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OFFICIAL RESPONSE STATEMENT **September 2019**

EMA Pharmacovigilance 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

UKTIS, in collaboration with the European Network of Teratology Information Services (ENTIS), have issued a joint statement (see below) in response to the recommendations from the EMA PRAC regarding the use of ondansetron in the first trimester of pregnancy[1].

In summary:

- The background risk for orofacial cleft is 11 per 10,000 pregnancies
- The risk of orofacial cleft is 14 per 10,000 pregnancies following ondansetron use in the first trimester[2]
- This equates to an additional 3 cases of orofacial cleft per 10,000 pregnancies exposed to ondansetron
- UKTIS recommend that ondansetron should be reserved as a **second line** agent for the treatment of nausea and vomiting in pregnancy (as currently recommended by the RCOG Green-top Guideline)[3].
- Patients must be adequately counselled regarding the benefits of ondansetron together with the small increase in risk of orofacial cleft which **may** exist.
- Ondansetron should still be considered an option for patients with severe vomiting in pregnancy in whom first line treatments have failed.

For more information please see our recently updated monograph 'Use of Ondansetron in Pregnancy' (available from www.uktis.org/docs/Ondansetron_2019.pdf and www.toxbase.org, Patient information is also available through BUMPS (www.medicinesinpregnancy.org/Medicine--pregnancy/Ondansetron). Health professionals can discuss patient specific enquiries by telephoning UKTIS (0344 892 0909, available Monday to Friday 9am to 5pm).

Dr Kenneth Hodson MD MRCP(UK) MRCOG
Head of UK Teratology Information Service

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Service commissioned by:

Public Health England on behalf of UK Health Departments

service hosted by

The Newcastle upon Tyne Hospitals NHS
NHS Foundation Trust

ENTIS
EUROPEAN NETWORK OF
TERATOLOGY INFORMATION SERVICES

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EMA Pharmacovigilance 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

Summary: Ondansetron is a 5HT-3 receptor antagonist licensed for prevention and treatment of nausea and vomiting, either postoperative or caused by chemotherapy. It is also commonly used to treat nausea and vomiting in early pregnancy, although it is not specifically licensed for this purpose.

In August 2019, the European Medicines Agency (EMA) published the minutes of a meeting of the Pharmacovigilance Risk Assessment Committee (PRAC)[1] where it was recommended that all Marketing Authorisation Holders (MAH) for ondansetron containing medicines were to update their product literature to state that:

- Based on human experience from epidemiological studies, ondansetron is suspected to cause orofacial malformations when administered during the first trimester of pregnancy (Summary of Product Characteristics)
- The available epidemiological studies on cardiac malformations show conflicting results (Summary of Product Characteristics)
- Ondansetron containing medicines should not be used in the first trimester (Summary of Product Characteristics and Package Leaflet)
- If you are a woman of childbearing potential you may be advised to use effective contraception (Summary of Product Characteristics and Package Leaflet)

The Pharmacovigilance Risk Assessment Committee (PRAC) of the EMA provided their recommendations following the publication of two studies which together included approximately 160,000 first trimester exposures to ondansetron[2, 3], one of which identified a small increased risk of cleft lip and/or palate[2] while the other described a small increased risk of cardiac malformation[3] (this study has several important limitations including possible selection bias and exposure/outcome misclassification as indicated by the high rate of cardiac defects observed in comparison to the background rate). Although the findings of the study identifying associations with cleft lip and/or palate appear robust, the absolute increase in risk of orofacial cleft following first trimester maternal ondansetron use was very small, affecting approximately 14 per 10,000 births, compared to a background rate of 11 per 10,000 unexposed pregnancies[2]. This equates to three additional cases of orofacial cleft per 10,000 women using ondansetron during first trimester. In addition, the same study, which represents the best evidence available to date, found no statistically significant increased risk of cardiac defects overall after adjusting the results for a large number of relevant co-variates (aRR 1.01, 95% CI; 0.92 to 1.12)[2].

Ondansetron use in the management of nausea and vomiting in pregnancy is common (up to 15% in some studies)[4-6] and has increased in recent years[6]. This may be due to the improved efficacy and less problematic side effect profile for ondansetron in comparison with other second-line antiemetic drugs like metoclopramide[7]. There is also much more information available about safety during pregnancy for ondansetron than other antiemetic drugs, with data now available from over 168,000 women treated during the first trimester.[2, 3, 8-16]. This allows provision of more detailed and accurate counselling to pregnant women who require anti-emetic treatment. Paradoxically, less is

known about the safety of first-line or licensed antiemetics such as cyclizine, promethazine or doxylamine/pyridoxine in terms of drug safety in pregnancy.

For these reasons the European Network of Teratology Information Services (ENTIS) does not support the recommendations made by the EMA PRAC. We believe these would result in less effective control of maternal nausea and vomiting, increased maternal morbidity and hospitalisation, and an increased risk of termination of wanted pregnancies. Additionally, we would like to minimise the inevitable and disproportionate concern generated by the proposed changes to product literature for women who have taken ondansetron in the first trimester.

In view of the most recently published data, ENTIS recommend that ondansetron should be reserved as a **second line** agent for the treatment of nausea and vomiting in pregnancy (as currently recommended by the UK RCOG Green-top Guideline)[7]. Patients must be adequately counselled regarding the benefits of ondansetron together with the small increase in risk of orofacial cleft which **may** exist. Ondansetron should still be considered an option for patients with severe vomiting in pregnancy in whom first line treatments have failed.

Letter drafted by:

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Letter endorsed* by the European Network of Teratology Information Services (ENTIS)

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*Hedvig Nordeng and Thierry Vial recused themselves given their prior involvement in providing input to PRAC on this topic

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