pasternak et al. study also has some methodological limitations, the authors did not detect any increased risk to the fetus. Furthermore, the study did not identify a single ondansetron-exposed cleft palate case, suggesting a lack of association.

All these studies suffer from various methodological limitations⁴² that preclude definitive conclusions about the safety of ondansetron use in pregnancy. The available evidence is not sufficient to conclude that there is an increased risk of birth defects, including cleft palate, among fetuses exposed to ondansetron. Moreover, the additional information we reviewed (e.g., results of an independent literature search and adverse event reports) does not provide evidence of a safety concern related to the use of ondansetron during pregnancy. When reviewed together, the totality of the available data does not support a determination that there is an increased risk of fetal adverse outcomes, including cleft palate, among fetuses exposed to ondansetron, because none of the other published studies corroborate the findings in the Anderka et al. or Danielsson, et al. studies. While a potential association between ondansetron use during pregnancy and cardiovascular malformations warrants continued vigilance, given the limitations of the Danielsson study, as well as the lack of consistent evidence for cardiovascular teratogenicity, the study does not support a change in pregnancy risk category at this time for those products

³⁸ Please also see note 30, above (discussing abstracts of unpublished data from a cohort study that the abstract authors state might indicate a risk of congenital anomalies related to antenatal ondansetron use).

³⁹ See discussion of the Anderka study on pp. 7-8, above.

⁴⁰ See discussion of the Danielsson study on pp. 10-11, above; see also note 30, above.

⁴¹ Supra note 15.

⁴² For example, small sample size, data confounders, recall bias, possibility of a chance finding, and other data and method limitations.

for which the labeling has not yet been revised consistent with the Pregnancy and Lactation Labeling Rule. For products for which the labeling is currently undergoing revision to be consistent with the new rule, the data reviewed do not provide sufficient evidence to support changes to the “Pregnancy” and “Lactation” (formerly “Nursing Mothers”) label subsections at this time.

Thus, we find that the available data are not sufficient to conclude that there is a safety concern with regard to the use of ondansetron during pregnancy that would warrant changes at this time to the pregnancy risk category (for labeling that has not yet been revised consistent with the Pregnancy and Lactation Labeling Rule), or to the “Pregnancy” or “Lactation” subsections in labeling that is being revised consistent with the new rule.

2. Risks to the Pregnant Patient

In addition to concerns regarding potential teratogenic risks to the fetus and neonate posed by ondansetron use during pregnancy, the Petition also raises concerns regarding risks specific to the pregnant woman.

a. Vision Loss

The first supplement to the Petition is a case report of one pregnant woman who experienced vision loss while being treated with ondansetron.⁴³ We reviewed the case report as well as other literature and adverse event reports from the FDA Adverse Event Reporting System (FAERS) database, in order to identify cases of vision loss related to ondansetron. FAERS is a computerized information database designed to support FDA's post-marketing safety surveillance program for all approved drug and therapeutic biologic products.⁴⁴ FDA requires sponsors of prescription products, including sponsors of ondansetron products, to report adverse events associated with their drug products.⁴⁵ In addition, individual health care providers and their patients are encouraged to voluntarily report serious adverse events to FDA.⁴⁶ Transient blindness and blurred vision are labeled as potential adverse reactions for any patient using ondansetron

⁴³ Davis, F, et al., “The Case Files: Vision Loss in a Pregnant Patient,” *Emergency Med News*; 2012.

⁴⁴ See FDA Adverse Event Reporting System (FAERS),
<http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/default.htm> .

⁴⁵ See, e.g., 21 CFR part 314.80(c)(1)(i) (among other things, requiring reports to FDA within 15 calendar days when sponsors of prescription products become aware of information that suggests that use of the drug product resulted in an adverse drug experience that is both serious and unexpected).

⁴⁶ See, e.g., MedWatch forms and other information regarding voluntary reporting by health professionals and consumers available at the FDA website (<http://www.fda.gov/Safety/MedWatch/HowToReport/default.htm>).

products.⁴⁷ We did not find evidence to support a potential safety signal for vision loss in pregnant women treated with ondansetron (as opposed to any patient treated with ondansetron).

b. Torsade de Pointes, QT Prolongation, and Use of Ondansetron with an Infusion Pump

The Petition raises a number of concerns regarding certain potential adverse reactions to ondansetron and the use of ondansetron with an infusion pump for treatment of NVP. In particular:

- The Petition states that Torsade de Pointes and QT prolongation are of particular concern when ondansetron is used in pregnant women (Petition at 4) and notes that women with NVP may already have electrolyte imbalances.
- The Petition states that use of a subcutaneous pump to administer ondansetron to pregnant women is particularly worrisome, citing a 2012 safety warning from FDA regarding the 32 mg IV dose of ondansetron⁴⁸ to support this concern and further states that it is “not uncommon” for patients to receive ondansetron doses approaching or exceeding 32 mg per day (Petition at 4).
- The Petition states that few obstetricians are aware of the FDA precautions and, therefore, are not following the safety recommendations (Petition at 4).

We discuss each of these issues below.

⁴⁷ See, e.g., labeling approved for Zofran injection on September 18, 2014, at Section 6.2 (Postmarket Experience), http://www.accessdata.fda.gov/drugsatfda_docs/label/2014/020007s046lbl.pdf.

⁴⁸ Drug Safety Communication: New information regarding QT prolongation with ondansetron (Zofran) (June 29, 2012), <http://www.fda.gov/Drugs/DrugSafety/ucm310190.htm>. The NDA sponsor announced immediate changes to the drug labeling to remove the 32 mg single IV dose. Id. Throughout 2012 and early 2013, FDA worked with brand name and generic drug sponsors on a voluntary recall of the 32 mg IV ondansetron product. See Drug Safety Communication: Updated information on 32 mg intravenous ondansetron (Zofran) dose and pre-mixed ondansetron products (December 4, 2012), <http://www.fda.gov/Drugs/DrugSafety/ucm330049.htm>. More recently, FDA published a determination that the 32 mg single IV dose was withdrawn for reasons of safety or effectiveness, see *Federal Register* Notice, “Determination That Ondansetron (Ondansetron Hydrochloride) Injection, USP in PL 2408 Plastic Container, 32 Milligrams in 50 Milliliters, Was Withdrawn From Sale for Reasons of Safety or Effectiveness” (80 FR 32962, June 10, 2015), and a related notice that FDA has withdrawn approval of the NDA (and four ANDAs) for that ondansetron product, see *Federal Register* Notice, “Baxter Healthcare Corporation et al.; Withdrawal of Approval of One New Drug Application and Four Abbreviated New Drug Applications” (80 FR 32966, June 10, 2015).

Current Labeling Regarding Torsade de Points, QT Prolongation, and Electrolytes

Both Torsade de Pointes and QT prolongation are already clearly identified on current ondansetron labeling as potential adverse reactions for health care providers to consider before treating any patient with ondansetron, whether pregnant or not.⁴⁹ The labeled information also includes a specific warning regarding additional monitoring recommended for patients with electrolyte imbalances.⁵⁰ OB/GYNs caring for pregnant women have access to, and should understand, this labeling. Moreover, OB/GYNs caring for women with NVP are likely to be especially aware of electrolyte balance concerns.

Use of an Infusion Pump to Administer Ondansetron for NVP

Ondansetron has not been approved to treat NVP (as noted in the Background section above) and no infusion pump has been cleared or approved for use in delivering ondansetron subcutaneously for treatment of NVP. Thus, such delivery of ondansetron to treat NVP would be an unapproved use of both ondansetron and the infusion pump used to deliver it.

FDA's 2012 safety communication regarding ondansetron communicated preliminary study results that suggested that a 32 mg single dose of intravenous ondansetron may affect the electrical activity of the heart by causing QT prolongation, which could predispose patients to develop Torsade de Pointes. In response, Zofran's sponsor (GlaxoSmithKline) voluntarily removed the 32 mg single intravenous dose of Zofran from the market. The FDA safety communication also noted that it did not apply to the oral dosing regimens or to the other lower intravenous dosing regimens.⁵¹ We also note that the FDA safety communication was related to the peak blood concentration after administering 32 mg in a single intravenous dose, not to 32 mg total ondansetron per day, which appears to be the concern raised in the Petition. In addition, under current labeling, the maximum amount of ondansetron (Zofran) that may be given per dose is 16 mg (every 4 hours for a total of three doses in adults with chemotherapy-induced nausea and vomiting), to be administered intravenously over 15 minutes. As noted above, there are specific labeled warnings regarding Torsade de Points, QT prolongation, and electrolyte imbalances.⁵²

⁴⁹ See, e.g., labeling approved for Zofran injection on September 18, 2014, at "Warnings and Precautions," and Sections 5.2 (QT Prolongation), 17 (Patient Counseling Information), http://www.accessdata.fda.gov/drugsatfda_docs/label/2014/020007s046lbl.pdf.

⁵⁰ Id. at Section 5.2 (QT Prolongation) ("... ECG [electrocardiogram] 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").

⁵¹ See note 49, above, Drug Safety Communication: New information regarding QT prolongation with ondansetron (Zofran) (stating, "[t]he new information on QT prolongation does not change any of the recommended oral dosing regimens for ondansetron. It also does not change the recommended lower dose intravenous dosing of ondansetron to prevent post-operative nausea and vomiting.").

⁵² See notes 48, 50, and 51, above.

The Petition states that it is “not uncommon” for infusion pump patients to receive ondansetron doses approaching or even exceeding 32 mg per day (Petition at 4). However, the Petition does not include sufficient data to support this statement and we are not independently aware of such data.⁵³

In summary, our review of your Petition did not find evidence to support your concerns regarding treatment of pregnant women with a total dose of 32 mg of ondansetron over a 24 hour period via infusion pump.

OB/GYN Awareness of FDA Precautions Regarding Ondansetron Use

The Petition states that few obstetricians are aware of FDA’s cautions regarding the use of ondansetron (Petition at 4). However, we did not receive or find in our own research sufficient data to support this statement. To the contrary, given the clear risk labeling with regard to QT prolongation, Torsade de Pointes, and electrolyte imbalances, as well as the existence of professional obstetrical advisories such as the *ACOG Practice Bulletin* on treatment of NVP,⁵⁴ we believe that OB/GYNs already have a significant amount of information available regarding these risks. Reviewing and applying such information to treat an individual patient is a routine part of a physician’s practice of medicine.

Although the Petition does not address post-marketing safety surveillance, we note that in addition to the drug product post-marketing surveillance discussed above (see section 2.A.2.a), FDA requires device manufacturers and device user facilities to report to us if they become aware of information that reasonably suggests that use of their infusion pump may have caused or contributed to a serious injury or death.⁵⁵ In addition, individual health care providers and their patients are encouraged to voluntarily notify the manufacturer or sponsor when they become aware of such events and to make reports to FDA. Such mandatory and voluntary reports provide an ongoing method to alert FDA to situations where an adverse outcome may have been caused by the use of an infusion pump to deliver ondansetron. As part of our consideration of this Petition, we reviewed relevant adverse event post-marketing surveillance data for ondansetron and for infusion pumps. As of May 1, 2015, we did not find any reports of adverse outcomes related to ondansetron administration to pregnant women via infusion pump.

⁵³ The Petition does not cite any specific source to support the statement that it is “not uncommon” for infusion pump patients to receive ondansetron doses approaching or even exceeding 32 mg per day. FDA reviewed the dosage instructions in the labeling, current practice guidelines for OB/GYNs, adverse event reporting for both drugs and devices, and other information. The reviewed data did not support the petition’s statement that patients commonly receive doses exceeding 32 mg per day.

⁵⁴ The American College of Obstetricians and Gynecologists (ACOG) Practice Bulletin, “Nausea and Vomiting of Pregnancy,” Number 153, September 2015.

⁵⁵ See, e.g., 21 CFR part 803 Subpart E. In addition, device user facilities, including outpatient treatment facilities and hospitals, are required to submit reports to both FDA and the manufacturer of the device, if known, when they become aware that a device has or may have caused or contributed to the death of a patient in their facility (section 519(b) of the Act and 21 CFR part 803 Subpart C).

B. Petition Requests

1. Request to Reclassify the Drug Ondansetron from Pregnancy Risk Category B to Category C, D, or X after Evaluation of “New Safety Information”

The Petition requests that FDA reclassify ondansetron from pregnancy risk category B to category C, D, or X after consideration of new safety information (Petition at 1). We have considered this request, and for the reasons discussed below, we have determined that the Petition has not provided sufficient information to justify changing the pregnancy category. Additionally, as noted, the recently published Pregnancy and Lactation Labeling Rule requires the removal of the pregnancy categories from prescription drug and biological product labeling.

We also note that, based on the available data reviewed in connection with this Petition⁵⁶ and the issues raised in the Petition, you have not provided sufficient evidence to support changes at this time to the new “Pregnancy” and “Lactation” (formerly “Nursing Mothers”) labeling subsections for ondansetron that are undergoing PLLR conversion. Safety evidence for ondansetron use during pregnancy consists of two large observational studies, supplemented by small non-interventional studies and case reports. In contrast, other than a single case-control study (Anderka et al.) and one recent retrospective cohort study (Danielsson et al.), none of the other published and reviewable sources cited in the Petition, supplements, and comments, or found in our own literature search, review of adverse event reports, and other data, found evidence of adverse pregnancy, fetal, or neonatal outcomes related to ondansetron use.

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 septal defects, among fetuses exposed to ondansetron. Because the new Pregnancy and Lactation Labeling Rule eliminates future use of the pregnancy risk categories, we have not discussed each category in detail. As discussed above, we believe pregnancy category B was the appropriate risk category for ondansetron when it was assigned and, to the extent that the pregnancy categories remain in the labeling for any ondansetron products until the Pregnancy and Lactation Labeling Rule is fully implemented, we believe pregnancy category B remains appropriate today.

As the labeling for ondansetron products is updated to comply with the new content and format requirements of the Pregnancy and Lactation Labeling Rule, it will include

⁵⁶ When discussing “available data” reviewed by FDA in connection with this Petition, we mean all materials submitted to the docket by the Petitioner, all third-party submissions to the docket, and additional information reviewed by FDA, including, but not limited to, post-marketing drug and device adverse event data, information submitted by the sponsor to support approval of the ondansetron NDA, and targeted searches of the published literature.

appropriate data to describe the known risks if taken during pregnancy.

Accordingly, this request is denied.

2. *Request to Notify OB/GYNs there is Insufficient Scientifically Acceptable Evidence that Ondansetron is Associated with Improved Treatment Outcomes and May Lead to Adverse Maternal and Fetal Events or Outcomes*

The Petition requests that FDA notify OB/GYNs that: (a) insufficient scientifically acceptable evidence has been published demonstrating safety, efficacy, or superiority of ondansetron over conventional treatments for NVP and (b) its use may lead to adverse maternal or fetal outcomes (Petition at 2).

a. *Notification Regarding Safety*

As discussed above in sections II.A.1.c, II.A.2.a-b, and II.B.1, we do not agree with the Petition that the available data reviewed by FDA in connection with the Petition warrant a conclusion that ondansetron use during pregnancy poses an increased risk of fetal or maternal adverse outcomes. Thus, a notification to OB/GYNs that ondansetron may lead to adverse maternal or fetal outcomes is not necessary and could be misleading. In particular, the available data do not support a conclusion that there are increased safety risks for the expectant mother, such as vision loss or QT prolongation (beyond the risks faced by any patient using ondansetron) (see section A.2), or for the fetus or neonate, including cleft palate (see section A.1).

b. *Notification Regarding Efficacy*

As noted, ondansetron is not approved for treatment of NVP, nor is there information in the labeling regarding ondansetron's efficacy as an NVP treatment or its relative efficacy as compared with other NVP treatments.

You have not provided a basis for us to notify OB/GYNs that there are insufficient data on the efficacy of ondansetron for treatment of NVP, or on its relative superiority or inferiority as compared with other NVP treatments. In particular, the Petition states that there are only a small number of studies regarding the efficacy of ondansetron in treating NVP or its relative efficacy for that use as compared with other NVP treatments (Petition at 2-3). While this may be true, ondansetron is not approved for use to treat NVP.

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 notification to health care providers regarding its relative efficacy as compared to other drug products for such unapproved use. FDA does not believe that such an unusual notification is warranted in this case.

In summary, we believe the data we reviewed do not warrant a special notification to OB/GYNs regarding safety concerns related to the use of ondansetron in the treatment of NVP or a notification regarding insufficient efficacy data regarding such use.

Accordingly, this request is denied.

3. *Request to Notify OB/GYNs that Promotion of Continuous Subcutaneous Ondansetron Pump for the Treatment of Nausea and Vomiting of Pregnancy is a Violation of FDA Regulations*

The Petition requests that FDA notify OB/GYNs that the “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 and that such promotion is a violation of FDA regulations (Petition at 1).

As stated in section A.2.b., above, based on the available data submitted to FDA in support of the Petition and information researched independently by FDA (e.g., adverse event data), FDA does not have reason to believe that the treatment of pregnant women with ondansetron via infusion pump is a safety concern warranting FDA action.

For this reason, we deny this request.

III. CONCLUSION

Based on our review of the Petition, supplements, additional submissions to the docket, and the scientific literature, as well as our review of other pertinent data and information, including published literature not referenced in the Petition, supplements, or docket, and adverse event reporting information, we deny the requests in the Petition for the reasons discussed above.

Although we have denied your requested actions, we nevertheless appreciate the information you provided. We will continue to monitor information regarding the use of ondansetron during pregnancy. As with all drug products, we will continue to engage in postmarketing surveillance and review other safety data regarding ondansetron and take any actions as appropriate.

Sincerely,



Janet Woodcock, M.D.
Director
Center for Drug Evaluation and Research