IN THE UNITED STATES DISTRICT COURT
FOR THE EASTERN DISTRICT OF TENNESSEE

KIMBERLY SHELTON, individually and on behalf of her minor child S. E.

Plaintiffs,

v.

Civil Action No.: _____
JURY TRIAL DEMANDED

GLAXCOSMITHKLINE LLC,

Defendant.

COMPLAINT

Now into Court, through undersigned counsel, comes Plaintiff, Kimberly Shelton, Individually and on behalf of her child, S. E., a minor, who files this Complaint with Jury Demand and alleges as follows:

NATURE OF THE CASE

1. This action is brought on behalf of Plaintiff Kimberly Shelton, individually and on behalf of her minor child, S. E., who seek compensatory and punitive damages, and such other relief as is just and proper arising from the injuries caused to S. E. as a result of her prenatal exposure to the prescription drug Zofran, also known as odansetron.

2. Zofran is a drug that was approved by the Food and Drug Administration (hereinafter "FDA") in 1991 to treat severe nausea in cancer patients undergoing chemotherapy and radiation treatments. To date, this remains the only FDA-approved use for Zofran.

3. GlaxoSmithKline (hereinafter "GSK") marketed Zofran "off label" as a safe and effective treatment for pregnancy-related nausea and vomiting, commonly called "morning sickness."

4. GSK engaged in this "off label" marketing despite never having conducted a single study on the effects of Zofran on pregnant women or their unborn children. GSK chose not to study Zofran in pregnant women or seek FDA approval before marketing the drug for treatment during pregnancy.

5. As a result, Zofran was prescribed to unsuspecting pregnant women throughout the United States. Pregnant women ingested Zofran because they were led to believe that Zofran was safe to use for the treatment of pregnancy-related nausea. Pregnant women who ingested Zofran had no way of knowing that their use of Zofran increased the risk that their unborn children would develop serious birth defects.

6. At the same time GSK was marketing Zofran to pregnant women, GSK knew that Zofran was unsafe for ingestion by pregnant women. GSK conducted animal studies in the 1980s which revealed evidence of toxicity, intrauterine deaths, and malformations in offspring. These studies also demonstrated that Zofran's active ingredient transferred through the placental barrier of pregnant mammals to fetuses. A later study conducted in humans confirmed that ingested Zofran readily crossed the human placenta barrier and exposed fetuses to substantial concentrations. GSK did not disclose this information to pregnant women or their physicians.

7. By 1992, GSK had a multitude of evidence linking Zofran to birth defects. GSK received at least 32 reports of birth defects associated with Zofran by 2000, and has received more than 200 such reports to date. Nevertheless, GSK did not disclose the reports to pregnant women or their physicians. In addition, scientists have conducted large-scale epidemiological studies that

have demonstrated an elevated risk of developing birth defects such as those suffered in this case. GSK has never disclosed this information to pregnant women or their physicians. Instead, GSK sales representatives continued to market and promote Zofran as a drug for pregnancy-related nausea at all times relevant to this case.

8. GSK pled guilty in 2012 to criminal charges brought by the U.S. Department of Justice regarding its "off-label" promotion of drugs for uses that were never approved by the FDA.

9. At or around the same time, GSK also entered into civil settlements with the United States that included more than $1 billion in payments to the federal government for its illegal marketing of various drugs, including Zofran specifically.

10. GSK's written agreement with the United States reports GSK's settlement of allegations that GSK:

> (a) "promoted the sale and use of Zofran for a variety of conditions other than those for which its use was approved as safe and effective by the FDA (including hyperemesis and pregnancy-related nausea)"
>
> (b) "made and/or disseminated unsubstantiated and false representations about the safety and efficacy of Zofran concerning the uses described in subsection (a) [hyperemesis and pregnancy-related nausea]"
>
> (c) "offered and paid illegal remuneration to health care professionals to induce them to promote and prescribe Zofran"

(Settlement Agreement, p. 5, July 2, 2012.)

11. GSK's fraudulent and unlawful conduct in the marketing and promotion of Zofran as a safe morning sickness drug to pregnant women has caused serious and irreversible damage to innocent children and their families, including Plaintiff and her minor child S. E.

12. GSK negligently and improperly failed to perform sufficient and adequate testing on pregnant women using Zofran during clinical trials. This inadequate testing evinced a callous, reckless, and willful indifference to the health, safety and welfare of pregnant women and their unborn children, including Plaintiff and her minor child S. E.

13. As a result of the foregoing acts and omissions, Plaintiff's minor child S. E. suffered serious and dangerous birth defects caused by exposure to Zofran while in utero. S. E.'s injuries include, but are not limited to pulmonary valve stenosis and atrial septum defect.

14. Therefore, Plaintiff seeks compensatory and punitive damages, and such other relief as is just and appropriate arising from injuries caused by Plaintiff's ingestion of Zofran while she was pregnant with her minor child.

JURISDICTION AND VENUE

15. This Court has jurisdiction over this action pursuant to 28 U.S.C. § 1332 because the amount in controversy exceeds $75,000.00, exclusive of interest and costs, and because there is complete diversity of citizenship between Plaintiff and Defendant GSK.

16. Venue is proper in this jurisdiction pursuant to 28 U.S.C. § 1391, because a substantial part of the events or omissions giving rise to the Plaintiff's claims occurred in this District, and because Defendant GSK conducts substantial business in this District.

17. This Court has personal jurisdiction over Defendant GSK because it has done business in the State of Tennessee, has committed a tort in whole or in part in the State of Tennessee, has substantial and continuing contact with the State of Tennessee, and derives substantial revenue from goods used and consumed with the State of Tennessee. Defendant GSK

actively advertises, sells, markets, distributes, and/or promotes its pharmaceutical product Zofran to physicians and consumers in the State of Tennessee on a regular and consistent basis.

PARTIES

18. Plaintiff and her minor child, S. E., are citizens and residents of the State of Tennessee and were citizens and residents of the State of Tennessee at all times relevant to the allegations in this Complaint. Plaintiff's minor child, S. E., upon information and belief, suffered severe personal injuries as a result of Plaintiff's use of Zofran while pregnant with S. E.

19. Defendant GSK is a limited liability company organized under the laws of the State of Delaware. GSK's sole member is GlaxoSmithKline Holdings, Inc., which is a Delaware corporation, and which has identified its principal place of business as Wilmington, Delaware.

20. GSK is the successor in interest to Glaxo, Inc. and Glaxo Wellcome Inc. Glaxo, Inc. was the sponsor of the original New Drug Application ("NDA") for Zofran. Glaxo, Inc., through its division Cerenex Pharmaceuticals, authored the original package insert and labeling for Zofran, including warnings and precautions attendant to its use. Glaxo Wellcome Inc. sponsored additional NDAs for Zofran, monitored and evaluated post-market adverse event reports arising from Zofran, and authored product labeling for Zofran. The term GSK used herein refers to GSK, its predecessors Glaxo, Inc. and Glaxo Wellcome Inc., and other GSK predecessors and/or affiliates that discovery reveals were involved in the testing, development, manufacture, marketing, sale and/or distribution of Zofran.

21. Upon information and belief, GSK has transacted and conducted business in the State of Tennessee.

22. Upon information and belief, GSK has derived substantial revenue from goods and products used in the State of Tennessee.

23. Upon information and belief, GSK expected or should have expected its acts to have consequence within the United States and the State of Tennessee, and derived substantial revenue from interstate commerce within the United States and the State of Tennessee, more particularly.

24. Upon information and belief, and at all relevant times, GSK was in the business of and did design, develop, research, manufacture, test, advertise, promote, market, sell, and/or distribute the drug Zofran for use by pregnant women as an anti-nausea, "morning sickness" medication.

ZOFRAN-SPECIFIC FACTUAL BACKGROUND

25. Zofran is a drug that was approved by the Food and Drug Administration (hereinafter "FDA") in 1991 to treat severe nausea in cancer patients undergoing chemotherapy and radiation treatments. To date, this remains the only FDA-approved use for Zofran.

26. The Zofran Prescribing Information as of September 2014 provides as follows:

> INDICATIONS AND USAGE
>
> 1. Prevention of nausea and vomiting associated with highly emetogenic cancer chemotherapy, including cisplatin ≥ 50 mg/m2.
>
> 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.

(GSK, Zofran Prescribing Information, Sept. 2014.)

27. Zofran is an anti-emetic (a drug that prevents or treats nausea and vomiting) belonging to a class of anti-emetics called selective serotonin 5HT3 receptor anatagonists. The active ingredient in Zofran is ondansetron hydrochloride, an antagonist at the 5-hydroxytryptamine receptor type 3 (5-HT3).

28. Serotonin triggers nausea and vomiting in the human body. Zofran works by inhibiting the body's serotonin activity.

29. Zofran is available as an injection (2 mg/mL), a premixed injection (32 mg/50ml and 4 mg/50 ml), oral tablets (4 mg, 8 mg and 24 mg), orally disintegrating tablets (4 mg and 8 mg) and an oral solution (4 mg/5 mL).

30. GSK has obtained FDA approval for the following formations of Zofran:

(a) NDA 20-007 – Zofran Injection (FDA approved January 4, 1991);

(b) NDA 20-103 – Zofran Tablets (FDA approved December 31, 1992);

(c) NDA 20-403 – Zofran Premixed Injection (FDA approved January 31, 1995);

(d) NDA 20-605 – Zofran Oral Solution (FDA approved January 24, 1997);

(e) NDA 20-781 – Zofran (a/k/a Zofran-Zydis) Orally Disintegrating Tablets (FDA approved January 27, 1999).

31. The FDA has never approved Zofran for the treatment of morning sickness or any other condition in pregnant women.

32. In order to lawfully market Zofran for treating morning sickness in pregnant women, GSK is required to adequately test the drug for that purpose (including to perform

appropriate clinical studies) and to submit formally evidence demonstrating that the drug is safe and effective for that purpose to the FDA. Without obtaining FDA approval to market a drug for the treatment of pregnant women, GSK may not legally market its drug for that purpose.

33. Despite having the resources and capability to perform appropriate studies, GSK has not performed any clinical studies to determine the effect on pregnant women who take Zofran.

34. Further, GSK has not submitted any data to the FDA demonstrating that Zofran is safe and effective for treating pregnancy-related nausea in pregnant women. Rather, GSK has illegally circumvented the FDA approval process by marketing Zofran for the treatment of pregnancy-related nausea in pregnant women without having applied for the FDA's approval to market Zofran to treat that condition or any other condition in pregnant women. This practice is known as "off-label" promotion, and in this case it constitutes fraudulent marketing.

35. At all times relevant to this case, GSK was in the business of and did design, research, manufacture, test, package, label, advertise, promote, market, sell and distribute Zofran; GSK continues to market and sell Zofran "off label" today.

36. Since at least the 1980s, when GSK received the results of the preclinical studies that it submitted in support of Zofran's NDA 20-007, GSK has known of the risk that Zofran ingested during pregnancy in mammals crosses the placental barrier to expose the fetus to the drug. For example, at least as early as the mid-1980s, GSK performed placental-transfer studies of Zofran in rats and rabbits, and reported that the rat and rabbit fetuses were exposed prenatally to Zofran during pregnancy.

37. The placental transfer of Zofran during human pregnancy at concentrations high enough to cause congenital malformations has been independently confirmed and detected in every sample of fetal tissue taken in a published study involving 41 pregnant patients. The average fetal

tissue concentration of Zofran's active ingredient was 41% of the corresponding concentration in the mother's plasma.

38. GSK reported four animal studies in support of its application for approval of NDA 20-0007: (1) Study No. R10937 I.V. Segment II teratological study of rats; (2) Study No. R10873 I.V. Segment II teratological study of rabbits; (3) Study No. R10590 Oral Segment II teratological study of rats; (4) Study No. L10649 Oral Segment II teratological study of rabbits. These preclinical teratogenicity studies in rats and rabbits were stated by the sponsor, GSK, to show no harm to the fetus, but the data also revealed clinical signs of toxicity, premature births, intrauterine fetal deaths, and impairment of ossification (incomplete bone growth).

39. Study No. R10937 was a Segment II teratological study of pregnant rats exposed to Zofran injection solution. Four groups of 40 pregnant rats (160 total) were reportedly administered Zofran through intravenous (I.V.) administration at doses of 0, 0.5, 1.5, and 4 mg/kg/day, respectively. Clinical signs of toxicity that were observed in the pregnant rats included "low posture, ataxia, subdued behavior and rearing, as well as nodding and bulging eyes." No observations were reported as teratogenic effects.

40. Study No. R10873 was a Segment II teratological study of pregnant rabbits exposed to Zofran injection solution. Four groups of 15 pregnant rabbits (60 total) were reportedly given Zofran doses of 0, 0.5, 1.5, and 4 mg/kg/day, respectively. The study showed an increase in the number of intra-uterine deaths in the 4 mg/kg group versus lower-dosage groups. The study also reported maternal weight loss in the exposed groups. Developmental retardation in offspring and fetuses were noted—namely, areas of the parietal (body cavity) were not fully ossified, and the hyoid (neck) failed to ossify completely.

41. Study No. R10590 was an Oral Segment II teratological study of rats. Four groups of 30 pregnant rats (120 total) were given Zofran orally at doses of 0, 1, 4, and 15 mg/kg/day, respectively. Subdued behavior, labored breathing (which is a symptom of congenital heart defects), and dilated pupils were observed in the 15 mg/kg/day group. Body weight, gestational duration, and fetal examinations were reported as normal, but "slight retardation in skeletal ossification" was noted in the offspring.

42. Study No. L10649 was an Oral Segment II teratological study of rabbits. Four groups of 14-18 pregnant rabbits (56-64 total) were given Zofran orally at doses of 0, 1, 5.5 and 30 mg/kg/day. The study reported lower maternal weight gain in all of the exposed groups, as well as premature delivery and "total litter loss," referring to fetal deaths during pregnancy in the 5.5 mg/kg/day group. Examination of the fetuses showed "slight developmental retardation as evident by incomplete ossification or asymmetry of skeleton."

43. Even assuming that these animal studies do not conclusively reveal evidence of potential harm to a fetus exposed to Zofran, GSK was aware that animal studies are not necessarily predictive of human response. For example, a drug formerly prescribed to alleviate morning sickness, thalidomide, is an infamous teratogenic in humans, but animal studies involving the drug failed to demonstrate such an increased risk of birth defects in animals. GSK conducted studies of thalidomide and its toxicity before GSK developed Zofran and before it marketed Zofran for the treatment of morning sickness in pregnant women. Moreover, since at least 1993, GSK has stated in its prescribing information for Zofran that "animal reproduction studies are not always predictive of human response." Therefore, GSK has been aware since at least when it began marketing and selling Zofran that GSK could not responsibly rely on its animal studies as a basis

for promoting Zofran use in pregnant women. GSK nevertheless went forward with marketing and promoting Zofran to pregnant women.

44. GSK began receiving reports of birth defects associated with the use of Zofran by pregnant women as early as 1992. By 2000, GSK had received at least 32 reports of birth defects associated with Zofran, including reports of congenital heart disease, dysmorphism, intrauterine death, stillbirth, kidney malformation, congenital diaphragmatic anomaly, congenital musculoskeletal anomalies, and orofacial anomalies, among others.

45. To date, GSK has received more than 200 reports of birth defects in children who were exposed to Zofran while in utero. Upon information and belief, the number of such events that were actually reported to GSK comprises only a small fraction of all such events.

46. Three recent epidemiological studies have examined the association between prenatal exposure to Zofran and the risk of congenital heart defects in babies. These studies include: (1) Pasternak, *et al.*, Ondansetron in Pregnancy and Risk of Adverse Fetal Outcomes, New England Journal of Medicine (Feb. 28, 2013) (the "Pasternak Study"); (2) Andersen, *et al.*, Ondansetron Use in Early Pregnancy and the Risk of Congenital Malformations—A Register Based Nationwide Control Study, presented as International Society of Pharmaco-epidemiology, Montreal, Canada (2013) (the "Andersen Study"); and (3) Danielsson, *et al.*, Ondansetron During Pregnancy and Congenital Malformations in the Infant (Oct. 31, 2014) (the "Danielsson Study").

47. Each of these studies employs methodologies tending to bias results toward under-reporting the true risk of having a child with a birth defect. Despite this, all three studies show elevated risk ratios for cardiac malformations, including risk ratios greater than 2.0. In other words, the studies report that a mother who ingested Zofran had more than a double risk of having a baby with a congenital heart defect compared to a mother who did not ingest Zofran while pregnant.

48. The Pasternak Study included data from the Danish National Birth Registry and examined the use of Zofran during pregnancy and risk of adverse fetal outcomes. Adverse fetal outcomes were defined as: spontaneous abortion, stillbirth, any major birth defect, pre-term delivery, low birth weight, and small size for gestational age. A total of 608,385 pregnancies between January 2004 and March 31, 2011, were studied. The unexposed group was defined as women who did not fill a prescription for ondansetron during the exposure time window. The exposure time window was defined as the first 12-week gestational period. Notably, the median fetal age at first exposure to Zofran was 10 weeks, meaning that half of the cases were first exposed to Zofran after organogenesis (organ formation). This characteristic of the study led to an under-reporting of the actual risk of prenatal Zofran exposure. The study's supplemental materials indicated that women taking Zofran during the first trimester, compared to women who did not take Zofran, were 22% more likely to have offspring with a septal defect, 41% more likely to have offspring with a ventricular septal defect, and greater than four-times more likely to have offspring with an atrioventricular septal defect.

49. The Andersen Study was also based on data collected from the Danish Medical Birth Registry and the National Hospital Register, the same data examined in the Pasternak Study. The Andersen study examined the relationship between Zofran use during the first trimester and subgroups of congenital malformations. Data from all women giving birth in Denmark between 1997 and 2010 were included in the study. A total of 903,207 births were identified in the study period with 1,368 women filling prescriptions for Zofran during the first trimester. The Andersen Study therefore used a larger data set (13 years) compared to the Pasternak Study (seven years). Exposure to the drug was also defined as filling a prescription during the first trimester, and prescription data were obtained from the National Prescription Registry. The Andersen study

reported that mothers who ingested Zofran during their first trimesters of pregnancy were more likely than mothers who did not to have a child with a congenital heart defect, and had a two- to four-fold greater risk of having a baby with a septal cardiac defect.

50. The Danielsson Study investigated risks associated with Zofran use during pregnancy and risk of cardiac congenital malformations from data available through the Swedish Medical Birth Registry. The Swedish Medical Birth Registry was combined with the Swedish Register of Prescribed Drugs to identify 1,349 infants born to women who had taken Zofran in early pregnancy from 1998-2012. The total number of births in the study was 1,501,434 infants, and 43,658 had malformations classified as major (2.9%). Among the major malformations, 14,872 had cardiovascular defects (34%) and 10,492 had a cardiac septum defect (24%). The Danielsson study reported a statistically significantly elevated risk for cardiovascular defects for mothers taking Zofran versus those who did not. The results reported that the mothers who took Zofran during early pregnancy had a 62% increased risk of having a baby with a cardiovascular defect. Further, mothers who took Zofran during pregnancy had a greater than two-fold increased risk of having a baby with a septal cardiac defect, compared to mothers who did not take Zofran during pregnancy.

51. It is clear that, since as early as 1992, GSK has been privy to mounting evidence that Zofran poses an unreasonable risk of harm to babies exposed to the drug while in utero. GSK has been aware that Zofran readily crosses human placental barriers during pregnancy. GSK has also been aware that the animal studies of Zofran cannot reliably support an assertion that Zofran can be used safely or effectively in pregnant women. Since 1992, GSK has received hundreds of reports of major birth defects associated with prenatal Zofran exposure. GSK also has had actual and/or constructive knowledge of the epidemiological studies reporting that prenatal Zofran

exposure can more than double the risk of developing congenital heart defects. As alleged below, GSK not only concealed this knowledge from healthcare providers and consumers in the United States, and failed to warn of the risk of birth defects, but GSK also illegally and fraudulently promoted Zofran to physicians and patients specifically for the treatment of morning sickness in pregnant women.

52. Federal law governs GSK's drug labeling obligations for its pharmaceutical products, including Zofran, and federal law requires GSK to "describe serious adverse reactions and potential safety hazards, limitations in use imposed by them, and steps that should be taken if they occur." 21 C.F.R. § 201.57(e).

53. Federal law also requires GSK to list adverse reactions that occurred with other drugs in the same class as Zofran. *Id.* at § 201.57(g).

54. In the context of prescription drug labeling, "an adverse reaction is an undesirable effect, reasonably associated with use of a drug that may occur as part of the pharmacological action of the drug or may be unpredictable in its occurrence." *Id.*

55. Federal law also required GSK to revise Zofran's labeling "to include a warning as soon as there is reasonable evidence of an association of a serious hazard with a drug; a causal relationship need not have been proved." *Id.* at § 201.57(e)

56. GSK has received hundreds of reports of birth defects associated with the non-FDA-approved use of Zofran in pregnant women. GSK has failed, however, to disclose these severe adverse events to healthcare providers or expectant mothers, including Plaintiffs and their prescribing healthcare providers.

57. Under 21 C.F.R. § 314.70(c)(2)(i), pharmaceutical companies were (and are) free to add or strengthen—without prior approval from the FDA—a contraindication, warning, precaution, or adverse reaction.

58. GSK thus had the ability and obligation to add warnings, precautions and notice of adverse reactions to the product labeling for Zofran without prior approval from the FDA. GSK failed to do so.

59. Under 21 C.F.R. § 201.128:

> [I]f a manufacturer knows, or has knowledge of facts that would give him notice, that a drug introduced into interstate commerce by him is to be used for conditions, purposes, or uses other than the ones for which he offers it, he is required to provide adequate labeling for such a drug which accords with such other uses to which the article is to be put.

60. GSK has known since at least 1998, on the bases of its off-label promotion and payments to doctors, its obvious increase in revenue from Zofran, and its market analyses of prescription data, that physicians were prescribing Zofran off-label to treat morning sickness in pregnant women and that such usage was associated with a clinically significant risk or hazard of causing birth defects.

61. GSK had the ability and obligation to state prominently in the Indications and Usage section of its drug label that there is a lack of evidence that Zofran is safe for the treatment of morning sickness in pregnant women. GSK failed to do so, despite GSK's knowledge that (a) the safety of Zofran for use in human pregnancy has not been established, (b) there have been hundreds of reports of birth defects associated with Zofran use during pregnancy, and (c) epidemiology studies report an increased risk of birth defects in babies exposed to Zofran during pregnancy.

62. From 1993 to the present, despite being privy to mounting evidence of the birth defect risk, GSK's prescribing information for Zofran has included the same statement concerning use of Zofran during pregnancy:

> **Pregnancy: Teratogenic Effects**: Pregnancy Category B. Reproduction studies have been performed in pregnant rats and rabbits at I.V. doses up to 4 mg/kg per day 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.

63. By contrast, the Product Monograph for Zofran in Canada states "the safety of ondansetron for use in human pregnancy has not been established" and that "the use of ondansetron in pregnancy is not recommended."

64. In the United States, including in Tennessee, GSK has at all relevant times failed to include any warning regarding the risk of birth defects arising from the use of Zofran during pregnancy in Zofran's prescribing information or other product labeling.

65. GSK's inclusion of the phrase "Pregnancy Category B" in Zofran's prescribing information refers the FDA's pregnancy categorization scheme applicable to prescription drugs in the United States. The FDA has established five categories to indicate the potential of a drug to cause birth defects if used during pregnancy. The current system consists of five letter-categories (A, B, C, D, and X, in order of increasing risk).

66. GSK had the ability, and indeed was required under federal law, to update Zofran's label to reflect at least a Pregnancy Category D designation, or alternatively a Category X designation for Zofran:

> **Pregnancy Category D** If there is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience or studies in humans, but the potential benefits from the use of the drug in pregnant women may be acceptable despite its potential risks (for example, if the drug is needed in a life-threatening situation or serious disease for which safer drugs cannot be used or are ineffective), the labeling must state: "Pregnancy Category D. See "Warnings and Precautions" section. Under the "Warnings and Precautions" section, the labeling must state: "[drug] can cause fetal harm when administered to a pregnant woman [. . . .] If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to a fetus."

21 C.F.R. § 201.57(f)(6)(i)(d).

> **Pregnancy Category X** If studies in animals or humans have demonstrated fetal abnormalities or if there is positive evidence of fetal risk based on adverse reaction reports from investigational or marketing experience, or both, and the risk of the use of the drug in a pregnant woman clearly outweighs any possible benefit (for example, safer drugs or other forms of therapy are available), the labeling must state: "Pregnancy Category X. See 'Contraindications' section." Under "Contraindications," the labeling must state: "(Name of drug) may (can) cause fetal harm when administered to a pregnant woman [. . . .] (Name of drug) is contraindicated in women who are or may become pregnant. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to a fetus."

Id. at § 201.57(f)(6)(i)(e).

67. Beginning at least in 1992, GSK had evidence of human fetal risk posed by Zofran ingestion based on more than 200 reports to GSK of birth defects, as well as epidemiology studies, and placental-transfer studies reporting on Zofran's teratogenic risk. GSK has never updated Zofran's labeling to disclose that Zofran can cause fetal harm when administered to a pregnant woman, and GSK has failed to warn of the potential hazards to a fetus arising from Zofran use during pregnancy.

68. The FDA recently promulgated a final rule declaring that, as of June 2015, it will require pharmaceutical manufacturers to remove the current A, B, C, D, or X pregnancy categorization designation from all drug product labeling and instead summarize the risks of using a drug during pregnancy, discuss the data supporting that summary, and describe relevant information to help health care providers make prescribing decisions and counsel women about the use of drugs during pregnancy and lactation. 79 Fed. Reg. 72064 (Dec. 4, 2014). In promulgating this rule, the FDA "determined that retaining the pregnancy categories is inconsistent with the need to accurately and consistently communicate differences in degrees of fetal risk."

69. In summary, many years before Plaintiff was exposed to Zofran, GSK marketed and sold Zofran without adequately warning healthcare providers and consumers that Zofran was associated with an increased risk of birth defects, and that GSK had not adequately tested Zofran to support marketing and promoting it for use in pregnant women. This rendered the warnings accompanying Zofran inadequate and defective.

70. Plaintiff hereby demands that GSK immediately cease the wrongful conduct alleged herein for the benefit of Plaintiff and other similarly situated mothers and mothers-to-be, as GSK continues to engage in the same wrongful conduct. Plaintiff further demands that GSK fully and fairly comply with removing the Pregnancy Category B designation from its drug product labeling for Zofran and fully and accurately summarizing the known risks of using Zofran during pregnancy, with fully and accurately describing the data supporting that summary, and fully and accurately describing the relevant information to help health care providers make informed prescribing decisions and with counseling women about the risks associated with use of Zofran during pregnancy.

CASE-SPECIFIC FACTUAL BACKGROUND

71. Plaintiff Kimberly Shelton is the mother and natural guardian of S. E. Plaintiff began using Zofran on or about August 1999, during her first trimester of pregnancy with S. E. Plaintiff ingested Zofran for the purpose of alleviating and preventing pregnancy-related nausea.

72. Plaintiff's physician would not have prescribed Zofran to Plaintiff had her physician known of the true risks associated with the use of Zofran.

73. At the time Plaintiff ingested Zofran, she was unaware of the dangers posed by ingesting Zofran during pregnancy, and she was unaware of the fraudulent nature of GSK's marketing of Zofran as a safe drug for the purpose of treating pregnancy-related nausea.

74. Plaintiff would not have elected to use Zofran had she known of the true risks associated with the use of Zofran. In other words, Plaintiff would not have elected to use Zofran had she known that Zofran posed a risk of causing birth defects in her unborn child, S. E.

75. S. E. was born on April 28, 2000.

76. As a direct and proximate result of her prenatal exposure to Zofran, S. E. was diagnosed with heart defects.

77. There is no known history of birth defects of the type suffered by S. E. in Kimberly Shelton's family. Before S. E. was born, Plaintiff gave birth to a daughter without heart defects following a pregnancy in which Plaintiff did not ingest Zofran.

78. As a direct and proximate result of GSK's conduct, Plaintiff and her daughter S. E. have suffered and incurred damages, including severe and permanent pain and suffering, mental anguish, medical expenses and other economic and non-economic damages, and will require more medical treatment than had they not been exposed to Zofran.

79. Plaintiff files this lawsuit within the applicable limitations period of first suspecting that Zofran caused the appreciable harm sustained by her daughter S. E. Plaintiff could not, by the exercise of reasonable diligence, have discovered the wrongful cause of the injuries at an earlier time. Plaintiff did not suspect, nor did Plaintiff have reason to suspect, the tortious nature of the conduct causing the alleged injuries, within a year before the filing of this action. Additionally, Plaintiff was prevented from discovering this information sooner because GSK has misrepresented to the public and to the medical profession that Zofran is safe for use in pregnancy, and GSK has fraudulently concealed facts and information that could have led Plaintiff to discover a potential cause of action.

CAUSES OF ACTION

COUNT I: NEGLIGENCE

80. Plaintiff hereby incorporates by reference the allegations of this Complaint contained in each of the preceding paragraphs as if fully stated herein.

81. GSK had a duty to exercise reasonable care in the designing, developing, researching, manufacturing, marketing, supplying, promoting, packaging, sale and/or distribution of Zofran into the stream of commerce, including but not limited to a duty to assure that the product would not cause users to suffer unreasonable and dangerous adverse side effects, to properly warn of all risks, and to comply with federal requirements.

82. GSK failed to exercise ordinary care in the designing, developing, researching, manufacturing, marketing, supplying, promoting, packaging, sale, testing, quality assurance, quality control, and/or distribution of Zofran into interstate commerce in that GSK knew or should have known that the use of GSK by pregnant women could cause significant harm to unborn

children, including but not limited to physical injuries of a permanent and disabling nature, physical pain and mental anguish, diminished enjoyment of life, and hospitalization and other medical expenses, and was therefore not safe for use by pregnant women.

83. GSK's negligent acts and/or omissions include, but are not limited to:

(a) Producing, manufacturing, formulating, designing, and/or advertising Zofran to pregnant women to treat morning sickness without sufficiently, thoroughly, and/or adequately testing it for that purpose;

(b) Selling Zofran to pregnant women without performing sufficient/adequate testing to determine the full range of dangers to pregnant women;

(c) Failing to warn Plaintiff, the general public, healthcare providers, and the FDA of the dangers associated with using Zofran during pregnancy;

(d) Failing to provide adequate instructions regarding safety precautions to be observed by users, handlers, and persons who would reasonably and foreseeably come into contact with and/or use Zofran;

(e) Failing to test Zofran and/or failing to adequately, sufficiently and properly test Zofran for use by pregnant women;

(f) Negligently advertising and recommending the use of Zofran to Plaintiff, the general public, and healthcare providers without sufficient knowledge as to its dangerous propensities in pregnant women;

(g) Negligently representing that Zofran was safe for use by pregnant women, when, in fact, it was unsafe;

(h) Negligently representing that Zofran was equally as safe and effective as other available forms of treatment for morning sickness in pregnant women;

(i) Negligently designing Zofran in a manner which was dangerous to users, including Plaintiff;

(j) Negligently manufacturing Zofran in a manner which was dangerous to users, including Plaintiff;

(k) Negligently producing Zofran in a manner which was dangerous to users, including Plaintiff;

(l) Negligently assembling Zofran in a manner which was dangerous to users, including Plaintiff;

(m) Knowingly concealing that Zofran was unsafe, dangerous, and/or non-conforming with FDA regulations from Plaintiff, the general public, and healthcare providers;

(n) Improperly concealing and/or misrepresenting information regarding the risks and dangers posed by using Zofran during pregnancy.

84. Despite the fact that GSK knew or should have known that Zofran significantly increased the risk of birth defects, GSK continued and continues today to manufacture and market Zofran for use by pregnant women and continues to fail to comply with federal requirements.

85. GSK knew or should have known that consumers such as Plaintiff and her minor child would foreseeably suffer injury as a result of GSK's failure to exercise ordinary care as described above, including the failure to comply with federal requirements.

86. It was foreseeable that GSK's product, as designed, would cause serious injury to consumers, including Plaintiff and her minor child.

87. As a direct and proximate result of GSK's negligence, Plaintiff and her minor child were caused to suffer serious and dangerous side effects including, but not limited to, heart defects, physical pain and mental anguish, diminished enjoyment of life, and financial expenses for hospitalization and medical care.

88. GSK's conduct evidences a flagrant disregard of human life so as to warrant the imposition of punitive damages. This conduct includes but is not limited to: failing to adequately design, test, and manufacture GSK for use by pregnant women; marketing and distributing Zofran to pregnant women when GSK knew or should have known of the serious health risks it posed to unborn children; and failing to comply with federal requirements.

COUNT II: NEGLIGENCE PER SE

89. Plaintiffs hereby incorporate by reference the allegations of this Complaint contained in each of the preceding paragraphs as if fully stated herein.

90. GSK had a duty to exercise reasonable care, and comply with existing laws, in the design, research, manufacture, marketing, supply, promotion, packaging, sale, testing, and/or distribution of Zofran into the stream of commerce, including a duty to ensure that the product would not cause users to suffer unreasonable, dangerous side effects.

91. GSK failed to exercise ordinary care and failed to comply with existing laws in the design, research, manufacture, marketing, supply, promotion, packaging, sale, testing, quality assurance, quality control, and/or distribution of Zofran into interstate commerce in that GSK knew or should have known that using Zofran created an unreasonable risk of dangerous birth defects, as well as other severe and personal injuries which are permanent and lasting in nature, physical pain and mental anguish, including diminished enjoyment of life, as well as the need for lifelong medical treatment, monitoring and/or medication.

92. GSK, its agents, servants, and/or employees, failed to exercise ordinary care and violated 21 U.S.C. § 331, 352; 42 U.S.C. § 1320a-7b; and 21 C.F.R. §§ 201.57, 201.128, in particular.

93. The laws violated by GSK were designed to protect Plaintiff and similarly situated persons and to protect against the risks and hazards that have actualized in this case. Therefore, GSK's conduct constitutes negligence *per se*.

94. Despite the fact that GSK knew or should have known that Zofran significantly increased the risk of birth defects, GSK continued and continues to negligently and misleadingly market, manufacture, distribute and/or sell Zofran to consumers, including Plaintiff.

95. GSK knew or should have known that consumers such as Plaintiff would foreseeably suffer injury as a result of GSK's failure to exercise ordinary care, as set forth above.

96. GSK's negligence was the proximate cause of Plaintiff's injuries, harm and economic loss, which Plaintiff suffered and/or will continue to suffer.

97. Had Plaintiff not taken Zofran, her minor child herein would not have suffered those injuries and damages as described in this Complaint.

98. As a result of the foregoing acts and omissions, Plaintiff and her minor child herein were caused to suffer serious and dangerous side effects including, but not limited to heart defects, physical pain and mental anguish, diminished enjoyment of life, and financial expenses for hospitalization and medical care.

COUNT III: NEGLIGENT MISREPRESENTATION

99. Plaintiff hereby incorporates by reference the allegations of this Complaint contained in each of the preceding paragraphs as if fully stated herein.

100. GSK falsely and fraudulently represented to pregnant women and the medical and healthcare community, including Plaintiff and her health care providers, that:

(a) Zofran was safe and effective for treating pregnancy-related nausea;

(b) Zofran had been adequately tested and studied in pregnant women;

(c) Zofran use during pregnancy did not increase the risk of bearing children with birth defects; and

(d) Zofran's "Pregnancy Category B" designation established the safety and efficacy of Zofran for treating pregnancy-related nausea.

101. The representations made by GSK were material, false and misleading.

102. GSK knew that the representations were false when it made the representations.

103. GSK made these representations with the intent of defrauding and deceiving the public in general, and the medical and healthcare community in particular, and with the intent of inducing the public in general, and the medical and healthcare community in particular, including Plaintiff and her health care providers, to recommend, prescribe, dispense and/or purchase Zofran to treat pregnancy-related nausea, all of which evinced a callous, reckless, willful, and depraved indifference to the health, safety and welfare of Plaintiff herein.

104. At the time the aforesaid representations were made by GSK and, at the time Plaintiff used Zofran, Plaintiff was unaware of the falsity of said representations and reasonably believed them to be true.

105. In reliance upon said representations, Plaintiff's prescriber was induced to prescribe Zofran to her, and Plaintiff was induced to and did use Zofran to treat pregnancy-related nausea.

106. GSK knew that Zofran had not been sufficiently tested for pregnancy-related nausea and that it lacked adequate warnings.

107. GSK knew or should have known that exposure to Zofran increases the risk that children in utero will develop birth defects.

108. As a result of the foregoing acts and omissions, Plaintiff and her minor child herein were caused to suffer serious and dangerous side effects including, but not limited to, heart defects, as well as physical pain and mental anguish, diminished enjoyment of life, and financial expenses for hospitalization and medical care.

COUNT IV: NEGLIGENT INFLICTION OF EMOTIONAL DISTRESS

109. Plaintiff hereby incorporates by reference the allegations of this Complaint contained in each of the preceding paragraphs as if fully stated herein.

110. GSK negligently inflicted severe emotional distress upon Plaintiff by its negligent and careless actions, including, but not limited to:

(a) Producing, manufacturing, formulating, designing, and/or advertising Zofran to pregnant women to treat morning sickness without sufficiently, thoroughly, and/or adequately testing it for that purpose;

(b) Selling Zofran to pregnant women without performing sufficient/adequate testing to determine the full range of dangers to pregnant women;

(c) Failing to warn Plaintiff, the general public, healthcare providers, and the FDA of the dangers associated with using Zofran during pregnancy;

(d) Failing to provide adequate instructions regarding safety precautions to be observed by users, handlers, and persons who would reasonably and foreseeably come into contact with and/or use Zofran;

(e) Failing to test Zofran and/or failing to adequately, sufficiently and properly test Zofran for use by pregnant women;

(f) Negligently advertising and recommending the use of Zofran to Plaintiff, the general public, and healthcare providers without sufficient knowledge as to its dangerous propensities in pregnant women;

(g) Negligently representing that Zofran was safe for use by pregnant women, when, in fact, it was unsafe;

(h) Negligently representing that Zofran was equally as safe and effective as other available forms of treatment for morning sickness in pregnant women;

(i) Negligently designing Zofran in a manner which was dangerous to users, including Plaintiff;

(j) Negligently manufacturing Zofran in a manner which was dangerous to users, including Plaintiff;

(k) Negligently producing Zofran in a manner which was dangerous to users, including Plaintiff;

(l) Negligently assembling Zofran in a manner which was dangerous to users, including Plaintiff;

(m) Knowingly concealing that Zofran was unsafe, dangerous, and/or non-conforming with FDA regulations from Plaintiff, the general public, and healthcare providers;

(n) Improperly concealing and/or misrepresenting information regarding the risks and dangers posed by using Zofran during pregnancy.

111. Had Plaintiff not taken Zofran, she and her minor child would not have suffered those injuries and damages as described hereinabove.

112. As a result of the foregoing acts and omissions, Plaintiff and her minor child herein were caused to suffer serious and dangerous side effects including, but not limited to, heart defects, as well as physical pain and mental anguish, diminished enjoyment of life, and financial expenses for hospitalization and medical care.

COUNT V: FRAUDULENT MISREPRESENTATION

113. Plaintiff hereby incorporates by reference the allegations of this Complaint contained in each of the preceding paragraphs as if fully stated herein.

114. GSK falsely and fraudulently represented to pregnant women and the medical and healthcare community, including Plaintiffs and their providers, that:

(a) Zofran was safe and effective for treating pregnancy-related nausea;

(b) Zofran had been adequately tested and studied in pregnant women;

(c) Zofran use during pregnancy did not increase the risk of bearing children with birth defects; and

(d) Zofran's "Pregnancy Category B" designation established the safety and efficacy of Zofran for treating pregnancy-related nausea.

115. The representations made by GSK were material, false and misleading.

116. When GSK made these representations, it knew they were false.

117. GSK made these representations with the intent of defrauding and deceiving the public in general, and the medical and healthcare community in particular, and were made with the intent of inducing the public in general, and the medical and healthcare community in particular, including Plaintiff and her health care providers, to recommend, prescribe, dispense and/or purchase Zofran to treat pregnancy-related nausea, all of which evinced a callous, reckless, willful, depraved indifference to the health, safety, and welfare of Plaintiff.

118. At the time the aforesaid representations were made by GSK and, at the time Plaintiff used Zofran, she was unaware of the falsity of said representations and reasonably believed them to be true.

119. In reliance upon said representations, Plaintiff's prescriber was induced to prescribe Zofran to her, and Plaintiff was induced to and did use Zofran to treat pregnancy-related nausea.

120. GSK knew that Zofran had not been sufficiently tested for pregnancy-related nausea and that it lacked adequate warnings.

121. GSK knew or should have known that Zofran increases expectant mothers' risk of developing birth defects.

122. As a result of the foregoing acts and omissions, Plaintiff and her minor child herein were caused to suffer serious and dangerous side effects including, but not limited to, heart defects, physical pain and mental anguish, diminished enjoyment of life, and financial expenses for hospitalization and medical care.

COUNT VI: FRAUDULENT CONCEALMENT

123. Plaintiff hereby incorporated by reference the allegations of this Complaint contained in each of the preceding paragraphs as if fully stated herein.

124. In representations to Plaintiff's healthcare providers, expectant mothers including Plaintiff, and the FDA, GSK fraudulently concealed and intentionally omitted the following material facts:

(a) GSK was illegally paying and offering to pay doctors remuneration to promote and prescribe Zofran;

(b) Zofran had not (and has not) been tested or studied in pregnant women at all;

(c) in utero Zofran exposure increases the risk of birth defects;

(d) the risks of birth defects associated with the consumption of Zofran by pregnant women were not adequately tested prior to GSK's marketing of Zofran;

(e) the safety and efficacy of Zofran for treating pregnancy-related nausea has not been established;

(f) Zofran is not safe and effective for treating pregnancy-related nausea; and

(g) GSK's internal data and information associated Zofran use during pregnancy with birth defects.

125. GSK's concealment and omissions of material facts concerning, among other things, the safety and efficacy of Zofran for pregnancy-related nausea were done purposefully, willfully, wantonly, and/or recklessly, to mislead physicians, hospitals and healthcare providers, and expectant mothers including Plaintiff into reliance and continued use of Zofran, and to cause them to promote, purchase, prescribe, and/or dispense Zofran.

126. GSK knew that physicians, hospitals, healthcare providers and expectant mothers such as Plaintiff had no way to determine the truth behind GSK's concealment and material omissions of facts surrounding Zofran, as set forth herein.

127. Plaintiff and her provider reasonably relied on GSK's promotional statements concerning Zofran's asserted safety and efficacy in pregnant women, from which GSK negligently, fraudulently, and/or purposefully omitted material facts.

128. Plaintiff also has sustained severe emotional distress and suffering as a result GSK's wrongful conduct and the injuries to her minor child herein.

129. As a result of the foregoing acts and omissions, Plaintiff and her minor child herein were caused to suffer serious and dangerous side effects including, but not limited to, heart defects, as well as physical pain and mental anguish, diminished enjoyment of life, and financial expenses for hospitalization and medical care.

COUNT VII: BREACH OF EXPRESS WARRANTY

130. Plaintiff hereby incorporates by reference the allegations of this Complaint contained in each of the preceding paragraphs as if fully stated herein.

131. GSK expressly warranted that Zofran was a safe and effective product to be used by pregnant women for treating pregnancy-related nausea, that Zofran had been adequately tested and studied in pregnant women, that Zofran use during pregnancy did not increase the risk of bearing children with birth defects, and that Zofran's Category B designation established the safety and efficacy of Zofran for treating pregnancy-related nausea.

132. GSK did not disclose the material fact that Zofran use by pregnant women creates an unreasonable risk of serious side effects, including birth defects and intrauterine death, which were not warned of by GSK. The representations regarding Zofran's purported safety were not justified by the performance of Zofran.

133. Members of the consuming public, including consumers like Plaintiff and her healthcare provider, were intended beneficiaries of the warranty.

134. Plaintiff and her healthcare provider reasonably relied on GSK's express representations pertaining to Zofran's purported safety.

135. GSK knew or should have known that, in fact, said representations and warranties were false, misleading and untrue in that Zofran was not safe and fit for the use promoted, expressly warranted, and intended by GSK, and, in fact, it produced serious injuries to pregnant women and their babies, which injuries were not accurately identified and disclosed by GSK.

136. Zofran did not conform to GSK's express representations regarding its purported safety because it caused serious injury to Plaintiff when used as recommended and directed, and these risks were not disclosed to Plaintiff or her healthcare provider. GSK's behavior in marketing the drug did not conform to that of a reasonably prudent manufacturer or seller under the circumstances.

137. As a direct and proximate result of GSK's breach of warranty, Plaintiff and her minor child herein were caused to suffer serious and dangerous side effects including, but not limited to, heart defects, as well as physical pain and mental anguish, diminished enjoyment of life, and financial expenses for hospitalization and medical care.

COUNT VIII: BREACH OF IMPLIED WARRANTY

138. Plaintiff hereby incorporates by reference the allegations of this Complaint contained in each of the preceding paragraphs as if fully stated herein.

139. When GSK designed, developed, manufactured, marketed, sold, and/or distributed Zofran for use by consumers like Plaintiff, GSK knew of the use for which Zofran was intended

and impliedly warranted the product to be of merchantable quality and safe for use in the treatment of pregnancy-related nausea, and that its design, manufacture, labeling, and marketing complied with all applicable federal requirements.

140. Plaintiff and her physician reasonably relied upon GSK's representations regarding Zofran's purported merchantable quality and its safety for use by pregnant women to treat pregnancy-related nausea, and, further, reasonably relied upon GSK's implied warranties, including that Zofran was in compliance with all federal requirements.

141. Contrary to GSK's implied warranty, Zofran was not of merchantable quality or safe for use by pregnant women to treat pregnancy-related nausea, because the product was defective, as described herein, and failed to comply with federal requirements. GSK's behavior in marketing the drug did not conform to that of a reasonably prudent manufacturer or seller under the circumstances.

142. As a direct and proximate result of GSK's breach of warranty, Plaintiff and her minor child herein were caused to suffer serious and dangerous side effects including, but not limited to, heart defects, as well as physical pain and mental anguish, diminished enjoyment of life, and financial expenses for hospitalization and medical care.

COUNT IX: STRICT PRODUCTS LIABILITY

143. Plaintiff hereby incorporates by reference the allegations of this Complaint contained in each of the preceding paragraphs as if fully stated herein.

144. Zofran was designed, formulated, produced, manufactured, sold, marketed, distributed, supplied and/or placed into the stream of commerce by GSK and was defective at the time it left GSK's control in that, and not by way of limitation, the drug failed to include adequate

warnings, instructions, and directions relating to the dangerous risks associated with the use of Zofran to treat pregnancy-related nausea. Zofran also was defective in its design because the foreseeable risks of harm posed by the product could have been reduced or avoided by the adoption of a reasonable alternative design. Safe and effective products were available for the purpose for which GSK marketed Zofran in pregnant women, and neither the safety nor the efficacy of Zofran for that purpose had been established.

145. GSK failed to provide adequate warnings to physicians and users, including Plaintiff, of the increased risk of birth defects associated with Zofran and aggressively promoted the product off-label to doctors, to hospitals, and directly to consumers. GSK's behavior in marketing the drug did not conform to that of a reasonably prudent manufacturer or seller under the circumstances.

146. Prescribing physicians, health care providers, and mothers-to-be neither knew, nor had reason to know, at the time of their use of Zofran of the existence of the aforementioned defects. Ordinary consumers would not have recognized the potential risks or side effects for which GSK failed to include appropriate warnings, and which GSK masked through unbalanced promotion of Zofran specifically for treatment of pregnant women.

147. At all times herein mentioned, because of GSK's off-label marketing of Zofran, the drug was prescribed and used as intended by GSK and in a manner reasonably foreseeable to GSK.

148. As a direct and proximate result of the defective nature of Zofran, Plaintiff's minor child herein was caused to suffer serious birth defects that are permanent and lasting in nature, including, but not limited to, heart defects, and physical pain and mental anguish, including diminished enjoyment of life, as well as the potential need for lifelong medical treatment, monitoring and/or medications.

149. Plaintiff has also sustained severe emotional distress and suffering as a result GSK's wrongful conduct and the injuries to her minor child herein.

150. As a result of the foregoing acts and omissions, Plaintiff and her minor child herein were caused to suffer serious and dangerous side effects including, but not limited to, heart defects, as well as physical pain and mental anguish, diminished enjoyment of life, and financial expenses for hospitalization and medical care.

COUNT X: TENNESSEE PRODUCTS LIABILITY ACT

151. Plaintiff hereby incorporates by reference the allegations of this Complaint contained in each of the preceding paragraphs as if fully stated herein.

152. At all times material to this action, GSK was engaged in the business of the design, development, manufacture, testing, packaging, promotion, marketing, distribution, labeling, and/or sale of Zofran.

153. At all times material to this action, Zofran was expected to reach, and did reach, consumers in the State of Tennessee and throughout the United States, including Plaintiff herein, without substantial change in the condition in which it was sold.

154. The subject product manufactured and/or supplied by GSK was defective in design in that an alternative design exists that would prevent serious side effects and severe and permanent injury to pregnant women and their unborn children. The product was unreasonably dangerous in design such that it would not have been put on the market by a reasonably prudent manufacturer or seller that knew of its dangerous condition.

155. The subject product manufactured and/or supplied by GSK was unreasonably dangerous because GSK did not provide an adequate warning about the use of Zofran by pregnant women. At the time the subject product left GSK's control, it possessed a characteristic that may cause damage to pregnant women and their unborn children, and GSK failed to use reasonable care to provide an adequate warning of such characteristic and its danger to users and handlers of the product. The product is not safe, has numerous and serious side effects, and causes severe and permanent injuries. The product was unreasonably dangerous because of inadequate warning such that it would not have been put on the market by a reasonably prudent manufacturer or seller that knew of its dangerous condition.

156. The subject product manufactured and/or supplied by GSK was unreasonably dangerous because it did not conform to an express warranty made by GSK regarding the product's safety and fitness for use. GSK's express warranty that Zofran was safe for use by pregnant women to treat pregnancy-related nausea induced Plaintiff to use the product, and Plaintiff's damages were proximately caused because GSK's express warranty was untrue. The product was unreasonably dangerous such that it would not have been put on the market by a reasonably prudent manufacturer or seller that knew of its dangerous condition.

157. As a result of the foregoing acts and omissions, Plaintiff and her minor child herein were caused to suffer serious and dangerous side effects including, but not limited to, heart defects, as well as physical pain and mental anguish, diminished enjoyment of life, and financial expenses for hospitalization and medical care.

PRAYER FOR RELIEF

Plaintiff respectfully requests judgment against GSK on each of the above counts as follows:

(a) Compensatory damages in the amount of Twenty Million Dollars and Zero Cents ($20,000,000.00), including, but not limited to pain, suffering, emotional distress, loss of enjoyment of life, and other noneconomic damages in an amount to be determined at trial of this action;

(b) Economic damages in the form of medical expenses, out of pocket expenses, lost earnings and other economic damages, including, but not limited to, all damages sustained as a result of the injury in an amount to be determined at trial of this action;

(c) Punitive and exemplary damages for the wanton, willful, fraudulent, and reckless acts of Defendant GSK, which demonstrated a complete disregard and reckless indifference for the safety and welfare of the general public and Plaintiffs, in an amount sufficient to punish Defendant GSK and deter future similar conduct;

(d) Pre-judgment and post-judgment interest as provided by law;

(e) Plaintiff's attorney fees;

(f) Plaintiff's costs of the proceedings; and

(g) Such other and further relief as this Court deems just and proper.

DEMAND FOR JURY TRIAL

Plaintiff hereby demands a trial by jury on all counts and as to all issues and allegations presented herein.

This the 10th day of December, 2015.

Respectfully submitted.

H. Douglas Nichol (BPR # 005080)
Nichol & Associates
6759 Baum Drive
Knoxville TN 37919
(865) 588-7465

and

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Counsel for Plaintiffs

SETTLEMENT AGREEMENT

This Settlement Agreement ("Agreement") is entered into by and among the United States of America, acting through the United States Department of Justice on behalf of the Office of Inspector General of the United States Department of Health and Human Services ("OIG-HHS"), the TRICARE Management Activity ("TMA"), the United States Department of Veteran's Affairs ("VA"), and the United States Office of Personnel Management ("OPM") (collectively the "United States"), Relators identified in the cases listed in Paragraph B of the Preamble to this Agreement ("Relators"), and GlaxoSmithKline LLC ("GSK"), through their authorized representatives. Collectively, all of the above will be referred to as "the Parties."

PREAMBLE

As a preamble to this Agreement, the Parties agree to the following:

A. GlaxoSmithKline LLC is a Delaware limited liability company and an indirect subsidiary of GlaxoSmithKline plc, a public limited company incorporated under English law with headquarters in Brentford, England. At all relevant times, GSK developed, manufactured, distributed, marketed and sold pharmaceutical products in the United States, including drugs sold under the trade names of Paxil, Wellbutrin, Advair, Lamictal, Zofran, Imitrex, Lotronex, Flovent and Valtrex (collectively the "Covered Drugs").

B. The Relators listed herein have filed the following qui tam actions against GSK (collectively the "Civil Actions"):

(1) United States et al. ex rel. Thorpe, et al. v. GSK et al., Civ. No. 11-10398 (D. Mass.);

(2) United States et al. ex rel. Gerahty, et al. v. GSK et al., Civ. No. 03-10641 (D. Mass.);

(3) United States ex rel. Graydon v. GSK et al., Civ. No. 11-10741 (D. Mass);

(4) United States et al. ex rel. LaFauci v. GSK, Civ. No. 11-10921 (D. Mass.);

Exhibit A

The United States filed a notice of intervention on January 14, 2011 and filed its Complaint-In-Intervention on October 26, 2011 ("Complaint-in-Intervention").

C. On such date as may be determined by the Court, GSK will enter a plea of guilty pursuant to Fed. R. Crim. P. 11(c)(1)(C) (the "Plea Agreement") to an Information to be filed in United States of America v. GlaxoSmithKline LLC., Criminal Action No. [to be assigned] (District of Massachusetts) (the "Criminal Action") that will allege: (i) violations of Title 21, United States Code, Sections 331(a), 333(a)(1) and 352, namely, the introduction into interstate commerce of the misbranded drugs Wellbutrin and Paxil; and (ii) a violation of Title 21, United States Code, Sections 331(e), 333(a)(1), and 355(k)(1), namely, that GSK failed to report data relating to clinical experience, along with other data and information, regarding Avandia to the Food and Drug Administration ("FDA") in mandatory reports, all in violation of the Food, Drug and Cosmetic Act ("FDCA").

D. GSK has entered into or will be entering into separate settlement agreements, described in Paragraph 1(b) below (hereinafter referred to as the "Medicaid State Settlement Agreements") with certain states and the District of Columbia in settlement of the Covered Conduct. States with which GSK executes a Medicaid State Settlement Agreement in the form to which GSK and the National Association of Medicaid Fraud Control Units ("NAMFCU") Negotiating Team have agreed, or in a form otherwise agreed to by GSK and an individual State, shall be defined as "Medicaid Participating States."

E. The United States alleges that GSK caused to be submitted claims for payment for the Covered Drugs to the Medicare Program, Title XVIII of the Social Security Act, 42 U.S.C. §§1395-1395kkk ("Medicare"), and to the Medicaid Program, Title XIX of the Social Security Act, 42 U.S.C. §§ 1396-1396w-5 ("Medicaid"). The United States further alleges that

GSK caused claims for payment for the Covered Drugs to be submitted to the TRICARE program, 10 U.S.C. §§ 1071-1110b; the Federal Employees Health Benefits Program ("FEHBP"), 5 U.S.C. §§ 8901-8914; the Federal Employees Compensation Act Program, 5 U.S.C. § 8101, et seq; and caused purchases of the Covered Drugs by the Department of Veterans' Affairs Programs, 38 U.S.C. §§ 1701-1743 (collectively, the "other Federal Health Care Programs").

F. The United States contends that it and the Medicaid Participating States have certain civil claims, as specified in Paragraph 2, below, against GSK for engaging in the conduct set forth in the Complaint-in-Intervention and as described as follows (hereinafter referred to as the "Covered Conduct"):

(1) **Paxil**: During the period January 1, 1998 through December 31, 2003, GSK knowingly: (a) promoted the sale and use of Paxil for conditions and for patients other than those for which its use was approved as safe and effective by the Food and Drug Administration ("FDA"), specifically for children and adolescents under the age of 18, and which uses were not medically-accepted indications as defined by 42 U.S.C. § 1396r-8(k)(6) for which the United States and state Medicaid programs provided coverage for Paxil; (b) made and/or disseminated unsubstantiated and/or false and/or misleading representations or statements about the safety and efficacy of Paxil concerning the uses described in section (a) of this sub-paragraph, including concealing, omitting or failing to disclose material information about the safety and efficacy of Paxil; and (c) offered and paid illegal remuneration to health care professionals to induce them to promote and prescribe Paxil, in violation of the Federal Anti-Kickback Statute, 42 U.S.C. § 1320a-7b(b). As a result of the foregoing conduct, GSK knowingly caused false or fraudulent claims for Paxil to be submitted to, or caused purchases by Medicaid and the other Federal Health Care Programs.

(2) **Wellbutrin**: During the period January 1, 1999 through December 31, 2003, GSK knowingly: (a) promoted the sale and use of Wellbutrin for conditions (including weight loss, the treatment of obesity, sexual dysfunction and in combination with other anti-depressants) and at dosages other than those for which its use was approved as safe and effective by the FDA, and some of which were not medically-accepted indications as defined by 42 U.S.C. §

1396r-8(k)(6) for which the United States and state Medicaid programs provided coverage for Wellbutrin; (b) made and/or disseminated unsubstantiated and/or false and/or misleading representations or statements about the safety and efficacy of Wellbutrin; and (c) offered and paid illegal remuneration to health care professionals to induce them to promote and prescribe Wellbutrin, in violation of the Federal Anti-Kickback Statute, 42 U.S.C. § 1320a-7b(b). As a result of the foregoing conduct, GSK knowingly caused false or fraudulent claims for Wellbutrin to be submitted to, or caused purchases by Medicaid and the other Federal Health Care Programs.

(3) **Advair**: During the period January 1, 2001 through June 30, 2010, GSK knowingly: (a) promoted the sale and use of Advair for conditions and dosing regimens other than those for which its use was approved as safe and effective by the FDA (including first line use for mild or all asthma, and for asthma previously treated by short-acting inhalers alone), and some of which were not medically-accepted indications as defined by 42 U.S.C. § 1396r-8(k)(6) for which the United States and state Medicaid programs provided coverage for Advair; (b) made and/or disseminated unsubstantiated and/or false and/or misleading representations or statements about the safety and efficacy of Advair (including that Advair was superior to the single component, inhaled corticosteroid alone, for patients previously treated by short-acting inhalers alone); and (c) offered and paid illegal remuneration to health care professionals to induce them to promote and prescribe Advair, in violation of the Federal Anti-Kickback Statute, 42 U.S.C. § 1320-7b(b). As a result of the foregoing conduct, GSK knowingly caused false or fraudulent claims for Advair to be submitted to, or caused purchases by Medicaid, Medicare and the other Federal Health Care Programs.

(4) **Lamictal**: During the period January 1, 1999 through December 31, 2003, GSK knowingly: (a) promoted the sale and use of Lamictal for a variety of conditions other than those for which its use was approved as safe and effective by the FDA (including bi-polar depression, neuropathic pain, and various other mental diseases), and some of which were not medically-accepted indications as defined by 42 U.S.C. § 1396r-8(k)(6) for which the United States and state Medicaid programs provided coverage for Lamictal; (b) made and/or disseminated unsubstantiated and/or false and/or misleading representations or statements about the safety and efficacy of Lamictal concerning the uses described in section (a) of this sub-paragraph; and (c) offered and paid illegal remuneration to health care professionals to induce them to promote and prescribe Lamictal, in violation of the Federal Anti-Kickback Statute, 42 U.S.C. § 1320-7b(b). As a result of the foregoing conduct, GSK knowingly caused

false or fraudulent claims for Lamictal to be submitted to, or caused purchases by Medicaid and the other Federal Health Care Programs.

(5) **Zofran**: During the period January 1, 2002 through December 31, 2004, GSK knowingly: (a) promoted the sale and use of Zofran for a variety of conditions other than those for which its use was approved as safe and effective by the FDA (including hyperemesis or pregnancy-related nausea), and some of which were not medically-accepted indications as defined by 42 U.S.C. § 1396r-8(k)(6) for which the United States and state Medicaid programs provided coverage for Zofran; (b) made and/or disseminated unsubstantiated and/or false representations or statements about the safety and efficacy of Zofran concerning the uses described in section (a) of this sub-paragraph; and (c) offered and paid illegal remuneration to health care professionals to induce them to promote and prescribe Zofran, in violation of the Federal Anti-Kickback Statute, 42 U.S.C. § 1320-7b(b). As a result of the foregoing conduct, GSK knowingly caused false or fraudulent claims for Zofran to be submitted to, or caused purchases by Medicaid and the other Federal Health Care Programs.

(6) **Imitrex, Lotronex, Flovent and Valtrex:** From January 1, 1999 through December 30, 2004, GSK paid illegal remuneration for speaker programs, mentorships, preceptorships, journal clubs, advisory boards (including Local and Regional Advisory Boards and Special Issues Boards), Reprint Mastery Trainings, and provided gifts (including entertainment, cash, travel and meals) to health care professionals to induce them to promote and prescribe the drugs Imitrex, Lotronex, Flovent and Valtrex, in violation of the Federal Anti-Kickback Statute, 42 U.S.C. § 1320a-7b(b). As a result of the foregoing conduct, GSK caused false claims to be submitted to, or caused purchases by Medicaid and certain other Federal Health Care Programs.

G. The United States also contends that it has certain administrative claims against GSK as specified in Paragraphs 4 through 6, below, for engaging in the Covered Conduct.

H. This Agreement is made in compromise of disputed claims. This Agreement is neither an admission of facts or liability by GSK. GSK expressly denies the allegations of the United States and the Relators as set forth herein and in the Civil Actions and the Complaint-In-Intervention, and denies that it engaged in any wrongful conduct in connection with the Covered Conduct, except as to such admissions GSK makes in connection with the Plea Agreement. This

Agreement is not a concession by the United States or the Relators that their claims are not well-founded. Neither this Agreement, nor the performance of any obligation arising under it, including any payment, nor the fact of settlement, is intended to be or shall be understood as, an admission of liability or wrongdoing, or other expression reflecting on the merits of the dispute, except as set forth in this Paragraph.

I. Relators claim entitlement under 31 U.S.C. § 3730(d) to a share of the proceeds of this Settlement Agreement and to reasonable expenses, attorneys' fees and costs, among other things. This agreement does not cover the claims of any Relator to a share of the proceeds or their attorneys' fees, costs, and expenses under 31 U.S.C. § 3730(d), and nothing in this Agreement shall constitute evidence or an admission that any Relator has filed a valid *qui tam* action under 31 U.S.C. § 3730 or is entitled to a share of the proceeds or attorneys' fees, costs, and expenses under 31 U.S.C. §3730(d).

J. To avoid the delay, expense, inconvenience and uncertainty of protracted litigation of these claims, the Parties desire to reach a final settlement as set forth below.

TERMS AND CONDITIONS

NOW, THEREFORE, in reliance on the representations contained herein and in consideration of the mutual promises, covenants, and obligations in this Agreement, and for good and valuable consideration, receipt of which is hereby acknowledged, the Parties agree as follows:

1. GSK agrees to pay to the United States and the Medicaid Participating States, collectively, the sum of one billion, forty-two million, six hundred twelve thousand, eight hundred dollars ($1,042,612,800), plus interest at the rate of 1.625% per annum from December 1, 2011, and continuing until and including the day before payment is made under this

Agreement (collectively, the "Settlement Amount"). The Settlement Amount is allocated to the drugs set forth in the Covered Conduct and at issue in the Civil Actions as follows:

Paxil:	$52,622,130
Wellbutrin:	$166,979,130
Advair-Asthma:	$686,049,841
Advair-COPD July 2008 to June 2010:	$25,273,910
Lamictal:	$54,729,862
Zofran:	$2,320,640
Kickbacks for Paxil, Wellbutrin, Advair, Lamictal, Zofran, Imitrex, Lotronex, Flovent, and Valtrex:	$54,637,287

The Settlement Amount shall constitute a debt immediately due and owing to the United States and the Medicaid Participating States on the Effective Date of this Agreement. This debt shall be discharged by payments to the United States and the Medicaid Participating States, under the following terms and conditions:

(a) GSK shall pay to the United States the sum of eight hundred thirty-two million, four hundred eighty-five thousand, four hundred and thirty-six dollars ($832,485,436), plus interest at the rate of 1.625% per annum from December 1, 2011, and continuing until and including the day before payment is made under this Agreement (the "Federal Settlement Amount"). The Federal Settlement Amount shall be paid by electronic funds transfer pursuant to written instructions from the United States no later than seven (7) business days after (i) this Agreement is fully executed by the Parties and delivered to GSK's attorneys; or (ii) the Court accepts a Fed. R. Crim. P. 11(c)(1)(C) guilty plea as described in Preamble Paragraph C in

connection with the Criminal Action and imposes the agreed upon sentence, whichever occurs later.

(b) GSK shall pay to the Medicaid Participating States the sum of two hundred and ten million, one hundred and twenty-seven thousand, three hundred and sixty-four dollars ($210,127,364), plus interest at the rate of 1.625% per annum from December 1, 2011, and continuing until and including the day before payment is made under this Agreement (the "Medicaid State Settlement Amount"). The Medicaid State Settlement Amount shall be paid by electronic funds transfer to an interest bearing account pursuant to written instructions from the NAMFCU Negotiating Team and under the terms and conditions of the Medicaid State Settlement Agreements that GSK will enter into with the Medicaid Participating States.

(c) If GSK's agreed-upon guilty plea pursuant to Fed. R. Crim. P. 11(c)(1)(C) in the Criminal Action described in Preamble Paragraph C is not accepted by the Court or the Court does not impose the agreed-upon sentence for whatever reason, this Agreement shall be null and void at the option of either the United States or GSK. If either the United States or GSK exercises this option, which option shall be exercised by notifying all Parties, through counsel, in writing within five (5) business days of the Court's decision, the Parties will not object and this Agreement will be rescinded. If this Agreement is rescinded, GSK will not plead, argue or otherwise raise any defenses under the theories of statute of limitations, laches, estoppel or similar theories, to any civil or administrative claims, actions or proceedings arising from the Covered Conduct that are brought by the United States within 90 calendar days of rescission, except to the extent such defenses were available on the day on which the qui tam complaints listed in Preamble Paragraph B, above, were filed.

2. Subject to the exceptions in Paragraph 7 below (concerning excluded claims), in consideration of the obligations of GSK set forth in this Agreement, conditioned upon GSK's payment in full of the Settlement Amount, the United States (on behalf of itself, its officers, agencies, and departments) agrees to release GSK, together with its predecessors, current and former parents, direct and indirect affiliates, divisions, subsidiaries, successors, transferees and assigns and their current and former directors, officers, and employees, individually and collectively, from any civil or administrative monetary claim that the United States has or may have for the Covered Conduct under the False Claims Act, 31 U.S.C. §§ 3729-3733; the Program Fraud Civil Remedies Act, 31 U.S.C. §§ 3801-3812; the Civil Monetary Penalties Law, 42 U.S.C. § 1320a-7a; the Food, Drug and Cosmetic Act, 21 U.S.C. § 301, et seq.; any statutory provision creating a cause of action for civil damages or civil penalties for which the Civil Division of the Department of Justice has actual and present authority to assert and compromise pursuant to 28 C.F.R. Part 0, Subpart I, 0.45(d) and common law claims for fraud, payment by mistake, breach of contract, disgorgement and unjust enrichment.

3. Conditioned upon the United States' receipt of the payments described in Paragraph 1(a) above, and in consideration of the obligations of GSK in this Agreement, Relators, for themselves and for their heirs, successors, attorneys, agents, and assigns and any other person or entity acting on their behalf or asserting their rights, release GSK together with its predecessors, and its current and former divisions, parents, direct and indirect affiliates, divisions, subsidiaries, transferees, successors, and assigns, and all of their current and former directors, officers, employees, representatives, servants, agents, consultants and attorneys, individually and collectively, from any civil monetary claim the United States has or may have under the False Claims Act, 31 U.S.C. §§ 3729-3733, for the Covered Conduct and from all

liability, claims, demands, actions or causes of action whatsoever, whether known or unknown, fixed or contingent, in law or in equity, in contract or in tort, under any federal or state statute or regulation, or in common law, that they, their heirs, successors, attorneys, agents and assigns otherwise would have standing to bring as of the date of this Agreement, including any liability to Relators arising from or relating to the claims Relator asserted or could have asserted in the Civil Actions. Provided, however, that Relators and Relators' counsel do not release GSK for any claims they may have for reasonable attorneys' fees, expenses and costs pursuant to 31 U.S.C. § 3730(d); or for any claims Relators may have pursuant to 31 U.S.C. § 3730(h).

4. In consideration of the obligations of GSK in this Agreement and the Corporate Integrity Agreement ("CIA") entered into between OIG-HHS and GSK, and conditioned upon GSK's full payment of the Settlement Amount, the OIG-HHS agrees to release and refrain from instituting, directing, or maintaining any administrative action seeking exclusion from Medicare, Medicaid, and other Federal health care programs (as defined in 42 U.S.C. § 1320a-7b(f)) against GSK under 42 U.S.C. § 1320a-7a (Civil Monetary Penalties Law) or 42 U.S.C. § 1320a-7(b)(7) (permissive exclusion for fraud, kickbacks, and other prohibited activities) for the Covered Conduct, or against GSK under 42 U.S.C. § 1320a-7(b)(1) based on GSK's agreement to plead guilty to the charges set forth in the Information in the Criminal Action referenced in Paragraph C above, except as reserved in Paragraph 7 (concerning excluded claims), below, and as reserved in this Paragraph. The OIG-HHS expressly reserves all rights to comply with any statutory obligations to exclude GSK from Medicare, Medicaid, and other Federal health care programs under 42 U.S.C. § 1320a-7(a) (mandatory exclusion) based upon the Covered Conduct. Nothing in this Paragraph precludes the OIG-HHS from taking action against entities

or persons, or for conduct and practices, for which claims have been reserved in Paragraph 7, below.

5. In consideration of the obligations of GSK set forth in this Agreement, conditioned upon GSK's full payment of the Settlement Amount, TMA agrees to release and refrain from instituting, directing, or maintaining any administrative action seeking exclusion or suspension from the TRICARE Program against GSK under 32 C.F.R. § 199.9 for the Covered Conduct, except as reserved in Paragraph 7 (concerning excluded claims), below, and as reserved in this Paragraph. TMA expressly reserves authority to exclude GSK under 32 C.F.R. §§ 199.9 (f)(1)(i)(A), (f)(1)(i)(B), and (f)(1)(iii), based upon the Covered Conduct. Nothing in this Paragraph precludes TMA or the TRICARE Program from taking action against entities or persons, or for conduct and practices, for which claims have been reserved in Paragraph 7, below.

6. In consideration of the obligations of GSK in this Agreement, conditioned upon GSK's full payment of the Settlement Amount, OPM agrees to release and refrain from instituting, directing, or maintaining any administrative action against GSK under 5 U.S.C. § 8902a or 5 C.F.R. Part 970 for the Covered Conduct, except as reserved in Paragraph 7 (concerning excluded claims), below, and except if excluded by the OIG-HHS pursuant to 42 U.S.C. § 1320a-7(a) or required by 5 U.S.C. § 8902a(b), or 5 C.F.R. Part 970. Nothing in this Paragraph precludes OPM from taking action against entities or persons, or for conduct and practices, for which claims have been reserved in Paragraph 7, below.

7. Notwithstanding any term of this Agreement, specifically reserved and excluded from the scope and terms of this Agreement as to any entity or person (including GSK and the Relators) are the following claims of the United States:

(a) Any civil, criminal, or administrative liability arising under Title 26, U.S. Code (Internal Revenue Code);

(b) Any criminal liability;

(c) Except as explicitly stated in this Agreement, any administrative liability, including mandatory exclusion from Federal health care programs;

(d) Any liability to the United States (or its agencies) for any conduct other than the Covered Conduct;

(e) Any liability based upon such obligations as are created by this Agreement;

(f) Any liability for express or implied warranty claims or other claims for defective or deficient products and services, including quality of goods and services;

(g) Any liability for personal injury or property damage or for other consequential damages arising from the Covered Conduct;

(h) Any liability for failure to deliver items or services due; or

(i) Any liability of individuals (including current or former directors, officers, employees, or agents of GSK) who receive written notification that they are the target of a criminal investigation, are criminally indicted or charged, or are convicted, or who enter into a criminal plea agreement related to the Covered Conduct.

8. (A) Each Relator and his/her respective heirs, successors, attorneys, agents, and assigns agree not to object to this Agreement and agree and confirm that this Agreement and the amounts set forth in Paragraph 1(a) are fair, adequate and reasonable under all the circumstances, pursuant to 31 U.S.C. § 3730(c)(2)(B). Each Relator and his/her respective heirs, successors, attorneys, agents, and assigns, expressly waives the opportunity for a hearing on any objection to this agreement pursuant to 31 U.S.C. § 3730(C)(2)(B).

(B) Of the federal and states drug claims listed in Paragraphs 1(a), the following were alleged in United States et al. ex rel. Thorpe, et al. v. GSK et al., Civ. No. 11-10398 (D. Mass.) and/or United States et al. ex rel. Gerahty, et al. v. GSK et al., Civ. No. 03-10461 (D. Mass): Paxil, Wellbutrin, Advair-Asthma, Lamictal, Zofran, Flovent, Imitrex, Lotronex, Valtrex, and kickbacks. Of the federal and state drug claims listed in paragraph 1(a), Advair-COPD (July 2008-June 2010) was alleged in United States ex rel. Graydon v. GSK et al., Civ. No. 11-10741 (D. Mass) and United States et al. ex rel. La Fauci v. GSK, Civ. No. 11-10921 (D. Mass). The Parties incorporate herein by reference the fairness, adequacy and reasonableness letters executed by each Relator and their counsel. Nothing in this subparagraph (B) is intended to address whether or to what extent any of the relators in these actions are entitled to a share of any of the proceeds allocated to the federal and state drug claims listed in Paragraph 1(a).

(C) All parties reserve all rights under the False Claims Act unless expressly waived or released herein. This Agreement does not resolve or in any manner affect any claims the United States has or may have against the Relators arising under Title 26, U.S. Code (Internal Revenue Code), or any claims arising under this Agreement.

9. GSK waives and shall not assert any defenses it may have to any criminal prosecution or administrative action relating to the Covered Conduct that may be based in whole

or in part on a contention that under the Double Jeopardy Clause in the Fifth Amendment of the Constitution, or under the Excessive Fines Clause in the Eighth Amendment of the Constitution, this Agreement bars a remedy sought in such criminal prosecution or administrative action. Nothing in this paragraph or any other provision of this Agreement constitutes an agreement by the United States concerning the characterization of the Settlement Amount for purposes of the Internal Revenue laws, Title 26 of the United States Code.

10. GSK fully and finally releases the United States, its agencies, employees, servants, and agents from any claims (including attorneys' fees, costs, and expenses of every kind and however denominated) which GSK has asserted, could have asserted, or may assert in the future against the United States, its agencies, employees, servants, and agents, related to the Covered Conduct or arising from the United States' investigation and prosecution of the Civil Actions and the Criminal Action.

11. Should this Agreement be challenged by any person as not fair, adequate or reasonable pursuant to 31 U.S.C. § 3730(c)(2)(B), the Parties agree that they will take all reasonable and necessary steps to defend this Agreement and the allocation set forth herein.

12. In consideration of the obligations of the Relators set forth in this Agreement, GSK, on behalf of itself, its predecessors, and its current and former divisions, parents, subsidiaries, agents, successors, assigns, and their current and former directors, officers and employees, fully and finally release, waive, and forever discharge the Relators and their respective heirs, successors, assigns, agents, and attorneys from any claims or allegations GSK has asserted or could have asserted, arising from the Covered Conduct and from all liability, claims, demands, actions or causes of action whatsoever, whether known or unknown, fixed or contingent, in law or in equity, in contract or in tort, under any federal or state statute or

regulation, or in common law, that they, their heirs, successors, attorneys, agents and assigns otherwise would have standing to bring as of the date of this Agreement, including any liability to GSK arising from or relating to the claims Relator asserted or could have asserted in the Civil Actions. Provided, however, that GSK expressly reserves any defenses or claims as to Relators' and Relators' counsel's claims for reasonable attorneys' fees, expenses and costs pursuant to 31 U.S.C. § 3730(d) and as to any claims Relators may have pursuant to 31 U.S.C. § 3730(h), which are reserved pursuant to Paragraph 3 above.

13. The Settlement Amount shall not be decreased as a result of the denial of claims for payment now being withheld from payment by any Medicare carrier or intermediary or any state payer, related to the Covered Conduct; and GSK agrees not to resubmit to any Medicare carrier or intermediary or any state payer any previously denied claims related to the Covered Conduct, and agrees not to appeal any such denials of claims.

14. GSK agrees to the following:

(a) Unallowable Costs Defined: that all costs (as defined in the Federal Acquisition Regulations (FAR) 48 C.F.R. § 31.205-47 and in Titles XVIII and XIX of the Social Security Act, 42 U.S.C. §§ 1395-1395kkk and 1396-1396w-5, and the regulations and official program directives promulgated thereunder) incurred by or on behalf of GSK, its present or former officers, directors, employees, shareholders, and agents in connection with the following shall be "Unallowable Costs" on government contracts and under the Medicare and Medicaid Programs and other Federal Health Care Programs:

(1) the matters covered by this Agreement and the related Plea Agreement;

(2) the United States' audit and civil and criminal investigation of the matters covered by this Agreement;

(3) GSK's investigation, defense, and any corrective actions undertaken in response to the United States' audit and civil and criminal investigation in connection with the matters covered by this Agreement (including attorneys' fees);

(4) the negotiation and performance of this Agreement, the Plea Agreement, and the Medicaid State Settlement Agreements;

(5) the payments GSK makes to the United States or any State pursuant to this Agreement, the Plea Agreement, or the Medicaid State Settlement Agreements and any payments that GSK may make to Relators (including costs and attorneys' fees);

(6) the negotiation of, and obligations undertaken pursuant to the CIA to: (i) retain an independent review organization to perform annual reviews as described in Section III of the CIA; and (ii) prepare and submit reports to OIG-HHS. However, nothing in this paragraph 14 affects the status of costs that are not allowable based on any other authority applicable to GSK.

(b) Future Treatment of Unallowable Costs: These Unallowable Costs shall be separately determined and accounted for by GSK, and GSK shall not charge such Unallowable Costs directly or indirectly to any contracts with the United States or any State Medicaid Program, or seek payment for such Unallowable Costs through any cost report, cost

statement, information statement, or payment request submitted by GSK or any of its subsidiaries or affiliates to the Medicare, Medicaid, TRICARE, or FEHBP Programs.

(c) Treatment of Unallowable Costs Previously Submitted for Payment: GSK further agrees that within 90 days of the Effective Date of this Agreement, it shall identify to applicable Medicare and TRICARE fiscal intermediaries, carriers, and/or contractors, and Medicaid, and FEHBP fiscal agents, any Unallowable Costs (as defined in this Paragraph) included in payments previously sought from the United States, or any State Medicaid Program, including, but not limited to, payments sought in any cost reports, cost statements, information reports, or payment requests already submitted by GSK or any of its subsidiaries or affiliates, and shall request, and agree, that such cost reports, cost statements, information reports, or payment requests, even if already settled, be adjusted to account for the effect of the inclusion of the Unallowable Costs. GSK agrees that the United States, at a minimum, shall be entitled to recoup from GSK any overpayment plus applicable interest and penalties as a result of the inclusion of such Unallowable Costs on previously-submitted cost reports, information reports, cost statements, or requests for payment.

Any payments due after the adjustments have been made shall be paid to the United States pursuant to the direction of the Department of Justice, and/or the affected agencies. The United States reserves its rights to disagree with any calculations submitted by GSK or any of its subsidiaries or affiliates on the effect of inclusion of Unallowable Costs (as defined in this Paragraph) on GSK's or any of its subsidiaries' or affiliates' cost reports, cost statements, or information reports.

(d) Nothing in this Agreement shall constitute a waiver of the rights of the United States to audit, examine or reexamine GSK's books and records to determine that no Unallowable Costs have been claimed in accordance with the provisions of this Paragraph.

15. This Agreement is intended to be for the benefit of the Parties only. The Parties do not release any claims against any other person or entity, except to the extent provided for in Paragraph 2 above and 16 below (waiver for beneficiaries paragraph).

16. GSK agrees that it waives and shall not seek payment for any of the health care billings covered by this Agreement from any health care beneficiaries or their parents, sponsors, legally responsible individuals, or third party payors based upon the claims defined as Covered Conduct.

17. GSK expressly warrants that it has reviewed its financial situation and that it is currently solvent within the meaning of 11 U.S.C. §§ 547(b)(3) and 548(a)(1)(B)(ii)(I), and will remain solvent following payment of the Settlement Amount. Further, the Parties warrant that, in evaluating whether to execute this Agreement, they (a) have intended that the mutual promises, covenants and obligations set forth herein constitute a contemporaneous exchange for new value given to GSK, within the meaning of 11 U.S.C. § 547(c)(1); and (b) conclude that these mutual promises, covenants and obligations do, in fact, constitute such a contemporaneous exchange. Further, the Parties warrant that the mutual promises, covenants, and obligations set forth herein are intended to and do, in fact, represent a reasonably equivalent exchange of value that is not intended to hinder, delay, or defraud any entity to which GSK was or became indebted to on or after the date of this transfer, within the meaning of 11 U.S.C. § 548(a)(1).

18. Within seven (7) business days following payment of the Settlement Amount, the Parties shall seek dismissal of the Complaint-in-Intervention and each of the Civil Actions. Each

dismissal shall be with prejudice as to all claims of the United States and the Relators with the exception of the following claims, if any, and over which the Court shall retain jurisdiction: (a) Relators' claims for a share of the proceeds of the Civil Actions pursuant to 31 U.S.C. § 3730(d); (b) Relators' claims against GSK for reasonable attorneys' fees, expenses, and costs pursuant to 31 U.S.C. § 3730(d); (c) Relators' claims against GSK under 31 U.S.C. § 3730(h); and (d) Relators' claims against the States for Relators' Shares. This provision shall not limit the rights of the United States to in any way challenge or contest claims under subsection (a) above, including but not limited to challenging or contesting those claims under 31 U.S.C. § 3730(b)(5) and/or 31 § U.S.C. 3730(e)(4), or as to GSK, to in any way challenge or contest claims under subsection (b) and (c) above.

19. Each party shall bear its own legal and other costs incurred in connection with this matter, including the preparation and performance of this Agreement, except Relators reserve their rights against GSK to seek attorneys' fees, costs and expenses under 31 U.S.C. § 3730(d).

20. The Parties each represent that this Agreement is freely and voluntarily entered into without any degree of duress or compulsion.

21. This Agreement is governed by the laws of the United States. The Parties agree that the exclusive jurisdiction and venue for any dispute arising between and among the Parties under this Agreement, including any issues regarding relators' share or payment of Relators' attorneys' fees, expenses and costs, shall be the United States District Court for the District of Massachusetts, except that disputes arising under the CIA shall be resolved exclusively under the dispute resolution provisions in the CIA.

22. For purposes of construction, this Agreement shall be deemed to have been drafted by all Parties to this Agreement and shall not, therefore, be construed against any party for that reason in any dispute.

23. This Agreement including any documents incorporated by reference herein constitutes the complete agreement between the Parties with respect to the issues covered by the Agreement. This Agreement may not be amended except by written consent of all the Parties.

24. The individuals signing this Agreement on behalf of GSK represent and warrant that they are authorized by GSK to execute this Agreement. The individuals signing this Agreement on behalf of each Relator represent and warrant that they are authorized by that Relator to execute this Agreement. The United States' signatories represent that they are signing this Agreement in their official capacities and they are authorized to execute this Agreement.

25. This Agreement may be executed in counterparts, each of which constitutes an original and all of which shall constitute one and the same Agreement.

27. This Agreement is binding on GSK's successors, transferees, heirs and assigns.

26. This Agreement is binding on Relators' successors, transferees, heirs, attorneys and assigns.

27. All Parties consent to the disclosure of this Agreement, and information about this Agreement, to the public after the Effective Date.

28. This Agreement is effective on the date of signature of the last signatory to the Agreement (Effective Date of this Agreement). Facsimiles or electronic versions of signatures shall constitute acceptable, binding signatures for purposes of this Agreement.

UNITED STATES OF AMERICA

CARMEN M. ORTIZ
United States Attorney

By: _____ Dated: 7/2/2012

SARA MIRON BLOOM
AMANDA STRACHAN
BRIAN PEREZ-DAPLE
Assistant United States Attorneys
District of Massachusetts

United States Attorney John Walsh

By: _____ Dated: July 2, 2012

EDWIN WINSTEAD
Assistant United States Attorney
District of Colorado

STUART F. DELERY
Acting Assistant Attorney General

By: _____ Dated: 7/2/12

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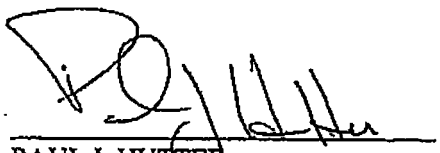
By: Abigail Cumings
for GREGORY E. DEMSKE
Chief Counsel to the Inspector General
Office of Counsel to the Inspector General
Office of Inspector General
U.S. Department of Health and Human Services

Dated: 6/28/2012

By: 

PAUL J. HUTTER
General Counsel
TRICARE Management Activity
United States Department of Defense

Dated: 6/27/12

By: _____
SHIRLY R. PATTERSON
Assistant Director for Federal Employee Insurance Operations
United States Office of Personnel Management

Dated: 6/7/12

By: _____
J. DAVID COPE
Debarring Official
Office of the Assistant Inspector General for Legal Affairs
United States Office of Personnel Management

Dated: 6/7/12

GLAXOSMITHKLINE LLC

By: _____ Dated: 6.28.12

ELPIDIO VILLARREAL
Senior Vice President, Global Litigation, GlaxoSmithKline LLC

By: _____ Dated: 6/28/12

GEOFFREY HOBART
MATTHEW O'CONNOR
Covington & Burling LLP
Counsel to GlaxoSmithKline LLC.

RELATOR GREG THORPE

By: _____ Dated: _____
GREG THORPE

RELATOR BLAIR HAMRICK

By: _____ Dated: _____
BLAIR HAMRICK

BRIAN KENNEY

By: _____ Dated: 6/27/12
BRIAN KENNEY
M.. TAVY DEMING
KENNEY & McCAFFERTY, PC
Counsel to Relators Greg Thorpe & Blair Hamrick

RELATOR GREG THORPE

By: _____ Dated: 6/27/12
GREG THORPE

RELATOR BLAIR HAMRICK

By: _____ Dated: _____
BLAIR HAMRICK

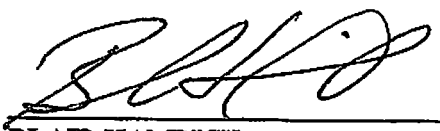
BRIAN KENNEY

By: _____ Dated: _____
BRIAN KENNEY
M. TAVY DEMING
KENNEY & McCAFFERTY, PC
Counsel to Relators Greg Thorpe & Blair Hamrick

RELATOR GREG THORPE

By: _____ Dated: _____
GREG THORPE

RELATOR BLAIR HAMRICK

By:  Dated: 6.27.12
BLAIR HAMRICK

BRIAN KENNEY

By: _____ Dated: _____
BRIAN KENNEY
M. TAVY DEMING
KENNEY & McCAFFERTY, PC
Counsel to Relators Greg Thorpe & Blair Hamrick

RELATOR THOMAS GERAHTY

By: _____ Dated: _____
THOMAS GERAHTY

RELATOR MATTHEW BURKE

By: Matthew Burke Dated: 6-26-12
MATTHEW BURKE

By: Erika Kelton Dated: 6/26/12
ERIKA KELTON
Phillips & Cohen
Counsel to Relators Thomas Gerahty and Matthew Burke

RELATOR THOMAS GERAHTY

By: _____ Dated: 6/26/2012
THOMAS GERAHTY

RELATOR MATTHEW BURKE

By: _____ Dated: _____
MATTHEW BURKE

By: _____ Dated: 6/26/2012
ERIKA KELTON
Phillips & Cohen
Counsel to Relators Thomas Gerahty and Matthew Burke

RELATOR LOIS GRAYDON

By: Lois Graydon Dated: 6/27/2012
LOIS GRAYDON

By: Dated: 6/26/2012
REUBEN GUTTMAN
Grant & Eisenhofer, PA
Counsel to Relator Lois Graydon

RELATOR MICHAEL LAFAUCI

By: _____ Dated: 6/27/12
MICHAEL LAFAUCI

By: _____ Dated: 6/27/12
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PRESCRIBING INFORMATION

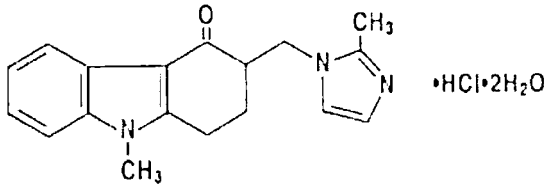
ZOFRAN®
(ondansetron hydrochloride)
Tablets

ZOFRAN ODT®
(ondansetron)
Orally Disintegrating Tablets

ZOFRAN®
(ondansetron hydrochloride)
Oral Solution

DESCRIPTION

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

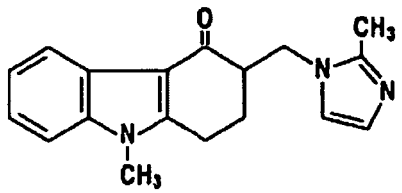


The empirical formula is $C_{18}H_{19}N_3O$•HCl•$2H_2O$, representing a molecular weight of 365.9.

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

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

Exhibit B



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

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

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

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

CLINICAL PHARMACOLOGY

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

In animals, the emetic response to cisplatin can be prevented by pretreatment with an inhibitor of serotonin synthesis, bilateral abdominal vagotomy and greater splanchnic nerve section, or pretreatment with a serotonin 5-HT_3 receptor antagonist.

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

Ondansetron does not alter the respiratory depressant effects produced by alfentanil or the degree of neuromuscular blockade produced by atracurium. Interactions with general or local anesthetics have not been studied.

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

Ondansetron systemic exposure does not increase proportionately to dose. AUC from a 16-mg tablet was 24% greater than predicted from an 8-mg tablet dose. This may reflect some reduction of first-pass metabolism at higher oral doses. Bioavailability is also slightly enhanced by the presence of food but unaffected by antacids.

Ondansetron is extensively metabolized in humans, with approximately 5% of a radiolabeled dose recovered as the parent compound from the urine. The primary metabolic pathway is hydroxylation on the indole ring followed by subsequent glucuronide or sulfate conjugation. Although some nonconjugated metabolites have pharmacologic activity, these are not found in plasma at concentrations likely to significantly contribute to the biological activity of ondansetron.

In vitro metabolism studies have shown that ondansetron is a substrate for human hepatic cytochrome P-450 enzymes, including CYP1A2, CYP2D6, and CYP3A4. In terms of overall ondansetron turnover, CYP3A4 played the predominant role. Because of the multiplicity of metabolic enzymes capable of metabolizing ondansetron, it is likely that inhibition or loss of one enzyme (e.g., CYP2D6 genetic deficiency) will be compensated by others and may result in little change in overall rates of ondansetron elimination. Ondansetron elimination may be affected by cytochrome P-450 inducers. In a pharmacokinetic study of 16 epileptic patients maintained chronically on CYP3A4 inducers, carbamazepine, or phenytoin, reduction in AUC, C_{max}, and $T_{½}$ of ondansetron was observed.[1] This resulted in a significant increase in clearance. However, on the basis of available data, no dosage adjustment for ondansetron is recommended (see PRECAUTIONS: Drug Interactions).

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

Gender differences were shown in the disposition of ondansetron given as a single dose. The extent and rate of ondansetron's absorption is greater in women than men. Slower clearance in women, a smaller apparent volume of distribution (adjusted for weight), and higher absolute bioavailability resulted in higher plasma ondansetron levels. These higher plasma levels may in part be explained by differences in body weight between men and women. It is not known whether these gender-related differences were clinically important. More detailed pharmacokinetic information is contained in Tables 1 and 2 taken from 2 studies.

Table 1. Pharmacokinetics in Normal Volunteers: Single 8-mg ZOFRAN Tablet Dose

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

Table 2. Pharmacokinetics in Normal Volunteers: Single 24-mg ZOFRAN Tablet Dose

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

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

In patients with mild-to-moderate hepatic impairment, clearance is reduced 2-fold and mean half-life is increased to 11.6 hours compared to 5.7 hours in normals. In patients with severe hepatic impairment (Child-Pugh[2] score of 10 or greater), clearance is reduced 2-fold to 3-fold and apparent volume of distribution is increased with a resultant increase in half-life to 20 hours. In patients with severe hepatic impairment, a total daily dose of 8 mg should not be exceeded.

Due to the very small contribution (5%) of renal clearance to the overall clearance, renal impairment was not expected to significantly influence the total clearance of ondansetron. However, ondansetron oral mean plasma clearance was reduced by about 50% in patients with severe renal impairment (creatinine clearance < 30 mL/min). This reduction in clearance is variable and was not consistent with an increase in half-life. No reduction in dose or dosing frequency in these patients is warranted.

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

Four- and 8-mg doses of either ZOFRAN Oral Solution or ZOFRAN ODT Orally Disintegrating Tablets are bioequivalent to corresponding doses of ZOFRAN Tablets and may be

used interchangeably. One 24-mg ZOFRAN Tablet is bioequivalent to and interchangeable with three 8-mg ZOFRAN Tablets.

CLINICAL TRIALS

Chemotherapy-Induced Nausea and Vomiting: *Highly Emetogenic Chemotherapy:* In 2 randomized, double-blind, monotherapy trials, a single 24-mg ZOFRAN Tablet was superior to a relevant historical placebo control in the prevention of nausea and vomiting associated with highly emetogenic cancer chemotherapy, including cisplatin $\geq$ 50 mg/m^2. Steroid administration was excluded from these clinical trials. More than 90% of patients receiving a cisplatin dose $\geq$ 50 mg/m^2 in the historical placebo comparator experienced vomiting in the absence of antiemetic therapy.

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

In the same trial, 56% of patients receiving oral ondansetron 24 mg once a day experienced no nausea during the 24-hour study period, compared with 36% of patients in the oral ondansetron 8-mg twice-a-day group ($P = 0.001$) and 50% in the oral ondansetron 32-mg once-a-day group.

In a second trial, efficacy of the oral ondansetron 24-mg once-a-day regimen in the prevention of nausea and vomiting associated with highly emetogenic cancer chemotherapy, including cisplatin $\geq$ 50 mg/m^2, was confirmed.

Moderately Emetogenic Chemotherapy: In 1 double-blind US study in 67 patients, ZOFRAN Tablets 8 mg administered twice a day were significantly more effective than placebo in preventing vomiting induced by cyclophosphamide-based chemotherapy containing doxorubicin. Treatment response is based on the total number of emetic episodes over the 3-day study period. The results of this study are summarized in Table 3:

Table 3. Emetic Episodes: Treatment Response

	Ondansetron 8-mg b.i.d. ZOFRAN Tablets[a]	Placebo	*P* Value
Number of patients	33	34	
Treatment response			
0 Emetic episodes	20 (61%)	2 (6%)	< 0.001
1-2 Emetic episodes	6 (18%)	8 (24%)	
More than 2 emetic episodes/withdrawn	7 (21%)	24 (71%)	< 0.001
Median number of emetic episodes	0.0	Undefined[b]	
Median time to first emetic episode (h)	Undefined[c]	6.5	

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

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

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

In 1 double-blind US study in 336 patients, ZOFRAN Tablets 8 mg administered twice a day were as effective as ZOFRAN Tablets 8 mg administered 3 times a day in preventing nausea and vomiting induced by cyclophosphamide-based chemotherapy containing either methotrexate or doxorubicin. Treatment response is based on the total number of emetic episodes over the 3-day study period. The results of this study are summarized in Table 4:

Table 4. Emetic Episodes: Treatment Response

	Ondansetron	
	8-mg b.i.d. ZOFRAN Tablets[a]	8-mg t.i.d. ZOFRAN Tablets[b]
Number of patients	165	171
Treatment response		
0 Emetic episodes	101 (61%)	99 (58%)
1-2 Emetic episodes	16 (10%)	17 (10%)
More than 2 emetic episodes/withdrawn	48 (29%)	55 (32%)
Median number of emetic episodes	0.0	0.0
Median time to first emetic episode (h)	Undefined[c]	Undefined[c]
Median nausea scores (0-100)[d]	6	6

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

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

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

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

Re-treatment: In uncontrolled trials, 148 patients receiving cyclophosphamide-based chemotherapy were re-treated with ZOFRAN Tablets 8 mg 3 times daily during subsequent chemotherapy for a total of 396 re-treatment courses. No emetic episodes occurred in 314 (79%) of the re-treatment courses, and only 1 to 2 emetic episodes occurred in 43 (11%) of the re-treatment courses.

Pediatric Studies: Three open-label, uncontrolled, foreign trials have been performed with 182 pediatric patients 4 to 18 years old with cancer who were given a variety of cisplatin or noncisplatin regimens. In these foreign trials, the initial dose of ZOFRAN® (ondansetron HCl) Injection ranged from 0.04 to 0.87 mg/kg for a total dose of 2.16 to 12 mg. This was followed by the administration of ZOFRAN Tablets ranging from 4 to 24 mg daily for 3 days. In these studies, 58% of the 170 evaluable patients had a complete response (no emetic episodes) on day 1. Two studies showed the response rates for patients less than 12 years of age who received ZOFRAN Tablets 4 mg 3 times a day to be similar to those in patients 12 to 18 years of age who received ZOFRAN Tablets 8 mg 3 times daily. Thus, prevention of emesis in these pediatric patients was essentially the same as for patients older than 18 years of age. Overall, ZOFRAN Tablets were well tolerated in these pediatric patients.

Radiation-Induced Nausea and Vomiting: ***Total Body Irradiation:*** In a randomized, double-blind study in 20 patients, ZOFRAN Tablets (8 mg given 1.5 hours before each fraction of radiotherapy for 4 days) were significantly more effective than placebo in preventing vomiting induced by total body irradiation. Total body irradiation consisted of 11 fractions (120 cGy per fraction) over 4 days for a total of 1,320 cGy. Patients received 3 fractions for 3 days, then 2 fractions on day 4.

Single High-Dose Fraction Radiotherapy: Ondansetron was significantly more effective than metoclopramide with respect to complete control of emesis (0 emetic episodes) in a double-blind trial in 105 patients receiving single high-dose radiotherapy (800 to 1,000 cGy) over an anterior or posterior field size of ≥ 80 cm^2 to the abdomen. Patients received the first dose of ZOFRAN Tablets (8 mg) or metoclopramide (10 mg) 1 to 2 hours before radiotherapy. If radiotherapy was given in the morning, 2 additional doses of study treatment were given (1 tablet late afternoon and 1 tablet before bedtime). If radiotherapy was given in the afternoon, patients took only 1 further tablet that day before bedtime. Patients continued the oral medication on a 3 times a day basis for 3 days.

Daily Fractionated Radiotherapy: Ondansetron was significantly more effective than prochlorperazine with respect to complete control of emesis (0 emetic episodes) in a double-blind trial in 135 patients receiving a 1- to 4-week course of fractionated radiotherapy (180 cGy doses) over a field size of ≥ 100 cm^2 to the abdomen. Patients received the first dose of ZOFRAN Tablets (8 mg) or prochlorperazine (10 mg) 1 to 2 hours before the patient received the first daily radiotherapy fraction, with 2 subsequent doses on a 3 times a day basis. Patients continued the oral medication on a 3 times a day basis on each day of radiotherapy.

Postoperative Nausea and Vomiting: Surgical patients who received ondansetron 1 hour before the induction of general balanced anesthesia (barbiturate: thiopental, methohexital, or thiamylal; opioid: alfentanil, sufentanil, morphine, or fentanyl; nitrous oxide; neuromuscular blockade: succinylcholine/curare or gallamine and/or vecuronium, pancuronium, or atracurium; and supplemental isoflurane or enflurane) were evaluated in 2 double-blind studies (1 US study, 1 foreign) involving 865 patients. ZOFRAN Tablets (16 mg) were significantly more effective than placebo in preventing postoperative nausea and vomiting.

The study populations in all trials thus far consisted of women undergoing inpatient surgical procedures. No studies have been performed in males. No controlled clinical study comparing ZOFRAN Tablets to ZOFRAN Injection has been performed.

INDICATIONS AND USAGE

1. Prevention of nausea and vomiting associated with highly emetogenic cancer chemotherapy, including cisplatin ≥ 50 mg/m^2.
2. Prevention of nausea and vomiting associated with initial and repeat courses of moderately emetogenic cancer chemotherapy.

3. Prevention of nausea and vomiting associated with radiotherapy in patients receiving either total body irradiation, single high-dose fraction to the abdomen, or daily fractions to the abdomen.
4. Prevention of postoperative nausea and/or vomiting. As with other antiemetics, routine prophylaxis is not recommended for patients in whom there is little expectation that nausea and/or vomiting will occur postoperatively. In patients where nausea and/or vomiting must be avoided postoperatively, ZOFRAN Tablets, ZOFRAN ODT Orally Disintegrating Tablets, and ZOFRAN Oral Solution are recommended even where the incidence of postoperative nausea and/or vomiting is low.

CONTRAINDICATIONS

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

ZOFRAN Tablets, ZOFRAN ODT Orally Disintegrating Tablets, and ZOFRAN Oral Solution are contraindicated for patients known to have hypersensitivity to the drug.

WARNINGS

Hypersensitivity reactions have been reported in patients who have exhibited hypersensitivity to other selective 5-HT_3 receptor antagonists.

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

The development of serotonin syndrome has been reported with 5-HT3 receptor antagonists alone. Most reports have been associated with concomitant use of serotonergic drugs (e.g., selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors (SNRIs), monoamine oxidase inhibitors, mirtazapine, fentanyl, lithium, tramadol, and intravenous methylene blue). Some of the reported cases were fatal. Serotonin syndrome occurring with overdose of ZOFRAN alone has also been reported. The majority of reports of serotonin syndrome related to 5-HT3 receptor antagonist use occurred in a post-anesthesia care unit or an infusion center.

Symptoms associated with serotonin syndrome may include the following combination of signs and symptoms: mental status changes (e.g., agitation, hallucinations, delirium, and coma), autonomic instability (e.g., tachycardia, labile blood pressure, dizziness, diaphoresis, flushing, hyperthermia), neuromuscular symptoms (e.g., tremor, rigidity, myoclonus, hyperreflexia, incoordination), seizures, with or without gastrointestinal symptoms (e.g., nausea, vomiting, diarrhea). Patients should be monitored for the emergence of serotonin syndrome, especially with concomitant use of ZOFRAN and other serotonergic drugs. If symptoms of serotonin syndrome

occur, discontinue ZOFRAN and initiate supportive treatment. Patients should be informed of the increased risk of serotonin syndrome, especially if ZOFRAN is used concomitantly with other serotonergic drugs (see PRECAUTIONS and OVERDOSAGE).

PRECAUTIONS

General: Ondansetron is not a drug that stimulates gastric or intestinal peristalsis. It should not be used instead of nasogastric suction. The use of ondansetron in patients following abdominal surgery or in patients with chemotherapy-induced nausea and vomiting may mask a progressive ileus and/or gastric distension.

Information for Patients: ***Phenylketonurics:*** Phenylketonuric patients should be informed that ZOFRAN ODT Orally Disintegrating Tablets contain phenylalanine (a component of aspartame). Each 4-mg and 8-mg orally disintegrating tablet contains < 0.03 mg phenylalanine.

Patients should be instructed not to remove ZOFRAN ODT Tablets from the blister until just prior to dosing. The tablet should not be pushed through the foil. With dry hands, the blister backing should be peeled completely off the blister. The tablet should be gently removed and immediately placed on the tongue to dissolve and be swallowed with the saliva. Peelable illustrated stickers are affixed to the product carton that can be provided with the prescription to ensure proper use and handling of the product.

Serotonin Syndrome: Advise patients of the possibility of serotonin syndrome with concomitant use of ZOFRAN and another serotonergic agent such as medications to treat depression and migraines. Advise patients to seek immediate medical attention if the following symptoms occur: changes in mental status, autonomic instability, neuromuscular symptoms with or without gastrointestinal symptoms.

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

Apomorphine: Based on reports of profound hypotension and loss of consciousness when apomorphine was administered with ondansetron, concomitant use of apomorphine with ondansetron is contraindicated (see CONTRAINDICATIONS).

Phenytoin, Carbamazepine, and Rifampicin: In patients treated with potent inducers of CYP3A4 (i.e., phenytoin, carbamazepine, and rifampicin), the clearance of ondansetron was significantly increased and ondansetron blood concentrations were decreased. However, on the basis of available data, no dosage adjustment for ondansetron is recommended for patients on these drugs.[1,3]

Serotonergic Drugs: Serotonin syndrome (including altered mental status, autonomic instability, and neuromuscular symptoms) has been described following the concomitant use of 5-HT3 receptor antagonists and other serotonergic drugs, including selective serotonin reuptake

inhibitors (SSRIs) and serotonin and noradrenaline reuptake inhibitors (SNRIs) (see WARNINGS).

Tramadol: Although no pharmacokinetic drug interaction between ondansetron and tramadol has been observed, data from 2 small studies indicate that ondansetron may be associated with an increase in patient controlled administration of tramadol.[4,5]

Chemotherapy: Tumor response to chemotherapy in the P-388 mouse leukemia model is not affected by ondansetron. In humans, carmustine, etoposide, and cisplatin do not affect the pharmacokinetics of ondansetron.

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

Use in Surgical Patients: The coadministration of ondansetron had no effect on the pharmacokinetics and pharmacodynamics of temazepam.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Carcinogenic effects were not seen in 2-year studies in rats and mice with oral ondansetron doses up to 10 and 30 mg/kg/day, respectively. Ondansetron was not mutagenic in standard tests for mutagenicity. Oral administration of ondansetron up to 15 mg/kg/day did not affect fertility or general reproductive performance of male and female rats.

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.

Nursing Mothers: Ondansetron is excreted in the breast milk of rats. It is not known whether ondansetron is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when ondansetron is administered to a nursing woman.

Pediatric Use: Little information is available about dosage in pediatric patients 4 years of age or younger (see CLINICAL PHARMACOLOGY and DOSAGE AND ADMINISTRATION sections for use in pediatric patients 4 to 18 years of age).

Geriatric Use: Of the total number of subjects enrolled in cancer chemotherapy-induced and postoperative nausea and vomiting in US- and foreign-controlled clinical trials, for which there were subgroup analyses, 938 were 65 years of age and over. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out. Dosage adjustment is not needed in patients over the age of 65 (see CLINICAL PHARMACOLOGY).

ADVERSE REACTIONS

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

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

Table 5. Principal Adverse Events in US Trials: Single Day Therapy With 24-mg ZOFRAN Tablets (Highly Emetogenic Chemotherapy)

Event	Ondansetron 24 mg q.d. n = 300	Ondansetron 8 mg b.i.d. n = 124	Ondansetron 32 mg q.d. n = 117
Headache	33 (11%)	16 (13%)	17 (15%)
Diarrhea	13 (4%)	9 (7%)	3 (3%)

The adverse events in Table 6 have been reported in ≥ 5% of adults receiving either 8 mg of ZOFRAN Tablets 2 or 3 times a day for 3 days or placebo in 4 trials. These patients were receiving concurrent moderately emetogenic chemotherapy, primarily cyclophosphamide-based regimens.

Table 6. Principal Adverse Events in US Trials: 3 Days of Therapy With 8-mg ZOFRAN Tablets (Moderately Emetogenic Chemotherapy)

Event	Ondansetron 8 mg b.i.d. n = 242	Ondansetron 8 mg t.i.d. n = 415	Placebo n = 262
Headache	58 (24%)	113 (27%)	34 (13%)
Malaise/fatigue	32 (13%)	37 (9%)	6 (2%)
Constipation	22 (9%)	26 (6%)	1 (<1%)
Diarrhea	15 (6%)	16 (4%)	10 (4%)
Dizziness	13 (5%)	18 (4%)	12 (5%)

Central Nervous System: There have been rare reports consistent with, but not diagnostic of, extrapyramidal reactions in patients receiving ondansetron.

Hepatic: In 723 patients receiving cyclophosphamide-based chemotherapy in US clinical trials, AST and/or ALT values have been reported to exceed twice the upper limit of normal in approximately 1% to 2% of patients receiving ZOFRAN Tablets. The increases were transient and did not appear to be related to dose or duration of therapy. On repeat exposure, similar transient elevations in transaminase values occurred in some courses, but symptomatic hepatic disease did

not occur. The role of cancer chemotherapy in these biochemical changes cannot be clearly determined.

There have been reports of liver failure and death in patients with cancer receiving concurrent medications including potentially hepatotoxic cytotoxic chemotherapy and antibiotics. The etiology of the liver failure is unclear.

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

Other: Rare cases of anaphylaxis, bronchospasm, tachycardia, angina (chest pain), hypokalemia, electrocardiographic alterations, vascular occlusive events, and grand mal seizures have been reported. Except for bronchospasm and anaphylaxis, the relationship to ZOFRAN was unclear.

Radiation-Induced Nausea and Vomiting: The adverse events reported in patients receiving ZOFRAN Tablets and concurrent radiotherapy were similar to those reported in patients receiving ZOFRAN Tablets and concurrent chemotherapy. The most frequently reported adverse events were headache, constipation, and diarrhea.

Postoperative Nausea and Vomiting: The adverse events in Table 7 have been reported in ≥ 5% of patients receiving ZOFRAN Tablets at a dosage of 16 mg orally in clinical trials. With the exception of headache, rates of these events were not significantly different in the ondansetron and placebo groups. These patients were receiving multiple concomitant perioperative and postoperative medications.

Table 7. Frequency of Adverse Events From Controlled Studies With ZOFRAN Tablets (Postoperative Nausea and Vomiting)

Adverse Event	Ondansetron 16 mg (n = 550)	Placebo (n = 531)
Wound problem	152 (28%)	162 (31%)
Drowsiness/sedation	112 (20%)	122 (23%)
Headache	49 (9%)	27 (5%)
Hypoxia	49 (9%)	35 (7%)
Pyrexia	45 (8%)	34 (6%)
Dizziness	36 (7%)	34 (6%)
Gynecological disorder	36 (7%)	33 (6%)
Anxiety/agitation	33 (6%)	29 (5%)
Bradycardia	32 (6%)	30 (6%)
Shiver(s)	28 (5%)	30 (6%)
Urinary retention	28 (5%)	18 (3%)
Hypotension	27 (5%)	32 (6%)
Pruritus	27 (5%)	20 (4%)

Preliminary observations in a small number of subjects suggest a higher incidence of headache when ZOFRAN ODT Orally Disintegrating Tablets are taken with water, when compared to without water.

Observed During Clinical Practice: In addition to adverse events reported from clinical trials, the following events have been identified during post-approval use of oral formulations of ZOFRAN. Because they are reported voluntarily from a population of unknown size, estimates of frequency cannot be made. The events have been chosen for inclusion due to a combination of their seriousness, frequency of reporting, or potential causal connection to ZOFRAN.

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

General: Flushing. Rare cases of hypersensitivity reactions, sometimes severe (e.g., anaphylaxis/anaphylactoid reactions, angioedema, bronchospasm, shortness of breath, hypotension, laryngeal edema, stridor) have also been reported. Laryngospasm, shock, and cardiopulmonary arrest have occurred during allergic reactions in patients receiving injectable ondansetron.

Hepatobiliary: Liver enzyme abnormalities

Lower Respiratory: Hiccups

Neurology: Oculogyric crisis, appearing alone, as well as with other dystonic reactions

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

Special Senses: Eye Disorders: Cases of transient blindness, predominantly during intravenous administration, have been reported. These cases of transient blindness were reported to resolve within a few minutes up to 48 hours.

DRUG ABUSE AND DEPENDENCE

Animal studies have shown that ondansetron is not discriminated as a benzodiazepine nor does it substitute for benzodiazepines in direct addiction studies.

OVERDOSAGE

There is no specific antidote for ondansetron overdose. Patients should be managed with appropriate supportive therapy. Individual intravenous doses as large as 150 mg and total daily intravenous doses as large as 252 mg have been inadvertently administered without significant adverse events. These doses are more than 10 times the recommended daily dose.

In addition to the adverse events listed above, the following events have been described in the setting of ondansetron overdose: "Sudden blindness" (amaurosis) of 2 to 3 minutes' duration plus severe constipation occurred in 1 patient that was administered 72 mg of ondansetron intravenously as a single dose. Hypotension (and faintness) occurred in a patient that took 48 mg of ZOFRAN Tablets. Following infusion of 32 mg over only a 4-minute period, a vasovagal episode with transient second-degree heart block was observed. In all instances, the events resolved completely.

Pediatric cases consistent with serotonin syndrome have been reported after inadvertent oral overdoses of ondansetron (exceeding estimated ingestion of 5 mg/kg) in young children. Reported

symptoms included somnolence, agitation, tachycardia, tachypnea, hypertension, flushing, mydriasis, diaphoresis, myoclonic movements, horizontal nystagmus, hyperreflexia, and seizure. Patients required supportive care, including intubation in some cases, with complete recovery without sequelae within 1 to 2 days.

DOSAGE AND ADMINISTRATION

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

Prevention of Nausea and Vomiting Associated With Highly Emetogenic Cancer Chemotherapy: The recommended adult oral dosage of ZOFRAN is 24 mg given as three 8-mg tablets administered 30 minutes before the start of single-day highly emetogenic chemotherapy, including cisplatin ≥ 50 mg/m^2. Multiday, single-dose administration of a 24 mg dosage has not been studied.

Pediatric Use: There is no experience with the use of a 24 mg dosage in pediatric patients.

Geriatric Use: The dosage recommendation is the same as for the general population.

Prevention of Nausea and Vomiting Associated With Moderately Emetogenic Cancer Chemotherapy: The recommended adult oral dosage is one 8-mg ZOFRAN Tablet or one 8-mg ZOFRAN ODT Tablet or 10 mL (2 teaspoonfuls equivalent to 8 mg of ondansetron) of ZOFRAN Oral Solution given twice a day. The first dose should be administered 30 minutes before the start of emetogenic chemotherapy, with a subsequent dose 8 hours after the first dose. One 8-mg ZOFRAN Tablet or one 8-mg ZOFRAN ODT Tablet or 10 mL (2 teaspoonfuls equivalent to 8 mg of ondansetron) of ZOFRAN Oral Solution should be administered twice a day (every 12 hours) for 1 to 2 days after completion of chemotherapy.

Pediatric Use: For pediatric patients 12 years of age and older, the dosage is the same as for adults. For pediatric patients 4 through 11 years of age, the dosage is one 4-mg ZOFRAN Tablet or one 4-mg ZOFRAN ODT Tablet or 5 mL (1 teaspoonful equivalent to 4 mg of ondansetron) of ZOFRAN Oral Solution given 3 times a day. The first dose should be administered 30 minutes before the start of emetogenic chemotherapy, with subsequent doses 4 and 8 hours after the first dose. One 4-mg ZOFRAN Tablet or one 4-mg ZOFRAN ODT Tablet or 5 mL (1 teaspoonful equivalent to 4 mg of ondansetron) of ZOFRAN Oral Solution should be administered 3 times a day (every 8 hours) for 1 to 2 days after completion of chemotherapy.

Geriatric Use: The dosage is the same as for the general population.

Prevention of Nausea and Vomiting Associated With Radiotherapy, Either Total Body Irradiation, or Single High-Dose Fraction or Daily Fractions to the Abdomen: The recommended oral dosage is one 8-mg ZOFRAN Tablet or one 8-mg ZOFRAN ODT Tablet or 10 mL (2 teaspoonfuls equivalent to 8 mg of ondansetron) of ZOFRAN Oral Solution given 3 times a day.

For total body irradiation, one 8-mg ZOFRAN Tablet or one 8-mg ZOFRAN ODT Tablet or 10 mL (2 teaspoonfuls equivalent to 8 mg of ondansetron) of ZOFRAN Oral Solution should be administered 1 to 2 hours before each fraction of radiotherapy administered each day.

For single high-dose fraction radiotherapy to the abdomen, one 8-mg ZOFRAN Tablet or one 8-mg ZOFRAN ODT Tablet or 10 mL (2 teaspoonfuls equivalent to 8 mg of ondansetron) of ZOFRAN Oral Solution should be administered 1 to 2 hours before radiotherapy, with subsequent doses every 8 hours after the first dose for 1 to 2 days after completion of radiotherapy.

For daily fractionated radiotherapy to the abdomen, one 8-mg ZOFRAN Tablet or one 8-mg ZOFRAN ODT Tablet or 10 mL (2 teaspoonfuls equivalent to 8 mg of ondansetron) of ZOFRAN Oral Solution should be administered 1 to 2 hours before radiotherapy, with subsequent doses every 8 hours after the first dose for each day radiotherapy is given.

Pediatric Use: There is no experience with the use of ZOFRAN Tablets, ZOFRAN ODT Tablets, or ZOFRAN Oral Solution in the prevention of radiation-induced nausea and vomiting in pediatric patients.

Geriatric Use: The dosage recommendation is the same as for the general population.

Postoperative Nausea and Vomiting: The recommended dosage is 16 mg given as two 8-mg ZOFRAN Tablets or two 8-mg ZOFRAN ODT Tablets or 20 mL (4 teaspoonfuls equivalent to 16 mg of ondansetron) of ZOFRAN Oral Solution 1 hour before induction of anesthesia.

Pediatric Use: There is no experience with the use of ZOFRAN Tablets, ZOFRAN ODT Tablets, or ZOFRAN Oral Solution in the prevention of postoperative nausea and vomiting in pediatric patients.

Geriatric Use: The dosage is the same as for the general population.

Dosage Adjustment for Patients With Impaired Renal Function: The dosage recommendation is the same as for the general population. There is no experience beyond first-day administration of ondansetron.

Dosage Adjustment for Patients With Impaired Hepatic Function: In patients with severe hepatic impairment (Child-Pugh[2] score of 10 or greater), clearance is reduced and apparent volume of distribution is increased with a resultant increase in plasma half-life. In such patients, a total daily dose of 8 mg should not be exceeded.

HOW SUPPLIED

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

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

ZOFRAN Tablets, 8 mg (ondansetron HCl dihydrate equivalent to 8 mg of ondansetron), are yellow, oval, film-coated tablets engraved with "Zofran" on one side and "8" on the other in daily unit dose packs of 3 tablets (NDC 0173-0447-04), and bottles of 30 tablets (NDC 0173-0447-00).

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

Unit Dose Packs: Store between 2° and 30°C (36° and 86°F).

ZOFRAN ODT Orally Disintegrating Tablets, 4 mg (as 4 mg ondansetron base) are white, round and plano-convex tablets debossed with a"Z4" on one side in unit dose packs of 30 tablets (NDC 0173-0569-00).

ZOFRAN ODT Orally Disintegrating Tablets, 8 mg (as 8 mg ondansetron base) are white, round and plano-convex tablets debossed with a "Z8" on one side in unit dose packs of 30 tablets (NDC 0173-0570-00).

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

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

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

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

ZOFRAN ODT Orally Disintegrating Tablets:
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554 September 2014
555 ZFT:xPI

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