NOVARTIS SANDOZ A Novartis Division

IMPORTANT MEDICINE SAFETY INFORMATION

ZOFRAN (ONDANSETRON)

18 May 2020

Dear Healthcare Professional

RE: WARNING ABOUT INCREASED RISK OF CLEFT LIP AND/OR CLEFT PALATE FOLLOWING THE USE OF ZOFRAN® (ONDANSETRON) IN THE FIRST 12 WEEKS OF PREGNANCY.

In collaboration with the South African Health Products Regulatory Authority (SAHPRA), the below listed companies would like to inform you of an increased risk of cleft lip and/or cleft palate following the use of ZOFRAN® (ondansetron) during the first 12 weeks of pregnancy.

The Professional Information (PI) and Patient Information Leaflet (PIL) of ondansetron containing medicines will be amended to reflect the above safety information.

Summary

- The use of ZOFRAN® (ondansetron) during the first 12 weeks of pregnancy can be associated with an increased risk of developing oral cleft palate and/or lip to the foetus.
- The use of ZOFRAN® is contraindicated during the first 12 weeks of pregnancy irrespective of indication.
- Healthcare professional must ensure that female patients of child bearing age are adequately counselled on the teratogenicity of the treatment with ZOFRAN®.

Background on the safety concern:

Three epidemiological studies assessed by Novartis related to the use of ondansetron 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.

- Ondansetron is a selective serotonin antagonist (5-hydroxy-tryptamine-3 receptor antagonist) used for management of nausea and vomiting induced by cytotoxic chemotherapy and radiotherapy, and for the prevention of postoperative nausea and vomiting.
- Based on literature and post marketing reports, Zofran® (ondansetron) has been used off-label for treatment of nausea and vomiting during pregnancy or hyperemesis gravidarum.

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.

Advice to Healthcare Professional:

- 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® is contraindicated during the first 12 weeks of pregnancy irrespective of indication.
- Advise women of childbearing potential to use contraception while taking ZOFRAN® and for 2 days after stopping treatment.
- Please consider the above data from recent epidemiological studies before prescribing ZOFRAN® for your patients.

Healthcare professionals are urged to report all suspected adverse events associated with all ondansetron containing products to SAHPRA via the eReporting link available on the SAHPRA website (www.sahpra.org.za). Alternatively, please complete the ADR reporting form accessible via the SAHPRA website at https://www.sahpra.org.za/documents/12e54dcaADRForms.pdf and email it to adr@sahpra.org.za or fax to (021) 448 6181. For more information on ADR reporting, please call the SAHPRA vigilance unit on (012) 842 7609/10 or National Adverse Events Monitoring Centre (NADEMC) on (021) 447 1618.

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	Zofran Zydis® 4 mg	Ondansetron	32/5.10/0461	
Sandoz SA (Pty) Ltd	Zofran® 4 mg tablet	Ondansetron	X/5.10/332	**Tel:** (+27) 11 347 6600 **Fax:** (+27) 11 929 2262 **Email:** patientsafety.sacg@novartis.com **Web:** https://www.report.novartis.com/
	Zofran® 8 mg tablet	Ondansetron	X/5.10/333	
	Zofran® 4 mg/ 2 ml Injection	Ondansetron	X/5.10/331	
	Zofran® 8 mg/ 4 ml Injection	Ondansetron	Y/5.10/170	

Yours faithfully

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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