

James P. Reichmann

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January 4, 2012

Food and Drug Administration
Division of Dockets Management
Room 1061 (HFA-305)
5630 Fishers Lane
Rockville, MD 20852

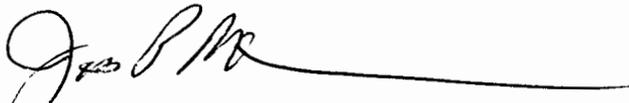
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To whom it may concern:

This citizen petition filed by me as a concerned individual, hereby petitions the Food and Drug Administration (FDA) pursuant to the Federal Food, Drug, and Cosmetic Act 21 U.S.C. Section 355(e) (3), and 21 C.F.R. 10.30, to reclassify the drug ondansetron (zofran®) from pregnancy risk category B to C,D, or X after consideration of "new safety information".

The petition seeks to have OB/GYNs notified that no scientifically acceptable evidence has been published demonstrating efficacy, safety, or superiority of ondansetron over conventional treatments for nausea and vomiting of pregnancy (NVP) and its use may lead to adverse maternal and/or fetal outcomes. Additionally it requests the FDA to notify OB/GYNs that continuous subcutaneous ondansetron pump may not be marketed or promoted in any way in the absence of FDA approval for the indication of treatment of nausea and vomiting of pregnancy.

Sincerely,


James P. Reichmann

FDA-2013-P-0048

2013-101

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Citizen Petition

“Ondansetron (Zofran®) Use in Pregnancy”

A. Action Requested

1. Reclassify the drug ondansetron (Zofran®) from pregnancy risk category B to category C, D, or X after evaluation of “new safety information”.
2. Notify 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 and promotion of continuous subcutaneous ondansetron pump (“Zofran® pump”) for the treatment of nausea and vomiting of pregnancy (NVP) is a violation of FDA regulations.

B. Statement of Grounds

Ondansetron (Zofran®) is one of the most commonly prescribed medications in pregnancy. It is estimated that millions of retail prescriptions for ondansetron were written by OB/GYNs over the last ten years. Those are for ondansetron tablet or ondansetron ODT presumably for outpatient treatment for nausea and vomiting of pregnancy, which is an off-label use. In addition to oral administration ondansetron may also be given intravenously and subcutaneously; both intermittently and continuously. In the late nineties physicians began prescribing continuous subcutaneous Zofran® (ondansetron) via a portable, programmable micro-infusion pump (MiniMed 404SP- MiniMed Technologies, Sylmar, CA. n.k.a. Medtronic Inc., Frindley, MN) similar to “Reglan® (metoclopramide) pump” a decade earlier. In the 1980s the FDA expressed concern with off-label use and promotion of the MinMed 404SP with terbutaline for the treatment of preterm labor, called “terbutaline pump”. A quick unrestricted internet search using the search engine Google with the search term “zofran® pump” yielded 36,600 results in 0.23 seconds and “Reglan® pump” yielded 764,000 results in 0.26 seconds. Reglan® pump has been in existence over ten years longer than Zofran® pump. Alere, 51 Sawyer Road, Waltham, MA is the largest provider of Zofran® pump for the treatment of nausea and vomiting of pregnancy.

Efficacy data is sorely lacking

Rigorous trials have yet to be published regarding the efficacy of ondansetron (Zofran®) used for the treatment of nausea and vomiting of pregnancy. Four case reports and one small randomized controlled trial (RCT) have been published in the medical literature regarding IV administration of ondansetron.^{1 2 3 4 5} The four reports all describe cases in

¹ Guikontes E, Spantideas A, Diakakis J. Ondansetron and hyperemesis gravidarum. *Lancet*. 1992 Nov 14;340(8829):1223.

² World MJ. Ondansetron and hyperemesis gravidarum. *Lancet*. 1993 Jan 16;341(8838):185.

which IV Zofran® was used in the hospital setting to arrest intractable Hyperemesis Gravidarum (HG) after previous pharmaceutical treatment attempts had failed. Sullivan et al was a double blind RCT (N=30) that compared 10mg of ondansetron administered intravenously every 8 hours to 50mg of promethazine (Phenergan®) administered intravenously every 8 hours in women who were hospitalized for HG. There was no difference in length of hospitalization, decrease in nausea, or total doses of medication.

Additionally five industry-sponsored and authored trials in support of “Reglan® pump” and “Zofran® pump” have been written from patients selected from an Alere (formerly Matria) controlled database.^{6 7 8 9 10} This petitioner published a review of all of the published data regarding continuous subcutaneous anti-emetic therapy which was adamantly, albeit falsely criticized by an Alere Medical Director; presumably to protect the off-label provision of the services.^{11 12} The Lombardi et al and Klauser et al studies were the only two trials that contained “Zofran® pump” recipients. Both are retrospective descriptive studies and embody all of the limitations inherent in that study design. This petitioner also published a review that addresses both the cost effectiveness as well as the efficacy of continuous subcutaneous anti-emetic therapy although the most recent Zofran® pump trial had not yet been published at the time of submission.¹³

Published safety data on ondansetron (Zofran®) for the treatment of NVP is scant

Pre-clinical evaluation of ondansetron that included various designs identified no end-organ toxicity in rats or dogs that were administered doses 30 – 100 times greater than

³ Trincello DG, Johnstone MJ. Treatment of hyperemesis gravidarum with the 5-HT₃ antagonist ondansetron (Zofran®). *Postgrad Med J.* 1996;72:688-9.

⁴ Siu SS, Yip SK, Chueng CW, Lau TK. Treatment of intractable hyperemesis gravidarum by ondansetron. *Eur J Obstet Gynecol Reprod Biol.* 2002 Oct 10;105(1):73-4.

⁵ Sullivan CA, Johnson MJ, Roach H, Martin RW, Stewart DK, Morrison JC. A pilot study of intravenous ondansetron for hyperemesis gravidarum. *Am J Obstet Gynecol* 1996;174:1565-8.

⁶ Buttino L, Gambon C. Home subcutaneous metoclopramide therapy for hyperemesis gravidarum. *Prim Care Update Ob Gyns.* 1998; 5(4):189.

⁷ Buttino L Jr., Coleman SK, Bergauer NK, Gambon C, Stanziano GJ. Home subcutaneous metoclopramide therapy for hyperemesis gravidarum. *J Perinatol.* 2000; 20(6):359-62.

⁸ Buttino L Jr., Gambon C, Coleman S, Home subcutaneous metoclopramide therapy for hyperemesis gravidarum. In: Koren G., Biashai R, editors. *Nausea and vomiting of pregnancy: state of the art 2000. First International Conference on Nausea and Vomiting of Pregnancy. Toronto:Motherisk; 2000 P84-9.*

⁹ Lombardi DG, Istwan N, Rhea D, O'Brien JM. Measuring outpatient outcomes of emesis and nausea management in pregnant women. *Manag Care.* 2004; 13(11):48-51.

¹⁰ Klauser CK, Fox NS, Istwan N, Rhea D, Rebarber A, Desch C, Palmer B, Saltzman D. Treatment of severe nausea and vomiting of pregnancy with subcutaneous medications. *Am J Perinatol.* 2011 Oct 28(9):715-22.

¹¹ Reichmann JP, Kirkbride MS. Continuous subcutaneous metoclopramide and ondansetron for treatment of nausea and vomiting of pregnancy: an evidence review. *Manag Care.* 2012 May; 21(5):44-7.

¹² Fernandez FM. Were some studies overlooked in nausea and vomiting paper? *Manag Care* 2012 Nov; 21(11): 5.

¹³ Reichmann JP, Kirkbride MS. Nausea and vomiting of pregnancy-cost effective pharmacologic treatments. *Manag Care.* 2008 Dec; 17(12):41-45.

those recommended for human use. Authors concluded ondansetron was not found to be genotoxic and had no reproductive or oncogenic potential.¹⁴ During the past decade and a half ondansetron has increasingly been used to treat nausea and vomiting of pregnancy (NVP). The fetal safety data for ondansetron rests on the outcomes of 235 births exposed to the drug in utero.^{15 16 17} Einerson et al addressed the safety of ondansetron in a study that examined 176 mostly American women through a prospective cohort study that could not detect a teratogenic risk. This trial ruled out a 5-fold increased risk of major malformations and the sample size limited the ability to examine specific malformations or detect a smaller risk. This is important because a later large study detected a 2.37 fold risk of cleft palate in infants exposed to ondansetron in utero in the first trimester. Asker et al retrospectively obtained information on drug use in pregnancy from the Swedish Medical Birth Register over a seven and a half year period. Women reporting use of ondansetron were compared to cohorts giving birth in the same period. 45 women exposed to the drug were identified; 21 in the first trimester and no malformations were present. Recently Ferreira et al published a case series containing the outcomes of 17 infants exposed to ondansetron in utero. Authors concluded that until more data is published on the safety of ondansetron it should be used only as a second-line agent in the management of HG.

Safety concerns acknowledged by the Food and Drug Administration (FDA) should be the heightened when ondansetron is given to pregnant women for NVP

The US Food and Drug Administration issued a warning about possible serious QT prolongation and Torsade de Pointes among the general population receiving ondansetron. More recently the 32mg IV dose of ondansetron was withdrawn from the market due to similar safety concerns. The side effect and therefore concern appears to be dose dependent and problematic with patients predisposed which makes the continuous subcutaneous ondansetron pump particularly worrisome. It is not uncommon for Zofran® pump patients to receive doses approaching and even exceeding 32mg per day. The FDA recommends strict follow up of patients receiving ondansetron to rule out long QT syndromes, electrolyte imbalance, congestive heart failure, or receiving concomitant medications that prolong the QT interval. Many pregnant women suffering with nausea and vomiting of pregnancy have electrolyte imbalances such as hypokalemia or hypomagnesemia. It appears the few Obstetricians are aware of the FDA precautions and therefore not following the recommendations.¹⁸

¹⁴ 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.

¹⁵ Einerson A, Maltepe C, Navioz Y, Kennedy D, Tan MP, Koren G. The safety of ondansetorn for nausea and vomiting of pregnancy: a prospective comparative study. *BJOG* 2004;111:940-3.

¹⁶ Asker C, Norstedt W, Wallen B. Use of antiemetic drugs during preganacy in Sweden. *Eur J Clin Pharmacol.* 2005 Dec; 61(12):899-906.

¹⁷ 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.

¹⁸ Koren G. Is ondansetron safe for use in pregnancy? Motherisk Update. *Can Fam Physician.* October 2012 58:1092-1093.

Fetal safety concerns may warrant a change in FDA pregnancy risk category

A study performed in China containing 41 women, scheduled to undergo a requested surgical pregnancy termination, were administered three doses of ondansetron 8mg intravenously prior to the surgery. It is noteworthy that post-surgical analysis of fetal tissue revealed ondansetron in all embryonic compartments.¹⁹ This trial which would have difficult to perform in the US may have served to forewarn of future potential fetal safety concerns.

Recommendations are made regarding the pharmacological treatments for nausea and vomiting of pregnancy however most medications have not been adequately tested for safe use in pregnancy. A recent large multi-site population based case control study detected over a two-fold increased risk of cleft palate associated with ondansetron taken for NVP in the first trimester of pregnancy (odds ratio 2.37 [95% CI 1.18 to 4.76]).²⁰

C. Environmental Impact

The requested actions would have no known impact on the environment.

D. Economic Impact

The requested actions would result in some loss of income for the manufacturers of ondansetron and for the companies that supply continuous subcutaneous anti-emetic pump to women with NVP. Savings would be realized by healthcare consumers who would be relieved of the cost burden associated with an unproven and expensive therapy. Additionally there could be healthcare savings from reduced follow on care from associated maternal/fetal side effects.

E. Certification

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



Signature

James P. Reichmann

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¹⁹ Siu SS, Chan M, Lau TK. Placental transfer of ondansetron during early human pregnancy. *Clin Pharmacokinet.* 2006; 45(4):419-23.

²⁰ Anderka M, Mitchell AA, Louik C, Werler MM, Hernandez-Diaz S, Rasmussen SA, et al. Medications used to treat nausea and vomiting of pregnancy and the risk of birth defects. *Birth Defects Res A Clin Mol Teratol.* 2012;94(1):22-30. Epub 2011 Nov 19.

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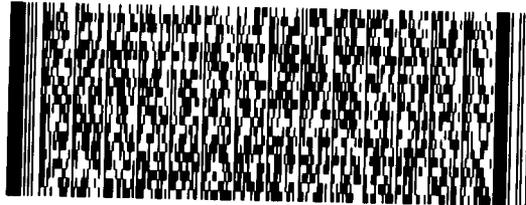
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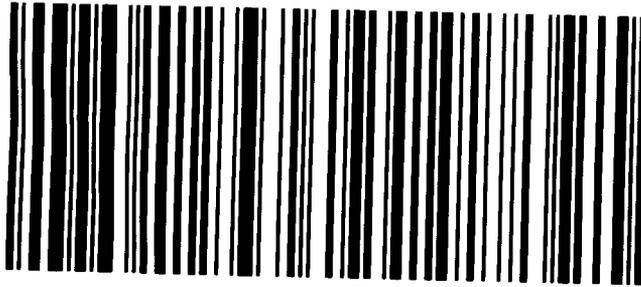


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