29 August 2019

Direct Healthcare Professional Communication on the risk of birth defects from the recently published epidemiological studies for Zofran® (Ondansetron)

Dear Healthcare Professional,

This is to inform you of new data from recently published epidemiological studies related to the risk of birth defects associated with Zofran® (Ondansetron). Zofran is licensed for the management of nausea and vomiting induced by cytotoxic chemotherapy and radiotherapy. Zofran is also indicated for the prevention and treatment of post-operative nausea and vomiting.

Background:

Two new epidemiological studies related to the use of Zofran in pregnancy were published by Zambelli-Weiner et al (2019) and Huybrechts et al (2018) that were based in the United States.

Ondansetron, a 5-HTE receptor antagonist was first approved in the US in 1991, and in the European Union in 1990 under the brand name Zofran®. Zofran® is not approved for the treatment of nausea and vomiting in pregnancy.

Currently in the EU, Ondansetron in not contraindicated in patients who are or may become pregnant. Given that the data emerging from these studies are of public health importance, Novartis is providing additional details to assist healthcare professionals to make an informed decision for patients. The European Medicines Agency (EMA) has reviewed these data and recommended additional details be provided in section 4.6 of the European Summary of Product Characteristics (SmPC), and Novartis has complied with this request taking into consideration the safety of our patients. The additional information is related to the risk of two birth defects: Orofacial cleft malformations and cardiac malformations.

The following information will be updated in the EU SmPC:

Section 4.6- Fertility, pregnancy and lactation

Women of Childbearing potential:

Women of childbearing potential should consider the use of contraception.

Pregnancy:

Based on human experience of epidemiological studies, ondansetron is suspected to cause orofacial malformations when administered during first trimester of pregnancy.

In one cohort study including 1.8 million pregnancies, first trimester ondansetron use was associated with an increased risk of oral clefts (3 additional cases per 10,000 women treated; adjusted relative risk, 1.24 (95% CI 1.03 to 1.48).

The available epidemiological studies on cardiac malformations show conflicting results. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity.

Ondansetron should not be used during the first trimester of pregnancy.

The package leaflet should also be amended to include the following information:

Section 2- What you need to know before you take Zofran®

Pregnancy and breast-feeding:

You should not use Zofran® during the first trimester of pregnancy. This is because Zofran® can slightly increase the risk of a baby being born with cleft lip and/or cleft palate (openings or splits in the upper lip and/or the roof of the mouth). If you are already pregnant, think you might be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking Zofran®. If you are a woman of childbearing potential, you may be advised to use effective contraception.

Considerations for you and your patients:

- The current Zofran® product has an established favorable benefit/risk profile for the approved indications.
- Zofran® is not approved for the treatment of nausea and vomiting in pregnancy.
- Ondansetron should not be used in the first trimester of pregnancy
- Women of childbearing potential should consider the use of contraception.
- Given that nausea and vomiting (NVP) during pregnancy or hyperemesis gravidarum (HG) is the most common medical condition during pregnancy which overlaps with the period of embryologic development and that ondansetron's off label prescription rate to pregnant women has been on the rise, there is a strong recommendation to follow practical guidelines regarding treatment of NVP/HG, taking into account new evidence of the risk of congenital malformations.
- Physicians must ensure that if the clinical condition of the women requires treatment with ondansetron, all female patients (to be) treated with ondansetron are informed of and understand the potential risks to a fetus associated with ondansetron during pregnancy.
- Please consider the above data from recent epidemiological studies before prescribing Zofran for your patients.

Call for Reporting:

The treating healthcare physicians are advised to report the adverse events in accordance with the national spontaneous reporting system of Republic of Armenia:

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Novartis places the highest priority on patient health.

Should you have any questions, please do not hesitate to contact company contact point in Armenia. We will keep you informed as further information becomes available.

Company contact point

Asteria Ltd, located at apt. 24, 28, T. Mets Str., Yerevan, phone: +374 105 19 070, e-mail: drugsafety.cis@novartis.com.

References:

1. Huybrechts KF et al. Association of Maternal First-Trimester Ondansetron use with cardiac malformations and oral clefts in offspring. JAMA 2018 Dec 18; 320 (23): 2429-2437
2. Parker SE, Van Bennekom C, Anderka M, Mitchell AA; National Birth Defects Prevention Study. Ondansetron for treatment of nausea and vomiting of pregnancy and the risk of specific birth defects. Obstet Gynecol 2018; 132(2): 385-394
3. Zambelli-Weiner A et al. First trimester Ondansetron exposure and risk of structural birth defects. Reprod Toxicol. 2019 Jan; 83: 14-20. DOI: [10.1016/j.reprotox.2018.10.010] (online 29 October 2018)