Ondansetron: small increased risk of oral clefts following use in the first 12 weeks of pregnancy

Your attention is drawn to the United Kingdom Medicines and Healthcare products Regulatory Agency’s (MHRA) announcement that recent epidemiological studies suggest exposure to ondansetron during the first trimester of pregnancy is associated with a small increased risk of the baby having a cleft lip and/or cleft palate.

Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity. There is a growing body of evidence on the use of ondansetron in pregnancy that does not suggest an increase in the risk of overall congenital malformations combined.

Recent epidemiological studies report a small increased risk of orofacial malformations in babies born to women who used ondansetron in early pregnancy. Key evidence was an observational study of 1.8 million pregnancies in the USA of which 88,467 (4.9%) were exposed to oral ondansetron during the first trimester of pregnancy. 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). These data were recently reviewed within Europe and considered to be robust. As for all licensed medicines, the safety of ondansetron will be continuously monitored by the MHRA and relevant emerging information will be considered as it becomes available.

Outside of its authorised indications, ondansetron is also used second line for treating women with hyperemesis gravidarum, a severe and potentially life-threatening condition. If a physician considers, based on their professional judgement, the available evidence and the risks for mother and
baby of malnutrition in early pregnancy, that a licensed treatment (for example doxylamine/pyridoxine, Xonvea) is not suitable or not sufficient alone to control severe nausea and vomiting in pregnancy, and there is a special clinical need to use ondansetron, then this decision should be made in consultation with the patient after she has been fully informed of the potential benefits and risks of the different treatment options. Prescribers should refer to clinical guidance if treatment with ondansetron is considered for severe nausea and vomiting in pregnancy.

Detailed findings of studies include a retrospective cohort study of a medical claims database in the USA included 1,816,414 pregnancies between 2000 and 2013, of which 88,467 (4.9%) were associated with a prescription of ondansetron during the first trimester. Exposure to ondansetron during the first 12 weeks of pregnancy was linked with a small but statistically significant increased risk of orofacial cleft defects (adjusted relative risk [aRR] 1.24, 95% CI 1.03–1.48).

A case-control study of another US medical claims database 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). This study also linked ondansetron use during the first trimester with an increased risk of cardiac defects (adjusted OR 1.43, 95% CI 1.28–1.61). However, this finding conflicts with results from other studies. For example, Huybrechts and colleagues did not find a significant association for cardiac defects after adjusting for pre-defined confounding factors (aRR 0.99, 95% CI 0.93–1.06).

The recent observational studies have some limitations inherent to the data sources, but the findings are considered sufficiently robust to indicate that use of ondansetron during the first trimester of pregnancy is associated with a small increased risk of the baby having a cleft lip and/or cleft palate.

If the clinical decision is to offer ondansetron in pregnancy, women must be counselled on the potential benefits and risks of use, both to her and to her unborn baby and the final decision should be made jointly.

Please refer to the following website in MHRA for details:

In Hong Kong, there are 28 registered pharmaceutical products containing ondansetron. All products are prescription-only medicines. So far, the Department of Health (DH) has received 3 cases of adverse drug reaction related to ondansetron, but these cases are not related to oral clefts in babies born to women who used ondansetron in early pregnancy. DH will remain vigilant on safety update of

We build a healthy Hong Kong and aspire to be an internationally renowned public health authority
the drug issued by other overseas drug regulatory authorities. Healthcare professionals are advised to balance the risk of possible adverse effects against the benefit of treatment.

Please report any adverse events caused by drugs to the Undesirable Medical Advertisements and Adverse Drug Reaction Unit of the DH (tel. no.: 2319 2920, fax: 2319 6319 or email: adr@dh.gov.hk). For details, please refer to the website at Drug Office under “ADR Reporting”: http://www.drugoffice.gov.hk/adr.html. You may wish to visit the Drug Office's website for subscription and browsing of "Drug News" which is a monthly digest of drug safety news and information issued by Drug Office.

Yours faithfully,

(Joseph LEE)
for Assistant Director (Drug)