IMPORTANT MEDICINE SAFETY INFORMATION

19 May 2020

Dear Healthcare Professional

RE: WARNING ABOUT INCREASED RISK OF CLEFT LIP AND/OR CLEFT PALATE FOLLOWING THE USE OF 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 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 ondansetron during the first 12 weeks of pregnancy is associated with an increased risk of developing oral cleft palate and/or lip to the foetus.
- The use of ondansetron is contraindicated during the first 12 weeks of pregnancy irrespective of indication.

The healthcare professional must ensure that female patients of childbearing age are adequately counselled on the teratogenicity of Ondansetron.

Background on the Safety Concern

- 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, ondansetron has been used for treatment of nausea and vomiting during pregnancy or hyperemesis gravidarum.
- Evidence from large observational studies suggest increase in risk of orofacial cleft malformation.

- In one US observational study[1], 88,467 women exposed to ondansetron during the first trimester were compared to 1,727,947 unexposed. The study reported that ondansetron use was associated with an additional 3 oral clefts per 10,000 births (14 cases per 10,000 births versus 11 cases per 10,000 births in the unexposed population).
- Another US observational study[2], included 864,083 mother infant pairs seen between 2000 and 2014, and found a non-statistically significant trend towards an increased risk of orofacial cleft defects in babies exposed to ondansetron compared with those not exposed to any antiemetic (adjusted odds ratio [OR] 1.30, 95% CI 0.75-2.25).

Healthcare professionals are urged to report any adverse drug reactions (ADRs) or product quality issues 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.

Company	Product Name	Active Ingredient(s)	Registration Number	Contact Details
Cipla Medpro (Pty) Ltd	Cipla Ondansetron 4	Ondansetron 4mg	A38/5.10/0435	***Tel:*** 021 943 4200 ***Fax:*** 021 914 1587 ***Email:*** drugsafetysa@Cipla.com
	Cipla Ondansetron 8	Ondansetron 8mg	A38/5.10/0436	
Mylan (Pty) Ltd	Mylan Ondansetron 4 mg / 2 ml	Ondansetron	A39/5.10/0509	***Tel:*** 071 281 2503 ***Email:*** medinfosa@mylan.com
	Mylan Ondansetron 8 mg / 4 ml	Ondansetron	A39/5.10/0510	
Fresenius Kabi South Africa (Pty) Ltd	Ondansetron Fresenius 2 mg/ml (4 mg/2 ml)	Ondansetron	43/5.10/0542	***Tel:*** 011 545 0154 ***Email:*** safety.fksa@fresenius-kabi.com
	Ondansetron Fresenius 2 mg/ml (8 mg/4 ml)	Ondansetron	43/5.10/0543	
Pharma Dynamics	Emistop 8	Ondansetron 8 mg/4ml	45/5.10/0387	***Tel:*** 021 707 7000 ***Fax:*** 021 702 0533

Company	Product Name	Active Ingredient(s)	Registration Number	Contact Details
	Emistop 4	Ondansetron 4 mg/2ml	45/5.10/0386	***Email:*** pharmacovigilance@pharmadynamics.co.za. p.vanvuuren@pharmadynamics.co.za
Ranbaxy Pharmaceuticals (Pty) Ltd.	Zofer 4 mg Injection	Ondansetron	A39/5.10/0448	***Tel***: 011 495 0100 011 495 0117 ***Email:*** barryjames.lewis@sunpharma.com susan.heritage@sunpharma.com Geeta.ghela@sunpharma.com
	Zofer 8 mg Injection	Ondansetron	A39/5.10/0449	
	Zofer 4 mg Tablets	Ondansetron	A39/5.10/0413	
	Zofer 8mg Tablets	Ondansetron	A39/5.10/0414	
	Zofer Rapitabs 4	Ondansetron	42/5.10/0662	
	Zofer Rapitabs 8	Ondansetron	42/5.10/0663	

Yours faithfully

Petra van Vuuren Deputy Responsible Pharmacist **Pharmadynamics (Pty) Ltd** PJ van Vuuren **Signature:**	Ansie Sarvrda Responsible Pharmacist **Mylan (Pty) Ltd** A Savrda **Signature:**	Dr Nic de Jongh Vice President – Chief Scientific Officer **Cipla Medpro (Pty) Ltd** **Signature:**
Geeta Ghela Responsible Pharmacist/ QA Head **Ranbaxy Pharmaceuticals (Pty) Ltd** **Signature:**	Sharon Davis Responsible Pharmacist **Fresenius Kabi South Africa (Pty) Ltd** **Signature:**	

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. Zambelli-Weiner A et al. First Trimester Ondansetron Exposure and Risk of Structural Birth Defects. Reprod Toxicol. 2019 Jan; 83: 14–20.