Citizen Petition

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I. ACTION REQUESTED

This petition is submitted on behalf of GlaxoSmithKline LLC ("GSK") pursuant to 21 C.F.R. § 10.30 to request that the Commissioner of Food and Drugs review four categories of information concerning the use of a prescription drug Zofran (ondansetron) in pregnancy. GSK understands that FDA may be reviewing or will soon review, together with Zofran's current NDA holder, Novartis, Zofran's safety profile and labeling as a result of newly available epidemiological studies and an assessment of Zofran's labeling by the Pharmacovigilance Risk Assessment Committee (PRAC). This petition does not address those developments. Rather, this petition presents FDA with four other categories of information and requests that FDA either refrain from taking action to alter Zofran's pregnancy-related labeling or take action to alter the labeling in light of these four categories of information, as the Agency deems appropriate. If the Agency deems it appropriate to alter the labeling, GSK respectfully requests that the Agency inform GSK and the public which categories of information (if any) necessitated a labeling change, whether the Agency believes it did not already have the information, and/or why the information is material to the Agency's labeling decision.

II. STATEMENT OF GROUNDS

A. Introduction

GSK is notifying FDA of certain information concerning the use of Zofran in pregnancy. On multiple occasions since Zofran's approval in 1991, FDA has examined Zofran's pregnancy labeling, including in response to an earlier Citizen Petition and in response to proposed labeling submitted under the Pregnancy and Lactation Labeling Rule (PLLR). In each case, FDA rejected proposals to add warnings concerning the use of Zofran in pregnancy.

Since 2015, lawsuits have been filed claiming that Zofran use in pregnancy causes a variety of birth defects. The plaintiffs have claimed that GSK failed to fully inform FDA of four categories of information relating to Zofran, which they contend would have caused FDA to change Zofran's pregnancy labeling. GSK believes that it complied with all regulatory disclosure requirements and that none of the cited information materially affects Zofran's safety profile or labeling. Nonetheless, GSK respects FDA's view on whether the four categories of information that the plaintiffs have identified contain any new and material information about Zofran. GSK also acknowledges that FDA has the authority to decide whether such information warrants inclusion in Zofran's labeling. *See* 21 U.S.C. § 355(*o*)(4)(A)-(B).

GSK understands that FDA may currently be engaging, or will soon engage, in an updated analysis of Zofran's safety profile and labeling in light of a recent PRAC assessment and newly available epidemiologic studies. GSK also understands that FDA may be discussing those developments with the current NDA holder, Novartis. This petition does not address those developments or their impact, if any, on Zofran's labeling.

GSK rather is submitting this Citizen Petition to FDA describing the four categories of information that plaintiffs in ongoing litigation have claimed warrant altering Zofran's labeling. GSK believes that it complied with all regulatory disclosure requirements and that none of the four categories of information materially affects Zofran's safety profile or labeling. GSK requests that FDA either refrain from taking action to alter Zofran's pregnancy-related labeling or take action to

alter the labeling in light of these four categories of information, as the Agency deems appropriate. If the Agency deems it appropriate to alter the labeling, GSK respectfully requests that the Agency inform GSK and the public which categories of information (if any) necessitated a labeling change, whether the Agency believes it did not already have the information, and/or why the information is material to the Agency's labeling decision.

B. Background

FDA approved Zofran in 1991. As part of FDA's determination that GSK had submitted the necessary safety and efficacy information to obtain approval, FDA assigned the drug a Pregnancy Category B designation based on its review of GSK's reproductive toxicity testing. Zofran remained a Pregnancy Category B medication for 25 years. In 2015, after analysis of human data, including epidemiology studies examining a potential association between Zofran and birth defects, FDA denied a Citizen Petition (the Reichmann Citizen Petition) requesting that Zofran's pregnancy category be changed from B to C, D, or X. In 2016, FDA approved new pregnancy labeling in accordance with the PLLR, which abolished the pregnancy categories. In approving the PLLR labeling, FDA again rejected proposals from the then-NDA holder Novartis to add precautionary language concerning a potential risk of birth defects. The approved PLLR labeling remains unchanged today.

In 2015, litigation was commenced alleging that Zofran causes birth defects, in particular cardiac malformations and orofacial cleft defects, when used in the first trimester of pregnancy. Currently, approximately 400 lawsuits are pending in a Massachusetts federal court. The plaintiffs claim that Zofran's assigned pregnancy category and pregnancy-related labeling were erroneous and misleading, and that GSK failed to fully inform FDA of four categories of information that, they claim, would have altered FDA's labeling decisions.

These four categories of information are:

(1) three animal reproductive toxicity studies performed to seek approval of Zofran in Japan;

(2) information regarding the potential of ondansetron to inhibit hERG ion channels, which was described in publicly available literature and which the plaintiffs claim demonstrates a teratogenic mechanism of action;

(3) the fact that GSK allegedly used multiple System Organ Class (SOC) codes from the MedDRA dictionary to code similar adverse events, such that "tabulations or analysis based on SOCs would dilute the total number of cardiac birth defects"; and

(4) information concerning GSK's assessment of, and GSK's alleged involvement in, a 2004 epidemiological study by Einarson *et al.*, as well as certain adverse events associated with that and other postmarketing studies.

GSK provides further information regarding these categories of information below.

Enclosed with this petition is an Appendix containing the information the plaintiffs contend supports revised pregnancy labeling and other background documents that provide additional context, including, among other materials, (1) reproductive toxicity study reports provided in submissions to FDA; (2) FDA's reviews of the submitted reproductive toxicity data; (3) FDA's

response denying the Reichmann Citizen Petition; and (4) FDA's comments on Novartis's proposed labeling.

C. Zofran's Approval and Pregnancy Labeling

Zofran (ondansetron) is a 5-HT3 receptor antagonist. It was first approved by FDA on January 4, 1991 for use in the prevention of chemotherapy-induced nausea and vomiting. It was subsequently approved for use in the prevention of nausea and vomiting associated with radiotherapy and the prevention of postoperative nausea and vomiting. *See*, *e.g.*, Zofran Label (Oct. 2016) (Appx. Tab 1, § 1). Zofran has been, and still is, used to treat conditions for which there has been no FDA-approved indication, such as gastroenteritis and nausea and vomiting in pregnancy (NVP).

At the time of Zofran's approval, FDA regulations required prescription drug labeling to include an assigned pregnancy category addressing potential teratogenic effects. Pregnancy Category B was assigned if reproductive toxicity studies in animals "failed to demonstrate a risk to the fetus and there are no adequate and well-controlled studies in pregnant women." 21 C.F.R. § 201.57(f)(6)(i)(b) (1980).

As part of the original Zofran NDA filed in 1989 (NDA 20,007), GSK submitted to FDA required clinical and preclinical data relating to safety and efficacy. This included eleven reproductive toxicity studies in two species of animals (rats and rabbits), of which four were definitive "Segment II" teratology studies. *See* NDA 20,007 Table of Contents (1989) (Appx. Tab 2, at -0378-79). The study investigators who performed the teratology studies uniformly concluded that there was no evidence of a teratogenic effect of Zofran.[1]

FDA reviewed the reproductive toxicity studies and agreed with the study investigators that there was no teratogenic effect. *See* FDA Pharmacologist's Review (NDA 20,007) (May 18, 1990) (Appx. Tab 3, at -7902-09; -7919-20). Accordingly, FDA assigned Zofran Pregnancy Category B. *See* NDA 20,007 Approval Package (Appx. Tab 4, at -5824). Zofran's labeling stated in relevant part:

> Pregnancy Category B. Reproduction studies have been performed in pregnant rats and rabbits . . . 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.[2]

GSK submitted additional Zofran NDAs for different formulations in 1992 (NDA 20,103), 1995 (NDA 20,605), and 1997 (NDA 20,781). In approving each NDA, FDA confirmed Pregnancy Category B as the appropriate designation.

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[1] *See* Study No. R10590 (Report WPT/84/150) (Appx. Tab 35, at -0070); Study No. R10937 (Report WPT/86/021) (Appx. Tab 36, at -9788); Study No. L10649 (Report WPT/85/031) (Appx. Tab 37, at -0480); Study No. L10873 (Report WPT/85/145) (Appx. Tab 38, at -0275).

[2] The original FDA-approved labeling did not contain the verbatim "Pregnancy Category B" language set forth in the regulations. In 1992, FDA requested that GSK amend the labeling to use the regulatory language. GSK complied with this request, and in 1993 FDA approved the amended labeling with the language set forth above.

D. FDA's Previous Conclusions That Zofran Does Not Pose a Risk to Fetal Safety

From the time of Zofran's approval until 2013, there was no FDA-approved medication for the treatment of NVP. Physicians began using Zofran to treat NVP. Although ondansetron is not indicated for the treatment of NVP, the American College of Obstetricians and Gynecologists (ACOG) has consistently recognized the drug as one of the options available to physicians. ACOG has included, and continues to include, ondansetron in its treatment recommendations for NVP. *See, e.g.,* ACOG Practice Bulletin No. 52. *Obstetrics & Gynecology* (2004); 103(4):803-815 (Appx. Tab 5, at 808); ACOG Practice Bulletin No. 189. *Obstetrics & Gynecology* (2018); 131(1), e15-e30 (Appx. Tab 6, at e20).

Recognizing that ondansetron was commonly used in pregnancy, in December 2010, FDA asked GSK to submit an analysis of available literature on the use of ondansetron during pregnancy and lactation, with a focus on the presence or absence of adverse pregnancy and/or neonatal outcomes. In response, in April 2011 GSK produced to FDA a detailed analysis of the then-available data, including published literature and adverse event reports. *See* Safety Evaluation and Risk Management, Ondansetron: Pregnancy (Apr. 20, 2011) ("2011 safety report") (Appx. Tab 7). GSK also provided details on 50 infants exposed to Zofran with reported congenital anomalies, including heart defects, musculoskeletal anomalies, and laryngomalacia. FDA did not require any changes to the pregnancy labeling.

In January 2013, an individual named James Reichmann submitted a Citizen Petition, seeking to change the Zofran pregnancy category from B to C, D, or X. *See* Reichmann Citizen Petition (Jan. 2013) (Appx. Tab 8). FDA denied the petition in 2015. FDA Response to the Reichmann Citizen Petition (Oct. 27, 2015) (Appx. Tab 9). In response to the petition, FDA conducted "targeted searches" of the published medical and scientific literature and reviewed relevant data, including large epidemiology studies, preclinical safety information, "post-marketing drug and device adverse event data," and third-party comments. Appx. Tab 9, at 18 & n.56. Based on that analysis, FDA concluded that "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." Appx. Tab 9, at 18. FDA also denied the petition's request to notify doctors that use of Zofran during pregnancy is not safe for the fetus, stating that such a notification "could be misleading" because "the available data do not support a conclusion that there are increased safety risks . . . for the fetus." Appx. Tab 9, at 19.

In December 2014, FDA enacted the PLLR, which eliminated the pregnancy categories. In early 2015, Novartis acquired Zofran from GSK and assumed responsibility for developing PLLR-compliant pregnancy labeling for Zofran. In September 2015, Novartis provided FDA with proposed PLLR labeling, which included precautionary language concerning a potential risk of fetal harm. *See* Letter from Novartis to FDA (Sept. 22, 2015) (Appx. Tab 10, at -2090, -2092). FDA deleted this language, noting that the available human data did not support it. *See* Draft label with FDA comments (Nov. 2015) (Appx. Tab 11, at -3945, -3947). Over the next several months, Novartis proposed a number of similar labeling statements, which FDA rejected. For example, Novartis proposed that the labeling state that "[c]ases of congenital malformations have been reported in infants whose mothers took ondansetron during pregnancy;" and "[t]he safety of ondansetron for use in human pregnancy has not been established." *See* Draft label with Novartis comments (Dec. 2015) (Appx. Tab 12, at -3902, -3903). FDA deleted both statements. *See* Draft label with FDA comments (Apr. 2016) (Appx. Tab 13, at -4051, -4052).

FDA explained that the scientific data did not support Novartis's proposed warnings and that there "is also no preponderance of evidence that the benefits [of Zofran] do not generally outweigh its risks." FDA also commented that warning prescribers of postmarketing cases of birth defects with use of Zofran in pregnancy "could be misleading in implying that FDA has some concerns about the role of Zofran in a variety of fetal malformations." *See* Draft label with FDA comments (June 2016) (Appx. Tab 14, at -4445, -4451). Novartis and FDA reached final, mutually agreed-upon labeling in September 2016.

The PLLR labeling for Zofran has remained unchanged since its approval in 2016. It states:

> **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 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 2 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.

Appx. Tab 1, § 8.1.[3]

E. The Four Categories of Information

1. Three Japanese Teratology Studies (Studies 100423, 100424 and 100441)

In connection with seeking approval of Zofran in Japan, GSK conducted a set of eight reproductive toxicity studies, including three definitive Segment II teratology studies; four preliminary Segment II teratology studies; and one definitive Segment I fertility study. The Segment II teratology studies are described in the chart below.

[3] The labeling for the intravenous formulation also mentions "a slight increase in the incidence of early uterine deaths at the high dose level in rabbits." Zofran Injection Label ZFJ 10PI (March 2017) (Appx. Tab 39, § 8.1.)

Segment II teratology studies conducted in Japan

Species	Route	Japanese Studies	
		Preliminary	Definitive
Rats	Oral	100421	100422
Rats	IV	100423	100424
Rabbits	Oral	881001 881002	100441

The study investigators who performed the definitive Segment II teratology studies uniformly concluded that was no evidence of a teratogenic effect of Zofran.[4] The Japanese definitive studies were published in 1992 in peer-reviewed scientific literature.[5] The conclusions of the published studies are consistent with the final study reports: no teratogenicity.

GSK disclosed to FDA the Japanese Segment II teratology studies by study title and number in 1993, as well as other preclinical studies done in connection with approval in Japan, in an IND annual report pursuant to 21 C.F.R. § 312.33. *See* 1993 IND 27,531 annual report (Appx. Tab 15, at -3819-21). GSK disclosed the Japanese regulatory approval studies under a sub-heading entitled "Studies performed specifically to satisfy Japanese regulatory requirements. These studies are either repetitive or provide no new significant safety information." GSK did not provide the final study reports to FDA with the annual report because it considered them duplicative of data FDA already had reviewed -- *i.e.*, the reproductive toxicity studies submitted with the original NDA, which also showed no teratogenicity.

In 1997, GSK sought FDA approval for a new formulation of ondansetron (NDA 20,781). FDA approved the formulation in 1999. GSK submitted the final study report of one of the three Japanese definitive Segment II teratology studies (Study No. 100422) as a reference to a repeat-dose toxicity study.[6] *See* NDA 20,781 Table of Contents (1997) (Appx. Tab 16, at -2490, -2494). In connection with that approval, FDA reviewed Study No. 100422. FDA agreed with the

[4] Study No. 100422 (Report NTX/90/006), (Appx. Tab 18, at -2508); Study No. 100424 (Report NTX/91/001) (Appx. Tab 19, at -7559); Study No. 100441 (Appx. Tab 20, at -7398).

[5] The published version of Study No. 100422 is: Shimizu M, *et al.* Reproduction Study (Seg. II) of ondansetron hydrochloride in rats by oral route. *Jpn Pharmacol Ther* (1992); 20:175-195 (Appx. Tab 40). The published version of Study No. 100424 is: Shimizu M, *et al.* Reproduction Study (Seg. II) of ondansetron hydrochloride in rats by intravenous route. *Jpn Pharmacol Ther* (1992); 20:155-174 (Appx. Tab 41). The published version of Study No. 100441 is: Ezaki H, *et al.* Reproduction Study (Seg. II) of ondansetron hydrochloride in rabbits by oral route. *Jpn Pharmacol Ther* (1992); 20:197-206 (Appx. Tab 42). In addition to these three teratology studies, two "Segment I" fertility studies conducted by GSK (one from the U.K. and one from Japan), and two "Segment III" pre-and postnatal studies conducted by GSK (both from the U.K.) were also published in the peer-reviewed Japanese journal. Sutherland MF, *et al.* Reproduction Study (Seg. I) of ondansetron hydrochloride in rats by oral route. *Jpn Pharmacol Ther* (1992); 20:141-154 (Appx. Tab 43); Kaneko Y, *et al.* Reproduction Study (Seg. I) of ondansetron hydrochloride in rats by intravenous route. *Jpn Pharmacol Ther* (1992); 20:129-140 (Appx. Tab 44); Secker RC, *et al.* Reproduction Study (Seg. III) of ondansetron hydrochloride in rats by oral route. *Jpn Pharmacol Ther* (1992); 20:221-236 (Appx. Tab 45); Secker RC, *et al.* Reproduction Study (Seg. III) of ondansetron hydrochloride in rats by intravenous route. *Jpn Pharmacol Ther* (1992); 20:207-219 (Appx. Tab 46). The peer-reviewed publications of the studies were translated into English by the parties in the litigation. Both sets of translations are attached and referenced for FDA's consideration.

[6] In the "Reproductive Toxicity Studies" section of NDA 20,781, GSK stated: "There are no new data in this section. Reproductive toxicity studies have been submitted and reviewed previously as part of the application for Zofran Injection (NDA 20-007) for the treatment of emesis, and thus, are incorporated into this NDA by reference." Appx. Tab 16, at -2780.

study investigators that there was no teratogenic effect of Zofran, and FDA noted that the results of the Japanese teratology study were materially similar to those of the teratology studies previously reviewed by FDA. *See* FDA Pharmacology Review (NDA 20,781) (Appx. Tab 17, at -2187, -2191).

The plaintiffs allege that GSK failed properly to supply FDA with the full study reports for the Japanese studies. They focus on three such studies: Study Nos. 100423, 100424 and 100441. Relying on opinions and an article published in 2018 by their expert, Dr. Bengt Danielsson, the plaintiffs further allege that those studies show teratogenic effect.[7] GSK has enclosed the full study reports for all eight Japanese studies and the 2018 Danielsson article with this Petition for FDA's consideration. Appx. Tabs 18-26.

GSK believes that Studies 100423, 100424, and 100441 do not demonstrate a teratogenic effect of Zofran. Moreover, GSK believes that these studies do not provide information that is materially different from the reproductive toxicology studies previously submitted and reviewed by FDA.

2. Mechanism of Action

The plaintiffs allege that GSK failed appropriately to disclose to FDA information supporting a theoretical mechanism of teratogenic action for ondansetron. This theory proposed by Dr. Bengt Danielsson posits that ondansetron has the potential to cause QT prolongation and cardiac arrhythmias, which can interrupt blood and oxygen supply to the embryo and cause birth defects. This mechanism theory was described in a published 2014 epidemiology study by Dr. Danielsson. Danielsson B, *et al.,* Use of ondansetron during pregnancy and congenital malformations in the infant, *Reprod. Toxicol.* 2014; 50:134-137 ("Danielsson (2014)") (Appx. Tab 27, at 137).

GSK cited Danielsson (2014) to FDA in an annual report submitted in 2015. Zofran Annual Report (2015) (Appx. Tab 28, at -4793). Additionally, this theory of teratogenic mechanism was described in a third-party comment submitted in conjunction with the Reichmann Citizen Petition. Comment from Simerpal Gill to James P. Reichmann Citizen Petition (Sept. 14, 2015) (Appx. Tab 29). In denying the Reichmann Citizen Petition, FDA devoted an entire page of the response to Danielsson (2014). Appx. Tab 9, at 10-11, 16.

Novartis's September 2015 submission included a clinical overview that contained a description of Danielsson (2014), as well as a 2007 study authored by Danielsson.[8] Novartis characterized Danielsson (2007) as having found that "hERG channel blockade could induce developmental toxicity generally due to embryonic heart arrhythmias leading to transient hypoxia and reperfusion injuries." As discussed above, FDA rejected Novartis's proposal to add a pregnancy warning to the Zofran label in 2015. FDA expressly concluded that "there is no evidence, nonclinical or mechanism of action, that raises concerns for adverse fetal outcomes with Zofran." Appx. Tab 14, at -4451.

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[7] *See* Danielsson *et al.*, Ondansetron and teratogenicity in rats: Evidence for a mechanism mediated via embryonic hERG blockade, *Reprod. Toxicol.*, 81 (2018). (Appx. Tab 26.)

[8] To protect the confidentiality of Novartis's analysis, Novartis has not authorized GSK to include its 2015 clinical overview in the publicly available Appendix to this Petition. GSK understands that Novartis submitted the clinical overview to FDA.

The plaintiffs also contend that GSK failed to advise FDA of earlier-published literature allegedly supporting Danielsson's theory. Specifically, they cite a 1994 study by de Lorenzi *et al.*; a 2000 study by Kuryshev *et al.*, and a 1994 study by Abrahamsson *et al.*[9] De Lorenzi studied the effect of ondansetron and another 5-HT3 receptor antagonist on IKr (hERG) and IKs currents in feline myocytes. Kuryshev studied the potential effect of ondansetron on cloned human hERG channels. Abrahamsson did not study ondansetron.

All of these studies were and are publicly available. GSK described de Lorenzi and Kuryshev in one or more periodic safety update reports for Zofran submitted to FDA.[10] GSK has enclosed all of these studies, along with Danielsson (2014), the comment submitted with the Reichmann Citizen Petition, FDA's denial of the Citizen Petition, and FDA's comment on mechanism of action in rejecting Novartis's proposed labeling.

3. Adverse Event Reports

From the time of Zofran's approval in 1991, GSK routinely supplied FDA with information about adverse events reported to the company. FDA also had access to adverse event report (AER) data submitted to its FAERs database. In its 2011 safety report to FDA, described above, GSK presented a detailed analysis of 765 pregnancy-related AERs from its database. Appx. Tab 7, at -4313-14. In 2015, Novartis provided FDA with a detailed analysis of more than 1,000 pregnancy-related AERs from the database, which Novartis then possessed. FDA considered AER data in making its pregnancy labeling determinations. In denying the Reichmann Citizen Petition, FDA stated that its denial was "[b]ased on [its] review of . . . adverse event reporting information." Appx. Tab 9, at 20. It also rejected Novartis's proposals to include a warning about reported adverse events, stating that it did not believe "there is any basis to suspect drug attribution to [reported] congenital malformation cases for them to qualify as 'adverse reactions.'" Appx. Tab 14, at -4450. FDA explained that "[i]t is not possible to rely on case reports of congenital anomalies to determine drug attribution given that the background incidence of major congenital anomalies is 2-4%." Appx. Tab 14, at -4450. FDA further observed that "the reported cases of congenital anomalies involve all different organ systems with distinct pathophysiology and embryological origins, making such observations unlikely to be due to a single drug." Appx. Tab 14, at -4450.

The plaintiffs' allegations about AERs are distinct from the rest of their allegations. Except as set forth in subpart II.E.4 below, the plaintiffs do *not* allege that GSK *failed* to disclose AERs to FDA. Instead, the plaintiffs allege that GSK used multiple System Organ Class codes from the MedDRA coding dictionary to code adverse event reports, meaning that "tabulations or analysis based on SOCs would dilute the total number of cardiac birth defects." On that basis, the plaintiffs claim that GSK miscoded AERs in two specific reports. The plaintiffs' criticisms are summarized below for FDA's consideration.

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[9] de Lorenzi FG, *et al*. Block of the delayed rectifier current (IK) by the 5-HT3 antagonists ondansetron and granisetron in feline ventricular myocytes. *Br J Pharmacol* 1994;113(2):527-35 (Appx. Tab 47); Kuryshev YA, *et al.* Interactions of the 5-hydroxytryptamine 3 antagonist class of antiemetic drugs with human cardiac ion channels. *J Pharmacol Exp Ther* 2000;295:614-620 (Appx. Tab 48); Abrahamsson C, *et al*. Induction of rhythm abnormalities in the fetal rat heart. A tentative mechanism for the embryotoxic effect of the class III antiarrhythmic agent almokalant. *Cardio Res* 1994;28:337-44 (Appx. Tab 49).

[10] *See, e.g.,* 2004 Annual Periodic Adverse Experience Report (Appx. Tab 50, at -4455, -4460); 2005 Annual Periodic Adverse Experience Report (Appx. Tab 51, at -0354, -0359); 2006 Annual Periodic Adverse Experience Report (Appx. Tab 52, at -2031, -2037, -2345-47); 2007 Annual Periodic Adverse Experience Report (Appx. Tab 53, at -3905, -3910); 2008 Annual Periodic Adverse Experience Report (Appx. Tab 54, at -5956, -5962).

First, the plaintiffs point to a 2005 document summarizing pediatric adverse events for the Medicines and Healthcare Regulatory Agency. The plaintiffs' only criticism of the document is that GSK categorized cardiac-related congenital adverse events under different SOCs. GSK used the MedDRA dictionary to code its AERs, consistent with FDA guidance. This coding system contemplates that a preferred term (PT) associated with an AER may be coded to one of several SOCs. The plaintiffs do not contend that GSK failed to disclose to FDA the AERs underlying this report.

Second, the plaintiffs cite a disproportionality analysis (DPA) GSK included in an internal signal evaluation report completed in 2015. The plaintiffs allege that the DPA was misleading because it was run on PTs within just two SOCs. The plaintiffs do not allege that GSK failed to include any particular PT related to a congenital anomaly within its analysis. As noted, Novartis provided its own detailed evaluation of the adverse event data and epidemiology to FDA in 2015, and FDA assessed such data when it denied the Reichmann Citizen Petition and rejected Novartis's proposed labeling.

4. Information Concerning the Einarson Study

Finally, the plaintiffs allege that GSK failed to disclose certain information concerning the 2004 Einarson study. In particular, they allege that GSK failed to disclose to FDA (1) GSK's supposed involvement in editing and advising on the study, (2) the opinions of GSK scientists that the study involved a small number of patients and was insufficiently powered, (3) the existence of a birth defect from the study (laryngomalacia) that was not described in the study publication, and (4) adverse events arising from this and two other studies.

The plaintiffs allege that GSK failed to disclose its involvement in the Einarson study. The Einarson study was submitted to the Agency by GSK in 2004 and 2011, and again by Novartis in 2015. The "Acknowledgements" section of the study publication states that the study was "supported by an unrestricted grant from GlaxoSmithKline, Mississauga, Canada." Einarson *et al*. The safety of ondansetron for nausea and vomiting of pregnancy: a prospective comparative study. *BJOG* 2004;940-943 (Appx. Tab 31, at 942). Although GSK communicated internally about the study, the plaintiffs have not identified evidence that GSK provided edits to the study authors or otherwise influenced the publication.

The plaintiffs also allege that GSK failed to disclose the study's limitations to FDA – including, notably, its small size and power. FDA referenced and discussed the study in its denial of the Reichmann Citizen Petition. FDA acknowledged that while the Einarson study showed no statistically significant differences regarding live births, miscarriages, or major malformations among the ondansetron exposure group and the controls, the study had limitations. FDA commented 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." Appx. Tab 9, at 9. In denying the petition, the Agency relied on other epidemiologic studies, such as Pasternak *et al.*, rather than Einarson, to conclude that the data did not warrant a label change. The current FDA-approved Zofran labeling addresses other epidemiological studies (Anderka, Danielsson, and Pasternak); it does not reference data from Einarson. Appx. Tabs 1, § 8.1; 39, § 8.1.

The plaintiffs have highlighted that the Einarson publication did not identify an observed case of laryngomalacia. The purpose of the Einarson study was "to determine whether this drug increases the baseline rate of major malformations," which the study notes included malformations that "require[] surgery." Appx. Tab 31, at 940, 942. Laryngomalacia is typically classified as a minor malformation in studies of this type because it resolves on its own in the majority of cases.[11] The occurrence of that defect was attributed to chance by the researcher who reported the case to GSK. GSK reported the occurrence of the defect to FDA in its April 2011 submission. Appx. Tab 7, at -4315.

The plaintiffs also have asserted that GSK failed properly to report fourteen AERs describing events arising from post-marketing studies, including Einarson. FDA was provided with information about these AERs in one or more ways.

Seven AERs came from the Einarson study. In 2004, shortly after the Einarson study was published, GSK submitted a 15-day alert report to FDA providing the full study publication, along with specific information on four adverse events from the study. *See* 15 day alert report to FDA (Oct. 19, 2004) (attaching Einarson publication) (Appx. Tab 32, at -1693-96). In its 2011 report to FDA, GSK discussed the study, described adverse events from the study, and listed the study in the reference list. Appx. Tab 7, at -4312-13, -4317, -4322. Novartis also described the Einarson study and its adverse events in its 2015 report to FDA.

Six AERs came from a study described in an abstract by McCauley *et al.*, which was publicly available. McCauley *et al.*, Safety and Efficacy of Ondansetron Therapy for Nausea and Vomiting of Pregnancy, *Obstetrics & Gynecology* (2002) Apr;99(4):24S (Appx. Tab 33). McCauley reported no birth defects out of 75 participants. Appx. Tab 33. GSK described adverse events from McCauley in its 2011 report to FDA. Appx. Tab 7, at -4317, -4322 . McCauley was also described in Novartis's 2015 report.

One AER came from a third study of Zofran and involved an inadvertent pregnancy occurring in a study participant, who then suffered a miscarriage. That event was described to FDA in Novartis's 2015 safety analysis.

GSK has enclosed its 2011 report, the 15-day alert report attaching the Einarson study publication, and the McCauley abstract. In addition, GSK has enclosed information about each of these fourteen AERs from GSK's safety database. Appx. Tab 34.

F. Conclusion

GSK believes that it complied with all regulatory disclosure requirements and that none of the cited information materially affects Zofran's safety profile or labeling. GSK respectfully requests that FDA review the four categories of information discussed above and either refrain from taking action to alter Zofran's pregnancy-related labeling or take action to alter the labeling

[11] CDC, Metropolitan Atlanta Congenital Defects Program (MACDP). Birth Defects and Genetic Diseases Branch 6-Digit Code for Reportable Congenital Anomalies. (2004); CDC, Metropolitan Atlanta Congenital Defects Program (MACDP). CDC/BPA 6-Digit Code for Congenital Anomalies. (2018); EUROCAT Guide 1.2, Instructions for the Registration of Congenital Anomalies. (2002); EUROCAT Guide 1.3, European Surveillance of Congenital Anomalies, Instructions for the Registration and Surveillance of Congenital Anomalies. (2005); EUROCAT Guide 1.4, European Surveillance of Congenital Anomalies. (2013). Appx. Tabs 55-59.

in light of these four categories of information, as the Agency deems appropriate. If the Agency deems it appropriate to alter the labeling, GSK respectfully requests that the Agency inform GSK and the public which category of information (if any) necessitated a labeling change, whether the Agency believes it did not already have the information, and/or why the information is material to the Agency's labeling decision.

III. ENVIRONMENTAL IMPACT

This Petition qualifies for a categorical exemption from the requirement to submit an environmental assessment under 21 C.F.R. § 25.31.

IV. ECONOMIC IMPACT

Information regarding economic impact will be submitted upon FDA's request following review of this Petition pursuant to 21 C.F.R. § 10.30(b).

V. CERTIFICATION

The undersigned certifies, that, to the best knowledge and belief of the undersigned, this petition includes all information and views on which the petition relies, and that it includes representative data and information known to the petitioner which are unfavorable to the petition.

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Appendix to Zofran - Citizen Petition

Tab	
1.	Zofran Tablets Label ZFT 9PI, October 2016.
2.	20-007 New Drug Application Table of Contents. (1989) (ZOFNDAA0000361-402) (Excerpt)
3.	FDA Pharmacologist Review (NDA 20-007). (ZFN03187830-861)
4.	20-007 Approval Package (ZOFNDAA0095829).
5.	American College of Obstetricians and Gynecologists (ACOG). Practice Bulletin No. 52. Nausea and Vomiting of Pregnancy. *Obstet Gynecol* 2004;103(4):803-815.
6.	American College of Obstetricians and Gynecologists (ACOG). Practice Bulletin No. 189. Nausea and Vomiting of Pregnancy. *Obstet Gynecol* 2018;131(1):e15-e30.
7.	Safety Evaluation and Risk Management, Ondansetron: Pregnancy. (April 2011) (ZOFNDAA0184304).
8.	James P. Reichmann Citizen Petition. (January 4, 2012)
9.	FDA Reply to Reichmann's Citizen Petition. (October 27, 2015)
10.	Letter from Novartis to FDA. (September 22, 2015) (NPCZOFR00002076)
11.	Draft label with FDA comments. (November 2015) (NPCZOFR00003937)
12.	Draft label with Novartis comments. (December 2015) (NPCZOFR00003895)
13.	Draft label with FDA comments. (April 2016) (NPCZOFR00004043)
14.	Draft label with FDA comments. (June 2016) (NPCZOFR00004442)
15.	27-531 Annual Report. (1993) (ZOFINDAC0013783)
16.	20-781 Table of Contents. (1997) (ZOFNDAE00002490-2494; 2780) (Excerpt)
17.	FDA Pharmacologist Review (NDA 20-781). (ZFN00002134-249)
18.	NTX/90/006: Reproduction Study on GR38032F (SN-307) in rats by oral administration during the period of organogenesis (Study No. 100422) (ZOFNDAE0002496).

19.	NTX/91/001: Reproduction Study on GR38032F (SN-307) in rats by intravenous administration during the period of organogenesis (Study No. 100424) (ZFN00077547).
20.	NTX/90/009: Reproduction Study (Seg II) on GR38032F (SN-307) in rabbits by oral route. (Study No. 100441) (ZFN00077391).
21.	NTX/95/009: Reproduction Study on GR38032F (SN307) in Rats by Intravenous Administration Prior to and during the Early Stage of Pregnancy (TRL Study No. 100425). (ZFN00077788-951)
22.	NTX/88/004: GR38032F (SN-307): Preliminary study for the reproduction study in rats by oral administration during the period of fetal organogenesis (Seg. II) (Study No. 100421). (ZFN00076968-029)
23.	NTX/88/005: GR38032F (SN-307): Preliminary study for the reproduction study in rats by intravenous administration during the period of fetal organogenesis (Seg. II) (Study No. 100423). (ZFN00077030-90)
24.	NTX/89/001: GR38032F: Preliminary study for the reproduction study in rabbits by oral administration during the period of fetal organogenesis (I) (Study No. T-881001). (ZFN00077091-113)
25.	NTX/89/002: GR38032F (SN-307): Preliminary study for the reproduction study in rabbits by oral administration during the period of fetal organogenesis (II). (Study No. T-881002). (ZFN00077114-145)
26.	Danielsson B, Webster WS, Ritchie HE. Ondansetron and teratogenicity in rats: evidence for a mechanism mediated via embryonic hERG blockade. *Reprod Toxicol* 2018;81:237-245.
27.	Danielsson, B, Wikner BN, Kallen B. Use of ondansetron in pregnancy and congenital malformations in the infant. *Repro Toxicol* 2014;50:134-137.
28.	Zofran Annual Report. (2015) (ZOFNDAB0154773)
29.	Gill, Simerpal. Comment on the Citizen's Petition of James P. Reichmann. (September 14, 2015)
30.	Intentionally Omitted
31.	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;940-943.
32.	15-Day Alert Reports to FDA. (October 19, 2004) (ZOFNDAA0161688)
33.	McCauley L, Coleman S, Jacques D, Palmer B, Stanziano G. Safety and efficacy of ondansetron therapy for nausea and vomiting of pregnancy. *Obstet Gynecol* 2002;99(4):24S.

34.	MedWatch Output, AERs from GSK's Safety Database. (October 23, 2019)
35.	WPT/84/150: GR38032B: Effect of oral administration on pregnant AHA rats and their progeny (Study No. R10590). (ZOFNDAA0010051)
36.	WPT/86/021: GR38032F: Effects of intravenous administration on pregnant AHA rats and their progeny. (Study No. R10937) (ZOFNDAA0009774)
37.	WPT/85/031: GR38032B: Effects of oral administration on pregnant New Zealand white rabbits and their progeny. (Study No. L10649) (ZOFNDAA0010471)
38.	WPT/85/145: GR38032F: Effects of intravenous administration on pregnant Dutch rabbits and their progeny. (Study No. L10873) (ZOFNDAA0010274)
39.	Zofran Injection Label ZFJ 10PI, March 2017.
40.	Shimizu M, Ota T, Kato S, Kobayashi Y, Yamashita Y, Asano M, Mori K, Koike T. Reproduction Study (Seg. II) of ondansetron hydrochloride in rats by oral route. *Jpn Pharmacol Ther* 1992;20:175-95. (Japanese version, GSK translation and plaintiffs' translation)
41.	Shimizu M, Ota T, Kato S, Kobayashi Y, Yamashita Y, Asano M, Mori K, Fujimura T. Reproduction Study (Seg II) of ondansetron hydrochloride in rats by intravenous route. *Jpn Pharmacol Ther* 1992;20:155-74. (Japanese version, GSK translation and plaintiffs' translation)
42.	Ezaki H, Yokoyama S, Takahashi N, Takamatsu M, Tokado Y, and Takeda K. Reproduction Study (Seg. II) of ondansetron hydrochloride in rabbits by oral route. *Jpn Pharmacol Ther* 1992;20:ss1187-96. (Japanese version, GSK translation and plaintiffs' translation)
43.	Sutherland MF, *et al.* Reproduction Study (Seg. I) of ondansetron hydrochloride in rats by oral route. *Jpn Pharmacol Ther* (1992); 20:141-154. (Japanese version, GSK translation and plaintiffs' translation)
44.	Kaneko Y, et al. Reproduction Study (Seg. I) of ondansetron hydrochloride in rats by intravenous route. *Jpn Pharmacol Ther* (1992); 20:129-140. (Japanese version, GSK translation and plaintiffs' translation)
45.	Secker RC, et al. Reproduction Study (Seg. III) of ondansetron hydrochloride in rats by oral route. *Jpn Pharmacol Ther* (1992); 20:221-236. (Japanese version, GSK translation and plaintiffs' translation)
46.	Secker RC, et al. Reproduction Study (Seg. III) of ondansetron hydrochloride in rats by intravenous route. *Jpn Pharmacol Ther* (1992); 20:207-219. (Japanese version, GSK translation and plaintiffs' translation)
47.	De Lorenzi FG, Bridal TR, Spinelli W. Block of the delayed rectifier current (IK) by the 5-HT3 antagonists ondansetron and granisetron in feline ventricular myocytes. *B J Pharmacol* 1995;113:527-535.

48.	Kuryshev YA, Brown AM, Wang L, Benedict CR, Rampe D. Interactions of the 5-hydroxytryptamine 3 antagonist class of antiemetic drugs with human cardiac ion channels. *J Pharmacol Experiment Ther* 2000;295:614-620.
49.	Abrahamsson C, Palmer M, Ljung B, Duker G, Baarnhielm C, Carlsson L, Danielsson B. Induction of rhythm abnormalities in the fetal rat heart. A tentative mechanism for the embryotoxic effect of the class III antiarrhythmic agent almokalant. *Cardiovascular Research* 1994;28:337-344.
50.	Annual Periodic Adverse Experience Report to FDA. (April 27, 2005) (Excerpt)
51.	Annual Periodic Adverse Experience Report to FDA. (April 28, 2006) (Excerpt)
52.	Annual Periodic Adverse Experience Report to FDA. (April 27, 2007) (Excerpt)
53.	Annual Periodic Adverse Experience Report to FDA. (April 28, 2008) (Excerpt)
54.	Annual Periodic Adverse Experience Report to FDA. (April 29, 2009) (Excerpy)
55.	CDC, Metropolitan Atlanta Congenital Defects Program (MACDP). Birth Defects and Genetic Diseases Branch 6-Digit Code for Reportable Congenital Anomalies. (2004)
56.	CDC, Metropolitan Atlanta Congenital Defects Program (MACDP). CDC/BPA 6-Digit Code for Congenital Anomalies. (2018)
57.	EUROCAT Guide 1.2, Instructions for the Registration of Congenital Anomalies. (2002)
58.	EUROCAT Guide 1.3, European Surveillance of Congenital Anomalies, Instructions for the Registration and Surveillance of Congenital Anomalies. (2005)
59.	EUROCAT Guide 1.4, European Surveillance of Congenital Anomalies. (2013)