



*This information has been gathered by The Cleft Lip & Palate Foundation of Smiles. We are responding to the fact that a number of our members have questions concerning the safety of medications that they had taken during pregnancy, or may take during a future pregnancy. These medications may be the cause of craniofacial differences. Our goal is to ensure that our families have resources and facts about the medications that may be taken during pregnancy, so you can have informed discussions with the treating doctors.*

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The Cleft Lip & Palate Foundation of Smiles provides research on craniofacial causes (genetics, environmental, prescription drugs), treatments (cleft palate teams, medical devices, therapies), and available support for families.

*This PDF is about Zofran and its similar generic versions containing Ondansetron. Zofran is often prescribed to pregnant women as an anti-nausea medication, commonly used to prevent morning sickness. Studies are linking the use of this drug to an increased chance of delivering a baby with cleft lip or palate, heart conditions, and other, more rare birth defects. View this infographic.*



## Causes of Cleft Lip and Palate: ZOFRAN

### What is Zofran?

Zofran is an anti-nausea drug manufactured by GlaxoSmithKline. Its active ingredient, ondansetron or ondansetron hydrochloride, is now being marketed in generic versions, too. In 1991, the FDA approved Zofran for the treatment of severe nausea and vomiting in cancer patients receiving chemotherapy and irradiation therapy, as well as those undergoing surgical anesthesia.

Zofran has never been approved as a treatment for morning sickness. Despite the fact that its manufacturer has never conducted clinical trials to demonstrate the drug's safety for a developing baby, it is widely prescribed as a treatment for morning sickness in pregnant women. In fact, Zofran and generic

ondansetron have become America's most popular prescription medications for women experiencing morning sickness.

### Why Are Pregnant Women Being Prescribed Zofran?

For a span of 30 years, there was no FDA approved drug for morning sickness. That all ended in 2013, when a Canadian drug called Diclegis was approved to treat nausea and vomiting of pregnancy. Diclegis has been found safe for fetal development in numerous clinical trials. But before that, many physicians ended up prescribing pregnant women Zofran. While Zofran was never approved for this purpose, it's not unlawful for doctors to prescribe drugs "off-label" when they believe that the benefits outweigh the risks.

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Recently, GlaxoSmithKline became the subject of an investigation conducted by the US Department of Justice. A number of the government's legal claims involved alleged fraudulent marketing of medications, including Zofran, for unapproved purposes. While the company continues to deny these allegations, it settled the DOJ's case for a record-breaking \$3 billion.

Neither Zofran's safety in pregnant women nor its efficacy in treating morning sickness have ever been studied in clinical trials by GlaxoSmithKline. The FDA requires such studies, which involve human subjects, before any medication can be approved for use during pregnancy.

### What Are The Links Between Zofran & Birth Defects?

Now, multiple research studies have begun to establish an association between Zofran's active ingredient ondansetron and several birth defects.

In a paper titled "Medications used to treat nausea and vomiting of pregnancy and the risk of selected birth defects," researchers at the Centers for Disease Control & Prevention and Harvard University's School of Public Health reviewed 10,383 pregnancies. Of those women, 67.1% reported experiencing nausea and vomiting during the first trimester, and 15.4% had symptoms so severe that they were prescribed a prescription drug. Comparing a group of 4,524 women who had delivered children with major birth defects to 5,859 who had not, the researchers found that women who took Zofran or generic ondansetron were 2.37 times more likely to deliver babies with cleft palate.

In 2013, Danish researchers reviewed every birth record filed in Denmark between 1997 and 2010. In the end, the study included more than 900,000 births. While only 1,368 of these women redeemed prescriptions for ondansetron in the first trimester, they were 4.8 times more likely to deliver babies with "atrioventricular septal defects." This form of congenital heart defect involves an incomplete barrier between two chambers of the heart, and drastically increases the risk of stroke and heart failure later in life. The study, published in the journal *Pharmacoepidemiology & Drug Safety*, was titled "Ondansetron use in early pregnancy and the risk of congenital malformations - a register based nationwide cohort study."

In a paper published as "Use of ondansetron during pregnancy and congenital malformations in the infant" in late 2014, researchers who used Swedish birth records found similar results. Reviewing every record made between 1998 and 2012, they identified a total of 1,349 infants born to women who had taken ondansetron during early pregnancy. Comparing the incidence of major birth defects within the group prescribed ondansetron to that of the pregnant population at-large, the researchers found that women who had taken ondansetron where 1.62 times more likely to deliver children with "cardiac septum defects," a category that includes atrioventricular septal defects. The study was published in the journal *Reproductive Toxicology*.

While these studies may not be the final conclusive evidence of danger, they are cause for concern. Especially since morning sickness generally occurs during the first trimester, when the risk of developing a birth defect is highest.

### What Has The FDA Said About Zofran?

The FDA has yet to make any public announcements about Zofran's potential link to birth defects. With that being said, the agency has instructed GlaxoSmithKline to alter the drug's warning label with major revisions twice in the past.

After a clinical trial found that Zofran can increase patients' risk of developing abnormal heart rhythms in 2012, the FDA instructed the drug's manufacturer to include warnings in relation to "Torsade de Pointes," a rare disorder of the heart's electrical activity that can result in cardiac failure. GlaxoSmithKline voluntarily recalled Zofran's 32 milligram intravenous dosage, which was found to be unacceptably dangerous.

On September 18, 2014, the FDA ruled that Zofran and several other drugs increase the risk of serotonin syndrome, a potentially fatal condition caused by abnormally high levels of serotonin, one of the body's key neurotransmitters. As a result, Zofran was placed on the FDA's "Adverse Event





Reporting System.” FAERS is a database of medications the FDA has identified as “potential safety issues.” Physicians, patients and drug manufacturers can report descriptions of adverse events associated with these medications directly to the FDA.

### Zofran Litigation

Lawsuits are being filed against the manufacturer of Zofran, alleging that Zofran caused a child birth defect. The first lawsuit alleging that Zofran caused a cleft palate was filed in April 2015. Click here to read a summary of the lawsuit.

### Do you have more questions? Do you need resources?

For questions and resources about cleft lip and cleft palate, please contact: The Cleft Lip and Palate Foundation of Smiles. Cleft lip or palate is one of the most common birth defects, currently affecting one in 600 children in the United States. The Foundation was formed by a young mother of twins both born with cleft lip and palate. The Foundation offers positive support to parents of children with craniofacial differences by offering news, information on cleft palate teams, state by state resources, birth registry listings, and a support group where you can meet other families in your local area who are going through the same or similar concerns and where you can share and express useful information.

### References

FDA.gov: [Zofran FDA Approvals & Drug Warning Label](#)

justice.gov: [GlaxoSmithKline to Plead Guilty and Pay \\$3 Billion](#)

Medications used to treat nausea and vomiting of pregnancy and the risk of selected birth defects. Marlene Anderka et al. © 2011 Wiley Periodicals, Inc. Birth Defects Research. Part A, Clinical & Molecular Teratology. 2012 Jan; 94(1):22-30. Abstract on [PubMed.gov](#).

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Andersen et al. International Society of Pharmaco-epidemiology. August 2013, Montreal, Canada. Abstract on [Motherisk.org](#).

Use of ondansetron during pregnancy and congenital malformations in the infant. B. Danielsson et al. © 2014 Elsevier Inc. Reproductive Toxicology. 2014 Dec; 50:134-7. Abstract on [PubMed.gov](#).

FDA.gov: [New information regarding QT prolongation with ondansetron \(Zofran\)](#)

FDA.gov: [Potential Signals of Serious Risks \(FAERS\)](#)

### Other Research from The Cleft Lip & Palate Foundation of Smiles

Research and Recent Studies:

[Causes of Cleft Lip and Palate: Birth Defects](#)

[Causes of Cleft Lip and Palate: Clomid](#)

[Causes of Cleft Lip and Palate: Hydrocodone](#)

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