May 2020

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

Dear Healthcare Professional,

In agreement with Saudi Food and Drug Authority (SFDA), Novartis would like to inform you of data from recently published epidemiological studies related to the risk of birth defects associated with Zofran® (Ondansetron).

Background:

Ondansetron, a $5HTE_3$ 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.

Three new epidemiological studies assessed by Novartis related to the use of Zofran in pregnancy were published in four publications by Parker et al (2019), Lemon et al (2019) and Huybrechts et al (2018, 2020). These studies assessed the risk of specific congenital anomalies, including orofacial clefts and cardiac malformations in children born to mothers exposed to ondansetron during the first trimester of pregnancy. Novartis has revised its company position and the local label under the SFDA review will reflect the information from these studies.

The four publications are summarized below:

1. One cohort study with 88,467 ondansetron exposed pregnancies showed an increased risk of oral clefts (three additional cases per 10,000 women treated, adjusted relative risk (RR), 1.24 (95% CI 1.03-1.48)) without an apparent increase in risk of cardiac malformations (Huybrechts et al 2018). A separately published subgroup analysis of 23,877 pregnancies exposed to intravenous ondansetron did not find an increased risk of either oral clefts or cardiac malformations (Huybrechts et al 2020).
2. One case-control study using population-based birth defect registries with 23,200 cases across two datasets reported an increased risk of cleft palate in one dataset and no increased risk in the other dataset. There was no increased risk of cardiac malformations in this study (Parker et al 2019).
3. Another cohort study with 3,733 ondansetron exposed pregnancies found a slightly increased risk of ventricular septal defect, adjusted RR 1.7 (95%CI 1.0-2.9), but no statistically significant increase in risk of cardiac malformations overall (Lemon et al 2019).

Based on the above data, an increase in orofacial clefts was observed in infants of women administered ondansetron during the first trimester of pregnancy. Regarding cardiac malformations, the epidemiological studies showed conflicting results.

Novartis is providing additional details to assist healthcare professionals to make an informed decision for patients in light of these new data.

Zofran® is licensed for use in:

- **Adults:** Zofran is indicated for the management of nausea and vomiting induced by cytotoxic chemotherapy and radiotherapy. Zofran is indicated for the prevention and treatment of post-operative nausea and vomiting (PONV). For treatment of established PONV, administration by injection is recommended.
- **Paediatric Population:** Zofran is indicated for the management of chemotherapy-induced nausea and vomiting (CINV) in children aged ≥6 months. No studies have been conducted on the use of orally administered ondansetron in the prevention and treatment of PONV in children aged ≥1 month, administration by IV injection is recommended for this purpose.

Considerations for you and your patients:

- The benefit - risk profile of Zofran® in its' approved indications is unchanged.
- Zofran® is not approved for the treatment of nausea and vomiting in pregnancy.
- The use of Zofran® in pregnancy is not recommended.
- Advise women of childbearing potential to use contraception.
- 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:

Patient Safety Department Novartis Pharma AG - Saudi Arabia -.
Toll Free Number: 8001240078
Phone: +966112658100
Fax: +966112658107
Email: adverse.events@novartis.com
Or by online: http://report.novartis.com/

Saudi Food and Drug Authority National Pharmacovigilance Center
Unified Contact Center: 19999
Toll Free Number: 8002490000
Fax: +966112057662
Email: npc.drug@sfda.gov.sa
Or by online: https://ade.sfda.gov.sa

Novartis places the highest priority on patient health. Should you have any questions, please do not hesitate to contact Novartis Patient Safety Department. We will keep you informed as further information becomes available.

Yours sincerely,

Malak Alowais
Patient Safety Manager / QPPV

Alowais Malak

Digitally signed by Alowais Malak
DN: dc=com, dc=novartis, ou=people, ou=GD, serialNumber=1834851, cn=Alowais Malak
Date: 2020.06.29 15:37:31 +03'00'

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. Huybrechts KF et al; Intravenous ondansetron in pregnancy and risk of congenital malformations. *JAMA* (IF51.273) Pub Date : 2020-01-28,*DOI: 10.1001/jama.2019.18587*
4. Lemon LS et al: Ondansetron use in the first trimester of pregnancy and the risk of neonatal ventricular septal defect. International Journal of Epidemiology, 2019, 1–9; doi: 10.1093/ije/dyz255