

2nd October 2019

Dear Dr Straus,

RE: EMA/516514/2019

Thank you for your reply dated 26th September. We appreciate the duty to highlight *possible* increase risk of cleft lip/palate (CLP) with ondansetron where it may be used in pregnancy for its licensed indications, specifically chemotherapy/radiotherapy and postoperative nausea and vomiting. However, in relation to those licensed indications the interpretation of the data and wording of the warning is still inaccurate and disproportional to the level of risk, particularly when considered in the context of those indications. The number of patients in both licensed categories is extremely small, in the case of chemotherapy it may be zero because these patients are required to delay chemotherapy or terminate the pregnancy and, bar emergency surgery, it is extremely rare to conduct elective surgery in the first trimester. The number of oral clefts prevented by the additional warning on packaging will be negligible and we would question the need to publish the warning at all given the 'knock on effect' is to put women and prescribers off using ondansetron for its unlicensed indication for hyperemesis gravidarum, which you are not advising on.

Furthermore, the data in the Huybrechts *et al* (2018) study were predominantly from patients with a diagnosis of pregnancy nausea and vomiting and excluded women who had used ondansetron in the 3 months prior to pregnancy and would therefore be unlikely to include those with a cancer diagnosis. Dr Huybrechts is checking the data for further information on the prescription indications to confirm this. To extrapolate data findings from one indication of off license use and apply it to the drugs licensed use in this context is inappropriate given the vast confounders that could be at play with the various indications.

While I appreciate the difference between licensed and unlicensed uses of medications and your relative responsibilities, I must press the issue of the real-world effect of your statements. Hospitals across the UK are already altering their guidelines to deny patients ondansetron in the first trimester and countries own medicine's agencies are releasing statements to the same effect. Women are already being told to stop taking it by their healthcare professionals because "*there is an alert out that its dangerous*". And we have had women calling our helpline facing no option other than termination because they are "not allowed" ondansetron anymore.

I would very much appreciate a teleconference on this matter, although myself and colleagues including Professor Nelson-Piercy, Dr Huybrechts and Dr Cleary will be in Amsterdam with myself and Dr Painter for a conference on Hyperemesis Gravidarum next week on the 10th-11th October, which could be a good opportunity to meet and discuss as you are Amsterdam based I believe?

I look forward to hearing from you on this urgent matter soon

Yours Sincerely,



Caitlin Dean, on behalf of

Dr Huybrechts, Prof Nelson-Piercy, Dr Kenneth Hodson, Dr Rebecca Painter, Ms Clare Murphy (bpas),
Dr Brian Cleary