Irish Medicines in Pregnancy Service: Position Statement on Ondansetron Use in Pregnancy

23rd October 2019

Summary: Ondansetron Market Authorisation Holders (MAH) recently wrote to health care professionals regarding the safety of ondansetron use during the first trimester of pregnancy.[1] The communication was issued on foot of recommendations from the European Medicines Agency (EMA) and Health Products Regulatory Authority (HPRA). It included recommendations that ondansetron should not be used during the first trimester of pregnancy. This recommendation applied to ondansetron's licensed indications. The Irish Medicines in Pregnancy Service (IMPS) recommend that ondansetron should remain as a treatment option for women with hyperemesis gravidarum where first-line agents, as outlined in national clinical guidelines, have not been effective. Women should be adequately counselled on the benefits and potential risks prior to beginning treatment.

Background: Ondansetron is a 5HT-3 receptor antagonist licensed for the management of nausea and vomiting induced by cytotoxic chemotherapy and radiotherapy or for the prevention of postoperative nausea and vomiting. Ondansetron is rarely used for licensed indications during pregnancy. The most common use of ondansetron in pregnancy is in the context of hyperemesis gravidarum, where other treatments have been ineffective. Hyperemesis Gravidarum is a complication of pregnancy characterised by severe, protracted nausea and vomiting associated with weight loss of more than 5% of pre-pregnancy weight, dehydration and electrolyte imbalances. In addition, the psychosocial burden of this can be heavy for women and their families.

The European Medicines Agency's Pharmacovigilance Risk Assessment Committee (EMA PRAC) adopted recommendations on the use of ondansetron in pregnancy at their July 2019 meeting.[2] The letter circulated this week suggested that ondansetron use was associated with orofacial malformations, that ondansetron should not be used in the first trimester and advised that women of childbearing potential who are taking ondansetron should use effective contraception.

The European Network of Teratology Information Services (ENTIS), a specialist network of clinicians and researchers who specialise in ensuring the safe and effective use of medicines in pregnancy, released an official response statement*.[3] This statement outlined that ENTIS does not support the recommendations made by the EMA PRAC and that if these recommendations were followed it might lead to less effective control of maternal nausea and vomiting, increased maternal morbidity and hospitalisation, and an increased risk of termination of wanted pregnancies.

*Two members of ENTIS recused themselves from the ENTIS response statement given their prior involvement in providing input to PRAC on this topic.

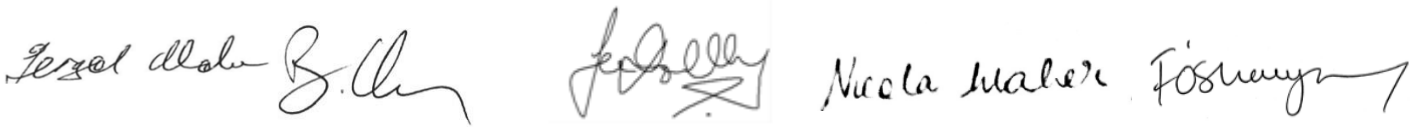
Ondansetron is included in clinical practice guidelines for the management of nausea and vomiting in pregnancy (NVP) published by the Institute of Obstetricians and Gynaecologists of Ireland, the Royal College of Physicians in Ireland and the Health Service Executive.[4] It is important to note that ondansetron will remain a treatment option in an updated version of these guidelines that is currently under development.

The EMA PRAC recommendations were based primarily on two epidemiological studies which together included approximately 160,000 women who took ondansetron during the first trimester of pregnancy.[5,6] In particular, one study[5] identified a small increased risk of cleft lip and/or palate in women who were exposed to ondansetron during the first trimester; the risk of orofacial clefts was 11 per 10,000 pregnancies in women who did not take ondansetron, compared with 14 per 10,000 pregnancies in women who did take ondansetron during the first trimester (adjusted relative risk 1.24 (95% CI 1.03-1.48)). As demonstrated in the visual risk summary below, the absolute increase in risk was very small, equating to three additional cases of orofacial cleft per 10,000 women using ondansetron during the first trimester. It is uncertain if this risk increase was caused by ondansetron or by the severity of the maternal condition or consequential nutritional deficiencies.

Response: The Irish Medicines in Pregnancy Service does not consider that currently available data support the conclusion that ondansetron causes congenital anomalies. It is important to differentiate between retrospective research that suggests a potential statistical association between an exposure and a disease, and prospective research designed to confirm a causative relationship between exposure and a disease. The data relied upon by the EMA PRAC are retrospective in nature and cannot confirm a causative link between ondansetron use and orofacial clefting. The available data on ondansetron safety should facilitate the provision of more detailed and accurate counselling to pregnant women regarding potential risks of ondansetron use during pregnancy. These potential risks should be balanced with the benefits of managing a severe underlying maternal condition that can also lead to a range of adverse pregnancy outcomes.

Therefore, The Irish Medicines in Pregnancy Service does not support the recommendations in the letter distributed on behalf of ondansetron MAH and approved by the HPRA. The implementation of these recommendations in the context of hyperemesis gravidarum may result in sub-optimal control of a serious medical condition leading to increased hospitalisation and potentially severe maternal morbidity. We believe the proposed changes to product literature and warnings may generate disproportionate anxiety and concern among women who have taken ondansetron in the first trimester. Such concerns are shared by members of ENTIS.[3]

Recommendations: IMPS recommends that ondansetron should still be considered a valid treatment option for select women with hyperemesis gravidarum in whom first-line treatments have failed, as per national clinical guidelines. We agree with ENTIS recommendations that patients must be adequately counselled regarding the benefits of ondansetron for the management of hyperemesis gravidarum together with the small increased risk of orofacial clefts which **<u>may</u>** exist. We believe that those who are best placed to make this decision are an individual patient and their healthcare provider.



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About the Irish Medicines in Pregnancy Service

Established in 2019, the Irish Medicines in Pregnancy Service (IMPS) is a multidisciplinary team that aims to support safe and effective medication use in pregnancy through clear, evidence-based risk communication. IMPS is based at the Rotunda Hospital, Dublin, and is an associate member of the European Network of Teratology Information Services (ENTIS).

Visual Risk Summary

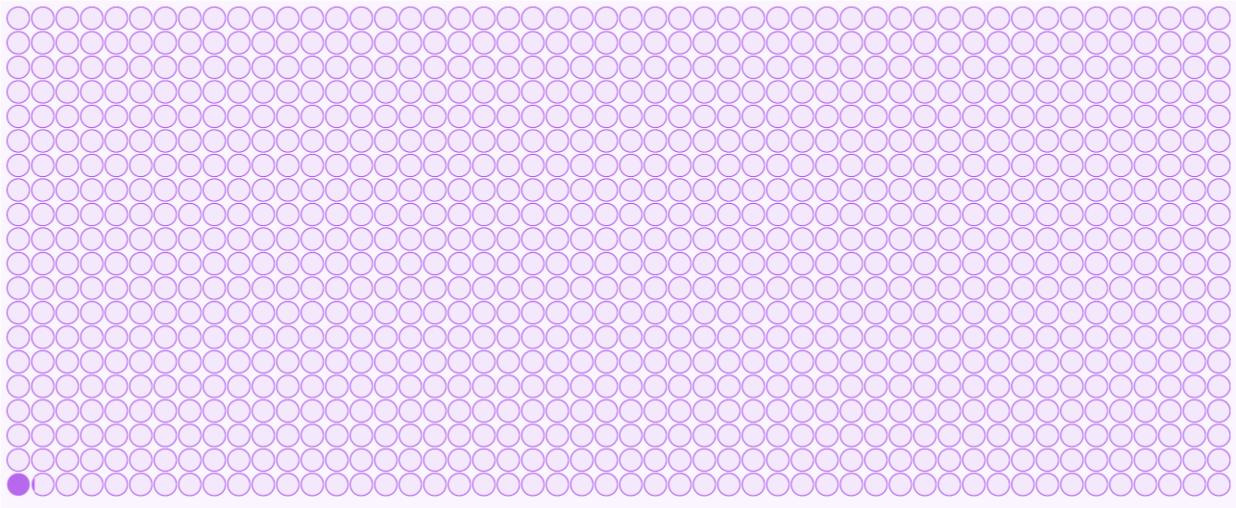

Figure 1. Rate of orofacial clefts in non-exposed pregnancies- 11 per 10,000

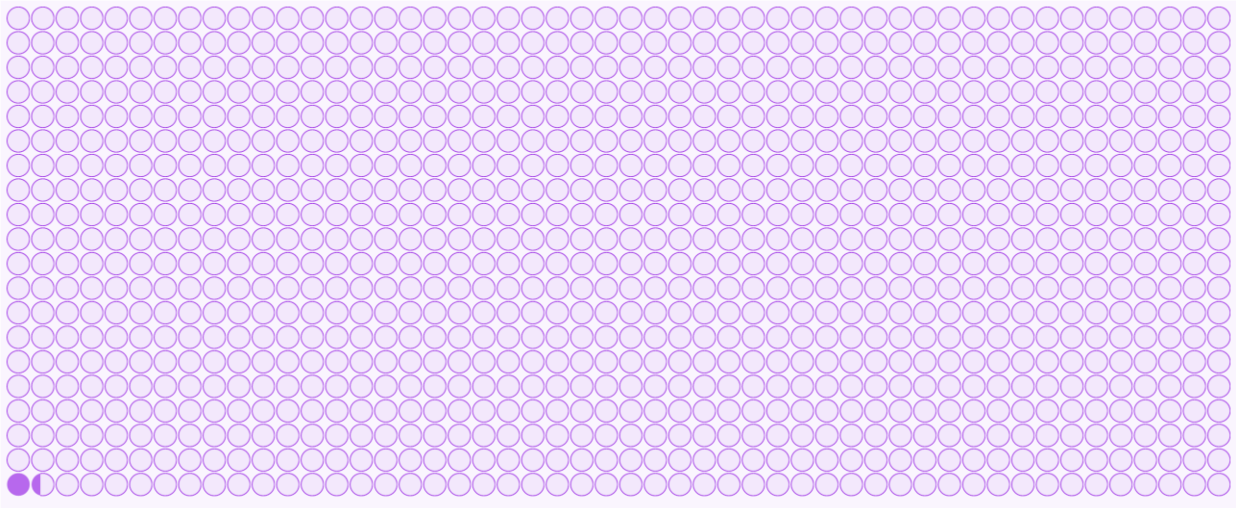

Figure 2. Rate of orofacial clefts in ondansetron-exposed pregnancies- 14 per 10,000

References:

1. Direct Healthcare Professional Communication. Ondansetron – risk of birth defects following in-utero exposure during the first trimester of pregnancy. Health Products Regulatory Authority. October 2019.
2. European Medicines Agency. PRAC recommendations on signals - Adopted at the 8-11 July 2019 PRAC meeting. 2019; Available from: https://www.ema.europa.eu/en/documents/prac-recommendation/prac-recommendations-signals-adopted-8-11-july-2019-prac-meeting_en.pdf.
3. European Network of Teratology Information Services (ENTIS). Official Response Statement. EMA Pharmarcovigilence Risk Assessment Committee (PRAC), Recommendations on signals adopted at the 8-11th July meeting. Ondansetron; Signal of birth defects following in-utero exposure during the first trimester of pregnancy arising from recent publications. September 2019.
4. Clinical practice guideline. Hyperemesis and Nausea/Vomiting in Pregnancy. Institute of Obstetricians and Gynaecologists, Royal College of Physicians of Ireland and the Clinical Strategy and Programmes Division, Health Service Executive. November 2015. Accessed online at: https://www.rcpi.ie/faculties/obstetricians-and-gynaecologists/national-clinical-guidelines-in-obstetrics-and-gynaecology/. Last accessed 16/10/19.
5. Huybrechts, K.F., S. Hernandez-Diaz, L. Straub, K.J. Gray, Y. Zhu, E. Patorno, R.J. Desai, H. Mogun, and B.T. Bateman, Association of Maternal First-Trimester Ondansetron Use With Cardiac Malformations and Oral Clefts in Offspring. JAMA, 2018. 320(23): p. 2429-2437. PMID: 30561479.
6. Zambelli-Weiner, A., C. Via, M. Yuen, D.J. Weiner, and R.S. Kirby, First trimester ondansetron exposure and risk of structural birth defects. Reproductive Toxicology, 2019. 83: p. 14-20. PMID: 30385129.