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Direct Healthcare Professional Communication (DHPC)

Ondansetron containing products – Signal of birth defects following in-utero exposure during the first trimester of pregnancy arising from recent publications

Dear Healthcare professional,

Accord Healthcare Ireland Ltd, Anfarm Hellas S.A., Aurobindo (Pharma) Malta Limited, Baxter Healthcare, Central Procurement & Supplies Unit, Fresenius Kabi Italia S.r.l., JV Healthcare Limited, Medical Logistics Ltd, Novartis Ireland Limited, Pinewood Laboratories Limited, Wockhardt UK Limited, in agreement with the European Medicines Agency and Malta Medicines Authority, would like to inform you of the following new safety information:

Summary:

- **Based on human experience from epidemiological studies, ondansetron is suspected to cause orofacial cleft malformations when administered during the first trimester of pregnancy**
- **The available epidemiological studies on cardiac malformations show inconclusive results**
- **Ondansetron should not be used during pregnancy, especially during first trimester**
- **Given that nausea and vomiting during pregnancy (NVP) 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**
- **The 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.**

Background on the safety concern

- Ondansetron is a selective serotonin antagonist (5-hydroxy-tryptamine-3 receptor antagonist) used for prevention of nausea and vomiting induced by cytotoxic chemotherapy and radiotherapy (CINV/RINV), and for the management of postoperative nausea and vomiting (PONV)
- Based on literature and post marketing reports, ondansetron is off-label used for treatment of nausea and vomiting during pregnancy (NVP) or hyperemesis gravidarum (HG)
- Its use in US increased from <1% of pregnancies in 2001 to 22.2% in 2014. In EU the use of ondansetron during pregnancy has increased (more or less) steadily over time, with reported

prevalence of 0 to 1,4 % and 2,2% in France and Germany (in gynaecological practices), respectively, from 2005 to 2018; and in United Kingdom from around 2003 to 2018 from 0 to 2%

- Evidence from the recently largest published observational studies suggest increase in risk of orofacial cleft malformation:

  One US observational study[1], based on 88,467 women exposed to ondansetron during the first trimester compared to 1,727,947 unexposed, identified three (14 vs 11) additional cases of oral clefts per 10,000 births, equal to a relative risk (RR) of 1.24 (95% CI 1.03-1.48) after adjustment for confounders. The increased risk was due mainly to a greater number of babies born with cleft palate. A second US observational study[2], based on 864,083 mother-child pairs including 76,330 pregnant women who received ondansetron during the first trimester (of those 5,557 in the medical office or hospital setting), found an adjusted odds ratio (OR) of 1.30 (95% CI 0.75-2.25) for orofacial clefting after adjustment for maternal age, infant year of birth and sex of infant
- The available epidemiological studies on cardiac malformations show inconclusive results:

  The first study found no increased risk for cardiac abnormalities after adjustment for confounders. However, the second study found a statistically significant increase in cardiac abnormalities (mainly septal defects) in infants born to mothers treated in the medical office or hospital setting (adjusted odds ratio (aOR) of 1.43 (95% CI 1.28-1.61) after adjustment for maternal age, infant year of birth and sex of infant).

Call for reporting

Reporting suspected adverse reactions after authorisation of a medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are reminded to continue to report suspected adverse reactions associated with ondansetron-containing medicinal products in accordance with the national spontaneous reporting system. Report forms can be downloaded from www.medicinesauthority.gov.mt/adrportal and posted to Post-licensing directorate, Medicines Authority, Sir Temi Żammit Buildings, Malta Life Sciences Park, San Ġwann SĠN 3000, Malta or sent by email to postlicensing.medicinesauthority@gov.mt

[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.

Company contact point

Should you have any questions or require additional information, please call Medical Information at:

Company	Product Name	Email	Phone
Accord Healthcare Ireland Ltd	Ondansetron 2mg/ml Solution for Injection or Infusion (2ml vial)	safety.eu@lambda-cro.com	+44(0)2089013370
	Ondansetron 2mg/ml Solution for Injection or Infusion (4ml vial)		
Anfarm Hellas S.A.	Odasen 8mg/4ml Solution for Injection	pharmacovigilance@pharmabide.gr phvigilance@anfarm.com	+30 210 6831632
Aurobindo (Pharma) Malta Limited	Ondansetron 4mg film-coated Tablets	Pharmacovigilance.Malta@aurobindo.com	+356 22294163
	Ondansetron 8mg film-coated Tablets		
Central Procurement & Supplies Unit	Ondansetron 4mg/5ml Syrup	richard.despott@gov.mt	+356 23439150
	Ondansetron Solution for Injection 2mg/ml		
	Ondansetron Tablet, film coated 8mg		
	Ondansetron Solution for Injection 2mg/ml		
Fresenius Kabi Italia S.r.l.	Ondansetron Kabi 2mg/ml Solution for Injection	paola.ragazzo@fresenius-kabi.com	T: +39 045 6649402 M: +39 3489710480
JV Healthcare Limited	Ondansetron Solution for Injection 2mg/ml	Damian.stellini@jvpharma.eu	+356 21437551
Medical Logistics Ltd	Ondansetron Orodispersible Tablet 4mg	info@ml.com.mt	+356 27559990
Novartis Pharma Services Inc Representative Office Malta on behalf of Novartis Ireland Limited	Zofran Tablet, film coated 8mg	novartis.malta@novartis.com	+356 22487231 +356 21222872
	Zofran Solution for Inj/Inf 4mg/2ml		
	Zofran Solution for Inj/Inf 8mg/4ml		
Peckforton Pharmaceuticals Limited	Ondansetron Solution for Injection 2mg/ml	summerfield@riemser.com shirleyann@redlinepv.co.uk medinfo@peckforton.com	+44 (0)1628 771800 +44 (0)330 1359 498
Pinewood Laboratories Limited	Ondansetron 4mg film-coated Tablet	Drug.safety@wockhardt.co.uk	+44 (0) 1978 669 272
	Ondansetron 8mg film-coated Tablet		

Company	Product Name	Email	Phone
	Ondansetron 2mg/ml Solution for Injection or Infusion (2ml amp)		
	Ondansetron 2mg/ml Solution for Injection or Infusion (4ml amp)		
Wockhardt UK Limited	Ondansetron 2mg/ml Solution for Inj/Inf 4mg in 2ml	Drug.safety@wockhardt.co.uk	+44 (0) 1978 669 272
	Ondansetron 2mg/ml Solution for Inj/Inf 8mg in 4ml		

Yours faithfully,

Post-Licensing Directorate

Medicines Authority

Disclaimer

This Direct Healthcare Professional Communication has been submitted to you on behalf of Accord Healthcare Ireland Ltd, Anfarm Hellas S.A., Aurobindo (Pharma) Malta Limited, Baxter Healthcare, Central Procurement & Supplies Unit, Fresenius Kabi Italia S.r.l., JV Healthcare Limited, Medical Logistics Ltd, Novartis Ireland Limited, Pinewood Laboratories Limited, Wockhardt UK Limited