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Pharmacovigilance Risk Assessment Committee (PRAC)

Updated Signal assessment report on birth defects following in-utero exposure during the first trimester of pregnancy arising from recent publications with ondansetron¹

EPITT no: 19353

Confirmation assessment report	07 February 2019
Adoption of first PRAC recommendation	14 March 2019
Preliminary assessment report on additional data ²	17 June 2019
Deadline for comments ³	1 July 2019
Updated rapporteur assessment report ³	4 July 2019
Adoption of second PRAC recommendation ³	11 July 2019

Note: Assessment report as adopted by the PRAC with all information of a commercially confidential nature deleted.

¹ In case there are several products authorised for the same active substance and the signal applies only to a specific product, please add the product name in brackets. For product classes, please only state the class and list the relevant active substances in the administrative information table.

² Please delete or repeat as applicable

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Administrative information

Active substance(s) (invented name)¹	Ondansetron
Strength(s)	<Text> [Only if relevant to the signal]
Pharmaceutical form(s)	<Text> [Only if relevant to the signal]
Route(s) of administration	<Text> [Only if relevant to the signal]
Indication(s)	<Text> [Only if relevant to the signal]
Marketing authorisation holder(s)	
Authorisation procedure [Tick the appropriate box(es) below.]	
<input type="checkbox"/>	Centralised
<input type="checkbox"/>	Mutual recognition or decentralised
<input checked="" type="checkbox"/>	National

Adverse event/reaction:³	Structural birth defects (cardiac defects and orofacial cleft) after first trimester exposure in pregnancy
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Signal validated by:	UK
Date of circulation of signal validation report:	10 January 2019
Signal confirmed by:	SI
Date of confirmation:	07 February 2019
PRAC Rapporteur appointed for the assessment of the signal:	Gabriela Jazbec (SI) gabriela.jazbec@jazmp.si

Declarations

The assessor confirms that the report does not contain any commercially confidential information (e.g. intellectual property, ongoing assessments, development plans) or reference to pharmacovigilance inspections.

Whenever the above box is un-ticked please indicate the section and page where the confidential information is located here:

Confidential information:

³ Please use MedDRA terminology whenever possible

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1. Background

This signal originates from the United Kingdom national competent authority (UK NCA), MHRA, and addresses new available data on the risk of birth defects in case of exposure to ondansetron during pregnancy, published by Zambelli-Weiner A et al. (2019)¹³ and Huybrechts KF et al. (2018)¹⁴.

Ondansetron, a 5-HT₃ receptor antagonist, was first approved in the US in 1991, and in the EU in 1990. It is indicated in the EU for the management of nausea and vomiting induced by cytotoxic chemotherapy and radiotherapy (adults and children > 6 months) and for the prevention and treatment of post-operative nausea and vomiting (adults and children > 1 month).

It is used off label for nausea and vomiting in pregnancy (NVP). However, this signal has potential public health importance and is also of relevance to the licensed indication in any cases where the patient may be or become pregnant.

The published studies were based in the United States, where ondansetron is one of 8 drugs currently recommended by the 2018 clinical guidelines from the American College of Gynecology (ACOG) for the treatment of NVP: ondansetron, Diclegis® (doxylamine succinate and pyridoxine hydrochloride), metoclopramide, promethazine, and methylprednisolone, prochloroperazine, chlorpromazine, and trimethobenzamide). In the US ondansetron is recommended as third line pharmacologic therapy. However, Zambelli et al. (2019)¹³ suggest that, as of 2014, it is the most frequently prescribed medication of nausea and vomiting in pregnancy (NVP) and hyperemesis gravidarum (HG) in the US, with use increasing from <1% of pregnancies in 2001 to over 22% in 2014.

UK NCA is also aware that in the UK, national clinical guidelines for NVP initially recommend dietary advice, rest, ginger extract, wrist acupressure, and avoidance of iron containing preparations; if these fail and the woman has persistent symptoms, drug treatment is suggested with antiemetic antihistamine or phenothiazine being recommended as first line approaches; if these fail an anti-emetic from a different class such as metoclopramide or oral ondansetron for no more than 5 days is suggested. The recommended ondansetron dose is aligned to that used for the indicated management of nausea and vomiting induced by cytotoxic chemotherapy and radiotherapy. CPRD⁴ usage analysis suggests that, in the UK *primary care* setting, the proportion of all eligible pregnancies in CPRD that had a record of ondansetron prescription during pregnancy was 0.25% in 2013 and rose to approximately 1% in 2017. Use in secondary care would add to this usage estimate. It is possible that similar off-label use occurs in other member states and published studies suggest that this may occur in Sweden and Denmark^{3,6}.

Previous epidemiological studies^{11,12} (briefly discussed in [Annex 1](#) of this signal paper) regarding ondansetron use in pregnancy have been performed which, although have not highlighted an overall risk of adverse fetal outcomes, have provided some data suggestive of the risk of specific outcomes - cardiac defects and cleft palate.

Currently in the EU ondansetron is not contraindicated in pregnancy. Although the SmPC section 4.6 suggests that ondansetron is not recommended in pregnancy, description is limited and there is no reference to data derived from published post marketing observational studies of ondansetron use in pregnancy (see [Annex 2](#) in this report). The PRAC is asked to consider whether the EU SmPC should be updated.

⁴ CPRD: Clinical Practice Research Datalink; UK data driving real-world evidence

Highlights

- Seriousness: Serious congenital anomaly
- Evidence:

1. A recently published large US based study suggests that first trimester medically administered ondansetron exposure is associated with an increased risk of cardiac defects (adjusted OR 1.43, 95%CI, 1.28-1.61) and with a (non-statistically significant) increased risk of orofacial cleft defects (aOR 1.30, 95%CI, 0.75-2.25).

Zambelli-Weiner A et al. First Trimester Ondansetron Exposure and Risk of Structural Birth Defects. *Reprod Toxicol.* 2019 Jan; 83: 14–20. DOI: [[10.1016/j.reprotox.2018.10.010](https://doi.org/10.1016/j.reprotox.2018.10.010)] (online 29 October 2018)¹³

2. Another large US based study, (published very recently at time of writing this signal document) also suggests that first trimester use of ondansetron in pregnancy is associated with a small but significant increased risk of orofacial cleft defects (aRR 1.24, 95%CI, 1.03 - 1.48), but found no statistically significant association between ondansetron and cardiac malformations (adjusted RR, 0.99; 95%CI, 0.93 - 1.06) or congenital malformations overall (aRR, 1.01; 95%CI, 0.98 - 1.05).

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. DOI:[[10.1001/jama.2018.18307](https://doi.org/10.1001/jama.2018.18307)]¹⁴

UK NCA presented evidence that is considered to contain new information on the malformation profile. Therefore, it is deemed justified to re-evaluate risk minimisation measures in place for the use of ondansetron during pregnancy in view of the currently available data.

2. Initial evidence

2.1. Signal validation

The UK NCA has provided the following evidence.

The Zambelli et al. (2019)¹³ study found that first trimester medically administered ondansetron exposure was associated with an increased risk of cardiac defects (adjusted OR:1.43, 95% CI: 1.28-1.61) and with a (non-statistically significant) increased risk of orofacial cleft defects (aOR: 1.30, 95% CI: 0.75-2.25).

Overall, UK consider this is a robust study which addresses the key limitations of previous observational studies which had assessed the safety of in-utero exposure to ondansetron such as: limited statistical power (in some studies); the assessment of congenital anomalies overall rather than individual birth defects; and exposure misclassification. This study had a large sample size which enabled assessment of pre-specified congenital defects of interest and the primary analysis was restricted to clinically administered ondansetron minimising the risk of exposure misclassification bias. A series of sensitivity analyses provide some reassurance regarding the potential for unmeasured confounding, potential confounding by indication, and potential detection bias.

However, despite the thorough design, there are limitations that create some uncertainties in the interpretation of results. The two main limitations are the potential for residual confounding (including possible differences in lifestyle factors, which were not captured by the source database, in women prepared to medicate during pregnancy compared to in women who were not) and potential for

outcome and exposure misclassifications (which may result in an underestimate of the risk). These limitations are inherent to the nature of the data source and information on key lifestyle factors could only be collected using active data collection which would be unfeasible given the large sample size needed to assess the risk of specific birth defects.

Full description and discussion on publication by Zambelli et al. (2019)¹³ and comments on more recently published Huybrechts et al. (2018)¹⁴ study is provided in [Annex 1](#).

The UK proposes to ask PRAC to consider whether the EU SmPC should be updated.

The UK also considers that some of the limitations of the Zambelli et al. (2019)¹³ study published may be addressed, if possible, by posing questions to the authors of the study. Questions for the consideration of the assessing member state are provided below.

Suggested question to the authors, if possible:

- With regards to the exposure definition for the primary analysis and the sensitivity analysis to address confounding by indication, there remains the question as to whether the patients who were administered ondansetron in a hospital or clinic setting were those patients presenting with the most extreme symptoms : therefore to what extent did the sensitivity analysis utilising unexposed patients with the diagnosis of hyperemesis gravidarum (HG) or nausea and vomiting in pregnancy (NVP) provide a balanced comparison in relation to the severity of condition? Could the authors provide any more information relating to this? What percentage of exposed cases had the diagnosis of HG and what percentage of the non-exposed patients used in the sensitivity analysis have diagnosis of HG? Did the authors consider a sensitivity analysis using women diagnosed with NVP/HG and treated with other antiemetic in pregnancy as a comparator?
- Are the authors able to provide the effect estimates from the model after including all pre-specified covariates?
- Are the authors able to comment on the effect estimate by a sensitivity analysis restricting the exposure window to weeks 0-8 in the first trimester, key to cardiovascular development?
- Could the author comment on the impact of missing cases due spontaneous abortions or pregnancy termination? Furthermore, could the author consider a sensitivity analysis assessing the impact of infant mortality within the first year on the effect estimates?
- For the sensitivity analysis assessing the impact of external adjustment to smoking, as presented in the supplementary data, are the authors able to provide confidence intervals? Are the authors able to provide a quantitative bias analysis accounting for the combined effect of multiple unmeasured confounders (such as smoking, alcohol consumption, OTC drug use, non-prescription folic acid intake, etc)

2.2. Signal confirmation

The association of congenital malformation with ondansetron use during pregnancy has already been the object of an evaluation in PSUSA (PSUSA/00002217/201502) procedure follow-up (i.e. PSUFU), discussed at PRAC in April 2016 and PSUSA/00002217/201802 in October 2018.

A detailed cumulative review and discussion on published literature in PSUFU and last PSUSA has concluded that there are no consistent and compelling results reported in published literature regarding the association between taking ondansetron during pregnancy and congenital anomalies. Studies done by Einarson et al. (2004)¹⁵, Asker et al. (2005)¹⁶, Colvin et al. (2013)⁵, Pasternak et al. (2013)⁶, and

Parker et al. (2018)⁹ found no statistically significant increased risk of major birth defects, while Danielsson et al. (2014)³ and Anderka et al. (2012)⁴ found increased risks of cardiac defects, more specifically cardiac septal defects, and cleft palates (but not cleft lip with or without cleft palate), respectively.

Limitations that have hampered above studies were small sample size (i.e. inadequate power, particularly for important subgroup analyses) and other methodological limitations (risk of bias from exposure misclassification due to reliance on filled prescriptions, recall bias, possibility of chance finding, confounding (either by indication or other data confounders and variables), exposure to the medication was not limited to sensitive windows of organogenesis).

The PRAC concluded at that time there is no consistent or compelling evidence indicating that the off-label exposure to ondansetron in early pregnancy causes major birth defects, including congenital cardiac defects. In addition, the PRAC agreed that the available data neither confirm nor refute an increased risk for congenital malformations. Therefore, no updates of product information, which states that use of ondansetron during pregnancy is not recommended, were necessary in light of the knowledge at that time.

This report addresses the signal which originates from the article published by Zambelli et al. (2019)¹³ and Huybrechts et al. (2018)¹⁴ and addresses new available data on the risk of birth defects in case of exposure to ondansetron during pregnancy.

In addition to the thorough review of the Zambelli et al. (2019)¹³, performed by UK NCA (see [Annex 1](#)), the review of Huybrechts et al. (2018)¹⁴ study and its strengths and limitations are evaluated below. Meta-analysis performed and sent by FR NCA, ANSM, as an additional evidence for this signal received very recently at time of writing this signal assessment report.

Study by Huybrechts et al. (2018)¹⁴ overview

Huybrechts and colleagues conducted a large **retrospective cohort study** based on data from the US nationwide Medicaid Analytic eXtract (MAX)⁵, a data set that included more than 1.8 million pregnancies resulting in live births between 2000 and 2013 among publicly insured pregnant women.

The cohort consisted of 1 816 414 pregnancies contributed by 1 502 895 women enrolled in Medicaid from 3 months before the last menstrual period through 1 month or longer after delivery; infants were enrolled in Medicaid for at least 3 months after birth. Excluded were pregnancies with chromosomal abnormalities and those exposed to known teratogenic medications (i.e., warfarin, antineoplastic agents, lithium, isotretinoin, misoprostol, thalidomide) during the first trimester.

Women were considered exposed if they filled at least 1 ondansetron prescription during the first 3 months of pregnancy. Women who did not fill a prescription for ondansetron during the 3 months before the start of pregnancy through the end of the first trimester were considered unexposed. Women who filled an ondansetron prescription during the 3 months before the start of pregnancy were excluded to avoid contaminating the reference group with women who still had medication available for ingestion after the start of pregnancy.

Primary outcomes were cardiac malformations and oral clefts diagnosed during the first 90 days after delivery. Secondary outcomes included congenital malformations overall and subgroups of cardiac malformations and oral clefts (i.e., palate, lip, or lip and palate).

⁵ MAX data include demographic and insurance enrollment information, medical visits and hospitalizations, diagnoses and procedures received as an inpatient or an outpatient, and prescriptions filled on an outpatient basis

From prescription data, it turned out that among 1 816 414 pregnancies, 88,467 (4.9 %) of pregnancies were exposed to ondansetron during the first trimester, the crucial period of fetal organ formation. Exposed women were more likely to be white, to have a diagnosis of psychiatric and neurological conditions, and to smoke. They were also more likely to fill a prescription for other medications used to treat nausea and vomiting during pregnancy (metoclopramide, promethazine, pyridoxine), for psychotropic medications, for corticosteroids, and for suspected teratogens.

Overall, 14 577 of 1 727 947 unexposed and 835 of 88 467 exposed infants were diagnosed with a cardiac malformation, for an **absolute risk** of 84.4 (95%CI, 83.0 to 85.7) in unexposed infants and 94.4 (95%CI, 88.0 to 100.8) per 10 000 births in exposed infants, and an unadjusted relative risk (RR) of 1.12 (95%CI, 1.04–1.20). Additionally, two fetal cardiac malformations had been linked to ondansetron in unadjusted analyses: *ventricular septal defects* (RR 1.14, 95%CI, 1.04-1.27; 400 exposed and 6826 unexposed infants) and *secundum atrial septal defects* (RR 1.37, 95%CI, 1.19-1.57; 216 exposed and 3080 unexposed infants).

The absolute risk of oral clefts was 11.1 per 10 000 births (95%CI, 10.6 to 11.6; 1921 unexposed infants) and was 14.0 per 10 000 births (95%CI, 11.6 to 16.5; 124 exposed infants), resulting in an unadjusted RR of 1.26 (95%CI, 1.05–1.51). The increased risk for oral clefts was attributable to *cleft palate* (65 exposed and 988 unexposed infants) with unadjusted RR, 1.29 (95%CI, 1.00-1.65). There was no evidence of an increased risk for cleft lip (33 exposed vs 620 unexposed cases; unadjusted RR, 1.04 (95%CI, 0.73-1.48) or cleft lip with cleft palate (48 exposed vs 925 unexposed cases; unadjusted RR, 1.01 (95%CI, 0.76-1.35)).

The absolute risk of any congenital malformation was 313.5 per 10 000 births (95% CI, 310.9 to 316.1; 54 174 unexposed infants) and was 370.4 (95%CI, 358.0 to 382.9; 3277 exposed infants), corresponding to an unadjusted RR of 1.18 (95%CI, 1.14 to 1.22). In addition, an exploratory analysis showed an uptick in *ear malformations* among ondansetron users. The absolute risks were 3.8 (95%CI, 2.7-5.4) per 10 000 exposed and 2.4 (95% CI, 2.2-2.7) per 10 000 unexposed pregnancies, corresponding to an adjusted RR of 1.64 (95%CI, 1.16-2.33) and an RD of 1.5 (95% CI, 0.2-2.8) per 10 000 births.

The results are shown in Table 2 and Figure 1 below (original from the manuscript):

Table 2. Absolute Risk of Congenital Malformations Among Infants Born to Mothers With and Without Exposure to Antiemetic Medications^a

Exposure Group	Total No. of Pregnancies	Primary Outcomes				Secondary Outcome	
		Cardiac Malformations		Oral Clefts		Any Congenital Malformation	
		Events, No. of Affected Infants	Risk, No./10 000 Infants (95% CI)	Events, No. of Affected Infants	Risk, No./10 000 Infants (95% CI)	Events, No. of Affected Infants	Risk, No./10 000 Infants (95% CI)
No exposure	1 727 947	14 577	84.4 (83.0-85.7)	1921	11.1 (10.6-11.6)	54 174	313.5 (310.9-316.1)
Ondansetron	88 467	835	94.4 (88.0-100.8)	124	14.0 (11.6-16.5)	3277	370.4 (358.0-382.9)
Other antiemetic	185 876	1629	87.6 (83.4-91.9)	219	11.8 (10.2-13.3)	6141	330.4 (322.3-338.5)
Metoclopramide	52 818	476	90.1 (82.1-98.2)	63	11.9 (9.0-14.9)	1732	327.9 (312.7-343.1)
Promethazine	139 932	1213	86.7 (81.8-91.5)	165	11.8 (10.0-13.6)	4634	331.2 (321.8-340.5)
Pyridoxine	9036	77	85.2 (66.3-104.2)	<11	7.6 (2.0-13.5)	283	313.2 (277.3-349.1)

^a Cell sizes with fewer than 11 are suppressed in accord with the Centers for Medicare & Medicaid Services cell size suppression policy.

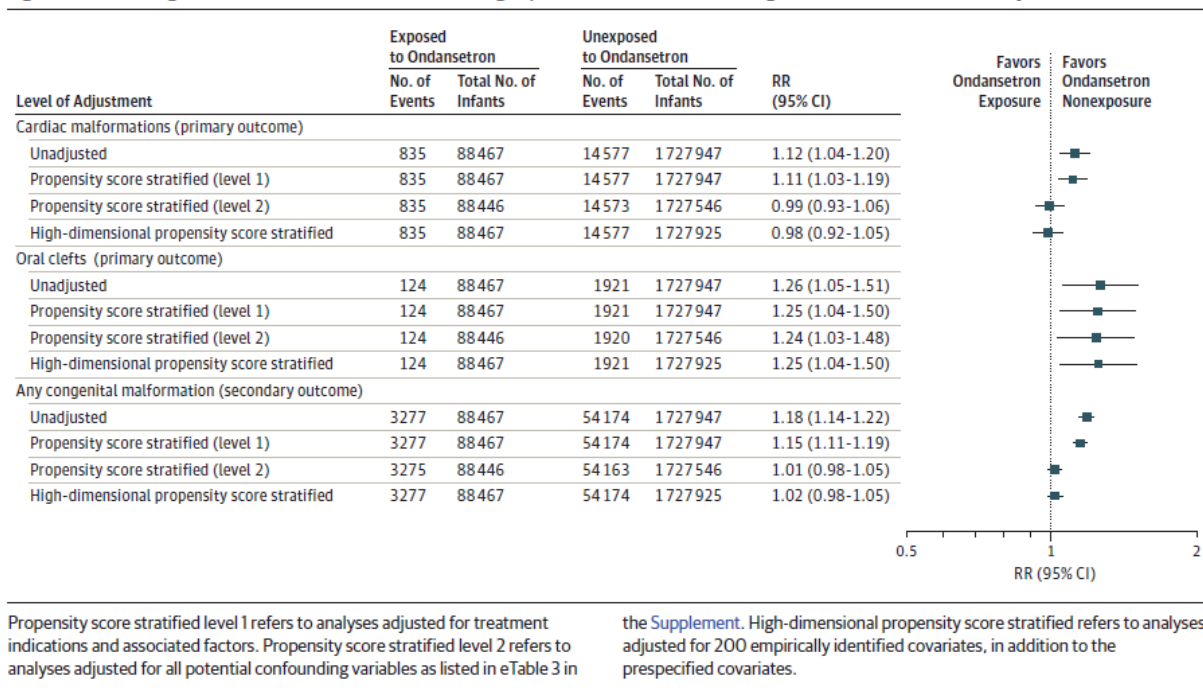
A broad range of potential confounders and proxies for confounders were considered, including treatment indication (nausea and vomiting during pregnancy, hyperemesis gravidarum) and associated conditions (weight loss, electrolyte and laboratory abnormalities, dehydration, gastroesophageal reflux), calendar year, state of residence, age, race, multiple gestation, maternal conditions, concomitant medication use, and general markers of the burden of illness. Maternal morbidity and concomitant medication use were measured from 3 months before the start of pregnancy to the end of the first trimester. Maternal conditions were assessed based on diagnostic codes and included psychiatric and neurological conditions (anxiety, depression, migraine, or other headache) and other

chronic conditions (diabetes, hypertension, renal disease, Crohn disease, irritable bowel syndrome, ulcerative colitis, overweight or obesity, underweight, illicit drug or alcohol abuse or dependence, smoking). Concomitant medications assessed included psychotropic medications (anticonvulsants, antidepressants, benzodiazepines), triptans, oral hypoglycemics, insulin, antihypertensives, progestins, corticosteroids, and suspected teratogens (fluconazole, methimazole, danazol, propylthiouracil, aminoglycosides, folic acid antagonists, potassium iodide, tetracycline). Propensity score stratification (using logistic regression) was used to control for treatment indication and associated factors (propensity score level 1), for all potential confounding variables (propensity score level 2) and 200 empirically defined covariates, in addition to the prespecified covariates (high-dimensional propensity score analyses, i.e. confirmatory analyses).

After stratification on the **propensity score**, all measured patient characteristics were balanced between the ondansetron-exposed and unexposed groups judged by an absolute standardized difference of less than 0.1. Although adjusting for the treatment indications and associated factors did not substantially change the crude risk estimates, accounting for all prespecified potential confounding variables (propensity score level 2) resulted in a null point estimate for cardiac malformations (adjusted relative risk (RR), 0.99; 95%CI, 0.93 to 1.06; risk difference (RD), -0.8; 95% CI, -7.3 to 5.7 per 10000 births) and for congenital malformations overall (RR, 1.01; 95%CI, 0.98 to 1.05; RD, 5.4; 95%CI, -7.3 to 18.2 per 10 000 births). For oral clefts, the adjusted RR remained statistically significant 1.24 (95%CI, 1.03 to 1.48) and the RD was 2.7 (95%CI, 0.2 to 5.2 per 10 000 births). These findings were confirmed in confirmatory analyses using high-dimensional propensity score analyses.

The results are shown in Figure 1 below (original from the manuscript):

Figure 1. Risk of Congenital Malformations in Infants Following Exposure to Ondansetron During the First Trimester: Main Analyses



Propensity score stratified level 1 refers to analyses adjusted for treatment indications and associated factors. Propensity score stratified level 2 refers to analyses adjusted for all potential confounding variables as listed in eTable 3 in

the Supplement. High-dimensional propensity score stratified refers to analyses adjusted for 200 empirically identified covariates, in addition to the prespecified covariates.

Additional **sensitivity analyses** were conducted to test the robustness of the primary results.

- The reference group was changed to women who filled a prescription for a different antiemetic medication (metoclopramide, promethazine and pyridoxine and other antiemetics) during the

first trimester because they might be more comparable with women exposed to ondansetron than women who were never treated with antiemetic agents during pregnancy.

⇒ Results when using women exposed to other antiemetics as the reference group were consistent with the main analyses:

- adjusted RR for cardiac malformations, 1.01; 95%CI, 0.92-1.12;
- aRR for oral clefts, 1.32; 95%CI, 1.03-1.70;
- aRR for any congenital malformation, 1.00; 95%CI, 0.95-1.05.

Results were similar across the individual antiemetic agents.

- To evaluate the potential effect of exposure misclassification, exposure was redefined as having filled 2 or more prescriptions for ondansetron during the first trimester.

⇒ The findings generally were not sensitive to changes in the exposure definition, except for oral cleft outcome, where no statistically significant association for oral clefts in comparison to the main analyses was observed:

- aRR for cardiac malformations, 1.06; 95%CI, 0.95-1.19;
- aRR for oral clefts, 1.15; 95%CI, 0.85-1.56;
- aRR for any congenital malformation, 1.02; 95%CI, 0.96-1.08.

- Because the period of greatest sensitivity to teratogens for oral clefts is likely the later part of the first trimester, the exposure window was redefined as 6 to 12 weeks after the date of last menstrual period.

⇒ The findings generally were not sensitive to changes in the exposure definition.

- aRR for cardiac malformations, 1.00; 95%CI, 0.93-1.07;
- aRR for oral clefts, 1.25; 95%CI, 1.03-1.51;
- aRR for any congenital malformation, 1.01; 95%CI, 0.98-1.05.

- In a negative control analysis, the risk of malformations was assessed in women who filled their first ondansetron prescription in gestational months 5 to 8, which is after the etiologically relevant window.

⇒ No increased risk was observed for oral clefts:

- aRR for cardiac malformations, 1.11; 95%CI, 0.98-1.26;
- aRR for oral clefts, 0.98; 95%CI, 0.66-1.45;
- aRR for any congenital malformation, 1.07; 95%CI, 1.00-1.14.

A null finding in this analysis provides indirect evidence of no substantial residual confounding. The authors also used this group with first ondansetron exposure in months 5 to 8 as an alternative reference group.

Focusing on cardiac malformations and oral clefts (the main congenital anomalies identified with any consistency in prior studies), the authors found no significant association between ondansetron and cardiac abnormalities (an adjusted relative risk, 0.99; 95%CI, 0.93 to 1.06). They also detected a small but statistically significant increased risk of oral clefts with first-trimester exposure to ondansetron (an adjusted RR, 1.24; 95%CI, 1.03 to 1.48). After multiple adjustments, the authors also found no difference in the risk of overall congenital malformations for infants of women exposed to ondansetron.

The authors concluded that among offspring of publicly insured pregnant mothers enrolled in Medicaid, first trimester exposure to ondansetron was not associated with increased risk of cardiac malformations or congenital malformations overall after accounting for measured confounders but was associated with a small increased risk of oral clefts.

Comments on study strengths and limitations

We consider Huybrechts et al. (2018)¹⁴ study (a large retrospective cohort study, including the measurement of multiple potential confounders) a robust study, which also addresses some limitations of previous observational studies which had assessed the safety of in-utero exposure to ondansetron including limited statistical power in some studies and consequently the assessment of congenital anomalies overall rather than individual birth defects; and residual or unmeasured confounding, such as the underlying indication or its severity, maternal comorbidities (e.g. diabetes) and concomitant medication use.

The **key strength** of Huybrechts et al. (2018)¹⁴ study lies in the size of the cohort. The study used data from more than 1.8 million pregnancies which enabled assessment of pre-specified congenital defects of interest and therefore carries strong statistical power.

The advantage with cohort studies is that identification of patients before the outcome is known will eliminate recall bias. Therefore, another strength in Huybrechts et al. (2018)¹⁴ study could be the fact that the information on ondansetron exposure was collected in prospective manner based on filled prescriptions, thereby negating any possible recall bias. However, the same strength is also the limitation of the study, as the assumption that just because a prescription was filled the medication was actually taken during the pregnancy, presents methodological problem. Especially because antiemetics are often prescribed prophylactically (as needed).

Additionally, the data source, Medicaid Analytic eXtract (MAX) contains rich patient-level information for confounding control, including maternal demographic characteristics, medical conditions, and medication exposures.

To minimise the possible confounding effect of the indication for treatment, in addition to comparing exposed to unexposed women, ondansetron-exposed women were compared with women exposed to other antiemetics. Consistent results with the primary analysis were documented.

The robustness of the primary analysis was assessed in a series of additional sensitivity analyses including changing the reference group to women exposed to any of the 3 other antiemetics; filling at least 2 ondansetron prescriptions; changing the exposure window to 6 to 12 weeks after last menstrual period; using pregnancies with first exposure to ondansetron 5 to 8 months after last menstrual period (reference); and changing the exposure window to 5 to 8 months after last menstrual period (negative control analysis). Results of sensitivity analyses were consistent with the main analyses, except for oral clefts where change in statistical power was observed.

The study has also several (typical) **limitations** that create some uncertainties in the interpretation of results.

Medicaid data have great potential for examining patterns of medication use and outcomes but pose some methodological difficulties.

1) Filling the prescription (exposure misclassification); use is not necessarily implied by filling of prescription and therefore presents the uncertainty of whether women who filled a prescription actually took the medication, which could bias the results toward the null.

However, it is a typical methodological limitation of databases which link prescriptions and birth defects, although they have a statistical power because they analyse large population datasets.

To address this limitation, sensitivity analyses in which women were required to have filled at least 2 prescriptions during the first trimester were conducted based on the notion that if a woman refills a prescription she is likely to have consumed the prescribed medication. This approach showed slightly increased risks for cardiac malformations and congenital malformations overall, however non-statistically significant.

2) There is always concern about residual confounding due to unmeasured or poorly measured characteristics.

In Huybrechts et al. (2018)¹⁴ study important confounding factors such as diabetes, overweight or obesity, underweight, illicit drug or alcohol abuse or dependence, and smoking were accounted for in the analyses, however, accounting for folic acid intake is missing. There is also the possibility that there might have been some other unrecognised factor involved especially since all the women in the study were uninsured and treated under Medicaid insurance and therefore included a higher percentage of women from disadvantaged communities.

Another example, highlighted by the authors: the absence of a recorded diagnosis is equated with absence of the disease, because it is possible, that the clinician did not record the diagnosis. This may have resulted in some misclassification of the confounder information and hence affect their ability to control for confounding. Although negative residual confounding is typically not a concern for null findings because drug exposure is not expected to be associated with factors protective against congenital malformations (i.e., cardiac malformations or congenital malformations overall), positive residual confounding could be a potential explanation for the increased risk in oral clefts.

To account for (potential residual) confounding, propensity score stratification, use of alternate reference groups, and a negative control analysis were used.

Given the detailed information collected on these women and their pregnancies, and the multiple analyses conducted on this data, the likelihood of unmeasured confounders affecting the findings was thought to be low.

3) Potential to selection bias due to the restriction of the cohort to livebirths.

The study cohort consisted of livebirths, and not pregnancies that ended in stillbirth, spontaneous or therapeutic abortions, so any birth defects that resulted in losing a pregnancy were not included.

If livebirth frequency is the same in the ondansetron exposed and unexposed pregnancies, within the levels of the covariates included as potential confounders, then the relative risk estimates obtained from the analyses are unbiased. However, if non-live births occur more frequently in the ondansetron-exposed pregnancies, then estimates from the main analysis may be biased towards the null. The authors quantified the potential for selection bias due to the restriction of the cohort to livebirths.

The most extreme scenario considered, using literature-based estimates, was a probability of livebirth of 80% among unexposed infants without a malformation, 55% among unexposed infants with a cardiac or any type of malformation, 70% among unexposed infants with oral clefts, and a 20% absolute decrease in the probability of livebirth in those exposed to ondansetron compared with those unexposed for both malformed and nonmalformed fetuses. Based on these assumptions, the RR estimate would remain below 1.2 for cardiac malformations and for any congenital malformation, and under the most extreme assumption, the RR estimate for oral clefts would shift from 1.24 to 1.30. The actual risks may therefore be slightly higher.

4) Focused on individuals with Medicaid insurance.

Medicaid data include demographic and insurance enrolment information, medical visits and hospitalizations, diagnoses and procedures received as an inpatient or an outpatient, and prescriptions

filled on an outpatient basis. Medicaid is the predominant payer for low-income Americans and is crucial for people with disabilities. In Medicaid data there is strong representation of vulnerable populations including racial/ethnic minorities. Data on treatments and diagnoses come from providers, avoiding self-report and nonresponse biases that are issues in interview-based studies.

However, a central limitation with many implications is that Medicaid data are collected for administrative rather than research purposes.

However, a key strength of Medicaid data is the very large number of individuals represented and corresponding statistical power for fine-grained analyses of important subgroups, rare conditions, complex patterns of comorbidity, and adverse events. Medicaid covers the medical expenses for approximately 50% of all pregnancies in the United States, making this an important population to study.

The cohort inclusion criteria in the Huybrechts et al. (2018)¹⁴ study resulted in the selection of a more disadvantaged subpopulation within Medicaid, mostly composed of low income adults, multiparae, and women with disabilities. Therefore, the study could have limited generalizability to the broader population given its focus on a more disadvantaged population on Medicaid. However, given the detailed information collected on these women and their pregnancies, and the multiple analyses conducted on this data, the likelihood of unmeasured confounders affecting the findings is thought to be low.

5) Newborns were followed for the first 3 months of life unless they died sooner.

Adverse outcome data of foetal exposure comprise both structural malformations, ('typical' birth defects, often – but not always – detected in the neonatal period) and non-structural or long-term functional effects (not easily detected in the immediate neonatal period) that can be potentially important but also difficult to detect or define. Some cardiac, renal and intestinal malformations are not always diagnosed immediately postpartum, and incidence is significantly influenced by duration of follow-up. Therefore, long-term follow-up is preferably to capture congenital malformations of interest.

The risk for cardiac defects in Huybrechts et al. (2018)¹⁴ study could therefore be underestimated (aRR 0.99 (0.93 – 1.06)), as study only captured outcomes diagnosed in the three months after birth, and after accounting additional cases, the risk could become borderline statistically significant.

6) One additional limitation of the data set could be that prescriptions for the current recommended first- line treatment, pyridoxine (with or without doxylamine), may not have been completely captured. The prescription combination of doxylamine and pyridoxine was approved by the US Food and Drug Administration in 2013, the final year the MAX data were queried. Many women may have obtained these components over-the-counter, and thus the true polypharmacy rates for nausea and vomiting treatment are not accounted for in the data set.

Conclusion

The epidemiological evidence regarding the risk of congenital malformations in association with the use of ondansetron during pregnancy to date was limited and conflicting. While some studies suggested no increase in birth defects in women who took ondansetron early in pregnancy^{5,6,15}, others raised safety concerns notably an increased risk of cleft palate and cardiac malformations^{4,8,9} (see [Annex 3](#) for short overview of prior studies).

Two recent largest epidemiological studies, which address some limitations of prior epidemiological studies, but are also affected by similar and additional limitations which future studies are unlikely to be able to address entirely, suggest an increased risk for specific structural birth defects in offspring in

association with the use of ondansetron in the first trimester of pregnancy, although the data is somewhat conflicting. The effect estimates are relatively low, but because of several strengths they both add to the body of evidence.

The Zambelli et al. (2019)¹³ study showed a possible association of the use of ondansetron in first trimester of pregnancy with a statistically significant increased risk of cardiac malformations (adjusted OR:1.43, 95%CI: 1.28-1.61) and with a (non-statistically significant) increased risk of orofacial cleft defects (aOR: 1.30, 95%CI: 0.75-2.25) (there is a significant variability around the estimates due to small sample size).

While Huybrechts et al. (2018)¹⁴ study found no statistically significant association between ondansetron and cardiac malformations (adjusted RR, 0.99; 95%CI, 0.93 to 1.06) or congenital malformations overall (aRR, 1.01; 95%CI, 0.98 to 1.05), and a small but statistically significant increased risk of orofacial cleft defects (aRR, 1.24; 95%CI, 1.03 to 1.48).

However, when taking into account the differences between studies and specifically when selecting the most comparable results, both studies suggest the same trend. For example, in Zambelli et al. (2019)¹³ study the unadjusted odds ratio from combined medical and prescription claims for cardiac defects was 1.11 (95%CI, 1.07-1.16), compared to unadjusted risk ratio for cardiac malformations (based on prescription data) of 1.12 (95%CI, 1.04-1.20), reported by Huybrechts et al. (2018)¹⁴.

In both studies, potential to selection bias due to the restriction of the cohort to livebirths could result in a slightly higher actual risks. Limitations regarding outcome and exposure misclassifications (newborns were followed for the first 1 year/3 months of life unless they died sooner; gestational age estimation; prescription data) would most likely lead to underestimation of the risk estimates. Adjusting for the treatment indications (nausea and vomiting during pregnancy, hyperemesis gravidarum) and associated factors (weight loss, electrolyte and laboratory abnormalities, dehydration, gastroesophageal reflux) in Huybrechts et al. (2018)¹⁴ study did not substantially change the crude risk estimates. In addition, to minimise the possible confounding effect of the indication for treatment, in addition to comparing exposed to unexposed women, ondansetron-exposed women were compared with women exposed to other antiemetics and results were consistent with the primary analysis. In Zambelli et al. (2019)¹³ study, by presenting results for both combined medical and prescription claims and medical claims alone, the impact of misclassification of exposure becomes clear, revealing a significant biasing of the risk estimate towards the null using prescription data.

In conclusion, limitations of studies might explain weak to moderate associations. Given that limitations of studies may result in an underestimation of the risk, current data suggests that ondansetron used in the first trimester of pregnancy increases the risk of congenital malformations, in particular an increase in the risk of cardiac malformations and oral clefts.

However, some of the limitations, especially of the Zambelli et al. (2019)¹³ study, may be addressed to minimize the uncertainties, by posing questions to the authors of the study.

To synthesize findings and to increase statistical power for rare outcomes such as congenital malformations, FR NCA performed meta-analysis within the framework of a request by marketing authorisation holder Novartis in December 2018 for type II variation concerning 4.6 and 5.3 of SmPC. After taking into account the exclusion criteria, 11 studies out of 27 articles have become eligible for meta-analysis (4 case-control studies and 7 cohort studies; including Zambelli and Huybrechts studies). Studies were excluded if there was no control group, or if the control group was also exposed to ondansetron (n = 1), if the exposure was to a class of drugs (antiemetics) and not to ondansetron only (n = 1), or on a substance other than ondansetron of the same class (n = 1), if the available data did not allow the calculation of OR (n = 3). Systematic reviews and meta-analysis (n = 6) were also

excluded (but were used to verify the completeness of the literature search), as were animal studies and case series (n = 1) and studies on efficacy or only describing use of ondansetron (n=3).

Very different levels of heterogeneity were observed and included observational studies were vulnerable to several potential sources of bias; but in conclusion, compared to non-exposed (disease free, sick or not specified), first trimester exposure to ondansetron was significantly associated with an increased risk of cardiac malformations (ORc= 1.45, 95%CI = 1.04-2.03, I² = 80%, n = 5 studies), cardiac septal defects (1.32, 95%CI = 1.12-1.56, I²= 59%; n = 4 studies), and oral clefts (1.30, 95%CI = 1.04-1.63, I² = 0%; 3 studies).

No statically significant association was found for major malformations (ORc= 1.07, 95%CI = 0.95-1.20; I²=20%; 5 studies), cleft lip with or without cleft palate (ORc = 1.01, 95%CI = 0.84-1.21; I²=0%; 7 studies) or cleft palate (ORc = 1.23, 95%CI = 0.83-1.84; I² = 72%; 6 studies).

Nausea and vomiting in pregnancy (NVP) is not without its risks and can result in a significant clinical, psychological, and economic burden because of missed work time, increased health care visits, and adverse effects on family relationships. Severe NVP can require hospitalization due to dehydration, weight loss, and electrolyte disturbances. We acknowledge, that early treatment of nausea and vomiting of pregnancy is recommended to prevent progression to hyperemesis gravidarum, but to minimize any potential risk, ondansetron should not be used as a first-line pharmacologic therapy for NVP. Additionally, the use of ondansetron should be avoided during the early stages of pregnancy (i.e., prior to 10 weeks' gestation) to further minimize any potential risk (however small) of teratogenicity, since the fetal cardiovascular system and palate forms very early in pregnancy (during the first 8 to 10 weeks, respectively).

Based on the above evidence the signal is confirmed, and re-evaluation of risk minimisation measures in place for the use of ondansetron during pregnancy is warranted.

2.3. Proposed recommendation

Although further discussion is needed at PRAC, the assessor agrees that due to the seriousness of potential congenital malformations and new body of evidence, the level of information provided in the current SmPCs for ondansetron is considered not adequate.

The assessor therefore recommends that the nationally authorized products containing ondansetron should be updated in section 4.6 of the SmPC (and respective sections of the PL) to reflect the new evidence of the risk of congenital malformations (new text underlined, text to be removed ~~struck through~~).

SmPC, section 4.6:

~~The safety of ondansetron for use in human pregnancy has not been established. Data from epidemiological studies suggest an increased risk, although small of cardiac malformations, particular septal defects and orofacial cleft defects in infants exposed to ondansetron in utero in the first trimester of pregnancy.~~

Evaluation of experimental animal studies does not indicate direct or indirect harmful effects with respect to the development of the embryo, or foetus, the course of gestation and peri- and post-natal development. However, as animal studies are not always predictive of human response
The use of ondansetron in pregnancy is not recommended.

Package leaflet, section 2:

Pregnancy and breast-feeding

~~*It is not known if <product name> is safe during pregnancy. <Product name> is not recommended for use during pregnancy. <Product name> may harm your unborn child. If you are pregnant, think you are pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking <product name>.*~~

The PRAC is asked to consider whether the EU SmPCs should be updated or considering the evidence, the questions to the authors of Zambelli et al. (2019)¹³ study should firstly be posed to minimize the uncertainties:

- With regards to the exposure definition for the primary analysis and the sensitivity analysis to address confounding by indication, there remains the question as to whether the patients who were administered ondansetron in a hospital or clinic setting were those patients presenting with the most extreme symptoms : therefore to what extent did the sensitivity analysis utilising unexposed patients with the diagnosis of hyperemesis gravidarum (HG) or nausea and vomiting in pregnancy (NVP) provide a balanced comparison in relation to the severity of condition? Could the authors provide any more information relating to this? What percentage of exposed cases had the diagnosis of HG and what percentage of the non-exposed patients used in the sensitivity analysis have diagnosis of HG? Did the authors consider a sensitivity analysis using women diagnosed with NVP/HG and treated with other antiemetic in pregnancy as a comparator?
- Are the authors able to provide the effect estimates from the model after including all pre-specified covariates?
- Are the authors able to comment on the effect estimate by a sensitivity analysis restricting the exposure window to weeks 0-8 in the first trimester, key to cardiovascular development?
- Could the author comment on the impact of missing cases due spontaneous abortions or pregnancy termination? Furthermore, could the author consider a sensitivity analysis assessing the impact of infant mortality within the first year on the effect estimates?
- For the sensitivity analysis assessing the impact of external adjustment to smoking, as presented in the supplementary data, are the authors able to provide confidence intervals? Are the authors able to provide a quantitative bias analysis accounting for the combined effect of multiple unmeasured confounders (such as smoking, alcohol consumption, OTC drug use, non-prescription folic acid intake, etc)?

2.4. Comments from Member States

1) MS1 comments

In general, we support the preliminary signal assessment on structural birth defects after first trimester exposure in pregnancy with ondansetron. We would, however, additionally suggest to consider the statements given in the "Guideline on Risk Assessment of Medicinal Products on Human Reproduction and Lactation: from Data to Labelling" (EMA/CHMP/203927/2005) for the proposed SmPC wording in section 4.6.

Assessor's comments:

MS1 generally endorses the assessment and proposes to amend the pregnancy section according to the CHMP Guideline.

The SmPC is modified as proposed (see section 2.5 for the updated wording). However, some minor editorial changes have been made to the recommended wording from the Guideline on risk assessment of medicinal products on Human reproduction and lactation: from data to labelling (EMA/CHMP/203927/2005), highlighting the first trimester exposure.

2) MS2 comments

Pending on the response to the LoQs, the need for updating section 4.6 of the SmPC is supported. While updating this section we propose to bring the wording in line with the CHMP guideline on risk assessment of medicinal products on human reproduction and lactation. It should also be discussed if further recommendations are needed on the use of the product in women of childbearing potential.

Furthermore, we consider the statement "increased risk, although small" along with the data from animal studies, not appropriately reflecting the teratogenic risks associated with the use of the product.

Assessor's comments:

MS2 comments are acknowledged. MS2 also supports the update of the SmPC according to the CHMP Guideline.

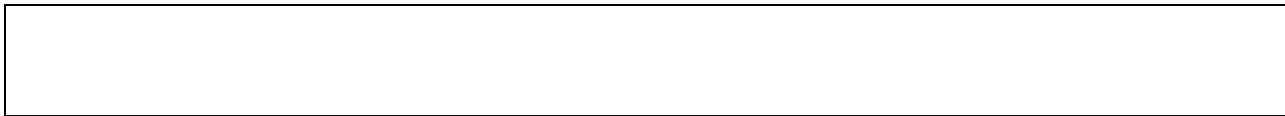
The SmPC is modified as proposed (see section 2.5 for the updated wording). However, some minor editorial changes have been made to the recommended wording from the Guideline on risk assessment of medicinal products on Human reproduction and lactation: from data to labelling (EMA/CHMP/203927/2005), highlighting the first trimester exposure.

Regarding the proposal to discuss the need for further recommendations on the use of the product in women of childbearing potential, this could be discussed at PRAC plenary. However, ondansetron is used primarily for prevention of nausea and vomiting associated with cytotoxic chemotherapy, radiotherapy, and for the prevention and treatment of postoperative nausea and vomiting.

In oncology care, screening of appropriate female patients for pregnancy prior to chemotherapy should already be a standard clinical practice, as the administration of chemotherapy is considered contraindicated until a gestational age of 10 weeks is reached due to the potential fetal risks associated with the use of cytotoxic treatment. The same recommendation is in place for radiotherapy treatment due to the possible risk of the ionizing radiation. Also, pregnancy checks before surgery in all women of childbearing potential and sexually active women should already be a standard clinical practice, because there are some risks related to anesthesia and other drugs administered during surgery in order to prevent the possibility of surgery on a woman who is unaware of her pregnancy.

The treatment with ondansetron is not considered as a long-term treatment. For highly emetogenic chemotherapy, treatment with ondansetron may be continued for up to 5 days after a course of treatment. It is not likely that woman of childbearing potential will become pregnant during that time. Also, the elimination half-life of ondansetron is relatively short - 5.7 hours (in adult cancer patients, the mean ondansetron elimination half-life was 4.0 hours).

Therefore, we believe that reproductive-age women with medical problems requiring administration of ondansetron would probably be screened for pregnancy due to the diagnosis itself and treatment required, and no further recommendations on the use of ondansetron in women of childbearing potential is warranted.



3) MS3 comments

We generally support the preliminary signal assessment on structural birth defects after first trimester exposure in pregnancy with ondansetron. However, we have some additional comments on proposed recommendation.

- Considering new evidences from literature data on birth defects, section 4.6 of SmPC (and respective sections of the PL) of products containing ondansetron should be updated without delay. Indeed:

- the two recent largest epidemiological studies of Huybrechts et al. (2018) and Zambelli et al. (2019) are robust and address some limitations of previous observational studies. Questions to the authors of Zambelli et al. study could help to minimize the uncertainties but would probably not help to conclude for sure on risk of birth defects;
- The meta-analysis conducted by the ANSM to address conflicting results in literature data showed an increased risk of cardiac malformations and oral clefts after in utero exposure to ondansetron;
- Recent data showed an important and increased off-label use of ondansetron during pregnancy;
- Some local SmPC present a less strict recommendation during pregnancy than others;
- In December 2018, MAH filed a type II variation procedure in several European countries to update SmPC of Zophren. In MS3, MAH proposed to upgrade the recommendation in pregnancy and mention in section 4.6 that some cases of congenital anomalies have been reported after in utero exposure to ondansetron. The procedure is still in progress.

- The proposed wording for section 4.6 of SmPC pertaining to nonclinical data should be revised taking into consideration results of an intravenous embryo-fetal development toxicity study conducted in rabbits (study no. WPT/85/145). Indeed, the latter showed a treatment-related increase in early foetal death at 4 mg/kg (i.e. 2.4-fold the maximal recommended human i.v. dose of 32 mg based on body surface area). This information is also reported in the approved FDA label for ZOFRAN injection: "In embryo-fetal development studies in rats and rabbits, pregnant animals received intravenous doses of ondansetron up to 10 mg/kg/day and 4 mg/kg/day, respectively, during the period of organogenesis. With the exception of short periods of maternal weight loss and a slight increase in the incidence of early uterine deaths at the high dose level in rabbits, there were no significant effects of ondansetron on the maternal animals or the development of the offspring" (see https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/020007s047lbl.pdf). For intravenous formulations, it is thus suggested to indicate "Studies in animals have shown reproductive toxicity".

- The updated SmPC should be labelled in accordance to the Guideline on risk assessment of medicinal product on human reproduction and lactation: from data to labelling" (EMA/CHMP/203927/2005).

Assessor's comments:

MS3 generally endorses the assessment and has some additional comments on proposed recommendations, which are acknowledged.

LMS agrees with the MS3 that questions to the authors of Zambelli et al. study could help to minimize the uncertainties but would probably not help to conclude for sure on risk of birth defects.

The SmPC is modified as proposed (see section 2.5 for the updated wording). However, some minor editorial changes have been made to the recommended wording from the Guideline on risk assessment

of medicinal products on Human reproduction and lactation: from data to labelling (EMA/CHMP/203927/2005), highlighting the first trimester exposure.

With regard to the proposed revision of section 4.6, based on non-clinical data for intravenous formulations, showing slight increase in the incidence of early uterine deaths at the high dose level in rabbits, LMS believes that this data should be further clarified. However, it should not be dealt with as part of this signal procedure. To date MAH Novartis never distinguished non-clinical data on reproductive toxicity according to the pharmaceutical form. Therefore, it is not clear, whether this data for intravenous formulation is new or just revealed in the FDA Labelling, due to the new rules about risks in pregnancy in product labeling for patients and providers to make informed decisions about the use of drugs during pregnancy, so called Pregnancy and Lactation Labeling Rule (PLLR), that came into force when FDA introduced narrative summary instead of pregnancy letter category system. Furthermore, revealed non-clinical data for intravenous formulations is not in contradiction (it is even in line with) to the proposed changes to SmPC based on human data and are not expected to fundamentally change the conclusions in terms of public health. Relevant human data should always prevail over non-clinical information.

As the effort to update the recommendations for use in pregnancy was made based on increasing human experience in exposed pregnancies, at this stage, we do not recommend any change in SmPC section 4.6 with regard to the data from animal studies.

4) MS4 comments

Please be informed that MS4 support the LMS conclusion and endorse the recommendation to consider the statements given in the "Guideline on Risk Assessment of Medicinal Products on Human Reproduction and Lactation: from Data to Labelling" (EMA/CHMP/203927/2005) for the proposed amendments of section 4.6 of the SmPC.

Assessor's comments:

The Member State supports the conclusion and proposes to amend the pregnancy section according to the CHMP Guideline.

The SmPC is modified as proposed (see section 2.5 for the updated wording). However, some minor editorial changes have been made to the recommended wording from the Guideline on risk assessment of medicinal products on Human reproduction and lactation: from data to labelling (EMA/CHMP/203927/2005), highlighting the first trimester exposure.

5) MS5 comments

We generally support the preliminary signal assessment on structural birth defects after first trimester exposure in pregnancy with ondansetron. In spite that questions to the authors of Zambelli et al. could help to minimize the uncertainties, the update of section 4.6 of the SmPC (and the respective sections of the PL) should be applied for the following reasons:

- The data from the two epidemiological studies analyzed in detail, the meta-analysis performed by ANSM and even other previous shorter studies are consistent with regard to the higher risk for specific congenital defects (cardiac malformations and orofacial clefts).
- It seems that there is an increased off-label use of ondansetron for the treatment of nausea/vomiting/hyperemesis during the pregnancy.
- The proposed warning in section 4.6 reflects clearly the level of evidence (data from epidemiological studies, small increase of the risks and the specific time of risk –first trimester of pregnancy-).

The updated SmPC should be labelled in accordance to the Guideline on risk assessment of medicinal product on human reproduction and lactation: from data to labelling" (EMA/CHMP/203927/2005).

Assessor's comments:

MS5 supports the assessment and proposes to amend the pregnancy section according to the CHMP Guideline.

The SmPC is modified as proposed (see section 2.5 for the updated wording). However, some minor editorial changes have been made to the recommended wording from the Guideline on risk assessment of medicinal products on Human reproduction and lactation: from data to labelling (EMA/CHMP/203927/2005), highlighting the first trimester exposure.

6) MS6 comments

We generally support the preliminary signal assessment on structural birth defects after first trimester exposure in pregnancy with ondansetron.

The study by Zambelli et al. addressed some of the major limitations associated with previous epidemiological studies such as small sample size and risk of bias from exposure misclassifications. As a result, the statistically significant association with first trimester exposure to ondansetron and increased cardiac defects merits further scrutiny. As outlined by UK colleagues, a number of uncertainties around the study finding remain, particularly confounding by indication, covariate adjustment, and treatment exposure window.

We are therefore supportive of the proposal for a list of questions to be sent to the study authors to help minimise the uncertainties around the study findings prior to updating the product information.

Assessor's comments:

MS6 comments are acknowledged.

7) MS7 comments

We support the preliminary signal assessment on structural birth defects after first trimester exposure in pregnancy with ondansetron and the recommendation to update section 4.6 of the SmPC to reflect the findings.

However, we have some additional comments relating to non-clinical aspects and the SmPC wording proposals. Depending on the level of detail to be included, it may be useful to await the response to the LoQs before finalizing the SmPC text.

Non-clinical Aspects

With regards to the comments received from MS3 relating to rabbit study (study no. WPT/85/145), and the wording in FDA PI:

"In embryo-fetal development studies in rats and rabbits, pregnant animals received intravenous doses of ondansetron up to 10 mg/kg/day and 4 mg/kg/day, respectively, during the period of organogenesis. With the exception of short periods of maternal weight loss and a slight increase in the incidence of early uterine deaths at the high dose level in rabbits, there were no significant effects of ondansetron on the maternal animals or the development of the offspring"

On the basis of this US text we do not agree that the EU wording change to “Studies in animals have shown reproductive toxicity” is warranted. Prior to any non-clinical wording change, careful consideration would need to be given to the data from WPT/85/145 to accurately put into context the meaning of ‘slight increase in the incidence of early uterine deaths”

Benefit-Risk Assessment

The MS7 considers that the questions proposed for the study authors would be valuable for a fuller understanding of the risk estimates that should be included in the SmPC and could help better understanding of the discrepancy between these two studies with regards to the risks of cardiac defects. These may also improve the comparability between the two studies (for example, if possible, comparing a 1 year follow up).

In addition to the questions proposed for the authors of the Zambelli Weiner study, the MS7 suggests further information should be sought from the authors of the Huybrechts et al. 2018 publication; the following questions are proposed:

1. Some potentially important confounders (e.g. diet, folic acid intake, other teratogens such as toxoplasmosis, syphilis, varicella-zoster, parvovirus B19, rubella, cytomegalovirus, and herpes (TORCH) infections) were not considered in the analysis. Please could the authors discuss the impact of not accounting for these and expand on how these could have been indirectly accounted for in the high dimensional PS models?
2. The completeness of the data for measured confounders is not discussed in the paper. Could the authors comment on the completeness and reliability of the data for smoking, alcohol intake or BMI?
3. Have the authors conducted a sensitivity analysis assessing the risk of cardiac malformations for infants with at least 1 year of follow up? If not, would they be able to do so?
4. Could the authors provide confidence intervals for the estimates derived from the additional analyses quantifying the potential effect of restriction to livebirths?

SmPC

The MS7 agrees that the SmPC 4.6 wording change should be in line with the CHMP guideline on risk assessment of medicinal products on human reproduction and lactation, but clear information on the specific anomalies and magnitude of the risk should be included to allow healthcare professionals and patients an informed choice when considering treatment. Regarding this the MS7 are working on a proposal for wording (if change is recommended now).

Assessor’s comments:

MS7 comments are acknowledged.

2.5. Updated proposed recommendation

The proposed recommendation of the LMS remains and proposals of the other PRAC members are taken into account.

Although further discussion is anticipated at PRAC, it is in the LMS’s opinion that due to the seriousness of potential congenital malformations and new body of evidence, the level of information provided in the current SmPCs for ondansetron is considered not adequate.

The LMS therefore recommends that the nationally authorized products containing ondansetron should be updated in section 4.6 of the SmPC (and respective sections of the PL) to reflect the new evidence of the risk of congenital malformations (new text underlined, text to be removed ~~struck through~~). Changes to the wording in AR section 2.3 are highlighted.

SmPC, section 4.6:

~~The safety of ondansetron for use in human pregnancy has not been established. Data from epidemiological studies suggest an increased risk, although small of cardiac malformations, particular septal defects and orofacial cleft defects in infants exposed to ondansetron in utero in the first trimester of pregnancy. Based on human experience from epidemiological studies, ondansetron is suggested to cause congenital malformations, particular cardiac malformations and orofacial clefts when administered during the first trimester of pregnancy.~~

~~Evaluation of experimental animal studies does not indicate direct or indirect harmful effects with respect to the development of the embryo, or foetus, the course of gestation and peri- and post-natal development. However, as animal studies are not always predictive of human response the use of ondansetron in pregnancy is not recommended.~~

~~Ondansetron should not be used during first trimester of pregnancy.~~

Package leaflet, section 2:

Pregnancy and breast-feeding

~~It is not known if <product name> is safe during pregnancy. <Product name> is not recommended for use should not be used during pregnancy. <Product name> ~~may~~ can cause harm to an ~~your~~ unborn baby child. If you are pregnant, think you are pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking <product name>.~~

The PRAC is asked to consider whether the EU SmPCs should be updated immediately or considering the evidence, the questions to the authors of Zambelli et al. (2019)¹³ study and Huybrechts et al. (2018)¹⁴ should firstly be posed to minimize the uncertainties and to help improve the comparability between the two studies:

LoQ to Zambelli et al. (2019)¹³:

- With regards to the exposure definition for the primary analysis and the sensitivity analysis to address confounding by indication, there remains the question as to whether the patients who were administered ondansetron in a hospital or clinic setting were those patients presenting with the most extreme symptoms : therefore to what extent did the sensitivity analysis utilising unexposed patients with the diagnosis of hyperemesis gravidarum (HG) or nausea and vomiting in pregnancy (NVP) provide a balanced comparison in relation to the severity of condition? Could the authors provide any more information relating to this? What percentage of exposed cases had the diagnosis of HG and what percentage of the non-exposed patients used in the sensitivity analysis have diagnosis of HG? Did the authors consider a sensitivity analysis using women diagnosed with NVP/HG and treated with other antiemetic in pregnancy as a comparator?

- Are the authors able to provide the effect estimates from the model after including all pre-specified covariates?
- Are the authors able to comment on the effect estimate by a sensitivity analysis restricting the exposure window to weeks 0-8 in the first trimester, key to cardiovascular development?
- Could the author comment on the impact of missing cases due spontaneous abortions or pregnancy termination? Furthermore, could the author consider a sensitivity analysis assessing the impact of infant mortality within the first year on the effect estimates?
- For the sensitivity analysis assessing the impact of external adjustment to smoking, as presented in the supplementary data, are the authors able to provide confidence intervals? Are the authors able to provide a quantitative bias analysis accounting for the combined effect of multiple unmeasured confounders (such as smoking, alcohol consumption, OTC drug use, non-prescription folic acid intake, etc)?

LoQ to Huybrechts et al. (2018)¹⁴:

- Some potentially important confounders (e.g. diet, folic acid intake, other teratogens such as toxoplasmosis, syphilis, varicella-zoster, parvovirus B19, rubella, cytomegalovirus, and herpes (TORCH) infections) were not considered in the analysis. Please could the authors discuss the impact of not accounting for these and expand on how these could have been indirectly accounted for in the high dimensional PS models?
- The completeness of the data for measured confounders is not discussed in the paper. Could the authors comment on the completeness and reliability of the data for smoking, alcohol intake or BMI?
- Have the authors conducted a sensitivity analysis assessing the risk of cardiac malformations for infants with at least 1 year of follow up? If not, would they be able to do so?
- Could the authors provide confidence intervals for the estimates derived from the additional analyses quantifying the potential effect of restriction to live births?

2.6. Adopted PRAC recommendation

Having considered the available evidence arising from recent publications on the signal of birth defects with ondansetron, the PRAC has concluded that this signal merits further investigation. The PRAC will request the authors of both studies (Zambelli et al. and Huybrechts et al.) to provide additional clarifications on the study findings by 11 April 2019 in order to minimize the uncertainties and assess the need for further actions on this issue. The PRAC has also agreed that Novartis, originator of ondansetron containing medicinal products should provide by 11 April 2019 response to the list of questions.

The following List of Questions (LOQs) for the Zambelli et al. study authors was agreed by the PRAC:

1. With regards to the exposure definition for the primary analysis and the sensitivity analysis to address confounding by indication, there remains the question as to whether the patients who were administered ondansetron in a hospital or clinic setting were those patients presenting with the most extreme symptoms: therefore to what extent did the sensitivity analysis utilising unexposed patients with the diagnosis of hyperemesis gravidarum (HG) or nausea and vomiting in pregnancy (NVP) provide a balanced comparison in relation to the severity of condition? Could the authors provide any more information relating to this? What percentage of

exposed cases had the diagnosis of HG and what percentage of the non-exposed patients used in the sensitivity analysis have diagnosis of HG? Did the authors consider a sensitivity analysis using women diagnosed with NVP/HG and treated with other antiemetic in pregnancy as a comparator?

2. Are the authors able to provide the effect estimates from the model after including all pre-specified covariates? Are the authors able to adjust for a propensity or a disease risk score?
3. Are the authors able to comment on the effect estimate by a sensitivity analysis restricting the exposure window to weeks 0-8 in the first trimester, key to cardiovascular development?
4. Could the author comment on the impact of missing cases due spontaneous abortions or pregnancy termination? Furthermore, could the author consider a sensitivity analysis assessing the impact of infant mortality within the first year on the effect estimates?
5. For the sensitivity analysis assessing the impact of external adjustment to smoking, as presented in the supplementary data, are the authors able to provide confidence intervals? Are the authors able to provide a quantitative bias analysis accounting for the combined effect of multiple unmeasured confounders (such as smoking, alcohol consumption, OTC drug use, non-prescription folic acid intake, etc)?

The following List of Questions (LOQs) for the Huybrechts et al. study authors was agreed by the PRAC:

1. Some potentially important confounders (e.g. diet, folic acid intake and other teratogens such as toxoplasmosis, syphilis, varicella-zoster, parvovirus B19, rubella, cytomegalovirus, and herpes (TORCH) infections) were not considered in the analysis. Could the authors discuss the impact of not accounting for these and expand on how these could have been indirectly accounted for in the high dimensional PS models?
2. The completeness of the data for measured confounders is not discussed in the paper. Could the authors comment on the completeness and reliability of the data for smoking, alcohol intake or BMI?
3. Have the authors conducted a sensitivity analysis assessing the risk of cardiac malformations for infants with at least 1 year of follow up? If not, would they be able to do so?

The following List of Questions for the MAH (Novartis) was agreed by the PRAC:

1. The MAH is requested to discuss the totality of evidence regarding potential risks with use of ondansetron in pregnancy, including the most recent observational studies (Zambelli et al. and Huybrechts et al.), and whether there is an increased risk for cardiac malformations and/or oral clefts. This should include a potential magnitude of the risk of oral clefts and cardiac malformations after first trimester exposure to ondansetron in a European setting. Which effect estimates are the most valid, and how does it translate to a European setting given baseline risks of oral clefts and cardiac malformations in Europe? Please provide absolute risks and number needed to harm.
2. The MAH should discuss whether there are any subgroups of pregnant women where the benefits of using ondansetron during the first trimester may outweigh the potential risks.
3. The MAH should discuss drug utilisation practices of ondansetron for nausea and vomiting in pregnancy (NVP) and Hyperemesis Gravidarum (HG) in a European setting.
4. The MAH should discuss the risks of treatment of severe NVP and HG with ondansetron.
5. The MAH is requested to discuss whether in the light of the responses to the questions above further risk minimisation measures are considered necessary, including amendment to the

product information. Furthermore, the MAH should comment on if communication is considered necessary, and if so, a draft DHPC and communication plan should be provided.

The PRAC will assess the responses from study authors and from the MAH within a 30/60 day timetable.

3. Additional evidence

During the PRAC meeting in March 2019 the authors of both studies (Zambelli et al. and Huybrechts et al.) were invited to submit additional clarifications on the studies, as per an agreed list of questions (LoQ). And MAH Novartis, originator of ondansetron containing medicines was requested to provide responses to LoQ.

Responses by the MAH were submitted on 3rd May 2019 and responses by author of the study Huybrechts et al. on 18th April 2019 and Zambelli-Weiner et al. on 31st May 2019. In addition, EMA provided small drug utilisation studies, showing the patterns of drug use in pregnancy in the in-house databases (for UK, Germany and France).

In addition, based on recommendation from French Health Authorities (ANSM), MAH shared to PRAC Rapporteur the Type II variation package and complementary data that are under review by ANSM for Type II variation regarding changes in SmPC section 4.6 and 5.3 and Patient Information Leaflets.

3.1. Assessment of additional data

3.1.1. Responses of the Zambelli-Weiner et al. (2019)¹³ study authors

The author informed us that GSK, as part of their ongoing litigation around ondansetron in the US, has subpoenaed her concerning the published study. Therefore, she sincerely apologizes that she is unable to fully answer our questions or provide any unpublished information regarding their study, or their larger PISCES project, at this point in time.

3.1.1.1. Question 1-5

- 1. With regards to the exposure definition for the primary analysis and the sensitivity analysis to address confounding by indication, there remains the question as to whether the patients who were administered ondansetron in a hospital or clinic setting were those patients presenting with the most extreme symptoms: therefore to what extent did the sensitivity analysis utilising unexposed patients with the diagnosis of hyperemesis gravidarum (HG) or nausea and vomiting in pregnancy (NVP) provide a balanced comparison in relation to the severity of condition? Could the authors provide any more information relating to this? What percentage of exposed cases had the diagnosis of HG and what percentage of the non-exposed patients used in the sensitivity analysis have diagnosis of HG? Did the authors consider a sensitivity analysis using women diagnosed with NVP/HG and treated with other antiemetic in pregnancy as a comparator?*
- 2. Are the authors able to provide the effect estimates from the model after including all pre-specified covariates? Are the authors able to adjust for a propensity or a disease risk score?*
- 3. Are the authors able to comment on the effect estimate by a sensitivity analysis restricting the exposure window to weeks 0-8 in the first trimester, key to cardiovascular development?*

4. *Could the author comment on the impact of missing cases due spontaneous abortions or pregnancy termination? Furthermore, could the author consider a sensitivity analysis assessing the impact of infant mortality within the first year on the effect estimates?*
5. *For the sensitivity analysis assessing the impact of external adjustment to smoking, as presented in the supplementary data, are the authors able to provide confidence intervals? Are the authors able to provide a quantitative bias analysis accounting for the combined effect of multiple unmeasured confounders (such as smoking, alcohol consumption, OTC drug use, non-prescription folic acid intake, etc)?*

Response

We learned many things about prescribing patterns of antiemetics as part of our larger PISCES project, which is our internal program in birth defects research. It is our scientific opinion that the analysis we presented on confounding by indication in the ondansetron paper is the least biased approach to addressing this given the strengths and limitations of our data source.

We have not seen any empirical data to suggest that women receiving medical administration were presenting with more extreme symptoms. In fact, in the US many EMS/ED protocols have ondansetron IV administration as a first-line therapy regardless of severity, prior diagnosis of NVP, pregnancy status, etc. Our data shows that the majority of women received a single injection of ondansetron, which is more consistent with episodic treatment of nausea or vomiting, such as related to flu. Furthermore, these are women who received only ondansetron. A woman who is being treated for chronic and severe NVP/HG is more likely to (1) be treated with multiple antiemetics, and (2) to receive more than a single dose of an antiemetic.

Of course, all studies have strengths and weaknesses and it's never possible to conduct all possible analyses within a single manuscript. It was always our hope that this paper would contribute in a meaningful way to the evidence base, the most significant contribution being the quantification of exposure misclassification that is likely present in any studies relying upon filled prescription data as a surrogate of ondansetron exposure.

PRAC Rapporteur's comment:

The response is noted.

3.1.2. Responses of the Huybrechts et al. (2018)¹⁴ study authors

3.1.2.1. Question 1

Some potentially important confounders (e.g. diet, folic acid intake and other teratogens such as toxoplasmosis, syphilis, varicella-zoster, parvovirus B19, rubella, cytomegalovirus, and herpes (TORCH) infections) were not considered in the analysis. Could the authors discuss the impact of not accounting for these and expand on how these could have been indirectly accounted for in the high dimensional PS models?

Response

Diet and folic acid intake are variables that are not available in our data source. The other diagnoses listed are available and could have been included, but we did not expect them to be imbalanced between ondansetron exposed and unexposed women (in which case they are not confounders). If they were important confounders, they would indeed have been identified by the hdPS approach which screens all diagnoses that are imbalanced between exposure groups and associated with the outcome. Finally, given the null finding for congenital malformations overall and for cardiac malformations, and

the findings from the negative control analysis for oral clefts (no association when evaluating exposure outside the etiologically relevant window) we are not concerned about residual confounding.

PRAC Rapporteur's comment:

The response is noted.

As the investigator could not present the data on diet and folic acid intake, the exact impact of potentially important confounders on the crude risk estimates remains unclear. Regarding TORCH infections, which include toxoplasmosis, syphilis, varicella-zoster, parvovirus B19, rubella, cytomegalovirus (CMV), and herpes infections, which are infections during pregnancy that are associated with congenital anomalies and possibly stillbirths, it is acknowledged that not taking into account those infections and not excluded those pregnancies could influence the study outcome. However, we could agree that significant imbalance regarding infection is not expected due to exposure/non-exposure to ondansetron.

3.1.2.2. Question 2

The completeness of the data for measured confounders is not discussed in the paper. Could the authors comment on the completeness and reliability of the data for smoking, alcohol intake or BMI?

Response

Claims data, such as MAX, are known to have incomplete information regarding lifestyle factors, such as smoking, alcohol intake and BMI. It is not as much an issue of missing data, as of these variables not being consistently coded. We addressed this in the paper and discussion as follows:

"Second, in non-randomized studies, there is always concern about residual confounding due to unmeasured or poorly measured characteristics (here we refer to variables such as smoking and BMI). ... This may result in some misclassification of the confounder information, and hence affect our ability to control for confounding. While negative residual confounding is typically not a concern for null findings because drug exposure is not expected to be associated with factors protective against congenital malformations (i.e., cardiac malformations or congenital malformations overall), positive residual confounding could be a potential explanation for the increased risk in oral clefts. An attempt was made to refute this alternative explanation using different strategies including adjustment for proxies of unmeasured confounders through high-dimensional propensity scores, use of alternate reference groups, and a negative control analysis. No increased risk of oral clefts was observed using the negative control exposure window, supporting the validity of this association."

PRAC Rapporteur's comment:

The author highlighted that claims data, such as MAX, are known to have incomplete information regarding lifestyle factors, such as smoking, alcohol intake and BMI. The ability of a given strategy to control confounding in studies based on these databases depends on completeness and validity of the recorded information on confounding factors.

As the investigator did not further discuss the completeness of the data for measured and poorly measured confounders, the extent of the residual confounding bias for each potential confounder remains unclear, although the authors overall controlled for measured confounding using propensity scores and addressed unmeasured confounding using high-dimensional propensity scores; and sensitivity analyses, including negative control.

3.1.2.3. Question 3

Have the authors conducted a sensitivity analysis assessing the risk of cardiac malformations for infants with at least 1 year of follow up? If not, would they be able to do so?

Response

We have conducted such analyses in prior studies (e.g., Huybrechts et al. NEJM 2014;370 (25):2397-2407), and concluded it tends to not change the findings. We therefore no longer consistently conduct this as a sensitivity analysis. We could in principle conduct such analysis, however. The cohort size would be slightly smaller as we would have to restrict the cohort to infants with at least one year of enrolment in MAX, unless they died sooner.

PRAC Rapporteur's comment:

The author pointed out another published study in which they investigated the use of selective serotonin-reuptake inhibitors (SSRIs) and other antidepressants during pregnancy and association with an increased risk of congenital cardiac defects. It was a large, population-based cohort study nested in the nationwide Medicaid Analytic eXtract for the period 2000 through 2007. The study included 949,504 pregnant women who were enrolled in Medicaid during the period from 3 months before the last menstrual period through 1 month after delivery and their liveborn infants. Congenital cardiac malformations were identified on the basis of the presence of inpatient or outpatient diagnostic codes from the ICD-9, in the maternal or infant records during the first 90 days after delivery. To evaluate the effect of potential misclassification of outcome, they restricted the outcome to inpatient diagnoses only and extended infant follow-up to 1 year. According to the authors findings, the overall findings were not qualitatively affected when they varied the exposure and outcome definitions. From the data presented it can be seen, that restriction to 12 months follow-up reduced the cohort to 65% of original cohort size.

Main analysis:

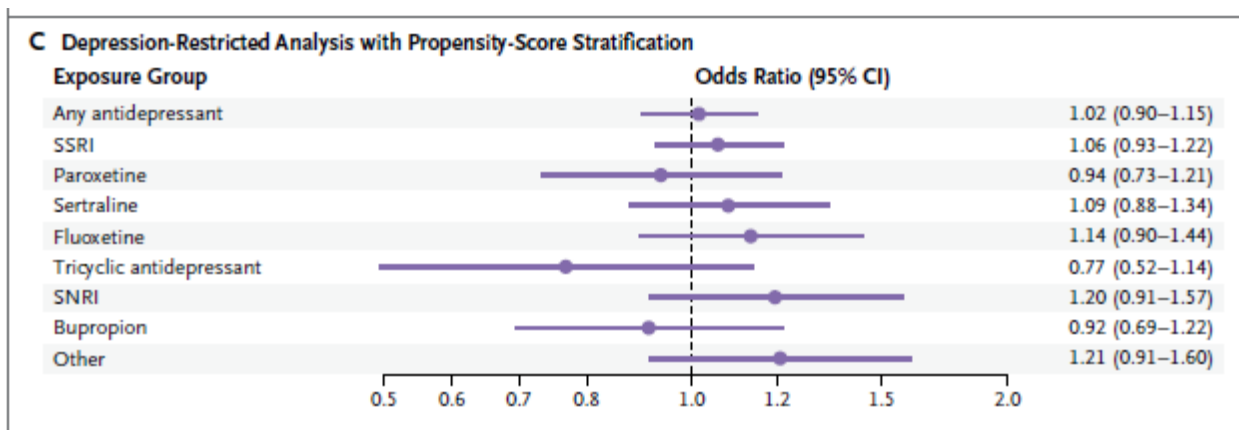


Figure 1. Risk of Cardiac Malformation in Infants, According to Maternal Exposure to Antidepressants.

Odds ratios and 95% confidence intervals are presented to show the risk of any cardiac malformation among infants born to women with exposure to antidepressants during the first trimester, as compared with the risk among infants born to women without such exposure. Panel A shows the unadjusted analysis, Panel B the analysis restricted to women with depression, and Panel C the analysis, restricted to women with depression, that used propensity-score stratification in order to adjust for confounders. Data are from the Medicaid Analytic eXtract for the period 2000 through 2007. SNRI denotes serotonin–norepinephrine reuptake inhibitor, and SSRI selective serotonin-reuptake inhibitor.

Sensitivity analysis:

Table S19 Relative risks and 95% confidence intervals comparing the risk for cardiac malformations between exposed and unexposed women, varying the outcome definitions; restricted to women with depression diagnosis with PS adjustment. Medicaid Analytic eXtract 2000-2007.

Exposure	Inpatient diagnosis of cardiac malformation					12 months follow-up to ascertain cardiac malformation ⁽³⁾				
	N Patients		N Outcomes		OR (95% CI)	N Patients		N Outcomes		OR (95% CI)
	Exp	Unexp	Exp	Unexp		Exp	Unexp	Exp	Unexp	
Any cardiac malformation										
ANTIDEP	49,527	180,422	335	1,128	0.96 (0.83, 1.11)	33,275	116,987	169	517	0.98 (0.80, 1.20)
SSRI	36,778	180,564	249	1,129	1.00 (0.85, 1.17)	24,918	117,042	116	517	0.91 (0.72, 1.15)
PAROXETINE	8,748	180,564	50	1,129	0.84 (0.62, 1.14)	6,274	117,040	17	517	0.53 (0.32, 0.89)
SERTRALINE	11,056	180,564	78	1,129	1.02 (0.80, 1.31)	7,507	117,042	43	517	1.16 (0.83, 1.62)
FLUOXETINE	8,664	180,563	66	1,129	1.18 (0.90, 1.54)	5,671	117,040	24	517	0.75 (0.48, 1.16)
TCAS	3,314	180,562	18	1,129	0.66 (0.41, 1.08)	2,217	117,034	17	517	1.33 (0.80, 2.23)
SNRIS	6,010	180,564	48	1,129	1.05 (0.76, 1.45)	4,007	117,042	27	517	1.25 (0.81, 1.93)
BUPROPION	6,691	180,563	43	1,129	0.89 (0.64, 1.24)	4,295	117,042	26	517	1.12 (0.73, 1.71)
OTHER	6,021	180,564	51	1,129	1.26 (0.92, 1.73)	3,988	117,042	17	517	0.93 (0.56, 1.57)

3.1.3. MAH's responses

For ease of review, the PRAC Question 1 has been broken down by the MAH to 3 sub-questions and all are addressed individually.

3.1.3.1. Question 1.a

The MAH is requested to discuss the totality of evidence regarding potential risks with use of ondansetron in pregnancy, including the most recent observational studies (Zambelli et al. and Huybrechts et al.), and whether there is an increased risk for cardiac malformations and/or oral clefts. This should include a potential magnitude of the risk of oral clefts and cardiac malformations after first trimester exposure to ondansetron in a European setting.

Response

A summary of the content of the MAH response is presented below (reference refer to the list of references given in the MAH response):

The Novartis PSUR for ondansetron containing products covering the reporting period from 01 March 2015 to 28 February 2018 (Procedure No.: PSUSA/00002217/201802) included a cumulative review of the published literature including case series, epidemiological studies and pre-clinical studies concerning reproductive toxicity associated with the use of ondansetron in pregnancy ([Appendix 1](#)).

Within the routine monitoring of published literature for ondansetron, Novartis identified 5 new articles relevant to assessment of adverse birth outcomes following use of ondansetron during pregnancy that were published since the data lock point of the last PSUR (28 February 2018) and until 15 March 2019 ([Appendix 2](#)).

1) Literature publications

The review is focused on five newly published articles relevant to assessment of adverse birth outcomes following use of ondansetron during pregnancy and are summarized in Table 3-1. These include:

- one systematic review without a formal synthesis of the results (Lavecchia et al. 2018) (not discussed in further detail by Novartis as it recaps information already presented in the previously submitted PSUR; the conclusion was that the results in the previously published literature have been conflicting and inconsistent - *Danielsson et al. 2014 found an increased risk for cardiovascular defects, specifically septal defects with an adjusted OR of 2.05 (95% CI, 1.19–3.28) and Anderka et al. 2012 found a potential increased risk of cleft palate with adjusted OR of 2.37 (95% CI, 1.18–4.76)*),
- one systematic review and meta-analysis (Kaplan et al. 2019) (which provided a formal synthesis of previously published data) and
- three new epidemiological studies, Zambeli-Weiner et al. 2019, Huybrechts et al. 2018 and one update (Parker et al. 2018) of a previously published analysis (Anderka et al. 2012), all of which were performed using secondary data in the US.

Table 3-1 Summary of studies published between 01 Mar 2018 and 15 Mar 2019

Article details	Objective	Population and study period	Conclusion
(Kaplan et al 2019) Search in PubMed/MEDLINE, Cochrane Central Register of Controlled Trials and Reprotox databases from inception to 21 Sep 2016	To assess whether ondansetron use in pregnancy is associated with an increase in the rate of major congenital malformations. Secondary objective: to analyze subgroups of malformations such as heart defects, orofacial clefts and isolated cleft palate, genitourinary malformations and hypospadias	Seven cohort studies and two case-control studies were identified as eligible for the meta-analysis. Two of the cohort studies originated from Denmark and two from Sweden registries, two were from Canada and the US. and one from Australia. Because two Danish studies investigated overlapping data and yielded conflicting results, one with a better methodological quality score was included in primary analysis, and another in sensitivity analysis only. Case-control studies originated from the US.	No significant increased risk for major malformations, heart defects, orofacial clefts, genitourinary malformations or hypospadias were identified in the primary analysis. A significant heterogeneity existed for isolated cleft palate. Elevated point estimates and altered statistical significances were present for some of the outcomes among secondary analyses

Article details	Objective	Population and study period	Conclusion
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<p>(Zambelli-Weiner et al 2019)</p> <p>US, nested case-control study in the Truven Health MarketScan Commercial Database</p>	<p>To investigate risk of specific structural birth defects associated with ondansetron exposure during the first trimester</p>	<p>Among 864,083 mother-child pairs, early exposure to ondansetron occurred in 76,330 mother-child pairs (8.8%), and early exposure to medical administration of ondansetron occurred in 5557 pairs (0.64%).</p> <p>Study period: 2000-2014</p>	<p>First trimester exposure to ondansetron (medical administration only) was associated with increased risk of cardiac (adjusted odds ratio [OR]=1.43, 95%CI 1.28–1.61) and orofacial cleft defects (adj OR=1.30, 95%CI 0.75–2.25) in offspring compared to women with no antiemetic exposure during pregnancy. Risk was attenuated in analyses of ondansetron prescription or medical administration: cardiac defects adj OR=1.04 (1.00-1.08); orofacial clefts adj OR=1.12 (0.95-1.33)</p>
<p>(Huybrechts et al 2018)</p> <p>US, retrospective cohort study nested in the nationwide Medicaid Analytic eXtract</p>	<p>To evaluate the association between ondansetron exposure during pregnancy and risk of congenital malformations</p>	<p>Among 1,816,414 pregnancies (mean age of mothers, 24.3 [5.8] years), 88,467 (4.9%) were exposed to ondansetron during the first trimester</p> <p>Study period: 2000-2013</p>	<p>The relative risk (RR) for cardiac malformations was 0.99 (95%CI 0.93-1.06). For oral clefts, adj RR=1.24 (1.03-1.48). The adjusted estimate for congenital malformations overall was RR=1.01 (0.98-1.05) and adjusted risk difference (RD) of 5.4 (95%CI, -7.3 to 18.2 per 10,000 births).</p>
<p>(Parker et al 2018)</p> <p>US, multi-site, population-based, case-control / National Birth Defects Prevention Study (NBDPS) and Slone Birth Defects Study (BDS)</p>	<p>To describe time trends in ondansetron use for the treatment of first-trimester nausea and vomiting of pregnancy and to investigate associations between first-trimester ondansetron use and major birth defects.</p>	<p>In the NBDPS and BDS, respectively, 6,751 and 5,873 control mothers and 14,667 and 8,533 case mothers who reported first-trimester nausea and vomiting of pregnancy (NVP) Among women in the control group, ondansetron exposure increased from <1% before 2000 to 13% in 2013–2014.</p> <p>Study period: NBDPS 1997-2011; BDS 1997-2014</p>	<p>Ondansetron use was not associated with an increased risk for most of the 51 defect groups analyzed. Modest increases in risk were observed for cleft palate (adjusted OR=1.6, 95%CI 1.1–2.3) in the NBDPS and renal agenesis–dysgenesis (adj OR=1.8, 1.1–3.0) in the BDS</p>
<p>(Lavecchia et al 2018)</p> <p>Systematic searches in Medline and Embase, performed in June 2017</p>	<p>To systematically review epidemiological evidence on the potential association of prenatal exposure to ondansetron and congenital malformations.</p>	<p>10 epidemiologic studies were included: 5 large retrospective cohort studies, 2 prospective studies, 2 population-based case-controls, 1 retrospective case series.</p> <p>Sample sizes ranged from 17 to 1,501,434 infants exposed to ondansetron.</p>	<p>1 case-control study identified an association between prenatal exposure to ondansetron and cleft palate (CP), and 1 cohort study found an increased risk of cardiovascular defects. These findings were not reproduced in the other studies.</p>

Results pertaining to specific categories of birth defects are summarized below. For cardiac defects and orofacial defects in addition to newly published articles, earlier epidemiological studies are also discussed.

Major malformations/birth defects

Among the recently published studies with primary data analysis, only Huybrechts et al. 2018 provided an analysis of the association between ondansetron use and all major malformations. The overall incidence of major malformations was 370.4 per 10,000 births (95%CI 358.0-382.9) among infants born to mothers exposed to ondansetron and 313.5 per 10,000 (310.9-316.1) among those unexposed, which corresponds to the previously cited estimate of 2-4% of all live births. A small increase in risk of overall malformations compared to unexposed infants was noted in the unadjusted analysis, RR=1.18 (95%CI, 1.14-1.22). However, propensity score (PS) stratification removed the apparent association; **aRR=1.01 (95%CI, 0.98-1.05)**, indicating that apparent association in unadjusted comparisons was attributable to confounding within the cohort. Results of high-dimensional propensity score (hdPS) adjustment confirmed this finding.

Meta-analysis by Kaplan et al. 2019 of overall major congenital malformation rates in ondansetron-exposed vs healthy controls identified six studies published between 2012 and 2016, assessing a total of 5148 ondansetron-exposed and 2,459,053 control infants. As two studies were conducted in overlapping populations in Denmark, primary analysis included only five studies leaving a total of 3914 ondansetron-exposed and 1,563,139 control infants. No significant increase in the rate of overall major congenital malformation was detected following ondansetron use during pregnancy (**OR=1.16; 95%CI 0.92–1.45**). However, the sensitivity analysis (including another Danish study with lower methodological quality score, Andersen et al. 2013) slightly elevated the point estimate and altered the statistical significance (OR=1.23; 95%CI 1.02–1.48). No significant heterogeneity among the studies were present for either analysis. The same publication reported another meta-analysis of the risk of overall major congenital malformations in ondansetron-exposed vs disease-matched controls. This secondary analysis included two studies and yielded statistically non-significant results (**OR=1.21, 95%CI 0.56–2.58**).

Conclusion: no increase in risk of overall malformations reported by Huybrechts et al. 2018 or Kaplan et al. 2019.

Cardiac defects

A variety of cardiac defects were assessed by the three newly published studies with primary data analysis (summarized in the following table). These include cardiac defects overall as well as ventricular septal defect (VSD), atrial septal defect (ASD), atrioventricular septal defect (AVSD) and hypoplastic left heart syndrome (HLHS).

Table 3-2 New epidemiological data on the association of cardiac defects with first-trimester ondansetron exposure

Specific defect type	Zambelli-Weiner et al 2019 Adjusted OR (95%CI), compared to unexposed; 2000-2014		Huybrechts et al 2018 Adjusted RR (95%CI), compared to unexposed; 2000-2013	Parker et al 2018 Adjusted OR (95%CI), compared to unexposed pregnancies with NVP	
	Medical administration	Prescription or medical administration		NBDPS, 1997-2011	BDS, 1997-2014
Any cardiac defect	1.43 (1.28-1.61)	1.04 (1.00-1.08)	0.99 (0.93-1.06)	NR	NR
ASD	1.49 (1.32-1.69)	1.04 (0.99-1.08)	NR	0.9 (0.6-1.3)	0.8 (0.5-1.2)
VSD	1.43 (1.28-1.61)	1.00 (0.93-1.07)	NR	0.9 (0.6-1.3)	1.1 (0.9-1.4)
AVSD	2.71 (1.62-4.52)	1.24 (1.00-1.53)	NR	0.7 (0.3-1.7)	NR
HLHS	2.12 (0.87-5.13)	1.31 (0.95-1.81)	NR	1.5 (0.9-2.5)	1.2 (0.6-2.4)

ASD - atrial septal defect; AVSD - atrioventricular septal defect; BDS – Birth Defects Study; HLHS - hypoplastic left heart syndrome; NBDPS - National Birth Defects Prevention Study; NR – not reported; VSD - ventricular septal defect

! There is a mistake in the presented table: for VSD should be 1.29 (1.03-1.61) instead of 1.43 (1.28-1.61).

In addition, Zambelli-Weiner et al. 2019 reported that “Other circulatory defects” were associated with first-trimester medical administration of ondansetron (**aOR=1.75, 95%CI 1.39-2.20**), but association was weaker for prescription or medical administration (**aOR=1.11, 95%CI 1.02-1.20**).

Meta-analysis by Kaplan et al. 2019 of the risk of any heart defects in ondansetron-exposed vs healthy controls identified six studies published between 2012 and 2016, assessing a total of 5148 ondansetron-exposed and 2,459,053 control infants. As two studies were conducted in overlapping populations in Denmark, primary analysis included only five studies leaving a total of 3914 ondansetron-exposed and 1,563,139 control infants. No significant increase in the rate of heart defects was detected following ondansetron use during pregnancy (**OR=1.26; 95%CI 0.90– 1.77**). However, the sensitivity analysis (including another study with lower methodological quality score, Andersen et al. 2013) slightly elevated the point estimate and altered the statistical significance (OR=1.59; 95%CI 1.14–2.21). No significant heterogeneity among the studies were present for either analysis. The same publication reported a meta-analysis of the risk of heart defects in ondansetron-exposed vs disease-matched controls. This secondary analysis included two studies and yielded statistically non-significant results (**OR=1.66, 95%CI 0.30-9.09**).

Conclusion: no increase in risk of *any cardiac defects* reported by (Huybrechts et al. 2018) or (Zambelli- Weiner et al. 2019) associated with prescription or administration of ondansetron. The latter study reported a slight increase in risk associated with medical administration only, however, this analysis may be reflective of more severe patients and is more prone to confounding by indication and surveillance bias. Parker et al. 2018 evaluated a number of cardiac defects but failed to find any association with first-trimester ondansetron exposure. Meta-analysis of previously published studies, conducted by Kaplan et al. 2019, did not find a statistically significant increase in overall heart defects in the primary analysis, although point estimate was slightly increased in secondary and sensitivity analyses, with OR around 1.6.

Cardiac septal defects: increase in risk of various septal defects reported by Zambelli-Weiner et al. 2019 but not confirmed by Parker et al. 2018.

Hypoplastic left heart syndrome: increase in risk reported by two studies (Parker et al. 2018, Zambelli-Weiner et al. 2019), with ORs ranging from 1.2 to 1.5 for prescription or medical administration.

Earlier larger epidemiology studies:

Danielsson et al. 2014, used data from the Swedish Medical Birth Register collected between 1998 and 2012. Of approximately 1.5 million births during the study period, there were 1,349 infants exposed to ondansetron during "early pregnancy." The authors found an increased risk for cardiovascular malformations, specifically septal defects. However, the comparison group is not clearly described. Of the 1,349 infants exposed to ondansetron in early pregnancy, the only malformations occurring more than once in the study were ventricular septum malformations, ventricular and atrium septum defects, and hypospadias. The majority of cardiac defects reported in this study were ventricular and/or septal defects (17 of 19 total). In addition to noting possible confounders and other limitations, the authors note that the clinical significance of the increased reported for atrial/ septal defects is unknown, and that "detailed clinical information on these cases is missing." Minor atrial/ septal defects are common, are often subclinical, and may resolve without intervention. Among women prescribed ondansetron in Danielsson's study, only 17% of women exposed to ondansetron filled their first prescription before 56 days' gestation. Following this time period, cardiac development of the fetus is complete. It is, therefore, unlikely that a drug thought to be associated with cardiac anomalies would have any role to play in this malformation.

In a large retrospective Danish analysis (Pasternak et al. 2013), the risk of adverse fetal outcomes associated with ondansetron administered during pregnancy were investigated from a historical cohort of 608,385 pregnancies in Denmark. Women who were exposed to ondansetron were matched to those who unexposed in a 1:4 ratio, in propensity-score matched analyses of spontaneous abortion, stillbirth, any major birth defect, preterm delivery, and birth of infants at low birth weight and small for gestational age. In addition, estimates were adjusted for hospitalization for NVP (as a proxy for severity) and the use of other antiemetics. Receipt of ondansetron was not associated with a significantly increased risk of spontaneous abortion, during gestational weeks 7 to 12 (hazard ratio, 0.49; 95% confidence interval [CI], 0.27 to 0.91) and spontaneous abortion during weeks 13 to 22 (hazard ratio, 0.60; 95% CI, 0.29 to 1.21). Ondansetron also conferred no significantly increased risk of stillbirth (hazard ratio, 0.42; 95% CI, 0.10 to 1.73), any major birth defect (prevalence odds ratio, **1.12; 95% CI, 0.69 to 1.82**), preterm delivery (prevalence odds ratio, 0.90; 95% CI, 0.66 to 1.25), delivery of a low-birthweight infant (prevalence odds ratio, 0.76; 95% CI, 0.51 to 1.13), or delivery of a small-for-gestational- age infant (prevalence odds ratio, 1.13; 95% CI, 0.89 to 1.44).

Andersen et al. 2013, published a study in abstract form in 2013. Data were obtained from the same database as the Pasternak study but examined the years 1997–2010. The authors examined a total of 897,018 births; of these, 1,248 women obtained a prescription for ondansetron. Fifty-eight congenital malformations (4.7%) were noted in the ondansetron-exposed group, and 31,357 congenital malformations (3.5%) were noted in the unexposed group. Exposure to ondansetron was associated with an **OR of 1.3 (95% CI 1.0–1.7)** for major malformations. An increased prevalence of heart defects (**OR 2.0, 95% CI 1.3–3.1**) accounted for the bulk of the increased malformations found. The data from this study have thus far been published only in abstract form, making it difficult to determine specific study methods, unlike other studies of similar size (such as Pasternak et al 2013).

The [ANSM meta-analysis](#) has found that first trimester exposure to ondansetron was significantly associated with an increased risk of cardiac malformations (**ORc = 1.45, 95% CI 1.04–2.03, I² = 80%, n = 5 studies**), although there was also significant heterogeneity in the results, and cardiac septal defects (**1.32, 95% CI = 1.12–1.56, I²= 59% ; n = 4 studies**).

After reviewing the methods of the analysis, Novartis believes that the article selection for the analysis of the cardiac malformations was skewed towards those studies showing less favourable results, despite lower methodological quality of these analyses. As a result, the summary odds ratio is likely an

overestimation of the true magnitude of the risk increase. For a more detailed discussion, please refer to the Novartis response to Question 1.b below.

Conclusion: earlier large epidemiology studies in Europe have provided inconsistent estimates of the risk of cardiovascular defects.

Orofacial clefts

All three newly published epidemiological studies in the US assessed the risk of orofacial clefts (OC); the findings are summarized in the following table and include OC overall as well as cleft palate (CP), cleft lip (CL) and cleft lip with or without cleft palate (CL/CP).

Table 3-3 New epidemiological data on the association of orofacial clefting with first-trimester ondansetron exposure

Specific defect type	Zambelli-Weiner et al 2019 Adjusted OR (95%CI), compared to unexposed; 2000-2014		Huybrechts et al 2018 Adjusted RR (95%CI), compared to unexposed; 2000-2013	Parker et al 2018 Adjusted OR (95%CI), compared to unexposed pregnancies with NVP	
	Medical administration	Prescription or medical administration		NBDPS, 1997-2011	BDS, 1997-2014
OC	1.30 (0.75-2.25)	1.12 (0.95-1.33)	1.24 (1.03-1.48)	NR	NR
CP	1.46 (0.81-2.65)	1.06 (0.87-1.30)	NR	1.6 (1.1-2.3)	0.5 (0.3-1.0)
CL	1.16 (0.48-2.81)	1.22 (0.96-1.56)	NR	NR	NR
CL/CP	1.69 (0.84-3.40)	1.07 (0.84-1.38)	NR	1.1 (0.8-1.5)	0.8 (0.5-1.2)

BDS – Birth Defects Study; CL – cleft lip; CL/CP - cleft lip with or without cleft palate; CP – cleft palate; NBDPS - National Birth Defects Prevention Study; NR – not reported; OC – orofacial clefts

Meta-analysis by Kaplan et al. 2019 of the risk of orofacial clefts in ondansetron-exposed vs healthy controls identified three studies, assessing a total of 2396 ondansetron-exposed and 104,280 control infants. No significant increase in the rates of orofacial clefts following ondansetron use during pregnancy were observed (**OR=0.89; 95%CI 0.32–2.50**) and no significant heterogeneity was present. In addition, the same publication investigated the risk of isolated cleft palate. This outcome was only investigated by two case-control studies. Cohort studies did not report the specific numbers of the infants with isolated cleft palate. Isolated cleft palate risk was not significantly associated with maternal ondansetron use (**OR=1.13; 95%CI, 0.43–2.97**), however, authors noted significant heterogeneity (P=0.0009; I²=86%). Results of sensitivity analysis were contradictory, as well.

Conclusion: a slight increase in risk of various types of oral clefts was reported by all three studies with primary data analysis, with the exception of the analysis of the BDS dataset that has shown no association. The other analyses provided risk estimates ranging from 1.1 to 1.7, with most estimates in the 1.1-1.3 range. Meta-analysis of previously published studies (Kaplan et al. 2019) did not find an increase of orofacial clefts or cleft palate, although significant heterogeneity was noted for the latter.

Earlier larger epidemiology studies:

A case-control study (Anderka et al. 2012) published an analysis of data from the U.S. National Birth Defects Prevention Study. The authors examined a total of 4,524 cases and 5,859 controls; they specifically looked at the incidence of four types of birth defects: cleft lip with and without cleft palate, cleft palate alone, hypospadias, and neural tube defects. In this study, there was not found to be an increased risk of cleft lip, neural tube defects, or hypospadias. However, the authors reported a roughly twofold increased risk of cleft palate in ondansetron-exposed neonates (**OR 2.37,95% CI 1.18–4.76**). There were 11 cleft palate cases in neonates exposed to ondansetron and 514 cases in unexposed neonates. The relatively small sample size in this study limits the interpretability of these

results. One limitation to the case-control study by Anderka et al. is the potential for recall bias. However, the limitation of most concern in this study is the possibility of a chance finding. Moreover, the authors noted that the medication exposure categories were not mutually exclusive (i.e., pregnant women taking ondansetron might also have been exposed to one or more other anti-NVP treatments). Thus, the association of risk with certain drugs may reflect confounding by other factors for which the authors did not control, including other potentially teratogenic medication use or genetic factors.

In a large retrospective Danish analysis (Pasternak et al. 2013) from a historical cohort of 608,385 pregnancies in Denmark, there were no cases of cleft palate in the group exposed to ondansetron.

Danielsson et al. 2014, found out that there were no infants with a cleft palate and only one infant with a cleft lip/palate.

The [ANSM meta-analysis](#) has found a significantly increased risk of oral clefts (**1.30, 95% CI = 1.04-1.63, I² = 0%; 3 studies**). No statistically significant association was found for major malformations (**ORc= 1.07, 95%CI = 0.95-1.20; I²=20%; 5 studies**), cleft lip with or without cleft palate (**ORc = 1.04, 95% CI = 0.84-1.21; I²=0%; 7 studies**) or cleft palate (**ORc = 1.23, 95% CI = 0.83-1.84; I² = 72%; 6 studies**).

Conclusion: earlier larger epidemiology studies in Europe have not provided evidence for the risk of orofacial clefts.

Hypospadias

One study with primary data analysis (Parker et al. 2018) reported the risk of hypospadias. The adjusted OR for 1st, 2nd or 3rd-degree hypospadias in BDS was **1.0 (95%CI, 0.6–1.5)**, compared to offspring of mothers with first-trimester NVP but no ondansetron exposure. In NBDPS, adjusted OR for 2nd or 3rd-degree hypospadias was **0.8 (95%CI, 0.5–1.1)**, using same control definition.

Meta-analysis by Kaplan et al. 2019 of the risk of hypospadias in ondansetron-exposed vs healthy controls identified four studies, assessing a total of 2565 ondansetron-exposed and 104,442 control infants. There was no significant increase in the rate of hypospadias following ondansetron use during pregnancy (**OR=1.61; 95%CI 0.69–3.75**) and no significant heterogeneity was present. The same publication reported a meta-analysis of the risk of hypospadias in ondansetron exposed vs disease-matched controls. This secondary analysis included two studies and yielded statistically non-significant results, although point estimate was increased owing to no events among 601 unexposed controls (**OR=4.01, 95%CI 0.48-33.52**).

Conclusion: Parker et al. 2018 did not note an increase in risk of hypospadias in either of the two study datasets. Meta-analysis of the risk of hypospadias in previously published studies did not find a statistically significant increase in risk, although point estimate was increased especially in secondary analysis limited to disease-matched controls.

Urinary defects

Risk of renal collecting system anomalies was reported by two studies with primary data analysis. Zambelli-Weiner et al. 2019 reported **aOR 1.24 (95%CI, 0.98-1.58)** for ondansetron medical administration only and **1.07 (95%CI, 1.00-1.16)** for prescription or medical administration, compared to women not exposed to ondansetron. Parker et al. 2018 reported **aOR 1.2 (95%CI, 0.9–1.6)** only in BDS dataset, compared to offspring of mothers with first-trimester NVP but no ondansetron exposure.

In addition, a number of other genitourinary defects was reported to BDS, but only renal agenesis-dysgenesis has shown an association with ondansetron use, **aOR=1.8 (95%CI, 1.1–3.0)** (Parker et al. 2018). This finding has been previously published using an earlier subset of BDS data: (van

Bennekom et al. 2015) reported **aOR=2.3 (95%CI, 1.3-4.0)**, so the updated analysis has shown a decrease in the effect estimate from the previously reported.

Meta-analysis by Kaplan et al. 2019 of the risk of genitourinary malformations in ondansetron-exposed vs healthy controls identified four studies, assessing a total of 2565 ondansetron-exposed and 104,442 control infants. There was no significant increase in the rate of genitourinary malformations following ondansetron use during pregnancy (**OR=1.55, 95%CI 0.89-2.69**) and no significant heterogeneity was present. The same publication reported a meta-analysis of the risk of genitourinary malformations in ondansetron-exposed vs disease-matched controls. This secondary analysis included two studies with 1121 exposed subjects and 601 unexposed controls and yielded statistically nonsignificant results, although point estimate was increased (**OR=2.01, 95%CI 0.40-10.20**).

Conclusion: a slight increase in risk of renal collecting system anomalies was reported by two studies (Parker et al. 2018, Zambelli-Weiner et al. 2019), with ORs between 1.1 and 1.2. In addition, increased risk of renal agenesis–dysgenesis was reported by Parker et al. 2018, consistent with an earlier publication using the same dataset. Meta-analysis of the risk of genitourinary malformations in previously published studies did not find a statistically significant increase in risk, although point estimate was increased especially in secondary analysis limited to disease-matched controls.

Diaphragmatic hernia

Zambelli-Weiner et al. 2019 reported possible association of diaphragmatic hernia with first trimester use of ondansetron (**aOR=2.5, 95%CI, 1.19-5.31** medical administration only, **1.40, 95%CI, 1.05-1.87** for prescription or medical administration). Of interest, risk of diaphragmatic hernia was also elevated in an analysis of an earlier subset of NBDPS data: reported **aOR=1.7 (95%CI, 0.9-3.5)** (van Bennekom et al. 2015). The updated analysis has shown a lower effect estimate than previously reported, but borderline statistically significant: **aOR=1.5 (95%CI, 1.0–2.4)** (Parker et al. 2018).

Conclusion: two studies (Parker et al. 2018, Zambelli-Weiner et al. 2019) reported increase in the risk of diaphragmatic hernia, with ORs between 1.4 and 1.5 for prescription or medical administration.

Clubfoot

Only one study (Parker et al. 2018) reported the risk of clubfoot, and only one of the two datasets (BDS) provided data on this malformation. The **adjusted OR was 0.9 (95%CI, 0.6– 1.3)**, compared to offspring of mothers with first-trimester NVP but no ondansetron or other antiemetic exposure.

Neural tube defects

One study (Parker et al. 2018) reported the risk of neural tube defects. The adjusted OR for spina bifida was **1.4 (95%CI, 0.8–2.5)** in BDS and **1.1 (95%CI, 0.6–1.8)** in NBDPS, compared to offspring of mothers with first-trimester NVP but no ondansetron exposure. In addition, adjusted OR for anencephaly and craniorachischisis in NBDPS was **1.1 (95%CI, 0.5–2.6)**.

Other malformations / birth defects

Zambelli-Weiner et al. 2019 reported no increase in risk of craniosynostosis, laryngeal clefts, limb reduction defects or “all other defects” (a combined category). Parker et al. 2018 evaluated about 40 birth defects in addition to those previously described in the literature, including craniosynostosis, limb deficiency and other brain, ear, eye, gastrointestinal and musculoskeletal defects, but did not find a significant increase in risk with any of these outcomes.

Conclusion: various other defects including clubfoot, neural tube defects, limb reduction etc. were evaluated by the three publications but no associations with ondansetron use in the first trimester were reported.

2) Preclinical studies

Ondansetron did not affect embryo-fetal development in the rat or rabbit and had no adverse effects on fertility or on the general reproductive performance and the post-natal development of rats.

Recent publication by Danielsson et al. (2018), aims to provide a mechanistic explanation for hERG block mediated teratogenicity in rat embryos in vitro. However, no embryo toxicity was observed in studies (oral or iv) performed by Shimizu et al (1992 a, b). There was also no effects on the post-implantation loss or the number of live fetuses. The teratogenicity of ondansetron referenced by Danielsson et al. (2018) from Shimizu et al (1992 a, b) is questionable and does not provide clear evidence of a teratogenic potential. Furthermore, two additional rat studies submitted to FDA did not show any effects albeit they were performed at lower doses. However, the oral high dose group in oral route of 15 mg/kg/d should have some findings as Danielsson reported both 10 and 40 mg/kg/d as teratogenic based on Shimizu et. al (2019 b) oral study. In a book entitled "Catalog of teratogenic agents by Shepard TH, Lemire R (2004)", both the Shimizu et al studies (oral and i.v.) were reported to be not teratogenic.

Taken together, there is no strong evidence or compelling pre-clinical data to state that ondansetron is teratogenic in rats.

3) Post-marketing data

Cumulative analysis of the cases (safety cut-off date 28 Feb 2018) from post marketing database regarding the adverse birth outcomes associated with the use of ondansetron during pregnancy was presented in latest Zofran PSUR ([Appendix 1](#)). Additional analysis of cases since the data lock point of latest Zofran PSUR 28 Feb 2018 until 10 Mar 2019 ([Appendix 4](#)) was performed to evaluate any new safety information for this important potential risk.

Of the cumulative 2,916 pregnancy and fetal cases, 2287 cases were received from the US (2287/2916, 78.4%). Of these 2916 cases, in 276 cases ondansetron was used for severe form of nausea and vomiting i.e. hyperemesis gravidarum.

It should be noted that there has been an increase of pregnancy cases (1,816 cases; 62% during 2015-2018 period) as a result of litigation in the US (n=1,586). In US, increase in trend of Zofran pregnancy cases was noted since 2015 which could be better explained by the stimulated reporting from US lawyers. Downward trend in pregnancy cases (including legal) from US was noticed from year 2017 onwards. There are numerous websites in the United States urging women who took ondansetron during pregnancy and whose babies have birth defects to contact them and file damages suits. This does not necessarily indicate that the drug is a teratogen but has certainly increased awareness and raised concerns about exposure to ondansetron during pregnancy (Kennedy et al. 2016).

In EU and rest of the countries, increasing trend of pregnancy cases was also noted from 2015 onwards however average number of cases in recent years (less than 40 per year) were significantly low compared to US (average more than 400 per year). No significant trend in pregnancy case reporting pattern was noted in all three regions (US, EU and rest of the countries) before year 2015.

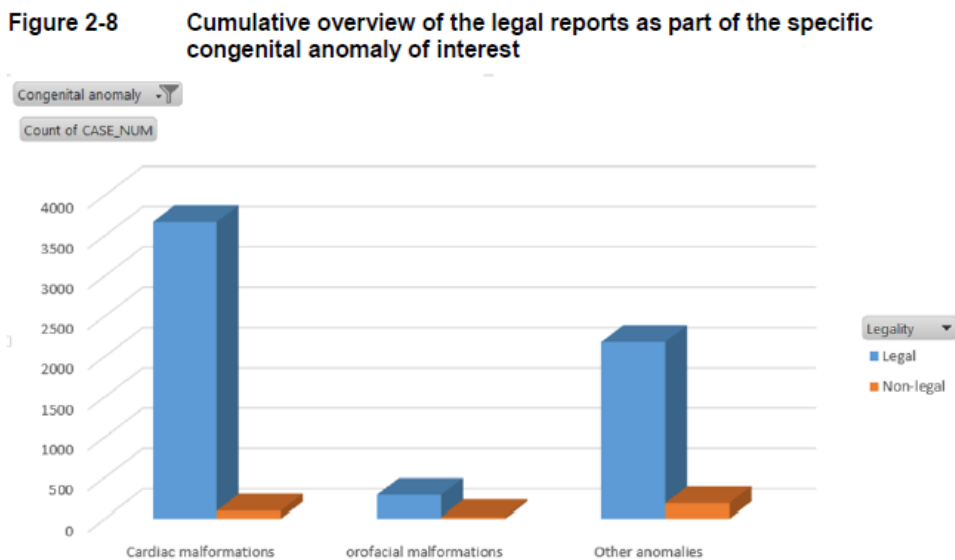
Of the total 2,916 cases, 804 case (27.5%) reported congenital malformations associated with the use of ondansetron during pregnancy. Overall the trend was similar to all pregnancy exposure cases with majority cases as legal case reports from US with increased reporting during 2015-17 followed by downward trend. EU and rest of the countries reported comparatively lower cases of congenital anomalies with an average case count of less than five cases in a year.

Among 804 cases with congenital anomaly, ondansetron was exposed during the first trimester in 680 cases (84.5%), exposure only after the first trimester were 19 cases (2.3%) The timing of ondansetron

exposure with respect to gestation could not be estimated or determined for the remaining 105 cases (13%).

Majority (n=1922; 66%) of the cumulative cases reporting exposure during pregnancy were reported during last five years (2014 until Mar 2019). Most of these recent reports contain very little information regarding precise timing and dosing of ondansetron, concurrent medications and medical conditions, and description of the identified anomalies and majority were stimulated reporting by the US lawyers.

A cumulative overview of the legal reports as part of the specific congenital anomaly reports involving different organs is presented in the Fig 2-8:



On cumulative analysis of post marketing cases of congenital anomalies, no particular pattern of anomalies was apparent, particularly after reports with limited information, including legal reports and reports where ondansetron use occurred after the susceptible period for reported anomaly, are excluded from consideration. Although congenital anomalies are reported with ondansetron, majority of these reports have limited information for a definitive association and precise time of exposure during the critical period of organogenesis [Appendix 1, Appendix 4](#).

Determining the rate of congenital anomalies from SRs is hindered by the lack of precise exposure data for a denominator, the actual number of exposed pregnancies (women prescribed off label ondansetron for NVP or HG or treated with ondansetron for approved indication while pregnant), and the outcomes of these exposed pregnancies, all of which are often not provided within the context of spontaneous adverse event reporting.

4) Conclusion (by MAH)

Conclusion of the cumulative review of data from available sources (preclinical studies, literature publications and post-marketing case reports) is as follows:

- No evidence of teratogenicity for preclinical studies.
- Published epidemiological studies suffer from various methodological limitations that preclude definitive conclusions about the safety of ondansetron use in pregnancy.
- No evidence of an association between ondansetron and overall risk of birth defects; however, evidence, including new information for an increased risk of specific defects, such as **cardiovascular defects are conflicting and remains contradictory. An increased risk of orofacial clefting was noted**, although the effect size appears to be small, with most studies

providing relative risk estimates between 1.1 and 1.3. Significant heterogeneity in the reported results regarding the risk of the cleft palate is evident both in the meta-analysis of earlier publications and newly published studies, with reported ORs ranging from 0.5 to 1.6.

- Quantitatively the cumulative number of cases of congenital malformation with ondansetron from the safety database appears high; however, the bias created by stimulated reporting including US legal cases noted (increase in trends since 2015 followed by downward trend). EU and rest of the countries reported comparatively lower cases of congenital anomalies with an average case count of less than five cases in a year. Majority of case reports have limited information for a definitive association and precise time of exposure during the critical period of organogenesis.

When reviewed together, the totality of the available data is not sufficient to conclude that there is an increased risk of birth defects, including cardiac malformation or oral clefts, among fetuses exposed to ondansetron. Although these results cannot definitively rule out the possibility of adverse effects in association with ondansetron hence use of ondansetron during pregnancy is not recommended during the first trimester of pregnancy with the available safety data.

PRAC Rapporteur's comment:

The MAH conclusion on risk of birth defects with maternal first-trimester ondansetron use is somewhat contradictory and inconclusive.

Literature review:

The MAH submitted summary of published literature on the adverse birth outcomes following use of ondansetron during pregnancy that were published since the data lock point of the last PSUR (28 February 2018) and until 15 March 2019. 5 new articles relevant to adverse birth outcomes were identified, Kaplan et al. (2019)¹⁸, Zambelli-Weiner et al. (2019)¹³, Huybrechts et al. (2018)¹⁴, Parker et al. (2018)¹⁹ and Lavecchia et al. (2018)²⁰. Based on the review, MAH concluded in [Appendix 2](#) and in response to the Question 1.b that the newly published epidemiological studies on the adverse birth outcomes following use of ondansetron in pregnancy provide further evidence that use of ondansetron during the first trimester is associated with an increased risk of orofacial clefting, although the effect size appears to be small. New information on the association of ondansetron with the risk of cardiovascular defects remains contradictory, and there appears to be no association with the overall risk of malformations.

Further, new data from the published studies links use of ondansetron in the first trimester with potential small increase in risk of hypoplastic left heart syndrome, renal collecting system anomalies, renal agenesis-dysgenesis and diaphragmatic hernia, although it cannot be excluded that these associations were due to residual confounding or chance findings.

It has to be highlighted, that Kaplan et al. (2019)¹⁸ and Lavecchia et al. (2018)²⁰ conducted a systematic review of the literature and in addition, Kaplan et al. (2019)¹⁸ conducted a meta-analysis to assess the risk of congenital malformations. Lavecchia et al. (2018)²⁰ neither included two most recently published studies (Zambelli and Huybrechts studies) nor study by Parker et al. (2018)¹⁹. In contrast, Kaplan et al. (2019)¹⁸ included study by Parker et al. (2018)¹⁹ (published first in the abstract form, Van Bennekom et al. (2015)¹⁹) and was aware of two new studies, however not included in meta-analysis, and therefore performed a brief summary of them and evaluation how data from those two studies would change their meta-analysis results and conclusions. According to the author it is considered unlikely that the addition of these new studies data would change the observations regarding overall and cardiac malformation risks, however, it is likely that they could have suggested a

small but statistically significant increased risk of orofacial cleft following maternal first trimester ondansetron use (see further below).

The meta-analysis by Kaplan et al. (2019)¹⁸ included 8 studies (2 case-control and 6 cohort studies) (Einarson et al. (2004)¹⁵, Colvin et al. (2013)⁵, Pasternak et al. (2013)⁶, Andersen et al. (2013)⁸, Danielsson et al. (2014)³, Fejzo et al. (2016)⁷; Anderka et al. (2012)⁴ and Van Bennekom et al. (2015)¹⁹). Asker et al. (2005)¹⁶ was excluded since it did not report the details of the control group and had overlapping data (Swedish Medical Birth Register) with the study by Danielsson et al. (2014)³, which was much more recent (1995–2002 vs 1995–2012, respectively). Because the two Danish studies, Pasternak et al. (2013)⁶, and Andersen et al. (2013)⁸, investigated largely overlapping data and yielded conflicting results, authors undertook a sensitivity analysis and presented two different forest plots for the outcomes of interest by including each Danish study one at a time. Of importance, the study by Andersen et al. (2013)⁸ was published as an abstract which provided very limited details that led to a relatively lower methodological quality score, according to the Newcastle-Ottawa scale used, and as such, the study by Pasternak et al. (2013)⁶ was included in the primary analysis. In the Newcastle-Ottawa scale, a 'star system' has been developed in which a study is judged on three broad perspectives: the selection of the study groups; the comparability of the groups; and the ascertainment of either the exposure or outcome of interest for case-control or cohort studies respectively.

Of note, Andersen et al. (2013)⁸ reported only a risk of major malformations and cardiac defects, including cardiac septal defects, associated with use of ondansetron during pregnancy. Andersen et al. also studied women exposed to metoclopramide and found no increased risk of congenital malformation. Interestingly, Andersen et al. published three abstracts. An inverse correlation can be observed in conference abstracts between the risk of major malformations and heart defects in infants exposed to ondansetron and the number of women taken ondansetron during pregnancy. The number of women went up from 1248 in the 2013 conference abstract to 1800 in the 2014b one, while the adjusted odds ratio of heart defects went down from 2.0 (95% CI: 1.3-3.1) in 2013 to 1.55 (95% CI: 1.02-2.37) in 2014b. The same pattern was observed for major malformations; 1.3 (95% CI: 1.0-1.7) in 2013 and 1.11 (95% CI: 0.85-1.44) in 2014b. Kaplan et al. (2019)¹⁸ used first published abstract in the meta-analysis.

Of note, Pasternak et al. (2013)⁶ did not calculate risks for specific defects (as the study was not designed or powered to study specific malformations), but major cardiac defects among infants exposed and unexposed to ondansetron in the first trimester of pregnancy were tabulated in the Appendix to the published paper. Among the cardiac defects reported, there were 6 and 17 VSDs, 4 and 18 ASDs, and 1 and 1 AVSDs among infants born to exposed (n=1233) and unexposed (n=4932) mothers, respectively. The calculation by Danielsson et al. (2014)³ from the supplemental data of Pasternak et al. gives crude OR of 1.04 (95% CI 0.52-1.95) for cardiovascular defect and crude OR of 1.22 (95% CI 0.56-2.47) for septal defect.

It should be mentioned, that Parker et al. (2018)¹⁹ reported two different risk estimates (for each of malformation investigating) from two separate datasets - National Birth Defects Prevention Study (1997–2011) and the Slone Birth Defects Study (1997–2014). Ondansetron use was not associated with an increased risk for most of the 51 defect groups analyzed. Modest increases in risk were observed for cleft palate (adjusted OR 1.6, 95% CI 1.1–2.4) in the NBDPS and renal agenesis-dysgenesis (adjusted OR 1.8, 95% CI 1.1–3.0) in the BDS, although these findings may be the result of chance. Parker et al. (2018)¹⁹ also reported opposite findings among two different datasets (NBDPS/BDS) regarding cleft palate - in BDS reported a significant decreased exposure rate among infants with cleft palate (aOR 0.5; 95% CI, 0.3 – 1.0). The author could not explain this discrepancy, in spite of conducting a number of sensitivity analysis, in their study.

Of note, Parker et al. (2018)¹⁹ included In the NBDPS participants with estimated delivery dates from 1997 to 2011. However, for the four defects (neural tube defects, cleft lip with or without cleft palate, cleft palate, hypospadias) that were previously analyzed by Anderka et al. (2012)⁴, Parker et al. (2018)¹⁹ restricted the repeat analyses to participants with estimated delivery dates from 2005 to 2011 only. Anderka et al. (2012)⁴, using earlier NBDPS data (1997-2004), report an adjusted OR of 2.37; 95% CI, 1.18–4.76 for cleft palate based on 11 exposed cases. In the more recent NBDPS data (2005 to 2011), Parker et al. (2018)¹⁹ observed an attenuated, yet still elevated, adjusted OR of 1.6; 95% CI, 1.1– 2.4 based on 40 exposed cases. Notwithstanding, it is not understood and clear, why Parker et al. (2018)¹⁹ did not use the whole set of data in their calculations (from 1997 to 2011) and used only data from 2005 to 2011 for neural tube defects, cleft lip with or without cleft palate, cleft palate and hypospadias.

Although the major congenital malformation rate was not suggested to be increased in any of the particular studies included in meta-analysis by Kaplan et al. (2019)¹⁸ and mentioned above, two prospective cohort studies have reported an increase in risk of heart defects [Andersen et al. (2013)⁸, Danielsson et al. (2014)³] while one case-control study identified a significant increase in the risk of isolated cleft palate [Anderka et al. (2012)⁴], and another reporting conflicting findings for this outcome in two different datasets [Van Bennekom et al. (2015)¹⁹/ Parker et al. (2018)¹⁹].

Meta-analysis by Kaplan et al. (2019)¹⁸ identified no significant increased risk for major malformations, heart defects, orofacial clefts (including isolated cleft palate), genitourinary malformations or hypospadias in primary analysis. However, a significant heterogeneity existed for **isolated cleft palate**, based on two case control studies (Anderka et al. (2012)⁴ and Van Bennekom et al. (2015)¹⁹). The issue of significant heterogeneity (P=0.0009; I²=86%) necessitated a sensitivity analysis which yielded a conflicting result; pooled data from NBDPS (1997–2009) demonstrated a significant association (OR, 1.77; 95% CI, 1.15–2.72, P=0.30; I²=7%) whereas BDS (1997–2013) data showed completely the opposite (OR, 0.40; 95% CI, 0.20-0.80). However, the later result is contributed by only one study - Van Bennekom et al. (2015)¹⁹, using BDS dataset.

Among secondary analyses in the meta-analysis by Kaplan et al. (2019)¹⁸ (the sensitivity analysis including Andersen et al. (2013)⁸ instead of Pasternak et al. (2013)⁶) slightly elevated point estimates and altered the statistical significances for major malformations and cardiac defects were present.

How data from Zambelli-Weiner et al. (2019)¹³ and Huybrechts et al. (2018)¹⁴ studies would impact the Kaplan et al. meta-analysis:

- Relating to overall malformation risk, it is probable that the weight of the Huybrechts et al. (2018)¹⁴ study would minimise any difference in the risk estimates following the substitution of the Pasternak study data with that provided from Andersen. As such, it is unlikely that either the primary or secondary meta-analysis would have identified increased risks for overall malformation rate. In support of this are results of ANSM meta-analysis, showing no increased risk for overall malformations; and substitution of named studies changed only heterogeneity between studies (I²=0% with Pasternak study and I²=20% with Andersen study), but not the results.

- Given that the findings of the two studies relating to risks of overall cardiac malformation are conflicting, the expected results from inclusion in a meta-analysis are less predictable. Given the slightly larger sample size of the Huybrechts et al. study, it is possible that the increased risk suggested from the Zambelli-Weiner et al. analysis would have been attenuated on combination. Furthermore, and as with the overall malformation data, it is likely that the sample sizes of the Zambelli-Weiner and Huybrechts studies would have limited any differences in risk estimates with

Pasternak and Andersen study data substitution. However, ANSM meta-analysis found an increased risk of cardiac malformations, with significant heterogeneity between studies.

- Finally, it is possible that combination of the data provided from Zambelli-Weiner et al., which described a non-significant but increased risk of orofacial clefts, with that provided from Huybrechts et al., which described a small but statistically significant increased risk, may have also described a small but statistically significant increased risk of orofacial clefts overall. In support of this are results of ANSM meta-analysis, showing a statistically significant increased risk of oral clefts.

We consider meta-analysis by Kaplan et al. (2019)¹⁸ a robust study with key strengths: some high quality cohort studies were used, which adequately dealt with the issue of confounding, the sample size of the exposed and control groups particularly for overall major congenital malformations and heart defects were quite large and yielded relatively narrow confidence interval, and the included studies retrieved data from three different geographical regions (Scandinavia, North America and Australia). However, this study is not without limitations: the exact information regarding the exposure time windows, dose and duration were not reported in the majority of the studies which limits the ability to discuss the exposure with regard to the sensitive periods for congenital malformations.

During the assessment of the signal we encountered an abstract on a population-based cohort study conducted by Bérard A et al. (2018)¹⁷, studying antiemetic use in pregnancy and the risk of major congenital malformations, as according to the authors conflicting information exists regarding its safety to the fetus.

Authors quantified the risk of major congenital malformations (MCM) associated with first-trimester exposure to antiemetics, using the Quebec Pregnancy Cohort [1998–2015]. First-trimester doxylamine-pyridoxine, metoclopramide and ondansetron exposures were assessed for their association with MCM overall and organ-specific malformations. Generalized estimating equations models were used to estimate odds ratios (OR), adjusting for potential confounding variables (aOR).

Results: Over 14 years of follow-up, the prevalence of antiemetic use during pregnancy increased by 76%. Within the cohort, 45,623 pregnancies were exposed to doxylamine-pyridoxine, 958 to metoclopramide, and 31 to ondansetron during the first-trimester of pregnancy. The mean gestational age at the first prescription filled was 8.2 weeks for doxylamine-pyridoxine exposed group, 9.4 weeks for metoclopramide exposed group, and 10.2 weeks for ondansetron exposed group. The mean number of exposed days during the first-trimester was 27.4 days among doxylamine-pyridoxine exposed-group, 17.7 days for metoclopramide exposed-group, and 12.8 days for ondansetron exposed-group. Doxylamine-pyridoxine and metoclopramide use were associated with an increased risk of overall MCM (aOR, 1.07, 95% CI: 1.03–1.11; 3,945 exposed cases and aOR, 1.27, 95% CI: 1.03–1.57; 105 exposed cases, respectively). Doxylamine-pyridoxine exposure was associated with increased risk of nervous system (aOR, 1.25, 95% CI: 1.06–1.47; 225 exposed cases) and musculoskeletal system defects (aOR, 1.08, 95% CI: 1.02–1.14; 1,735 exposed cases). Metoclopramide exposure was associated with increased risk of genital organ defects (aOR, 2.26, 95% CI: 1.14–4.47; 10 exposed cases). No statistically significant association was found between first-trimester ondansetron exposure and the risk of overall MCM, however, they only had 31 exposed pregnancies in their cohort.

The Quebec Pregnancy Cohort (QPC) is an ongoing population-based cohort with prospective data collection built with the linkage of four administrative databases from the province of Quebec, Canada: RAMQ (medical and pharmaceutical data), Med-Echo (hospitalizations), ISQ (births/deaths), and MELS (Ministry of Education data). The QPC is a tool for the study of the risk and benefit of drug use during the perinatal period. This cohort has the advantage of including a validated date of beginning of

pregnancy giving the possibility of assigning the exact gestational age at the time of maternal exposure.

The abstract of the Bérard A et al. (2018)¹⁷ study highlighted low exposure to ondansetron during pregnancy (probably because of in hospital use only in Canada) and no statistically significant association between first-trimester ondansetron exposure and the risk of overall major congenital malformations, however caution in the interpretation of results is warranted due to only 31 ondansetron exposed pregnancies. From the abstract it is also evident, that first-trimester exposure to other antiemetics was associated with an increased risk of overall MCM. However, grouping malformations into a single outcome category is problematic because teratogens increase risks of specific birth defects rather than birth defects overall (Mitchell AA⁶).

Preclinical studies

The findings from animal studies have not established that ondansetron can cause birth defects.

From the preclinical safety data, it is known, that a study in cloned human cardiac ion channels has shown ondansetron has the potential to affect cardiac repolarisation via blockade of hERG potassium channels. However, the clinical relevance of this finding is uncertain. Recent publication by Danielsson et al. (2018)²¹ suggest that ondansetron can have teratogenic potential in rats and humans mediated via hERG block and severe heart rhythm disturbances in the embryo, in a dose-dependent manner.

Whilst this plausible biological mechanism may add weight to the notion that ondansetron use in early pregnancy increases the risk of cardiac anomalies in humans, especially if additional risk factors are present, such as hypokalemia, further epidemiological surveillance is needed.

Post-marketing data

Based on additional questions from ANSM within the ongoing type II variation regarding high number of prospective cases with no outcome of pregnancy, cases of congenital anomalies, where chromosomal anomalies/genetic syndromes were not specified, cases of multiple anomalies, where specific birth defects were not specified, regarding reported indication for pregnancy cases and quantification of increased off-label use in EU and outside EU, the MAH Novartis clarified uncertainties and presented additional data with regard to post-marketing data. The data did not reveal any substantially new data related to risk of birth defect with ondansetron, except that disproportionality scores within the WHO Vigibase database are high for ondansetron and specific congenital cardiac and facial anomalies. We agree with the MAH that data mining scores do not provide sufficient evidence on causality but instead suggest the necessity of extending the evaluation to other data sources. In addition, off-label uses of ondansetron are evident from post-marketing data and increasing trend of pregnancy cases was noted.

In conclusion, no reliable conclusion on causal association from post-marketing data can be reached, based on the limitation of spontaneous data in relation to pregnancy cases, e.g. missing important information for a definitive association and precise time of exposure during pregnancy.

In summary, based on the assessment of available data, especially on the evidence from available epidemiological studies and meta-analysis, we do not agree with the MAH concluding that available data are not sufficient to conclude that there is an increased risk of birth defects, including cardiac malformation or oral clefts, among fetuses exposed to ondansetron.

⁶ Mitchell AA. Special considerations in studies of drug-induced birth defects. In: Strom BL, editor. *Pharmacoepidemiology*. 2nd ed. Chichester (United Kingdom): John Wiley and Sons, 1994. p. 595–608.

There is enough good data suggesting that small increase in the absolute risk of oral cleft malformation may exist, however data to date does not suggest statistically significant increased risks of overall major or cardiovascular malformation. For the later outcome the data are limited and inconclusive.

3.1.3.2. Question 1.b

Which effect estimates are the most valid?

Response

The data about exposure to ondansetron during pregnancy has come from either retrospective case-controlled studies or has been derived from large prescription/ birth defects databases and population cohorts which have inherent problems in their methodology. Databases which link prescriptions and birth defects are being increasingly used worldwide to determine pregnancy outcomes following exposures, although they were never designed or intended to assess drug safety. The relative paucity of exact timing of the first trimester exposure is another problem. It is important to emphasize that 'first trimester' means exposure up to 13 completed weeks of pregnancy, but this certainly does not mean that all first trimester exposures occurred prior to 10 weeks i.e. during the period of organogenesis. In reality, a significant proportion of ondansetron exposures actually occurred after this period and thus any birth defects in the exposed group are unrelated to the exposure i.e. would have occurred anyway and were already there prior to the commencement of ondansetron therapy. Thus, a birth defect cannot necessarily be attributed to any exposure without accurate timing information and 'first trimester' is not a precise enough description of timing in this context. The vast majority of women with NVP, and particularly those with severe symptoms generally take numerous medications and therefore ondansetron is part of a polypharmacy and polytherapy regimen, making it extremely difficult to attribute adverse outcomes to any single agent. Given the paucity of details about the pregnancy outcomes and malformations reported in many of these studies, it is also very difficult to assess the severity and clinical significance of these defects and thus contextualize the risks in a meaningful way for both patients and their health care providers (Kennedy et al. 2016).

Recently published study by Parker et al. 2018 use data from two large studies of birth defects to describe time trends in ondansetron use for the treatment of first-trimester nausea and vomiting of pregnancy and to investigate associations, either previously reported or undescribed, between first-trimester ondansetron use and major birth defects. National Birth Defects Prevention Study (NBDPS) is one of the largest studies on birth defects ever undertaken in the United States. NBDPS has made key contributions toward understanding the risk of having a baby with a birth defect when specific medications are used just before and during pregnancy.

Slone Pregnancy Health Interview Study (Birth Defects Study) was a study of factors in pregnancy that may be related to the health of newborns focusing on the safety and risks of a wide range of environmental exposures (primarily medications) in pregnancy. The outcomes of primary interest included birth defects and complications of pregnancy such as prematurity and pregnancy-induced hypertension. All three recent studies (Parker et al. 2018, Huybrechts et al. 2018 and Zambelli-Wiener et al. 2019) with primary data analysis were performed in the United States in the comparable time period, however they used different data sources and different analytic approaches. A summary of key methodological aspects is presented in the following table.

Table 2-3 Methodological comparison of three new epidemiological studies of ondansetron pregnancy safety

Design aspect	Zambelli-Weiner et al 2019	Huybrechts et al 2018	Parker et al 2018
Study design	Nested case-control study using secondary data source	Cohort study using secondary data source	Prospective case-control study
Study period	2000-2014	2000-2013	NBDPS 1997-2011 BDS 1997-2014
Data source	US administrative health care database (Truven Health Marketscan Commercial Database) <i>Representative sample of Americans with employer-provided health insurance</i>	Nationwide administrative health care database (Medicaid) <i>More disadvantaged population, mostly composed of low-income adults, multiparae, and women with disabilities.</i>	Prospective studies specifically designed to investigate risk factors for birth defects <i>Representative of the total population in the corresponding geographic areas</i>
Study population	Mother-child pairs resulting from all live births from 2000 to 2014 who had 1 year of follow-up for the infant(s). Mothers with continuous enrollment for 16 months prior to delivery, aged 15-49 on the date of delivery. <i>Not included in the analysis: Miscarriages, stillbirths, pregnancies terminated due to fetal anomalies, and infants who didn't survive birth defect up to 1 year of age</i>	Mothers with Medicaid coverage for 3 months prior to delivery, aged 12-55 on the date of delivery. <i>Not included in the analysis: miscarriages, stillbirths and pregnancies terminated due to fetal anomalies</i>	NBDPS: live births, stillbirths, elective terminations (in some sites) with defects from surveillance programs in 10 US states. BDS: live births, stillbirths, elective terminations with defects identified by review of hospital discharge records or birth registry data in 5 US states.

			<p>Controls: liveborn neonates without malformations identified from study hospitals and birth certificates in same regions as cases.</p> <p><i>Not included in the analysis:</i> miscarriages, elective terminations (in some NBDPS sites)</p>
Exclusion criteria	<p>Chromosomal birth defects in previous offspring</p> <p>Exposure to known teratogens (infections, thalidomide or isotretinoin) pre-birth</p> <p>Exposure to antiemetics other than ondansetron anytime during pregnancy</p> <p>Ondansetron exposure exclusively outside the first trimester</p>	<p>Infants were required to have coverage through Medicaid for the first 3 months of life unless they died sooner</p> <p>Ondansetron prescription in 3 months before the start of pregnancy</p>	<p>Analysis restricted to women reporting first trimester nausea and vomiting of pregnancy (NVP)</p>
Exposure definition	<p>Primary: administration of ondansetron in the medical office or hospital setting during first trimester</p> <p>Secondary: ondansetron filled prescription or medical administration during first trimester</p>	<p>Ondansetron dispensing during the first trimester</p>	<p>Self-reported during standardized interviews</p> <p>Primary: ondansetron (with or without other antiemetics)</p> <p>Secondary: other prescription antiemetic drugs or intravenous (IV) fluids</p>
Reference group	<p>No exposure to ondansetron or other antiemetic anytime during pregnancy</p>	<p>Women who did not fill a prescription for ondansetron during the 3 months before the start of pregnancy through the end of the 1st trimester</p>	<p>NVP not treated with any medication (prescription medications, IV fluids, over-the-counter, herbal products, supplements)</p>
Conception date assessment	<p>Estimated from the date of birth - <i>can lead to misclassification of the exposure window</i></p>	<p>Estimated from the date of birth - <i>can lead to misclassification of the exposure window</i></p>	<p>Estimated from the last menstrual period</p>

Outcome assessment	Malformations identified using ICD-9-CM codes. Cases were identified as having one or more claims with a relevant diagnosis code within 365 days of the date of birth	Malformations identified using algorithms based on inpatient/outpatient diagnoses and procedure codes in maternal (1 st month after delivery) or infant (3 months after date of birth) record, which have shown high specificity	NBDPS: selected major birth defects identified through surveillance programs BDS: major birth defects identified by review of hospital discharge records or birth registry data
Study size	864,083 mother-child pairs Any ondansetron exposure: 76,330 (8.8%) Medical administration of ondansetron (primary analysis): 5557 (0.64%)	816,414 pregnancies Ondansetron exposed: 88,467 (4.9%)	NBDPS: 14,667 cases, 6,751 controls BDS: 8,533 cases, 5,873 controls
Analysis	Logistic regression models used to calculate prevalence ORs and 95% CIs. Stepwise adjustment for confounders: if the risk estimate changed by $\geq 10\%$ that variable was included in the multivariable models	PS estimated using logistic regression. After trimming non-overlapping regions of the PS distribution, 50 equally sized strata were created, untreated observations weighted using the distribution of the treated among PS strata. HDPS analyses included 200 additional empirically defined covariates. Adjusted RR and RD estimated using a log-binomial model.	Logistic regression models used to calculate adjusted ORs and 95% CIs. The adjusted models included all covariates selected a priori.

A side by side comparison of the three recently published observational studies (Parker et al. 2018, Huybrechts et al. 2018 and Zambelli-Wiener et al. 2019) indicates that the study by Parker et al. 2018 is characterized with the highest methodological quality, for the following reasons:

- Among the newly published studies, two were analyzing secondary data collected for administrative purposes and the study by Parker et al (2018) was the only one conducted using a framework of primary data collection for a specific purpose of studying birth defects. This conferred the following advantages:
 - Minimization of misclassification bias in the ascertainment of the outcomes (birth defects verified through surveillance programs or directly from hospital records) as well as exposure to antiemetic products during the first trimester (standardized interview of mothers, although this also confers a possibility of recall bias)
 - More precise assessment of the conception date reduced possibility of exposure misclassification
 - Analysis was not restricted to live births, and the studied defects included those that resulted in stillbirths and elective terminations
 - More representative of the population

- Choice of exposure and reference group definitions was the most appropriate in the Parker et al (2018) study as it included all women with recorded NVP. This improved the baseline comparability between the exposure groups and reduced confounding by indication.

The two remaining studies (Huybrechts et al. 2018, Zambelli-Weiner et al. 2019) used similar data sources and thus suffer from the similar basic limitations related to the nature of these administrative datasets. However, among the two Huybrechts et al. 2018 is characterized with higher and Zambelli-Weiner et al. 2019 with lower methodological quality, due to the following design aspects:

- Study population in Zambelli-Weiner et al (2019) excluded birth defects associated with high mortality (as infants were only included if surviving up to 1 year). This should not have an effect on e.g. orofacial clefting outcome, but may potentially bias analysis of such outcomes as cardiac defects
- Outcome ascertainment was more robust in Huybrechts et al (2018) as it was based on validated algorithms rather than ICD-9 codes alone
- Exposure ascertainment is also expected to be more robust in Huybrechts et al (2018) as the authors note in the discussion that population served by Medicaid is more likely to obtain prescriptions for drugs available over the counter, thus decreasing risk of misclassification.
- Zambelli-Weiner et al (2019) focus on medical administration of ondansetron as primary analysis, arguing that prescription-based exposure definition is prone to misclassification due to women potentially not taking their prescribed pills. However, to test this assumption, Huybrechts et al (2018) performed sensitivity analyses using ≥ 2 prescriptions in the first trimester as exposure definition. It did not result in stronger associations, indicating that this bias did not play a large role in the results. At the same time, choice of "medical administration only" as the primary exposure definition by Zambelli-Weiner et al (2019) is associated with the following issues:
 - This approach selects only a small subset of the population (0.64% of all pregnancies or 7.3% of all ondansetron users). Although reference population remained large, only 5557 exposed mother-child pairs were available for the primary analysis, which made it prone to chance findings due to rarity of the studied outcomes. The strongest associations in the primary analysis were reported based on only a few cases (HLHS N=5; AVSD N=15; CL N=5; CP N=11), where addition or removal of a single case would have resulted in a drastic change of effect estimates, thus these estimates should be interpreted with caution.
 - This subpopulation is more likely to have more severe HG/NVP or other medical issues that have necessitated medical administration of ondansetron e.g. during hospitalization for high-risk pregnancy, potentially amplifying the issue of cohort non-comparability and residual confounding.
- Although both studies suffer from potential residual confounding, PS stratification and hdPS adjustment used by Huybrechts et al (2018) is expected to result in better confounding control through including multiple proxies for unmeasured confounders.

Finally, a limitation inherent to all studies that evaluated multiple outcomes was lack of multiplicity adjustment, which increases the possibility that some results would be statistically significant by chance. With conventional alpha-level of 0.05 there is a high likelihood that a study assessing more than 40 individual outcomes in two separate datasets (as was the case with Parker et al, 2018) a few outcomes will be statistically significant by chance alone. The publication by Zambelli-Weiner et al (2019) that evaluated 17 outcomes in 2 separate analyses is also prone to this issue.

It is also to be noted that identified birth defects (cardiac septal defects and oral clefts) are not rare occurrence during pregnancy. Congenital heart defects (CHD) are the most common cause of major congenital anomalies. In the EUROCAT study, they accounted for 28 % of major defects. Ventricular septal defects were the most commonly encountered CHD. Significant geographical differences also occurred, being highest in Asia (birth prevalence of 9.3 per 1000 live births) and significantly higher in Europe (8.2 per 1000) than in North America (6.9 per 1000). Isolated orofacial clefts, or clefts that occur with no other major birth defects, are one of the most common types of birth defects in the United States (Parker et al. 2010).

For any given agent it is difficult to categorically prove or disprove teratogenicity. Shepard devised 7 criteria (the first 3 being regarded as essential and 5–7 as being helpful but not essential) to prove teratogenicity (Fig 2-9) and essentially ondansetron fails to meet any of these criteria (Kennedy et al. 2016).

Figure 2-9 Shepard’s criteria for proof of human teratogenicity with specific reference to ondansetron

Criterion	In relation to ondansetron
1. Proven exposure to agent at a critical time(s) in prenatal development (prescriptions, physicians records, dates)	No – extremely difficult with mainly registry data and many with uncertain exposure timing or exposure after embryogenesis.
2. Consistent findings by at least 2 high-quality epidemiological studies a) control of confounding factors b) sufficient numbers (adequate power) c) exclusion of positive and negative bias factors d) prospective studies if possible e) relative risk of 6 or more (?)	No Only 1 prospective study with relatively small numbers. Mainly case-control retrospective studies.
3. Careful delineation of clinical cases. Description of a specific defect or syndrome if present is very helpful	No specific malformation syndrome has been described.
4. Rare environmental exposure associated with a rare defect	No – ondansetron is not a rare exposure and the defects of concern are cardiac septal defects and orofacial clefts which are not considered rare.
5. Teratogenicity in experimental animals important but not essential	No – Intravenous doses up to 4 mg/kg/day did not result in any adverse effects on fertility or fetal anomalies in rats and rabbits.
6. The association between exposure and teratogenic effect should make biological sense (biological plausibility)	No – Evidence in rat and mouse whole-embryo culture that serotonin plays a role in cardiac development. Theory about prolongation of QT interval and cardiac arrhythmias resulting in embryonic cardiac hypoperfusion and reperfusion anomalies such as septal defects. However, these have not been demonstrated in animal models.
7. Proof in an experimental system that the agent acts in an unaltered state	Ondansetron has not been definitively shown to cross the placenta – although its molecular weight of 293 and elimination half-life of 4.5 h suggest it would. However extensive hepatic metabolism may limit the amount of parent drug crossing the placenta.

In summary, all published studies evaluating the risk of adverse birth outcomes with use of ondansetron during pregnancy have various methodological limitation that preclude definitive conclusion about the safety of ondansetron use during pregnancy. However, the review of large epidemiological studies with better methodological quality from EU (Pasternak B et al. 2013) and US (Parker et al. 2018) did not reliably support the increased risk of congenital malformations with the use of ondansetron.

Available information including the information from the recent publications on the association of ondansetron with the risk of cardiac septal defects remains contradictory, and there appears to be no association with the overall risk of malformations.

The newly published epidemiological studies on the adverse birth outcomes following use of ondansetron in pregnancy provide further evidence that use of ondansetron during the first trimester is associated with an increased risk of orofacial clefting, although the effect size appears to be small, with

most studies providing relative risk estimates between 1.1 and 1.3. Significant heterogeneity in the reported results regarding the risk of the cleft palate is evident both in the meta-analysis of earlier publications and newly published studies, with reported ORs ranging from 0.5 to 1.6.

Further summary and discussion of the validity and the limitations of the earlier publications is available in the Novartis PSUR Appendix 1 for ondansetron containing products covering the reporting period from 01 March 2015 to 28 February 2018 (Procedure No.: PSUSA/00002217/201802).

ANSM meta-analysis

After reviewing the methods of the meta-analysis, Novartis believes that the article selection for the analysis of the cardiac malformations was skewed towards those studies showing less favorable results, despite lower methodological quality of these analyses.

This conclusion is based on the following analysis aspects:

- The effect estimates from the Zambelli-Weiner et al (2019) were drawn from the “medical administration of ondansetron” analysis only, which used a specific subset of ondansetron-exposed women. As discussed in detail above, this small subpopulation is not representative of ondansetron-exposed pregnancies in the first trimester and is more prone to residual confounding. Further, this exposure definition is different from those used in the analyses in other publications. To avoid comparing “apples to oranges” the “Prescription or medical administration” analyses from Zambelli-Weiner et al (2019) should have been used in the meta-analysis.
- Although the study by Pasternak et al (2013) was using data from the same database as the Andersen et al (2013), the results were discrepant, with Pasternak not finding an association between use of ondansetron and cardiovascular events. As the Andersen et al (2013) abstract does not provide sufficient information regarding the methods used, it is difficult to pinpoint the source of the discrepancy, but one possible explanation lies in the use of adjustment methods. Estimates from Andersen et al are unadjusted, while the Pasternak et al (2013) study used propensity score matching methods to balance the cohorts, thus potentially removing a source of confounding that was present in the Andersen et al study. For the ANSM meta-analysis, only the Andersen et al (2013) study was selected for the meta-analysis. No clear rationale for the selection of the Andersen et al study was provided by the authors, and it appears to have been chosen for conservative reasons. Authors state that Andersen et al (2013) estimates were selected because they were unadjusted, however, PS-adjusted estimates would actually be preferable to avoid confounding. As the Andersen et al (2013) study does not provide sufficient information to assess methodological validity, in one previous meta-analysis was used for sensitivity rather than primary analysis as it was judged to have lower methodological quality compared to Pasternak et al (2013). As shown in this meta-analysis, a choice of one or the other study for inclusion has a significant effect on the overall results (Kaplan et al 2019), so for full transparency inclusion of the Pasternak et al (2013) study should have been done at least as a secondary analysis.
- The estimate from Andersen et al (2013) selected for the meta-analysis was later revised by the authors and moved from 2.0 (95%CI 1.3-3.1) to 1.6(CI95%1.1-3.1) with increased number of exposures (Andersen et al 2014). However, the ANSM meta-analysis included the larger estimate rather than the most recent one.

In conclusion, the summary odds ratio obtained for the cardiac malformations analysis is likely an overestimation of the true magnitude of the risk increase and needs to be interpreted with caution in light of the limitations above.

PRAC Rapporteur's comment:

The MAH submitted methodological assessment of recently published literature.

With respect to the comparison of the three recently published studies, which were all performed in the United States in the comparable time period, however they used different data sources and different analytic approaches, we agree with the MAH around the strengths of Parker et al. (2018)¹⁹ study:

- It is a prospective case-control study using data sources (NBDPS and BDS) which were specifically designed to investigate risk factors for birth defects.
- Study population was not restricted to only live births, but included live births, stillbirths, and (in selected sites) elective terminations.
- Birth defects were identified through surveillance programs or directly from hospital discharge records or registry data at participating hospitals or birth defect registries.
- In the BDS the last menstrual period date was used to estimate the date of conception.
- The analysis was restricted to women with first-trimester nausea and vomiting in pregnancy (exposure and reference group). However, a computer-assisted telephone interview was used to collect data on occurrence of nausea and vomiting in pregnancy, conducted up to 24 months and 6 months after delivery in the NBDPS and BDS, respectively.

The MAH evaluated study by Parker et al. (2018)¹⁹ as the study with the highest methodological quality. However, there are also some limitations of Parker et al. (2018)¹⁹ study:

- Interviews of mothers around collecting information on occurrence of nausea and vomiting in pregnancy, on estimated date of conception in NBDPS, and on collection information regarding treatments with prescription and nonprescription medications, herbal products, and supplements among women with NVP, confer a possibility of recall bias.
- Adjusted models include only following covariates, selected a priori: maternal age, maternal education, periconceptional folic acid use, study year, and study site.
- Exposure to ondansetron is defined as with or without other prescription antiemetics.

It should be mentioned, that Parker et al. (2018)¹⁹ reported two different risk estimates (for each of malformation investigating) from two separate datasets - National Birth Defects Prevention Study (1997–2011) and the Slone Birth Defects Study (1997–2014), reporting conflicting findings for cleft palate in those two different datasets. Even author could not explain this discrepancy, in spite of conducting a number of sensitivity analysis.

In the first round of the assessment, we already thoroughly discussed strengths and limitations of Zambelli-Weiner et al. (2019)¹³ and Huybrechts et al. (2018)¹⁴ studies and identified some uncertainties.

The MAH opposes the results of Zambelli-Weiner et al. (2018)¹³ as their primary analysis examined medical administration of ondansetron. This subgroup addresses classification bias found in other studies based on prescription data only and the risk of exposure misclassification in this subgroup is very low if not null. In addition, it is acknowledged, that vast majority of women with NVP, and

particularly those with severe symptoms generally take numerous medications and therefore ondansetron is part of a polypharmacy and polytherapy regimen, making it extremely difficult to attribute adverse outcomes to any single agent. Therefore, from the response of the authors it is clear, that the majority of women in Zambelli-Weiner et al. (2018)¹³ received a single injection of ondansetron and that these women received only ondansetron. And according to the author, a woman who is being treated for chronic and severe NVP/HG is more likely to be treated with multiple antiemetics, and to receive more than a single dose of an antiemetic. Notwithstanding the consequential small subset of the population, the results have a great value and represent the strength of the study.

In addition, according to the authors there is no empirical data to suggest that women receiving medical administration were presenting with more extreme symptoms.

The MAH highlights the fact that ondansetron doesn't meet any of the set seven criteria by Shepard's as proof of human teratogenicity, however, Shepard's criteria do not include recently large published studies, which are considered robust enough studies showing that the pattern of cardiac anomalies and orofacial clefts appear plausible.

Regarding MAH's comments on ANSM meta-analysis it should be mentioned that although ANSM meta-analysis used Andersen et al. (2013)⁸ study in the primary analysis (as adjusted data were available for the risk of major malformations and cardiac defects), supplementary analysis showed that results were not significantly changed including Pasternak et al. (2013)⁶ study instead of Andersen et al. study. According to the Kaplan et al. (2019)¹⁸ a choice of one or the other study for inclusion has in contrast a significant effect on the results. However, relating to overall malformation risk, the weight of the Huybrechts et al. (2018)¹⁴ study would in Kaplan et al. meta-analysis minimise any difference in the risk estimates following the substitution of the Pasternak et al. study data with that provided from Andersen et al. And as with the overall malformation data, it is likely that the sample sizes of the Zambelli-Weiner et al. (2018)¹³ and Huybrechts et al. (2018)¹⁴ studies would in Kaplan et al. meta-analysis have limited any differences in risk estimates of overall cardiac malformation with Pasternak et al. and Andersen et al. study data substitution (see comments to Question 1.a).

In addition to that, Kaplan et al. also used first published abstract of Andersen et al. study in their meta-analysis.

Although we agree that the data about exposure to ondansetron during pregnancy has come from studies which have inherent problems in their methodology, this is the best available evidence and it is unlikely that future studies will be able to address limitations entirely.

3.1.3.3. Question 1.c

How does it translate to a European setting given baseline risks of oral clefts and cardiac malformations in Europe? Please provide absolute risks and number needed to harm.

Response

Most of the large observational studies evaluating the risk of congenital malformations with the use of ondansetron during pregnancy were based on the data from US. The methodological assessment of these articles including recent publications is presented in previous section. When reviewed together, the totality of the available data is not sufficient to conclude that there is an increased risk of birth defects, including cardiac malformation or oral clefts, among fetuses exposed to ondansetron. Although

these results cannot definitively rule out the possibility of adverse effects in association with ondansetron hence use of ondansetron during pregnancy is not recommended with the available safety data.

In general, if there is enough evidence to support the risk of teratogenicity with drug then the risk is unlikely to be different across geographical region. Prevalence of congenital malformations in EU setting is provided in [Appendix 3](#).

Cardiac malformations:

According to EUROCAT data, the prevalence of congenital heart defects in Europe in 2012-2016 was 66.02 per 10,000 births (95%CI, 65.16 - 66.89), excluding genetic conditions. This estimate includes in the denominator all live births, fetal deaths / stillbirths from 20 weeks gestation and termination of pregnancy for fetal anomaly following prenatal diagnosis (LB+FD+TOPFA) (EUROCAT 2018, [Appendix 3](#)).

Number needed to harm (NNH) was calculated using formula $1/(\text{rate in exposed} - \text{rate non-exposed})$, and 95%CI was obtained by inverting and exchanging the confidence limits for the absolute risk increase, as described in (Bender 2001). This approach results in valid confidence interval as the continuity condition was not violated for the selected values of RR, however, it fails to account for the variability in the underlying (non-exposed) baseline rate.

The absolute risk increase was estimated conservatively, using risk estimates reported in the ANSM meta-analysis: OR=1.45 (95%CI 1.04 - 2.03):

Absolute rate in non-exposed:	66.0 per 10,000
Absolute rate in exposed:	95.7 per 10,000 (95%CI, 68.7 – 134.0)
NNH:	337 (95%CI, 147-3787)

When interpreting the NNH, the large uncertainty around the estimate needs to be taken into account. Even though the confidence limits ignore the variation of the baseline risk estimate, the upper limit of the CI is an order of magnitude higher than the NNH itself.

Further, as indicated in the discussion above, Novartis believes that the RR=1.45 is an overestimation of the true increase in risk of cardiac malformations, therefore, the true value of the risk increase lies below 1.45 and the corresponding NNH is also higher.

Orofacial clefts:

According to EUROCAT data (2012-2016), the prevalence of orofacial clefts in Europe (LB+FD+TOPFA) was 12.47 per 10,000 births (95%CI, 12.10 - 12.85), excluding genetic conditions (EUROCAT 2018, [Appendix 3](#)).

NNH was calculated using the estimate from the ANSM meta-analysis OR=1.30 (95%CI 1.04 - 1.63):

Absolute rate in non-exposed:	12.5 per 10,000
Absolute rate in exposed:	16.5 per 10,000 (95%CI, 13.0 – 20.3)
NNH:	2673 (95%CI, 1273 - 20048)

When interpreting the NNH, the large uncertainty around the estimate needs to be taken into account. Even though the confidence limits ignore the variation of the baseline risk estimate, the upper limit of the CI is more than 20,000, 7.5-fold higher than the NNH estimate.

PRAC Rapporteur's comment:

The MAH used EUROCAT as the source for the baseline epidemiology of congenital malformations. EUROCAT collects data from numerous population-based registries for the epidemiologic surveillance of congenital anomalies in European countries and it covers affected live births, foetal deaths after 20-week gestation and termination of pregnancy for foetal anomaly following prenatal diagnosis. According to the data on website, 29% of European birth population is covered in EUROCAT.

Based on EUROCAT criteria (excluding genetic conditions) the prevalence in the general population from 2013 to 2017 are slightly higher than from 2012 to 2016: 66.66 per 10,000 births (95%CI, 65.76 - 67.56) for congenital heart defects and 12.66 per 10,000 births (95 % CI, 12.27 - 13.06) for orofacial clefts.

To calculate an absolute rate in ondansetron exposed pregnancies, the MAH used risk estimates from the ANSM meta-analysis conducted in February 2019.

It is interesting, that Huybrechts et al. (2018)¹⁴ reported higher absolute risk for cardiac malformations in unexposed pregnancies than the EUROCAT, 84.4 per 10,000 births comparing to 66.66 per 10,000 births. However, the calculation of absolute rate in exposed pregnancies using EUROCAT data and risk estimates reported in the ANSM meta-analysis yielded similar results – 95.7 per 10,000 births in comparison to the reported Huybrechts et al. (2018)¹⁴ absolute risk for ondansetron exposed pregnancies, 94.4 per 10,000 births.

Although, the number needed to harm (NNH) is an important measure in evidence-based medicine and presents the average number of patients that would need to be exposed in order to see an adverse outcome, a definitive quantification of the risk of congenital anomalies in association with ondansetron use during pregnancy is not possible, as the reliable confidence intervals could not be provided. Data should be interpreted with caution.

It should also be mentioned, that a limitation of both the absolute risk increase and NNH is that they are not sensitive to changes to the underlying event rates. Practically, this means that an absolute risk increases of 2% may be clinically significant if the event rates are 1% and 3%, but less so if the rates are 40% and 42%.

3.1.3.4. Question 2

The MAH should discuss whether there are any subgroups of pregnant women where the benefits of using ondansetron during the first trimester may outweigh the potential risks.

Response

There are no controlled studies assessing the benefit risk of ondansetron in first trimester of pregnancy. The studies referred to in the PRAC assessment report (Huybrechts et al., 2018; Zambelli-Weiner et al., 2019) do not provide any further information in this regard or in terms specific subgroups with positive benefit risk profile. Treatment guidelines from Obstetrics and Gynecology societies globally recommend ondansetron use as a second line therapy, to be used after the first trimester of pregnancy.

When reviewed together, the totality of the available data is not sufficient to conclude that there is an increased risk of birth defects, including cardiac malformation or oral clefts, among fetuses exposed to ondansetron. Although these results cannot definitively rule out the possibility of adverse effects in association with ondansetron hence use of ondansetron during the first trimester of pregnancy with the available safety data is not recommended.

PRAC Rapporteur’s comment:

MAH did not highlight any subgroups of pregnant women where the benefits of using ondansetron during the first trimester may outweigh the potential risks.

3.1.3.5. Question 3

The MAH should discuss drug utilisation practices of ondansetron for nausea and vomiting in pregnancy (NVP) and Hyperemesis Gravidarum (HG) in a European setting.

Response

Treatment guidelines from Obstetrics and Gynecology societies globally recommend ondansetron use as a second line therapy, to be used after the first trimester of pregnancy.

Information in guidelines from Ireland and UK, in the European context, are summarized below:

Royal College of Obstetrics and Gynecology, UK 2016 (Maltepe et al., 2013), recommends ondansetron as second line pharmacologic therapy. Further noting that the use of ondansetron should be limited to patients who are not adequately managed with other antiemetics (such as antihistamines (histamine H1 receptor antagonists) such as promethazine, cyclizine, cinnarizine, doxylamine and dimenhydrinate; phenothiazines including prochlorperazine, chlorpromazine and perphenazine; and dopamine antagonists including metoclopramide and domperidone) and preferably used after the first trimester of pregnancy.

Appendix III: Recommended antiemetic therapies and dosages

First line	<ul style="list-style-type: none">• Cyclizine 50 mg PO, IM or IV 8 hourly• Prochlorperazine 5–10 mg 6–8 hourly PO; 12.5 mg 8 hourly IM/IV; 25 mg PR daily• Promethazine 12.5–25 mg 4–8 hourly PO, IM, IV or PR• Chlorpromazine 10–25 mg 4–6 hourly PO, IV or IM; or 50–100 mg 6–8 hourly PR
Second line	<ul style="list-style-type: none">• Metoclopramide 5–10 mg 8 hourly PO, IV or IM (maximum 5 days’ duration)• Domperidone 10 mg 8 hourly PO; 30–60 mg 8 hourly PR• Ondansetron 4–8 mg 6–8 hourly PO; 8 mg over 15 minutes 12 hourly IV
Third line	<ul style="list-style-type: none">• Corticosteroids: hydrocortisone 100 mg twice daily IV and once clinical improvement occurs, convert to prednisolone 40–50 mg daily PO, with the dose gradually tapered until the lowest maintenance dose that controls the symptoms is reached

IM intramuscular; IV intravenous; PO by mouth; PR by rectum.

Ondansetron is also afforded a grade C* recommendation, noting- “There is evidence that ondansetron is safe and effective, but because data are limited it should be used as second-line therapy.”

*A body of evidence including studies rated as 2+ directly applicable to the target population and demonstrating overall consistency of results; or Extrapolated evidence from studies rated as 2++

Institute of Obstetricians and Gynecologists, Ireland, 2015

Ondansetron is recommended as second line pharmacologic therapy.

“Recommendations on the use of ondansetron in pregnancy include reserving it for use where other treatments have failed (Schaefer 2015) and delaying use until after 10 weeks’ gestation (Briggs 2014).”

Overall the ondansetron utilization during pregnancy in US has increased from approximately 1% of all pregnancies in 2001 to nearly a quarter of pregnancies in 2014 (Lockwood G et al. 2017). However, there is no drug utilization data in EU setting available from literature publications. In a large retrospective Danish analysis (Pasternak et al. 2013), the risk of adverse fetal outcomes associated

with ondansetron administered during pregnancy were investigated from a historical cohort of 608,385 pregnancies in Denmark. Exposure to ondansetron was reported in 1970 (0.3%) of these pregnancies.

Post marketing case reports (adverse events reports associated with exposure during pregnancy) do not reliably provide estimate of actual number of off-label use in pregnant patients. Majority (approx. 78%) of the cumulative case reports with adverse events following ondansetron in pregnant patients were reported from US. However, increase in trend in case reporting was noted from year 2015 mainly due to stimulated reporting from US legal cases. In EU and rest of the countries, increasing trend of pregnancy case reports was also noted from 2015 onwards (Fig 2-3 and 2-4) however average number of cases (less than 40 per year) were significantly low compared to US (average more than 400 per year).

PRAC Rapporteur's comment:

The drug utilization review is defined as a review of prescribing, dispensing and use of medication in a society. The MAH shortly presented two national guidelines and trend in case reporting in Europe. However, the MAH did not properly discuss what would be the most interesting, e.g. the pattern of ondansetron use in pregnancy or the quality of use (compliance with national prescription guidelines) and prescriber characteristics in European setting.

3.1.3.6. Question 4

The MAH should discuss the risks of treatment of severe NVP and HG with ondansetron.

Response

NVP is the most prevalent medical condition in pregnancy affecting up to 85% of pregnant women. Typical symptoms of NVP tend to commence between 4 and 9 weeks of pregnancy, and peak between 7 and 12 weeks of pregnancy. The most severe form of NVP, HG, affects between 0.3 and 2% of pregnant women. HG typically leads to hospitalization because of severe and persistent symptoms, weight loss of greater than 5% of pre-pregnancy weight, dehydration, electrolyte imbalances, and nutritional deficiencies. In cases of severe NVP and HG, there are apparent increased fetal risks for adverse pregnancy outcomes such as small for gestational age, low birth weight, preterm delivery, low 5-min Apgar score and neuro developmental delay (Koren G et al 2017).

Cumulative evidence from literature publications and post marketing reports was reviewed for any new safety information or risks in this population.

Literature publications

Relevant published literatures discussing ondansetron use for HG was searched in PubMed, Embase and with cut-off date of 10 Mar 2019. Pure efficacy related articles were excluded, and articles related to safety was focused. Relevant publications were retrieved cumulatively from the three publicly accessible bibliographic databases Medline, Embase and Biosis on the use of ondansetron in severe nausea and vomiting and hyperemesis gravidarum and were reviewed to identify any important new safety information.

There were no robust articles with larger sample size specifically evaluating the safety of ondansetron in severe NVP and HG. However, there were many articles including RCTs, meta-analysis and review articles where safety of antiemetics including ondansetron was studied as a secondary outcomes and drug efficacy was the primary endpoint. In these studies no major adverse event were reported following use of ondansetron in hyperemesis gravidarum.

A brief description about each of these studies are mentioned below.

Mc Parlin et al (2016), Treatments for Hyperemesis Gravidarum and Nausea and Vomiting in Pregnancy: A Systematic Review.

Seventy-eight studies (n = 8930 participants) evaluating the hyperemesis gravidarum and nausea and vomiting in pregnancy (treatment medications compared included metoclopramide, pyridoxine-doxylamine combinations, pyridoxine plus doxylamine and ondansetron). The author concluded that ondansetron appears to be safe in pregnancy, but evidence is limited and more research is needed.

Boelig et al (2016), Interventions for treating hyperemesis gravidarum: a Cochrane systematic review and meta-analysis

Twenty-five trials (2052 women) were studied. Primary endpoint was efficacy and secondary outcomes included adverse maternal/fetal/neonatal outcomes, quality of life measures, and economic costs. A comparison between metoclopramide and ondansetron showed that more women taking metoclopramide complained of drowsiness and dry mouth (RR 2.40, 95% CI 1.23–4.69, and RR 2.38, 95% CI 1.10–5.11, respectively). There were no clear differences between groups for other side effects. In a single trial with 30 women, those receiving ondansetron had no difference in duration of hospital admission compared to those receiving promethazine (mean difference (MD) 0.00, 95% CI –1.39–1.39), although there was increased sedation with promethazine (RR 0.06, 95% CI 0.00–0.94).

O'Donnell A et al (2016), Treatments for hyperemesis gravidarum and nausea and vomiting in pregnancy: a systematic review and economic assessment

A total of five trials and one cohort study compared the serotonin antagonist (ondansetron) against a range of alternatives for the treatment of women experiencing various severities of nausea in pregnancy. Of these, one study focussed on the safety of ondansetron versus the usual treatment regimen (Einarson A et al), with symptom severity not specified. Three trials tested ondansetron against metoclopramide. The remaining two trials compared ondansetron with antihistamines. Given the differences between trials in patient populations, settings, interventions and, in particular, the heterogeneous nature of the reported outcomes across trials, the study did not attempt to perform meta-analyses and have thus reported a narrative summary only for each intervention and comparator set. Sullivan et al noted that, hospital stay (days) were, similar between groups (ondansetron 4.47 ± 2.3 vs. promethazine 4.47 ± 1.5 days; $p = 1.00$) and the only reported side effect was sedation; eight women in the promethazine group vs. none in ondansetron group ($p = 0.002$). No adverse events were reported in the trial of Kashifard and colleagues, in terms of either pregnancy outcomes or side effects. Ghahiri and colleagues found no significant difference between groups in relation to minor side effects [headaches, dizziness, sedation or anxiety ($p > 0.05$)]. Abas and colleagues also reported some minor side effects (difficulty sleeping, dizziness, diarrhoea, headache, palpitations and skin rash) in similar proportions across the trial arms ($p > 0.5$), significant differences were found in self-reported drowsiness ($p = 0.011$) and dry mouth ($p = 0.003$) in favour of ondansetron. No pregnancy outcomes or adverse event data were reported in the trial of Eftekhari and Mehralhasani. In the trial of Sullivan and colleagues, eight women reported sedation versus none in the ondansetron group ($p = 0.002$). Novartis comment: *No new major safety findings were identified in pregnant patients with Nausea Vomiting and HG while using ondansetron.*

Abas MN et al (2014), Ondansetron compared with metoclopramide for hyperemesis gravidarum: a randomized controlled trial.

Total 160 women with hyperemesis gravidarum were randomized to intravenous 4 mg ondansetron or 10 mg metoclopramide every 8 hours for 24 hours. Eighty women each were randomized to ondansetron or metoclopramide. Reported rates of drowsiness (12.5% compared with 30%; $P = .01$;

number needed to treat to benefit, 6), xerostomia (10.0% compared with 23.8%; $P < .01$; number needed to treat to benefit, 8), and persistent ketonuria at 24 hours (12.5% compared with 30%; $P = .01$; number needed to treat to benefit, 6) were less frequent with ondansetron. Length of hospital stay was similar. The author concluded that the overall profile, particularly regarding adverse effects, was better with ondansetron.

London V et al (2017), Hyperemesis Gravidarum: A Review of Recent Literature.

In this article author mentions that metoclopramide and Zofran are the mainstays of current hyperemesis gravidarum therapy and no new safety information is reported specific to ondansetron use in severe NVP or HG.

Cohen et al (2014), Intestinal obstruction in pregnancy by ondansetron

Describes about a case report of intestinal obstruction by ondansetron in HG along with review of Vigibase database and possible mechanism for the event. The case was documented in company database (PHHY2014IL182089) and was presented in the previous two EU PSUR (01Mar2012-28Feb2015 and 01Mar2015-28Feb2018). Assessment of Cohen case shows that no clear temporal association can be drawn up (ondansetron was taken orally for continuous period of 3 months prior diagnosis of intestinal obstruction), constipation is common in pregnancy and the incidence of intestinal obstruction during pregnancy is estimated at 1:1500-1:66400 pregnancies and is diagnosed in II and III trimester in most cases. Since defecation is affected both by bowel movement and hydration, a possible mechanism might be a combination of low intestinal peristalsis, caused by ondansetron and dehydration related to Hyperemesis gravidarum. However, the possible causal association of ondansetron cannot be ruled out.

In response to this article, Fejzo MS et al (2015) described that they have been collecting extensive survey data on women with severe nausea of pregnancy and currently we have 877 women in our database reporting on 1193 pregnancies exposed to ondansetron. Among the 1193 ondansetron exposures, there have been 3 (0.25%) reports of hospitalization for intestinal obstruction. Delayed gastric emptying was reported in 107 (8.97%) of pregnancies exposed to ondansetron. Severe constipation was reported in 36 (3.02%) pregnancies. The author concluded that intestinal obstruction in pregnancies exposed to ondansetron is rare, and that the antiemetic benefit outweighs the risk of intestinal obstruction for the majority of pregnant women with severe nausea and vomiting.

Fejzo MS et al (2016) performed an analysis of fetal outcome in pregnancies exposed to ondansetron to treat HG. In this retrospective cohort study, U.S. data on outcome were collected on 1070 pregnancies exposed to ondansetron and compared to outcomes in two control groups: 771 pregnancies in women with a history of HG with no ondansetron exposure and 1555 pregnancies with neither a history of HG nor ondansetron exposure. Ventricular septal defects were reported in 2/952 of infants in the HG/Ondansetron-exposure group and 4/1286 in the No HG/No Ondansetron-exposure group. Cleft palate was reported in 1/952 live births in the HG/Ondansetron and 2/1286 in the No HG/No Ondansetron-exposure groups. Women with a history of HG who took ondansetron reported less miscarriages and terminations, and higher live birth rates. The overall results do not support evidence of teratogenicity of ondansetron.

Post marketing reports

From cumulative post marketing data (safety cut-off date 10 Mar 2019), an attempt was made to identify the severe cases of Nausea and Vomiting or HG, however none of the cases reported indications based on the severity of nausea and vomiting symptoms. Further analysis was focused on the cases reporting use of ondansetron for severe form of nausea and vomiting i.e. HG and the safety profile of ondansetron use in this population was studied. In order to ascertain the risks associated

with the use of ondansetron in hyperemesis gravidarum the medical review was focused only on cases reporting serious events (including congenital malformations).

Cumulatively there were 276 post marketing case reports of use of ondansetron in patients with HG. Of these 66 cases reporting 168 serious adverse events were evaluated further for evidence of any risks in this population. Overview of reported preferred terms (PTs) for serious events in this population is presented in a Table 2-4 below.

Table 2-4 Overview of serious events reported in patients with hyperemesis gravidarum (event count>2)

Preferred Terms	Event Count
Maternal exposure during pregnancy, Exposure during pregnancy, Off label use	31
Premature delivery/ Premature baby	14
Drug ineffective, Hyperemesis gravidarum	8
Dehydration	3
Foetal death	3
Hydronephrosis	3
Nephrolithiasis	3

Most commonly reported event terms were related off-label use in pregnancy. Other commonly reported events were drug ineffective, hyperemesis gravidarum and dehydration which were better explained by underlying indication of HG.

Total 14 events of premature delivery/premature baby were reported in six cases. Of these six cases, one case was reported from EU while remaining five were legal cases reported from US. HG itself is a risk factor for premature delivery. There was either insufficient information for proper medical assessment or had one or more of potential confounders such as maternal diabetes mellitus, Hepatitis B infection, pre-eclampsia and substance/alcohol abuse.

Of the three cases reporting fetal death, in one case the fetal death was attributed to congenital anomaly without any further details, whereas in the remaining two cases exact cause of intrauterine death of fetus was not mentioned. These cases either had limited information for adequate medical assessment (maternal history, past obstetric history, exposure trimester, diagnosis for fetal death and maternal concomitant medications) or/and cases had one or more of potential confounders such as gestational diabetes mellitus, severe hyperemesis gravidarum, high maternal age (38 years), maternal exposure to other confounding medications (anti-emetic, tacrolimus, lorazepam which preclude causality assessment in isolation), past history of fetal loss and congenital anomaly.

Hydronephrosis and nephrolithiasis events (three each) were reported from three US legal cases of which two cases had concurrent condition of nephrolithiasis as better alternative explanation and the remaining case had limited information for adequate medical assessment (maternal history, past obstetric history, exposure trimester, investigation details and maternal concomitant medications).

No unusual trend of serious events (frequency <2 events) or new safety information were noted from remaining 103 serious events.

Conclusions:

From the currently available evidences from published literature articles and post marketing data, there appears to be no reasonable evidence of any specific safety concerns/risks with the use of ondansetron for severe NVP or hyperemesis gravidarum. Few national treatment guidelines recommend the use of ondansetron as second- or third-line antiemetic therapy in nausea and vomiting during pregnancy which indicate severe nature of indication. Most of the local treatment practice guidelines (US, UK and Ireland) recommend the use of ondansetron as second- or third-line antiemetic

therapy in pregnant patients not responding to the first line antiemetics (Pyridoxine alone or combination with doxylamine, dimenhydrinate, diphenhydramine, promethazine). Hence it is anticipated that all reported cases of off-label use for nausea and vomiting during pregnancy were severe or not responding to conventional first line antiemetic therapies. The summary of cumulative analysis of all pregnancy cases is presented in section 2.1.1 (details in [Appendix 1](#) and [Appendix 4](#)). The Post marketing data did not reveal any unusual trend or new safety information associated with the use of ondansetron in patients with hyperemesis gravidarum. One epidemiology study (Fejzo MS et al 2016) observed that women with a history of HG who took ondansetron reported less miscarriages and terminations, and higher live birth rates and the overall results do not support evidence of teratogenicity of ondansetron. However, the available data is insufficient to establish any specific safety concerns/risk with the use of ondansetron in patients with severe nausea and vomiting or hyperemesis gravidarum hence use of ondansetron is not recommended in pregnant population.

PRAC Rapporteur's comment:

The MAH presented a review of the literature discussing ondansetron use for hyperemesis gravidarum (HG), which included 7 studies; 3 systematic reviews and 1 meta-analysis. These studies did not report any specific safety concerns/risks with the use of ondansetron for severe NVP or HG. Within the response, the MAH did not specifically discuss if severe NVP or HG in addition to the use of ondansetron could increase any risks to the pregnant women.

There are two main aspects to medication safety in NVP. The fetal safety of drugs used to treat NVP symptoms, and the risks of untreated NVP. According to Koren et al. (2017)²³, there is increasing evidence that HG increases maternal and fetal risks, and hence, by choosing not to treat, or delaying treatment of HG one may increase the child's risks for intrauterine growth restrictions and developmental delay. And there is no evidence that adverse maternal effects using antiemetic drugs occur more frequently in pregnancy or increase maternal risks more than among other adult patients.

Headache, fatigue, constipation, and drowsiness are the most common ondansetron-related side effects. Ondansetron can cause QT prolongation, particularly in patients with underlying arrhythmia risk factors, such as a personal or family history of long QT syndrome, hypokalemia or hypomagnesemia, heart failure, administration of concomitant medications that lead to QT prolongation, and use of multiple doses or intravenous ondansetron. Serotonin syndrome is a potentially life-threatening condition associated with use of serotonergic agents and manifested by increased serotonergic activity in the central nervous system.

According to Mc Parlin et al. (2016)²⁴, the treatment of NVP/HG with ondansetron should be contraindicated in pregnant women at risk of cardiac arrhythmias, history of prolonged QT interval, heart failure, hypokalaemia, hypomagnesemia, use of concomitant medications that lead to prolongation of QT interval. Mc Parlin et al. (2016)²⁴ also highlighted that reported common adverse effects using ondansetron for the treatment of NVP/HG include anxiety, dizziness, constipation, dry mouth, confusion, headache, hyperventilation, tachycardia, irritability, restlessness, muscle spasms and insomnia. In addition, Kennedy et al. (2016)¹¹ highlighted that reported side effects using ondansetron for the treatment of NVP/HG include diarrhoea and fatigue and there are theoretical concerns about potential QT prolongation and torsade de pointes as well as serotonin syndrome, although no reports of these complications with regard to treatment of NVP were identified in the literature.

In the context of NVP, quite a few women with severe NVP may have electrolyte abnormalities (hypokalemia or hypomagnesemia).

Serotonin syndrome is most often reported with the use of selective serotonin reuptake inhibitors and concomitant use of 5-HT₃ receptor antagonists. Because a large number of pregnant women are on selective serotonin reuptake inhibitors (antidepressants) and up to 85% experience morning sickness, a possible interaction with ondansetron leading to serotonin syndrome should be considered.

3.1.3.7. Question 5

The MAH is requested to discuss whether in the light of the responses to the questions above further risk minimization measures are considered necessary, including amendment to the product information. Furthermore, the MAH should comment on if communication is considered necessary, and if so, a draft DHPC and communication plan should be provided.

Response

The review of totality of data regarding the risk of congenital malformations associated with the use of ondansetron during nausea and vomiting of pregnancy (Question 1.a) is not sufficient to conclude that there is an increased risk of birth defects, including cardiac malformation or oral clefts, among fetuses exposed to ondansetron.

No evidence of teratogenicity was identified in ondansetron preclinical studies.

A side by side comparison of the three recent large observational studies (Huybrechts et al. 2018, Zambelli-Weiner et al. 2019 and Parker et al. 2018) indicates that the study by Parker et al. 2018 is characterized with the highest methodological quality. Two recently published studies (Huybrechts et al. 2018, Zambelli-Weiner et al. 2019) were performed using secondary data sources and have various methodological limitations which preclude meaningful interpretations of the results. In comparison, recently published Parker et al. 2018 was a prospective case control study using data sources (NBDPS and BDS) which were specifically designed to investigate risk factors for birth defects.

The review of large epidemiological studies with better methodological quality from EU (Pasternak et al. 2013) and US (Parker et al. 2018) did not reliably support the increased risk of congenital malformations including cardiac malformations or oral clefts with the use of ondansetron. Other previous epidemiological studies did not reveal consistent and compelling evidence to support the risk of congenital malformation including cardiac septal defects and oral clefts with the use of ondansetron. However, these results cannot definitively rule out the possibility of adverse effects in association with ondansetron hence the use of ondansetron during the first trimester of pregnancy is not recommended with the available safety data.

Considering above findings, the MAH believes that there is no reasonable evidence to update product information for an association of congenital malformations in particular cardiac malformations and orofacial clefts associated with the use of ondansetron during first trimester of pregnancy. The safety data from epidemiology studies is inconsistent however results cannot definitively rule out the possibility of adverse effects in association with ondansetron hence use of ondansetron during pregnancy is not recommended during the first trimester of pregnancy with the available safety data. The MAH propose following text in the pregnancy section of product information consistent with the pregnancy guidance provided in Zofran Core Data Sheet (CDS). This text has been submitted to the various EU national Agencies by means of respective local variations and has already been approved in majority while in few, it is approved with alternate wording for section 4.6.

Novartis Core Data Sheet (CDS)

Risk Summary

The safety of ondansetron for use in human pregnancy has not been established.

Reproductive studies in rats and rabbits did not show evidence of harm to the fetus when ondansetron was administered during organogenesis at approximately 6 and 24 times the maximum recommended human oral dose of 24 mg/day, based on body surface area, respectively. However as animal studies are not always predictive of human response, the use of ondansetron in pregnancy is not recommended (see Animal data).

Safety data of ondansetron in pregnancy are limited, and findings from available pharmaco-epidemiologic studies are inconsistent.

Post-marketing reports describe cases of congenital malformations with use of Zofran during pregnancy; however the reports are insufficient to establish a causal relationship.

Animal Data

In embryo-fetal development studies in rats and rabbits, pregnant animals received oral doses of ondansetron up to 15 mg/kg/day and 30 mg/kg/day, respectively, during the period of organogenesis. With the exception of a slight decrease in maternal body weight gain in the rabbits, there were no significant effects of ondansetron on the maternal animals or the development of the offspring. At doses of 15 mg/kg/day in rats and 30 mg/kg/day in rabbits, the maternal dose was approximately 6 and 24 times the maximum recommended human oral dose of 24 mg/day, respectively, based on body surface area. In a pre- and postnatal developmental toxicity study, pregnant rats received oral doses of ondansetron up to 15 mg/kg/day from Day 17 of pregnancy to litter Day 21. With the exception of a slight reduction in maternal body weight gain, there were no effects upon the pregnant rats and the pre- and postnatal development of their offspring, including reproductive performance of the mated F1 generation. At a dose of 15 mg/kg/day in rats, the maternal dose was approximately 6 times the maximum recommended human oral dose of 24 mg/day based on BSA.

The MAH has also proposed additional guidance text in label (routine risk minimization measure) for females of reproductive potential as follows;

Females and males of reproductive potential

Pregnancy testing

Pregnancy status should be verified for females of reproductive potential prior to starting the treatment with Zofran.

Contraception

Females of reproductive potential should be advised that it is possible that Zofran can cause harm to the developing fetus. Sexually active females of reproductive potential are recommended to use effective contraception (methods that result in less than 1 % pregnancy rates) when using Zofran during the treatment and for two days after stopping treatment with Zofran.

Basic Patient leaflet (BPL):

Pregnancy and breast-feeding

Zofran is not recommended for use during pregnancy.

- *Tell your doctor if you are pregnant or planning to become pregnant. Zofran may harm your unborn baby.*
- *If you do become pregnant during treatment with Zofran tell your doctor.*

Breast-feeding is not recommended during treatment with Zofran. The ingredients can pass into your breast milk, and may affect your baby. Talk to your doctor about this.

Females of child-bearing potential and male patients

Zofran may harm your unborn baby. If you are a woman of childbearing age, your doctor or healthcare provider will check if you are pregnant and perform a pregnancy test if necessary before starting treatment with Zofran. If you may become pregnant, you should use effective birth control during treatment with Zofran.

Ask your doctor about options of effective birth control.

Post-marketing reports suggestive of quantitatively higher pregnancy exposure cases (including congenital malformations) mostly due to stimulated reporting of pregnancy cases from US with increasing trend after 2015 and downward trend was thereafter. In EU, overall reporting of pregnancy exposure cases (including congenital malformations) is significantly low compared to US. Few local national guidelines (e.g. UK, Ireland) recommend ondansetron as second line antiemetic therapy preferably after first trimester of pregnancy. It was noted that some local SmPC (e.g. Germany) have a less strict recommendation during pregnancy. Considering overall lower reporting from EU, the MAH suggest that the proposed update to the SmPC pregnancy section and additional guidance on contraception and pregnancy testing for females of reproductive potential consistent with Zofran CDS is sufficient to mitigate the risk of off-label use during pregnancy and no additional risk minimization measure (including DHCP letter) is required in EU at present.

The important potential risk of adverse birth outcomes following the use of ondansetron during pregnancy would continue to be closely monitored in the next Zofran PSUR for further characterization.

PRAC Rapporteur's comment:

In light of the responses to the previous questions the MAH believes there is no reasonable evidence to update the product information for an association of congenital malformations, however the MAH proposed extensive update of the product information, already submitted in various member states across EU. Although the MAH believes that there is not sufficient evidence to conclude that there is an increased risk of birth defects, as a precautionary measure the MAH further proposes effective contraceptive use (methods that result in less than 1% pregnancy rates) and pregnancy testing during ondansetron use, which is not risk-proportionate.

The provided proposal for an update of product information is not appropriate. The current wording of section 4.6 of the SmPC should be updated according to the "Guideline on Risk Assessment of Medicinal Products on Human Reproduction and Lactation: from Data to Labelling" (EMA/CHMP/203927/2005) to reflect the new evidence of the risk of congenital malformations and to include a statement that ondansetron should not be used during pregnancy.

Lower reporting rate claimed by the MAH is not the evidence there is no harm. It has to be mentioned that the absence of data cannot be used as a strong argument for the absence of risk.

The MAH considers that further risk minimisation measures is not necessary.

However, in case the product information is amended as proposed by the Rapporteur, a communication to inform the prescribers of the new evidence of the risk of congenital malformations as a basis for their decision regarding use in pregnancy is considered warranted.

3.1.4. Drug utilisation studies by EMA

Following the PRAC recommendation on March 2019, the EMA performed two small drug utilisation studies with the aim to identify use of ondansetron in women during pregnancy and to study the yearly proportion of women with a diagnosis of excessive vomiting of pregnancy treated with ondansetron between 2005 and 2018 in France and Germany; and to estimate the exposure to 5HT3 antagonists in women during pregnancy in the UK and to assess the potential for further research using the THIN dataset of general practice data.

1) Use of ondansetron in pregnant female patients in the IMS Disease Analyzer databases in France and Germany (summary)

Methods: In the IMS DA databases it is not possible to identify mother-child pairs. Use during pregnancy instead needs to be identified on the basis of a diagnosis code suggestive of pregnancy, and then linking this diagnosis in time to a prescription of a drug of interest.

The codes have been selected in order to identify women at all stages of pregnancy and after giving birth among women 12 to 60 years of age. A subset of these ICD 10 codes (ICD code O21) identifies women with excessive vomiting in pregnancy. The start and end of pregnancy is not recorded in the IMS DA databases. Therefore, the number of days that a woman could have been pregnant and the number of days that a woman could still be pregnant at the time of a recorded pregnancy-related diagnosis has been estimated for each pregnancy and post-partum diagnosis code please see Appendix 1 in the report. Use of ondansetron during this time period is considered to have taken place during pregnancy. Women with a diagnosis of cancer (ICD codes C00-C97) prior to the recorded pregnancy-related code are excluded. Any use of ondansetron in pregnant women with a diagnosis of cancer up to the time of the ondansetron prescription is also excluded.

The IMS DA databases use EphMRA ATC codes and all prescriptions have an attributed EphMRA ATC code. Ondansetron is identified using the EphMRA ATC code A04A01 for serotonin antagonists and selecting products containing ondansetron on the basis of the substance name.

The study uses version December 2018 of the IMS DA databases. The study period is defined as January 2005 to December 2018.

All pregnant women with no prior diagnosis of cancer are identified, and all use of ondansetron during pregnancy in women with no prior diagnosis of cancer is captured. Pregnant women with excessive vomiting in pregnancy are then specifically identified, and use of ondansetron in these women is captured. Data is provided for the entire study period as well as annually. The time point is determined by the recorded pregnancy-related event. The existence of an ondansetron prescription relates to the specified time window for a possible pregnancy based on the recorded pregnancy-related event, and is expressed as a proportion of pregnant women. In IMS DA Germany, general practitioner (GP) practices and gynaecologist practices are selected for the analysis. Results are presented separately by type of practice.

Results: IMS DA France

Women with a pregnancy-related code between 2005 and 2018

In IMS DA France a total of 75,539 women 12-60 years of age had a pregnancy-related code between 2005 and 2018 and no prior diagnosis of cancer (89 women were excluded due to a prior diagnosis of cancer). A diagnosis of excessive vomiting in pregnancy was identified in 8476 women.

Total use of ondansetron between 2005 and 2018

A total of 634 patients had received a total of 853 prescriptions for ondansetron between 2005 and 2018 of which 400 patients (63.1%) and 544 prescriptions (63.8%) concerned women.

Use of ondansetron in women with a pregnancy-related code between 2005 and 2018 and no prior diagnosis of cancer

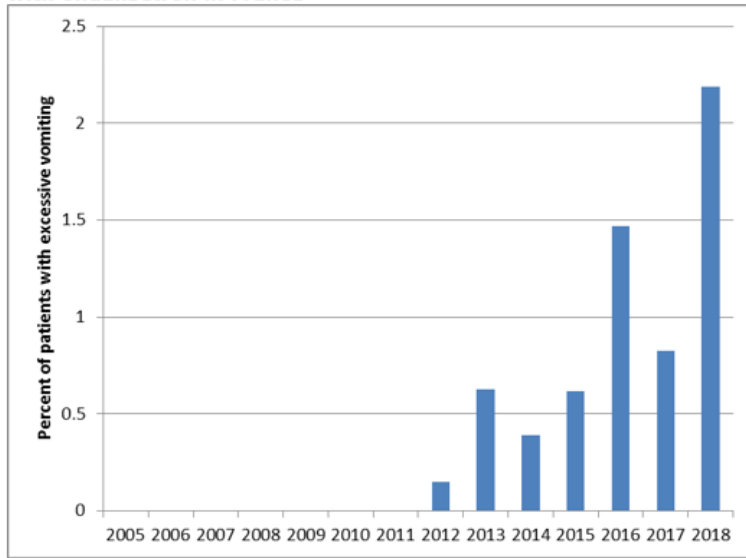
A total of 59 women with a pregnancy-related code between 2005 and 2018 and no prior diagnosis of cancer had received a prescription for ondansetron during pregnancy; 43 of the women had a diagnosis of excessive vomiting in pregnancy, see Table 1. The percentage of women with a diagnosis of excessive vomiting in pregnancy that had received a prescription for ondansetron appeared to increase over time, see Figure 1.

Table 1 Use of ondansetron in women with a pregnancy-related diagnosis between 2005 and 2018 and no prior diagnosis of cancer in France

Year	No. of women a pregnancy-related diagnosis (no. of women with excessive nausea) ¹	No. of women with ondansetron during pregnancy (no. of women with ondansetron for excessive nausea) ¹
2005	3499 (421)	0 (0)
2006	4184 (521)	0 (0)
2007	4469 (560)	0 (0)
2008	4780 (602)	0 (0)
2009	5251 (617)	0 (0)
2010	5480 (581)	0 (0)
2011	5583 (626)	0 (0)
2012	6466 (665)	1 (1)
2013	7876 (638)	5 (4)
2014	9724 (768)	8 (3)
2015	10597 (810)	6 (5)
2016	10352 (749)	15 (11)
2017	10376 (727)	15 (6)
2018	10153 (731)	23 (16)

¹ No prior diagnosis of cancer.

Figure 1 Proportion of women with excessive vomiting during pregnancy treated with ondansetron in France



Results: IMS DA Germany

Women with a pregnancy-related code between 2005 and 2018

In IMS DA Germany a total of 505,312 women 12-60 years of age in gynaecological practices and 141,158 women 12-60 years of age in GP practices had a pregnancy-related code between 2005 and 2018 and no prior diagnosis of cancer (9082 women in gynaecological practices and 1841 women in GP practices were excluded due to a prior diagnosis of cancer). A diagnosis of excessive vomiting in pregnancy was identified in 57,248 women in gynaecological practices and 7944 women in GP practices.

Use of ondansetron between 2005 and 2018

A total of 9769 patients in GP practices had received a total of 21,263 prescriptions for ondansetron between 2005 and 2018 of which 5844 patients (59.8%) and 12,543 prescriptions (59.0%) concerned women. A total of 2134 patients in gynaecological practices had received a total of 5292 prescriptions for ondansetron between 2005 and 2018 of which 2097 patients (98.3%) and 5231 prescriptions (98.8%) concerned women.

Use of ondansetron in women with a pregnancy-related code between 2005 and 2018 and no prior diagnosis of cancer

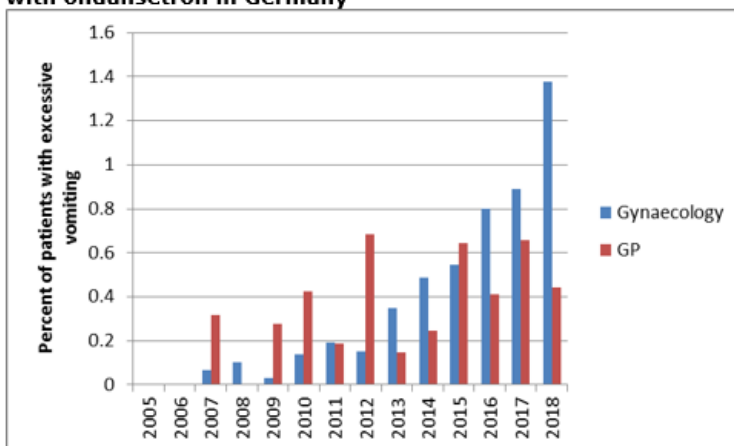
A total of 349 women in gynaecological practices and 47 women in GP practices with a pregnancy-related code between 2005 and 2018 and no prior diagnosis of cancer had received a prescription for ondansetron during pregnancy; 271 of the women in gynaecological practices and 26 in GP practices had a diagnosis of excessive vomiting in pregnancy, see Table 2. The percentage of women with a diagnosis of excessive vomiting in pregnancy that had received a prescription for ondansetron increased over time in gynaecological practices, whereas there was no clear trend over time in GP practices, see Figure 2.

Table 2 Use of ondansetron in women with a pregnancy-related diagnosis between 2005 and 2018 and no prior diagnosis of cancer in Germany

Year	No. of women with a pregnancy-related diagnosis in gynaecological practices (no. of women with excessive nausea) ¹	No. of women with ondansetron during pregnancy in gynaecological practices (no. of women with ondansetron for excessive nausea) ¹	No. of women with a pregnancy-related diagnosis in GP practices (no. of women with excessive nausea) ¹	No. of women with ondansetron during pregnancy in GP practices (no. of women with ondansetron for excessive nausea) ¹
2005	33826 (2244)	0 (0)	4968 (232)	0 (0)
2006	39246 (2612)	1 (0)	5936 (256)	0 (0)
2007	45145 (3034)	4 (2)	7181 (317)	1 (1)
2008	47250 (2886)	8 (3)	7410 (333)	2 (0)
2009	50920 (3322)	15 (1)	8651 (360)	1 (1)
2010	53424 (3657)	14 (5)	9553 (470)	2 (2)
2011	56065 (4190)	14 (8)	11048 (528)	2 (1)
2012	63562 (4651)	15 (7)	12807 (583)	4 (4)
2013	68730 (5421)	33 (19)	13862 (681)	1 (1)
2014	74128 (5943)	40 (29)	15313 (810)	2 (2)
2015	80865 (6625)	58 (36)	17343 (934)	12 (6)
2016	83507 (6480)	77 (52)	18653 (976)	9 (4)
2017	81567 (6525)	110 (58)	17917 (915)	9 (6)
2018	76546 (6239)	131 (86)	17201 (907)	9 (4)

¹ No prior diagnosis of cancer.

Figure 2 Proportion of women with excessive vomiting during pregnancy treated with ondansetron in Germany



Discussion: Prescribing of serotonin antagonist ondansetron for excessive nausea during pregnancy appeared to increase over time between 2005 and 2018, at least in France and in gynaecological practices in Germany. In 2018, the percentage of women with a diagnosis of excessive nausea during pregnancy that had received ondansetron was around 1.4% in gynaecological practices in Germany and 2.2% in France, an increase from 0.0% in 2005 and 2006. Also, in GP practices in Germany there was no prescribing of ondansetron identified in women with a diagnosis of excessive nausea in 2005 and 2006, but apart from this there was no clear trend towards increased prescribing over time. It is possible that these analyses underestimate use of ondansetron during pregnancy because of the possibility that pregnant woman may visit different healthcare providers for the pregnancy itself and for the treatment of nausea during pregnancy (the same person cannot be identified across different

healthcare providers), and due to the possibility that longitudinal data for a pregnant woman may not cover the entire estimated pregnancy time period.

PRAC Rapporteur's comment:

Although there is no direct data of interests in the IMS® Disease Analyzer database (which provides real world evidence via anonymized disease and therapy pathways) and therefore there is a lot of compilation of data and estimations, it can be concluded that off-label ondansetron use among pregnant women is on a steep rise.

According to the presented data, 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.

In the presented study, data is provided for the entire study period as well as annually. For the clarity of the data, as the sum of the number of women during each year is not equal to the total number of women during the entire study period, it should be taking into account that when splitting data over time periods the same woman can contribute to more than one time period, e.g the same pregnancy can be recorded in two consecutive years or the same woman can have more than one pregnancy recorded.

2) Exposure to 5HT3 antagonists in pregnancy in the UK

Data source: The study uses data from UK general practice electronic medical records collected in the THIN Database between 1 January 1990 and 24 September 2018. At September 2018 the data contained records on 15.0 million patients considered to meet acceptable standards for research of whom 3.0 million were still under observation. The data for each patient form a record of visits and interactions with their general practitioner (GP). In particular, all prescriptions issued by the GP and clinical events discussed are routinely recorded using formal coding dictionaries together with the date of the consultation. Data are representative of the UK population in terms of age, deprivation, and geographical distribution.

Population for analysis: The study is restricted to women with identifiable live offspring registered in THIN practices. No explicit link is made between babies registered with practices and mothers, but a family identification number is coded that allows potential mothers for babies registered with the practice to be identified. Babies are defined as new registrations that occurred within 150 days of the date of birth. For children older than 15 at the point of last data collection the date of birth is masked by coding the month to July and, in these cases an imputed value was used to increase the accuracy of identification. Potential mothers were considered to be female with the same family identification number who were between the age of 12 and 55 at the date of birth. When more than one potential mother was found a hierarchical list of tests was used to discriminate the most likely mother. In particular we looked for and last menstrual period code between 6 months and a year before the birth, any record of a clinical visit on the days of registration for the baby and any one of a list of pregnancy related codes in the year before the birth.

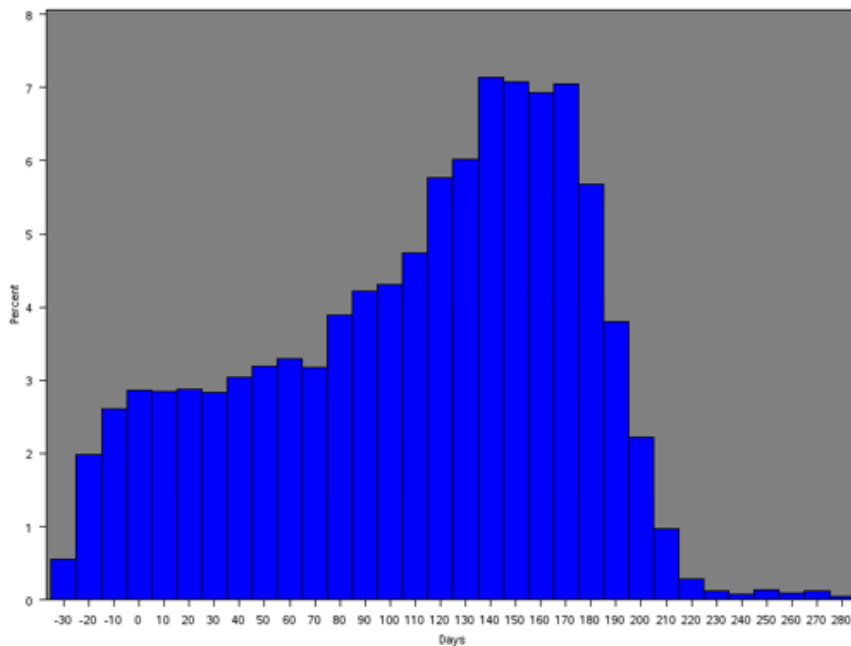
Using this procedure 981,821 registered babies were linked to 706,259 mothers.

Use of 5HT3 antagonists in THIN practices: Over the year 1990 to 2018 four 5HT3 antagonists were prescribed by UK GPs in THIN practices. Annex 1 shows the numbers of prescriptions by year. 96.6% of prescriptions were for ondansetron and 3.1% for granisetron. Dolasetron and tropisetron accounted for only 0.3% of use. Use of these products in pregnant women is further skewed towards

ondansetron (99.9%) with granisetron accounting for the remaining 0.1%. Thus, although we include all 5HT3 antagonists, the figures in this report should be viewed primarily as ondansetron usage.

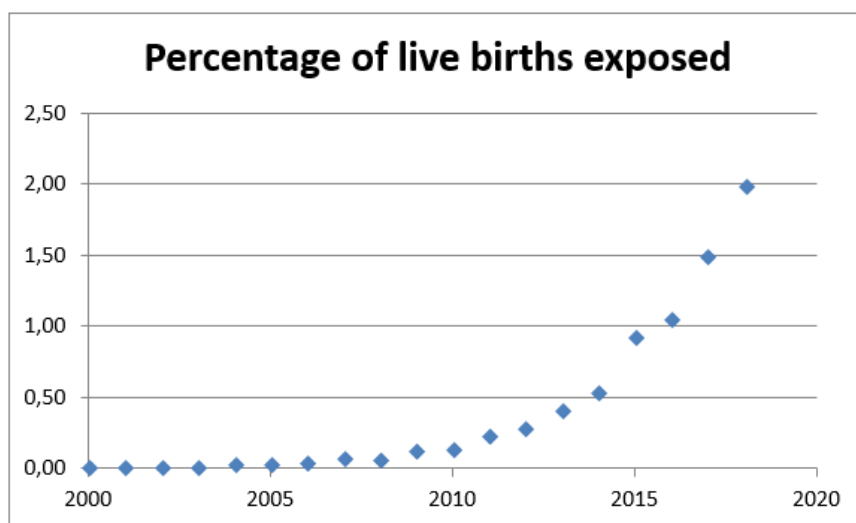
Exposure of live births in THIN: Using all live births that could be matched to a mother in the September 2018 version of THIN there were 2674 children whose mothers received a prescription for 5HT3 antagonists between 310 days before the date of birth and the date of birth. 310 days was used to allow a window of 30 days before the likely date of conception.

The distribution of times throughout the pregnancy when these prescriptions were issued are shown in the histogram:



It should be noted that the matching of babies to mothers and the predominantly accurate records of date of birth – 97.75% were recorded to the month – allows accurate attribution of time of exposure. Thus, the predominance of prescriptions during the second trimester is accurate and may reflect the second line use of ondansetron, mothers having previously tried other treatments for nausea.

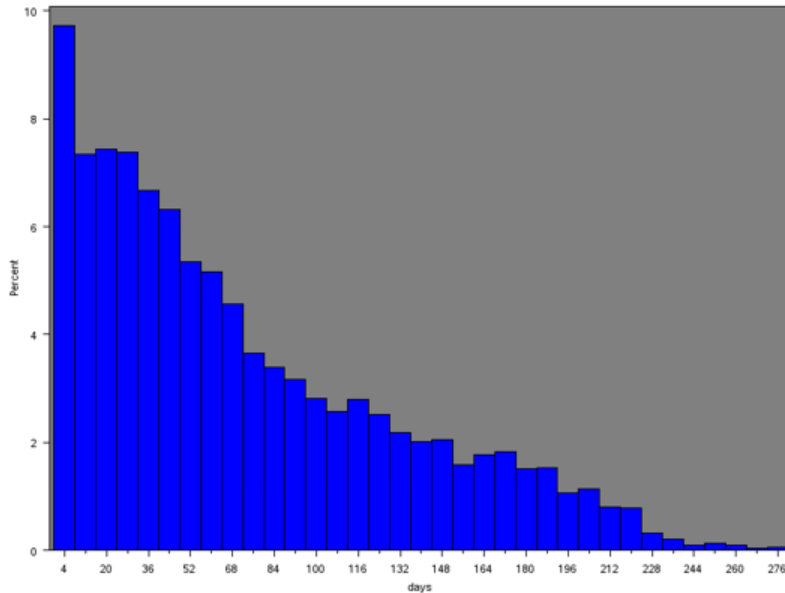
The percentage of live births exposed during pregnancy over the years 2000 to 2018 are illustrated below.



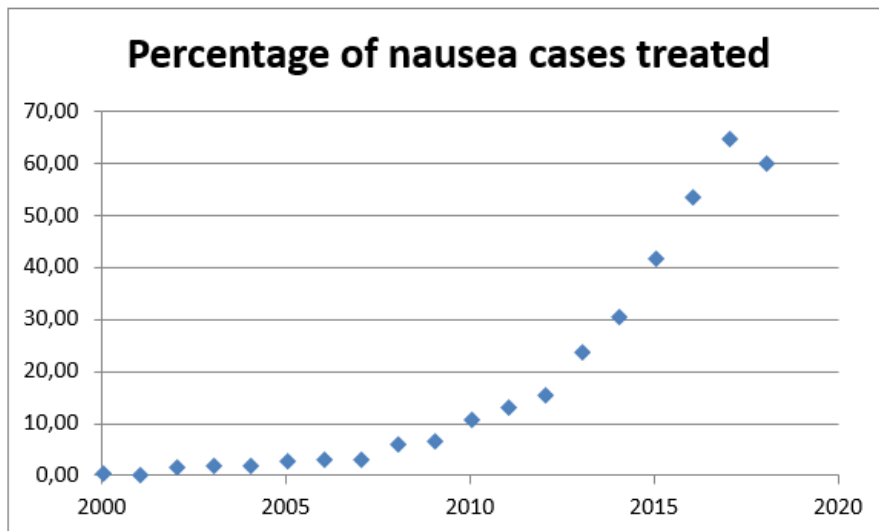
Exposure in women with new episodes of pregnancy related nausea: We also considered the timing of use of 5HT3 antagonists relative to recording of nausea during pregnancy. We define a new episode of pregnancy related nausea as one of the codes listed in Annex 2 not preceded by another code in the list for 280 days. This will exclude a number of pregnancies that did not go to term but only those that were followed soon by a further conception.

A total of 4499 such cases of nausea exposed to 5HT3 antagonists were found in the dataset.

The distribution of times from the index date for nausea to any prescription are shown below.



The graph below shows the percentage of women who reported nausea in pregnancy that were treated with 5HT3 antagonists.



Potential for study of structural birth defects in THIN

Study population: Of the mother-baby pairs identified in THIN between 2000 and September 2018, 2674 (0.3%) infants were exposed at any stage of the pregnancy to a 5HT3 antagonist, predominantly ondansetron. Although the use of ondansetron has historically been much less in the UK than in the US

there has been an accelerating rise in use in recent years, the estimate for 2018 being 2%. Thus, it was considered worth examining the THIN data for possible effects of exposure on infants.

Sample size considerations: The low overall exposure to 5HT3 antagonists restricts the power of this study to examine rare effects. We calculate that, in order to detect an increase in odds of 50% with exposure to 5HT3 antagonists with 95% confidence given the exposure level of 0.3% we would need to restrict our investigation to events occurring in about 6500 infants. Thus, in general, we are only in a position to examine either common specific abnormalities or wider groups of abnormalities. The primary outcomes used in this study are based largely on the widest categories examined by Huybrecht et al (eTable 2 in ref 2). Some secondary analyses could be performed of other frequent congenital anomalies based on feasibility and these are identified as exploratory.

Outcome variables: The outcomes of this study would be selected congenital defects identified within the first year of life. These can be assessed from Read codes in the records of the infant. As discussed, we will consider fairly wide groupings of codes with sufficient numbers present in the dataset to make detection of a treatment effect of similar size to those found in the previous studies feasible. The table in Annex 3 gives details of the codes. Note that there are insufficient oral clefts recorded for reliable detection of an OR of 1.5 but this is included as it is primary outcome in the recent studies.

Analysis: The primary analysis would be a logistic regression for the presence of congenital defects within the first year. The main comparison of interest is of infants exposed in utero to 5HT3 antagonists with those not exposed. The analysis would be adjusted for the same variables used by Zambelli-Weiner; maternal age, infant year of birth and infant gender.

A secondary analysis could examine the time to diagnosis over available follow-up or to 5 years of age since, for those defects that are not necessarily apparent from visual inspection, it is possible that some delay in diagnosis could occur. This analysis will use a Cox proportional hazards model of time to the first relevant Read code.

Conclusions: Exposure of pregnant women in the UK to 5HT3 antagonists is currently around 2%. An accelerating trend in exposure has been discernible since the time of first marketing of these products. The exposure extends through the first and second trimester with more in the second.

Exposure of women suffering from nausea during pregnancy is about 60% and has also been rising strongly in recent years.

A study of more common structural birth defects would be possible in the THIN data using the mother child linkage.

PRAC Rapporteur's comment:

Although there is no direct link of mothers and babies in THIN database (which is a large database of anonymised electronic medical records collected at Primary Care clinics throughout the UK; of note, most prescribing in the UK is performed by general practitioners), and therefore compilation of data is needed and some calculations (e.g. start dates and durations of pregnancies using the last menstrual period date), it can be concluded, that off-label 5HT3 antagonists use among pregnant women is on a steep rise. From the presented data it can also be concluded, that most likely used 5HT3 antagonist during pregnancy is ondansetron (99,9%). Granisetron accounted for the remaining 0.1%.

According to the presented data, the use of ondansetron during pregnancy has increased over time, with reported percentage of live births exposed from 0 to 2% in UK from around 2003 to 2018, with the highest rise from 2014 onwards.

It is interesting to note that from the THIN dataset of general practice data the predominance of prescriptions of ondansetron is during the second trimester of pregnancy.

As the questions remain concerning whether there are sufficient European data to further investigate an association with these or other structural birth defects, the potential for such study in THIN was evaluated.

In epidemiologic studies sample size calculation has an important role to detect an effect and to achieve a desired precision in estimates of parameter of interest, EMA colleagues calculated that we would need the sample size of 6500 infants to examine rare effects. As there were 'only' 2674 exposed infants identified in 18 years (from 2000 to 2018), we are not convinced, the estimated sample size of 6500 is feasible in reasonable time. Another obstacle are confounding factors. The analysis would be able to be adjusted for the variables as maternal age, infant year of birth and infant gender; and would not be able to account for some important confounding factors such as folic acid intake, life-style factors including diet, smoking, alcohol consumption, BMI or over the counter drug use. So, the extent of the residual confounding would be unclear.

As the main limitation of all studies to date is the paucity of information about dose, duration of exposure, and actual exposure to ondansetron (gestational age), it would be beneficial that future studies would address those missing data, as these factors impact on fetal safety and would increase the ability to assess the safety more accurately.

3.2. Rapporteur's discussion

The use of ondansetron in pregnant women is controversial. However, ondansetron is commonly and increasingly prescribed during pregnancy to relieve nausea and vomiting. Its use in US increased from <1% of pregnancies in 2001 to 22.2% in 2014, with much of the increase attributable to oral ondansetron beginning in 2006 (Taylor et al. (2017)²²). 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 UK from around 2003 to 2018 from 0 to 2%.

Despite its prevalence, data on the safety of the drug and any effects on the developing fetus have been limited and inconsistent.

Recent studies expand the evidence available to date and represent the largest published studies of tens of thousands of women and fetal outcomes. These results suggest that use of ondansetron in early pregnancy is not associated with a high risk of congenital malformations, but a small absolute increase in risk of cardiovascular malformations (especially septum defects) and orofacial clefts (especially cleft palate) may exist. Representative human studies include the following:

- A retrospective cohort study including over 1.8 million pregnancies of women enrolled in Medicaid, **Huybrechts et al. (2018)**¹⁴ concluded that first trimester ondansetron exposure (defined by pharmacy dispensing records) was not associated with an increased risk of cardiac malformations or congenital malformations overall after adjustment for known confounders in comparison with either unexposed population or disease-matched (exposed to other antiemetics) controls. There appeared to be an increased risk of oral clefts (aRR 1.24, 95% CI 1.03-1.48) in comparison with both of these control groups, but the absolute risk difference

was low (risk difference 2.7 per 10,000 births, 95% CI 0.2-5.2). The increased risk for oral clefts was attributable to cleft palate with unadjusted RR, 1.29 (95%CI, 1.00-1.65). This study, which included almost 90,000 first trimester ondansetron exposures, is the largest study of this issue, which utilises propensity score methods to account for a large number of possible data confounders.

- A retrospective nested-case control study including over 800,000 mother-child pairs (early exposure to ondansetron in over 75,000 mother-child pairs) enrolled in large US administrative claims database, **Zambelli-Weiner et al. (2019)¹³** concluded that first trimester medically administered ondansetron exposure (5557 mother-child pairs) is associated with an increased risk of cardiac defects (aOR 1.43, 95%CI, 1.28-1.61) and with a (non-statistically significant) increased risk of orofacial cleft defects (aOR 1.30, 95%CI, 0.75-2.25) in comparison to women with no antiemetic exposure during pregnancy. Risk estimates were especially elevated for septal defects overall (aOR 1.44, 95% CI: 1.28-1.62); atrial septal defects (aOR: 1.49, 95% CI: 1.32-1.69), ventricular septal defects (aOR: 1.29, 95% CI: 1.03-1.61) and atrioventricular septal defects (aOR: 2.71, 95% CI: 1.62-4.52). However, when exposure was defined by prescription and medical administration data combined, these findings only remained of borderline statistical significance for septal defects overall and atrioventricular septal defects specifically. No statistically significant increased risks of orofacial clefts overall or specifically cleft lip alone, cleft palate alone, or cleft lip with or without cleft palate were observed.
- Data from two case-control studies, the National Birth Defects Prevention Study (NBDPS) and Slone Birth Defects Study (SBDS) studies in the United States (**Parker et al. (2018)¹²**) included, respectively, 6,751 and 5,873 control mothers and 14,667 and 8,533 case mothers who reported first-trimester nausea and vomiting of pregnancy. As a reference group, women with untreated first-trimester NVP were used. A secondary exposure group of other prescription antiemetics was used to address confounding by indication. Ondansetron use was not associated with an increased risk for most of the 51 defect groups analysed (a number of cardiac defects were evaluated but failed to find any association with first-trimester ondansetron exposure). Modest increases in risk were observed for cleft palate (adjusted OR 1.6, 95% CI 1.1-2.3) in the NBDPS and renal agenesis-dysgenesis (adjusted OR 1.8, 95% CI 1.1-3.0) in the BDS.

Available data from published studies to date in summary:

- The **major congenital malformation** rate was not suggested to be increased in any of the studies to date, except one cohort study found increased risk with ondansetron (Andersen et al. (2013)⁸, aOR 1.3, 95% CI, 1.0-1.7).
- Two prospective cohort studies (Andersen et al. (2013)⁸, aOR 2.0, 95% CI, 1.3-3.1, and Danielsson et al. (2014)³, aOR 1.62, 95% CI, 1.04-2.14, particularly a cardiac septum defect (OR 2.05, 95% CI, 1.19-3.28)) and one large case-control study (Zambelli-Weiner et al. (2019)¹³, see above) have reported an increase in risk of **heart defects**.
- One case-control study (Anderka et al. (2012)⁴, aOR 2.37, 95% CI, 1.18-4.76) identified a significant increase in the risk of isolated **cleft palate**, and one large retrospective cohort study (Huybrechts et al. (2018)¹⁴, see above) reported small increased risk of **oral clefts**, in particular cleft palate, and another study (Parker et al. 2018, see above) reporting conflicting findings for this outcome in two different datasets, where modest increase risk was observed in one dataset, whereas the other dataset reported a significantly decreased exposure rate among infants with cleft palate. Parker et al. (2018)¹² could not explain this discrepancy, in spite of conducting a number of sensitivity analysis, in their study.

- The findings from animal studies have not established that ondansetron can cause birth defects.

In the first round of the assessment, we already thoroughly discussed strengths and limitations of Zambelli-Weiner et al. (2019)¹³ and Huybrechts et al. (2018)¹⁴ studies and identified some uncertainties.

The responses of the authors to the posed questions did address some of the limitations identified in the first round of assessment, but the authors were unable to provide further analyses that the PRAC would have found useful to clarify certain studies outcomes. Notwithstanding remaining uncertainties, the studies are considered well conducted and because of several strengths they both add to the body of evidence.

Considering those two studies, Kaplan et al. (2019)¹⁸ conclude the following in their meta-analysis:

Relating to overall malformation risk, it is probable that the weight of the Huybrechts et al. (2018)¹⁴ study would minimise any difference in the risk estimates following the substitution of the Pasternak et al. (2013)⁶ study data with that provided from Andersen et al. (2013)⁸. As such, it is unlikely that either the primary or secondary meta-analysis would have identified increased risks for overall malformation rate. In support of this are results of ANSM meta-analysis, showing no increased risk for overall malformations; and substitution of named studies changed only heterogeneity between studies (I²=0% with Pasternak study and I²=20% with Andersen study), but not the results.

Given that the findings of the two studies relating to risks of overall cardiac malformation are conflicting, the expected results from inclusion in a meta-analysis are less predictable. Given the slightly larger sample size of the Huybrechts et al. (2018)¹⁴ study, it is possible that the increased risk suggested from the Zambelli-Weiner et al. (2019)¹³ analysis would have been attenuated on combination. Furthermore, and as with the overall malformation data, it is likely that the sample sizes of the Zambelli-Weiner and Huybrechts studies would have limited any differences in risk estimates with Pasternak et al. (2013)⁶ and Andersen et al. (2013)⁸ study data substitution. However, ANSM meta-analysis found an increased risk of cardiac malformations, with significant heterogeneity between studies.

Finally, it is possible that combination of the data provided from Zambelli-Weiner et al. (2019)¹³, which described a non-significant but increased risk of orofacial clefts, with that provided from Huybrechts et al. (2018)¹⁴, which described a small but statistically significant increased risk, may have also described a small but statistically significant increased risk of orofacial clefts overall. In support of this are results of ANSM meta-analysis, showing a statistically significant increased risk of oral clefts.

The majority of the studies to date, however did not report the exact information regarding the exposure time windows, dose and duration, which limits the ability to discuss the exposure with regard to the sensitive periods for congenital malformations (Kaplan et al. (2019)¹⁸) and remains limitation of all studies. Notwithstanding, taking all together, they represent the best available evidence on suggested increased risk that cannot be excluded. These results suggest that ondansetron does not meaningfully increase the risk of congenital malformations, although an increase in the risk of oral clefts cannot be excluded.

Of note, according to Taylor et al. (2017)²², use of any antiemetics in US, including ondansetron, is most common in the first trimester and decreases throughout pregnancy, while in EU (according to the THIN database) the exposure extends through the first and second trimester with more in the second trimester. The reason behind could be compliance with the clinical guidelines for NVP/HG which globally recommend ondansetron use as a second or third line therapy, to be used after the first trimester of pregnancy.

Given that NVP 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.

Taken all together, recent large observational studies and meta-analysis are of adequate scientific quality, each of them with strengths and limitations, to conclude that first-trimester ondansetron use does not appear to suggest statistically significant increased risks of overall major or cardiovascular malformation. However, a very small increase in the absolute risk of oral cleft malformations may exist.

Based on that it is considered justified to update section 4.6 of the SmPC (and respective sections of the PL) to reflect the new evidence of the risk of congenital malformations.

In case the product information is amended as proposed, a communication to inform the prescribers of the new evidence of the risk of congenital malformations as a basis for their decision regarding use in pregnancy is considered warranted.

The Guideline on risk assessment of medicinal products on Human reproduction and lactation: from data to labelling (EMA/CHMP/203927/2005) gives also an option to mention contraception: <Women of childbearing potential have to use effective contraception <during <and up to {number} weeks after)> treatment. >

According to the Guideline on Summary of Product Characteristics (Rev.2) recommendations on the use of the medicinal product in women of childbearing potential should be given when appropriate including the need for pregnancy test or contraceptive measures. It also recommends that if contraceptive measures are recommended, there should also be a cross-reference to section 4.5 (and possibly 4.4) in case of interaction with oral contraceptives.

With respect to the above recommendations, available data, a risk-proportionate approach and indication of the medicinal product, and the fact that formal studies about potential interactions between ondansetron and oral contraceptives are not available, it is not considered warranted to mention a request for use of effective contraception measures during treatment with ondansetron.

Instead of requiring strict contraception during the use of ondansetron, we suggest in the SmPC, if warranted using "Woman of childbearing potential should consider the use of contraception."

From the MSs comments in the previous round it was highlighted that SmPC 4.6 wording should include clear information on the specific anomalies and magnitude of the risk to allow healthcare professionals and patients an informed choice when considering treatment.

3.3. Rapporteur's proposed recommendation

In most European countries, the current SmPC section 4.6 for ondansetron states "The safety of ondansetron for use in human pregnancy has not been established. Evaluation of experimental animal studies does not indicate direct or indirect harmful effects with respect to the development of the embryo, or the foetus, the course of gestation and peri- and post-natal development. However, as animal studies are not always predictive of human response, the use of ondansetron in pregnancy is not recommended."

Based on the totality of evidence from epidemiological studies assessed and due to the seriousness of potential congenital malformations, it is recommended that the nationally authorized products containing ondansetron should be updated in section 4.6 of the SmPC (and respective sections of the

PL) in line with the Guideline on risk assessment of medicinal products on Human reproduction and lactation: from data to labelling (EMA/CHMP/203927/2005), to reflect the new evidence of the risk of congenital malformations (new text underlined, text to be removed ~~struck through~~).

SmPC, section 4.6:

The safety of ondansetron for use in human pregnancy has not been established.

Based on human experience from epidemiological studies, ondansetron is suspected to cause orofacial cleft malformations when administered during the first trimester of pregnancy.

Evidence from the largest studies suggest increased risk. One US observational study was based on 88,467 women exposed to ondansetron during the first trimester compared to 1,727,947 not exposed. A second US observational study was based on 864,083 mother-child pairs including 5,557 pregnant women who received ondansetron during the first trimester.

The first study found the risk of oral clefts in infants born of women exposed to ondansetron was 14 per 10,000 births compared to 11 per 10,000 births for unexposed women (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.

Data from the second study 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 exposed mothers (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).

Evaluation of experimental animal studies does not indicate direct or indirect harmful effects with respect to the development of the embryo, or foetus, the course of gestation and peri- and post-natal development. However, ~~as animal studies are not always predictive of human response the use of ondansetron in pregnancy is not recommended.~~

Ondansetron should not be used during first trimester of pregnancy.

Woman of childbearing potential should consider the use of contraception.

Package leaflet, section 2:

Pregnancy and breast-feeding

~~*It is not known if <product name> is safe during pregnancy. <Product name> should not be used during pregnancy. <Product name> can cause harm to an unborn baby. If you are pregnant, think you are pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking <product name>.*~~

In case the product information is amended as proposed, a communication to inform the prescribers of the new evidence of the risk of congenital malformations as a basis for their decision regarding use in pregnancy is considered warranted.

3.4. Comments from other PRAC members and MAH(s)

3.4.1. Comments from other PRAC members (in chronological order)

MS8:

We agree with the rapporteur's conclusions and recommendations.

In particular, we support the need for a communication to inform the prescribers of the new evidence of the risk of congenital malformations.

We also have a comment on the SmPC and on the PIL:

As noted by the Rapporteur, according to the Guideline on Summary of Product Characteristics (Rev.2), recommendations on the use of the medicinal product in women of childbearing potential should be given when appropriate including the need for pregnancy test or contraceptive measures. It also recommends that if contraceptive measures are recommended, there should also be a cross-reference to section 4.5 (and possibly 4.4) in case of interaction with oral contraceptives.

We agree with the rapporteur that a cross-reference to section 4.5 is not warranted as formal studies about potential interactions between ondansetron and oral contraceptives are not available.

We also agree with the proposed wording "*Woman of childbearing potential should consider the use of contraception*" which seems more appropriate than a requirement for strict contraception during the use of ondansetron.

However, we are of the opinion that a cross-reference between sections 4.4 and 4.6 should be added because this is important information that should be read before the pregnancy occurs (cfr Guideline on Summary of Product Characteristics (Rev. 2)).

Concerning the wording proposed for the PIL section 2, **we propose the following alternative wording :**

Pregnancy and breast-feeding

~~It is not known if <product name> is safe during pregnancy. You should not use <product name> if you are pregnant or might become pregnant. This is because <product name> can cause harm to an unborn baby.~~

If you are pregnant, think you are pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking <product name>.

PRAC Rapporteur's comment:

MS8 agrees with the conclusions and recommendations. The position on communication and further comments are acknowledged.

We do not object with the proposal regarding section 4.4 and we agree with the amended wording for the PIL section 2. However, please note, that the wording recommended to be included in the product information has been amended and as far as possible aligned with the comments from other Member States (see AR section 3.5 for the updated wording).

For section 4.4, we propose:

Section 4.4 Special warnings and precautions for use

Woman of childbearing potential should consider the use of contraception (see section 4.6).

With regard to the communication, we propose that a decision on the need for a communication in the form of a DHPC or any other type of communication (e.g. it could lead to update national guidelines on treatment of NVP/HG regarding new evidence of the risk of congenital malformations) should be considered at national level by Member States. However, key messages can be agreed by the PRAC.

MS2:

Considering the response of the authors did not fully address the concerns with regard to the role of confounders and the lower 95%CI bound being close to unity, questions remain about the robustness of the observed increased risk of oral clefts. Also, in view of the importance of antiemetic treatment for patients to tolerate cytotoxic chemotherapy and radiotherapy, we consider that the proposed recommendation that ondansetron should not be used during first trimester of pregnancy, is too rigid and could deprive patients from lifesaving treatment. We would therefore consider that the possibility to give ondansetron as a last resort should be maintained.

Furthermore, considering the extend of exposure and the current available data in human, a reference to animal studies in section 4.6 is not needed as human data prevail.

Lastly, we propose to shorten the 4.6 wording to ensure that the main message does not get lost amidst detailed study data.

Therefore, we propose the following wording:

SmPC, section 4.6:

Epidemiological studies (based on more than 80,000 ondansetron exposed pregnancies) suggest an increased risk of oral clefts in infants born of women exposed to ondansetron during the first trimester of pregnancy (relative risk (RR) of 1.24 (95% CI 1.03-1.48)). The available epidemiological studies on cardiac malformations show inconclusive results.

The use of ondansetron during first trimester of pregnancy is not recommended.

PRAC Rapporteur's comment:

The position and comments from MS2 are acknowledged.

Although in light of the limitations of the data from studies we agree with the comment, we are still of the opinion that ondansetron should not be used during pregnancy, especially during the first trimester of pregnancy and that stricter wording should apply. Current wording regarding not recommended use during pregnancy led to increased off-label use in the last years.

We understand the rationale behind the proposal, however, we believe, that the wording 'should not be used' does not prevail over the physician's decision and individual benefit/risk assessment by physicians, taking into account the risks of untreated maternal conditions and the suspected teratogenic potential of ondansetron.

Considering the relevant available data in human, we agree that human data prevail over non-clinical information, however the wording has been slightly amended following the comments from another Member State (see AR section 3.5 for the updated wording) and it is agreed by PRAC Rapporteur.

We agree with the proposal to shorten the 4.6 wording to ensure that the main message does not get lost among detailed study data and to increase the readability. However, please note, that the wording recommended to be included in the product information has been amended and as far as possible aligned with the comments from other Member States (see AR section 3.5 for the updated wording).

MS7:

We fully endorse the PRAC Rapp assessment and have some comments.

PRAC endorsed guidance on communication is welcome. The MS7 proposes that a decision on need for a final DHPC communication on a national level, with key messages agreed by the PRAC, may be most appropriate to maximise the message while accounting for local clinical guidelines and practices.

The existing SPC wording states that use in pregnancy is not recommended, whereas the Rapporteur's proposed wording amends this warning to advise not to use ondansetron during the first trimester of pregnancy. Whilst it is agreed that the evidence concerns harms associated with exposure during the first trimester, and this should be specifically highlighted, it can't be excluded that there may be harm associated with exposure during later stages of pregnancy and thus avoiding use throughout pregnancy is advisable.

It also can't be excluded that use during pregnancy may be necessary in some cases where no other options exist. Therefore, the MS7 considers that this should be reflected in the SPC wording as proposed below (which would also be consistent with the CHMP data to labelling guidelines).

Some more detailed information for the patient is recommended regarding the nature of the risk in order to support discussions between HCPs and female patients regarding treatment options in the case the woman is pregnant. Pregnant women will be more familiar with referring to the stages of pregnancy in number of weeks rather than trimesters.

Therefore, based on the rapporteur's proposals, the MS7 proposes the following wording for the Product Information with amendments (as discussed above) highlighted in bold for the rapporteur's and PRAC members' convenience:

SmPC, section 4.6:

The safety of ondansetron for use in human pregnancy has not been established.

Based on human experience from epidemiological studies, ondansetron is suspected to cause orofacial cleft malformations when administered during the first trimester of pregnancy.

Evidence from the largest studies suggest increased risk. One US observational study was based on 88,467 women exposed to ondansetron during the first trimester compared to 1,727,947 not exposed. A second US observational study was based on 864,083 mother-child pairs including 5,557 pregnant women who received ondansetron during the first trimester.

The first study found the risk of oral clefts in infants born of women exposed to ondansetron was 14 per 10,000 births compared to 11 per 10,000 births for unexposed women (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.

Data from the second study 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 exposed mothers (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).

Evaluation of experimental animal studies does not indicate direct or indirect harmful effects with respect to the development of the embryo, or foetus, the course of gestation and peri- and post-natal development.

Ondansetron should not be used in pregnancy, especially during the first trimester, unless the clinical condition of the woman requires treatment and other options are unsuitable or ineffective.

Woman of childbearing potential should consider the use of contraception.

Package leaflet, section 2:

Pregnancy and breast-feeding

Ondansetron may slightly increase the risk of a baby being born with a cleft palate when administered during the first 13 weeks of pregnancy. It is recommended to avoid becoming pregnant while taking ondansetron.

Ondansetron should not be used during pregnancy, **unless other treatment options are not suitable or effective**. If you are **already** pregnant, think you **might be** pregnant or are planning to have a baby, ask your **doctor** for advice before taking ondansetron.

PRAC Rapporteur's comment:

MS7 fully endorses the assessment. The position on communication and further comments on the proposed SmPC and PL wording are acknowledged.

With regard to the communication, we agree and propose that a decision on the need for a communication in the form of a DHPC or any other type of communication (e.g. it could lead to update national guidelines on treatment of NVP/HG regarding new evidence of the risk of congenital malformations) should be considered at national level by Member States. However, key messages can be agreed by the PRAC.

The PRAC Rapporteur agrees with the opinion and proposal that ondansetron should not be used during pregnancy, especially during the first trimester of pregnancy.

As ondansetron should be as any other medicinal product used during pregnancy only if clinical condition of the women requires it and should be subject to the individual benefit/risk assessment by physicians, taking into account the risks of untreated maternal conditions and the suspected teratogenic potential of ondansetron, we would not agree to highlight universally valid remit of physicians as it could be misinterpreted and could be understood as promotion of off-label use. Therefore, 'unless the clinical condition of the woman requires treatment and other options are unsuitable or ineffective' is not supported.

Please note, that the wording recommended to be included in the product information has been amended and as far as possible aligned with the comments from other Member States (see AR section 3.5 for the updated wording).

MS9:

In general, MS9 supports the PRAC Rapporteur's AR and have additional comments on the proposed SmPC and PL wording.

MS9 proposed updates are in **bold**.

SmPC, section 4.6:

~~The safety of ondansetron for use in human pregnancy has not been established.~~

~~Based on human experience from epidemiological studies, ondansetron may increase risk of is suspected to cause orofacial cleft malformations when administered during the first trimester of pregnancy. Evidence from the largest studies suggest increased risk. In one US observational study was based on 88,467 women exposed to ondansetron during the first trimester compared to 1,727,947 not exposed, three (14 vs 11) additional cases of oral clefts per 10,000 births were identified, and the estimated. A second US observational study was based on 864,083 mother-child pairs including 5,557 pregnant women who received ondansetron during the first trimester.~~

~~The first study found the risk of oral clefts in infants born of women exposed to ondansetron was 14 per 10,000 births compared to 11 per 10,000 births for unexposed women (equal to a relative risk (RR) was 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.~~

~~Data from the second study 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 exposed mothers (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).~~

~~Evaluation of experimental animal studies does not indicate direct or indirect harmful effects with respect to the development of the embryo, or foetus, the course of gestation and peri- and post-natal development. However, as animal studies are not always predictive of human response the use of ondansetron in pregnancy is not recommended.~~

~~Ondansetron should not be used during first trimester of pregnancy.~~

~~Woman of childbearing potential should consider the use of contraception.~~

- In addition, the recommendation on the use of contraception in WOCBP needs to be followed with a recommendation on duration of the use of contraception. We suggest that the MAH is asked to propose this recommendation.

Package leaflet, section 2:

Pregnancy and breast-feeding

*It is not known if <product name> is safe during pregnancy. <Product name> should not be used during **the first trimester** of pregnancy. <Product name> can cause harm to an unborn baby. If you are pregnant, think you are pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking <product name>.*

PRAC Rapporteur's comment:

In general, MS9 supports the assessment report. Further comments on the proposed SmPC and PL wording are acknowledged.

With regard to the recommendation on the use of contraception in woman of childbearing potential, we believe that instead of requiring strict contraception during the use of ondansetron according to the Guideline on risk assessment of medicinal products on Human reproduction and lactation: from data to labelling (EMA/CHMP/203927/2005), the proposed wording seems more appropriate with respect to the available data, a risk-proportionate approach and indication of the medicinal product and no further recommendations on the contraception measures in women of childbearing potential is warranted.

We agree with the helpful proposal to shorten the 4.6 wording to ensure that the main message does not get lost among detailed study data and to increase the readability. However, please note, that the wording recommended to be included in the product information has been amended and as far as possible aligned with the comments from other Member States (see AR section 3.5 for the updated wording).

FR:

We generally support the rapporteur's assessment but have some additional comments about the baseline risks and the proposed wording in the PI. The ANSM meta-analysis was also updated.

ANSM Meta-analysis:

Based on the comments provided by the MAH, the Rapporteur and several PRAC members, the ANSM updated the meta-analysis to strengthen its conclusions. It should also be noted that another team worked on a meta-analysis on the use of ondansetron during pregnancy. The study is not published yet but it has been presented during a congress in France in June 2019 (<https://onlinelibrary.wiley.com/doi/epdf/10.1111/fcp.12468> (réf.CO-054)). The results are also in favor of an increased risk of oro-facial cleft and septal defect.

About baseline risks of oral clefts and cardiac malformations in Europe (question 1.c to MAH):

Based on post-marketing data provided by MAH during the type II variation procedure, 809 cases of live births with congenital anomalies including 236 cases exposed in the 1st trimester, 32 in the 2nd or 3rd trimesters, 408 during the whole pregnancy and 133 at an unknown period. 42 cases were excluded by the MAH because not related to a congenital anomaly. The distribution of congenital anomalies of the remaining 767 cases was as follows:

Type of anomaly (Total number of cases)	Known exposure during the first trimester	Known exposure post first trimester	Specific week of exposure unknown
Isolated cardiac defect (264)	216	7	41
Isolated neurologic anomalies (14)	7	2	5
Isolated facial anomalies (75)	63	0	12
Isolated dental anomalies (2)	1	0	1
Isolated respiratory tract (5)	4	0	1
Isolated gastrointestinal anomalies (12)	8	0	4
Isolated renal anomalies (16)	10	1	5
Isolated genitourinary anomalies (10)	5	2	3
Isolated musculoskeletal and/or limb anomalies (41)	28	0	13
Isolated dermatologic anomalies (5)	3	1	1
Isolated Sensory anomalies (5)	1	0	4
Multiple congenital anomalies (311)	279	9	23
Other potential (7)	4	1	2
Total	629	23	115

Excluding post-first trimester exposures or unknown exposure and cases with multiple or undefined anomalies, compared to the expected distribution (EUROCAT data), according to the SOC, the distribution of congenital anomalies reported by MAH is as follow:

	<i>EUROCAT data (%) excluding genetic conditions</i>	<i>Novartis data (%) excluding multiple congenital anomalies cases</i>
<i>Cardiac defect</i>	<i>32,34</i>	63,3
<i>Nervous system</i>	<i>10,8</i>	<i>2,1</i>
<i>Face</i>	<i>0,73</i>	18,5
<i>Respiratory</i>	<i>1,8</i>	<i>1,2</i>
<i>Gastrointestinal</i>	<i>7,52</i>	<i>2,4</i>
<i>Renal</i>	<i>15,9</i>	<i>2,9</i>
<i>Géni-to-urinaire</i>	<i>10,1</i>	<i>1,5</i>
<i>Squelettique</i>	<i>19,4</i>	<i>8,2</i>

Cardiac abnormalities are the most represented (63.3%) and are far in excess of what is expected in the general population according to EUROCAT data (32.3%) for ondansetron exposure in Q1 of pregnancy (excluding multiple anomalies). 18.5% of the total malformations are facial malformations, which is also much higher than the expected rate in the general population (less than 1% of malformations). These elements support the existence of a pattern of malformations associated with exposure to ondansetron during pregnancy.

SmPC, section 4.6 and package leaflet, section 2:

We agree with the rapporteur to upgrade the recommendation regarding use of ondansetron during pregnancy, considering:

- the important off-label use during pregnancy in patients not under chemotherapy or radiotherapy
- that women of childbearing potential are not targeted by the restriction of use and can therefore benefit from the treatment,
- that pregnant women who need ondansetron to treat nausea or vomiting induced by chemotherapy or radiotherapy are already under treatment with a level of recommendation during pregnancy equal or even stronger than ondansetron.

SmPC should mention the risk of cardiac malformations which has been highlighted in recent meta-analysis and reflect all available data.

In accordance to the "Guideline on risk assessment of medicinal products on human reproduction and lactation: from data to labelling", SmPC should reflect all available data. Only 3 studies are described here. It seems not necessary to keep paragraphs describing these studies. SmPC should be shortened to highlight the main message. Package leaflet should inform the patient about risks for her and her fetus. Moreover, we propose to keep the sentence mentioned in the Guideline regarding animal data. Therefore, SmPC section 4.6 and package leaflet section 2 could be as follow (new proposed text underlined, text to be removed ~~struck through~~, based on rapporteur's proposal):

SmPC, section 4.6:

The safety of ondansetron for use in human pregnancy has not been established.

Based on human experience from epidemiological studies, ondansetron is suspected to cause oro-facial cleft malformations and cardiac malformations when administered during the first trimester of pregnancy.

~~*Evidence from the largest studies suggest increased risk. One US observational study was based on 88,467 women exposed to ondansetron during the first trimester compared to 1,727,947 not exposed. A second US observational study was based on 864,083 mother-child pairs including 5,557 pregnant women who received ondansetron during the first trimester.*~~

~~*The first study found the risk of oral clefts in infants born of women exposed to ondansetron was 14 per 10,000 births compared to 11 per 10,000 births for unexposed women (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.*~~

~~*Data from the second study 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 exposed mothers (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).*~~

~~*Evaluation of experimental/Animal studies does do not indicate direct or indirect harmful effects with respect to reproductive toxicity the development of the embryo, or foetus, the course of gestation and peri- and post-natal development.*~~

~~*Ondansetron should not be used during first trimester of pregnancy.*~~

~~*Woman of childbearing potential should consider the use of contraception.*~~

Package leaflet, section 2:

Pregnancy and breast-feeding

<Product name> should not be used during pregnancy. <Product name> can cause harm, especially face and cardiac anomalies, to an unborn baby. If you are pregnant, think you are pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking <product name>.

PRAC Rapporteur's comment:

FR generally supports the assessment but have some additional comments about the baseline risks and the proposed wording in the PI. The ANSM meta-analysis was also updated in line with the comments provided in the first round.

As pointed out, in addition to the ANSM meta-analysis, there is another meta-analysis, performed by another French team, accessible from the public website (<http://metapreg.org/viewMA.aspx?exposition=281>), which includes 10 studies (3 case-control and 7 cohort studies) - the same 8 studies as Kaplan et al. (2019) and additional two - Huybrechts et al. (2018) and Zambelli-Weiner et al. (2019). However, in contrast to the meta-analysis by Kaplan et al., this meta-analysis used Andersen et al. (2013) in the primary analysis (as adjusted data were available for the risk of major malformations and cardiac defects), the same as ANSM meta-analysis, which showed that results were not significantly changed including Pasternak et al. study instead of Andersen et al. study.

In this meta-analysis risk of bias (due to confounding and other aspects of methodological quality such as participant selection, measurement of intervention, missing data, measurement in outcomes and selection of the reported results) is assessed with the Risk of Bias Tool for Non-Randomized Studies of Interventions (ROBINS-I). Based on the quality assessment by the ROBINS-I tools, majority of the studies can be considered as critical risk of bias.

Results showed that the use of ondansetron during pregnancy was associated with a borderline statistically significant increased risk of **ventricular septal defect** (pooled OR 1.11 (95%CI, 1.00 - 1.23), $I^2 = 0\%$, $n = 6$ studies) and **orofacial clefts** (pooled OR 1.32 (95% CI, 1.05 - 1.66], $I^2 = 0\%$, $n = 3$ studies). Despite results from several studies, exposure to ondansetron in pregnancy was not found associated with cleft palate (OR 1.28 (95%CI, 0.86 - 1.89), $I^2 = 64\%$, $n = 6$ studies), **overall cardiac malformations (OR 1.34 (95%CI, 0.98 - 1.83), $I^2 = 68\%$, $n = 5$ studies)**, atrial septal defects (OR 1.08 (95%CI, 0.83 - 1.41), $I^2 = 77\%$, $n = 5$ studies), major congenital malformations (OR 1.07 (95%CI, 0.95 - 1.21), $I^2 = 21\%$, $n = 5$ studies) and cleft lip with or without cleft palate (OR 1.00 (95%CI, 0.83 - 1.20), $I^2 = 0\%$, $n = 7$ studies).

A high heterogeneity was observed for some outcomes of interest (overall cardiac malformations, atrial septal defects and cleft palate). In an attempt to explain possible heterogeneity between studies, several sensitivity analyses by study design (cohort/case control), type of comparator groups, use of adjusted/unadjusted estimates, first trimester /over pregnancy exposure were conducted. No significant difference in results was observed.

FR comments regarding baseline risks of oral clefts and cardiac malformations in Europe are acknowledged and appreciated. We agree that the pattern of cardiac malformation and orofacial clefts appear plausible. However, regarding the risk of cardiac malformation and proposed inclusion in the SmPC/PIL, we do not agree, as inconsistent results and high heterogeneity was observed in meta-analyses, therefore caution is warranted.

In addition, we agree with the proposal to shorten the 4.6 wording to ensure that the main message does not get lost among detailed study data and to increase the readability. We also agree with the amended wording regarding animal data.

However, please note, that the wording recommended to be included in the product information has been amended and as far as possible aligned with the comments from other Member States (see AR section 3.5 for the updated wording).

MS1

We generally agree with the Rapporteur's proposed recommendation but have further comments as to the PI wording and other aspects.

Considering the seriousness of the approved indications (nausea and vomiting induced by cytotoxic chemotherapy and radiotherapy; post-operative nausea and vomiting) in relation to the observed extent of risk, we propose to include a less stringent recommendation on the use during the first trimester of pregnancy by adding: "unless the clinical condition of the women requires treatment with ondansetron". Furthermore, it is suggested to specify the duration of the recommended contraceptive measures for women of childbearing potential.

Our proposal is in line with the "Guideline on Risk Assessment of Medicinal Products on Human Reproduction and Lactation: from Data to Labelling" (EMA/CHMP/203927/2005).

Additionally, we would prefer a shorter warning in order to increase the readability.

SmPC, section 4.6:

~~The safety of ondansetron for use in human pregnancy has not been established.~~

~~Based on human experience from epidemiological studies, ondansetron is suspected to cause orofacial cleft malformations when administered during the first trimester of pregnancy.~~

~~Evidence from the largest studies suggest increased risk. One US observational study, was based on 88,467 women exposed to ondansetron during the first trimester compared to 1,727,947 not unexposed, found a risk for oral clefts in infants of 14 per 10,000 births and 11 per 10,000 births respectively (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, was based on 864,083 mother-child pairs including 5,557 pregnant women who received ondansetron during the first trimester, 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 first study found the risk of oral clefts in infants born of women exposed to ondansetron was 14 per 10,000 births compared to 11 per 10,000 births for unexposed women (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.~~

~~Data from the second study 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 exposed mothers (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).~~

~~Evaluation of experimental animal studies does not indicate direct or indirect harmful effects with respect to the development of the embryo, or foetus, the course of gestation and peri- and post-natal~~

~~development. However, as animal studies are not always predictive of human response the use of ondansetron in pregnancy is not recommended.~~

Ondansetron should not be used during first trimester of pregnancy **unless the clinical condition of the women requires treatment with ondansetron.**

Woman of childbearing potential should consider the use of contraception **<during <and up to {number} weeks after) treatment>.**

Package leaflet, section 2:

Pregnancy and breast-feeding

~~It is not known if <product name> is safe during pregnancy. <Product name> should not be used during pregnancy **unless the treatment is absolutely necessary.** <Product name> can cause harm to an unborn baby. If you are pregnant, think you are pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking <product name>.~~

Other aspects:

Data provided in the signal AR show that a certain level of exposure of pregnant women, although small, is also observed for another serotonin 5HT3 antagonist (granisetron).

Therefore, it is considered reasonable to evaluate the risk of birth defects for pharmacologically and chemically related substances at the next regulatory opportunity, e.g. in the upcoming PSURs.

The following related substances + PSUR submission dates were extracted from the EURD list:

granisetron (other formulations except for transdermal patch) → 19.05.2021
granisetron (transdermal patch) → 28.12.2019 [please see MS1 comment on PSUSA/00010101/201810]
netupitant / palonosetron → 19.12.2019
palonosetron → 22.10.2019

PRAC Rapporteur's comment:

MS1 generally agrees with the proposed recommendation. Further comments on the proposed SmPC/PIL wording and related substances are acknowledged.

With regard to a less stringent recommendation on the use of ondansetron, we understand the rationale behind the proposal, however, we believe that ondansetron should be, as any other medicinal product, used during pregnancy only if clinical condition of the women requires it and should be subject to the individual benefit/risk assessment by physicians, taking into account the risks of untreated maternal conditions and the suspected teratogenic potential of ondansetron. And a decision for treatment is in the remit of physicians. We would not agree to highlight universally valid remit of physicians as it could be misinterpreted and could be understood as promotion of off-label use. Therefore, 'unless the clinical condition of the woman requires treatment with ondansetron' is not supported.

With regard to the recommendation on the use of contraception in woman of childbearing potential, we believe that instead of requiring strict contraception during the use of ondansetron according to the Guideline on risk assessment of medicinal products on Human reproduction and lactation: from data to labelling (EMA/CHMP/203927/2005), the proposed wording seems more appropriate with respect to

the available data, a risk-proportionate approach and indication of the medicinal product and no further recommendations on the contraception measures in women of childbearing potential is warranted.

We agree with the helpful proposal to shorten the 4.6 wording to ensure that the main message does not get lost among detailed study data and to increase the readability. However, please note, that the wording recommended to be included in the product information has been amended and as far as possible aligned with the comments from other Member States (see AR section 3.5 for the updated wording).

Based on the THIN data, the exposure of pregnant women to other serotonin 5HT3 antagonists is low (ondansetron (99.9%) and granisetron accounting for the remaining 0.1%). We agree with the proposal to evaluate the risk of birth defects for pharmacologically and chemically related substances at the next regulatory opportunity, e.g. in the upcoming PSURs. Therefore, we propose to LMSs for PSUSA to carefully consider the topic in upcoming PSUSA procedures. For granisetron, transdermal patch (ongoing PSUSA), we propose to follow-up in the next PSUR, as two cases of major congenital malformations (ventricular septal defect and diaphragmatic hernia) and one case of neurodevelopmental delay after exposure to granisetron during the first or second trimester of pregnancy were detected in an observational study published during the relevant PSUR interval (Shapira et al, 2018).

MS4

MS4 fully endorses the PRAC Rapporteur's assessment report and conclusions. In particular from the Zambelli-Weiner's study it is believed relevant that the majority of women received a single injection of ondansetron as the only drug and "sensitivity analysis restricting exposure to women who filled at least 2 prescriptions of ondansetron in the first trimester showed results consistent to the primary analysis".

Finally, MS4 has no additional comments on the proposed SmPC and PL wording and supports the need for a communication to inform the prescribers of the new evidence of the risk of congenital malformations.

PRAC Rapporteur's comment:

MS4 fully endorses the assessment report and conclusions and also supports the need for a communication.

With regard to the communication, we propose that a decision on the need for a communication in the form of a DHPC or any other type of communication (e.g. it could lead to update national guidelines on treatment of NVP/HG regarding new evidence of the risk of congenital malformations) should be considered at national level by Member States. However, key messages can be agreed by the PRAC.

3.4.2. Comments from MAH Novartis

Novartis agrees with the PRAC proposals and finds them overall consistent with the outcome of Novartis' assessment. The Assessor recommended a label update to include clear information on

specific anomalies and the magnitude of the risk. The purpose is to allow healthcare professionals and patients to make an informed choice when considering treatment.

Novartis proposes to include some additional detail from the Parker et al. 2018 publication to provide clearer information in the SmPC. Parker et al. 2018 was the largest study from a US database specially designed to evaluate birth defects and is considered an important source of data on this subject.

Additionally, Novartis proposes to retain a strict recommendation on the use of contraception given the possibility of off-label use of ondansetron.

Please find attached draft proposal with rationale from Novartis.

PRAC proposal 17 Jun 2019

SmPC, section 4.6:
The safety of ondansetron for use in human pregnancy has not been established.

Based on human experience from epidemiological studies, ondansetron is suspected to cause orofacial cleft malformations when administered during the first trimester of pregnancy.

Evidence from the largest studies suggest increased risk. One US observational study was based on 88,467 women exposed to ondansetron during the first trimester compared to 1,727,947 not exposed. A second US observational study was based on 864,083 mother-child pairs including 5,557 pregnant women who received ondansetron during the first trimester.

Novartis proposal 01 Jul 2019

SmPC, section 4.6:
The safety of ondansetron for use in human pregnancy has not been established.

Based on human experience from epidemiological studies, ondansetron is suspected to cause orofacial cleft malformations when administered during the first trimester of pregnancy.

Evidence from the three largest studies to date suggest a small increase in increased risk of orofacial cleft malformations. One US observational study was based on 88,467 women exposed to ondansetron during the first trimester compared to 1,727,947 not exposed. A second US observational study was based on 864,083 mother-child pairs including 76,330 5,557 pregnant women who received ondansetron during the first trimester (of those, 5,557 in the medical office or hospital setting). In a third study,

Novartis rationale

Novartis acknowledges the assessor's recommendation to make a label update including clear information on specific anomalies and the magnitude of the risk to allow healthcare professionals and patients to make an informed choice when considering treatment. The proposed wording is consistent with the results of two large epidemiological studies and the conclusion of the Novartis assessment on this topic. However, we would like to propose a few edits and additional text as per below discussion.

Epidemiology studies result

an analysis was performed from two population-based birth defect registries in the US which included 6,751 and 5,873 control mothers and 14,667 and 8,533 case mothers, respectively.

The first study found the risk of oral clefts in infants born of women exposed to ondansetron was 14 per 10,000 births compared to 11 per 10,000 births for unexposed women (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.

Data from the second study 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 exposed mothers (adjusted odds ratio (OR) of 1.43 (95% CI 1.28-1.61) after adjustment for maternal age, infant year of birth and sex of infant).

Evaluation of experimental

The first study found the risk of oral clefts in infants born of women exposed to ondansetron was of 14 per 10,000 births compared to 11 per 10,000 births for unexposed women (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. However, the sensitivity analyses performed for women who were required to have filled at least two prescriptions during the first trimester (more likely to have consumed the prescribed medication) did not strengthen the association for oral clefts (adjusted RR, 1.15; 95%CI,0.85-1.56).

Data from the second study 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 in the subset treated in the medical office or hospital setting, and OR of 1.12 (95% CI 0.95-1.33) in all pregnancies exposed to ondansetron in the first trimester.

The analyses of the association between first trimester ondansetron use and individual orofacial clefting outcomes reported by the third study were inconsistent, ranging from OR of 0.5 (95%CI 0.3-1.0) to OR of 1.6 (95%CI 1.1-2.3) in individual comparisons.

The available epidemiological studies on cardiac malformations show inconclusive results.

Novartis proposes to provide more clarity on magnitude of the risk based on the results of the three largest epidemiology studies including Parker et al 2018. We propose to include results of Parker et al 2018, which used two databases National Birth Defects Prevention Study (NBDPS) and Slone Pregnancy Health Interview Study (Birth Defects Study) and is of better methodological quality. NBDPS is one of the largest studies on birth defects ever undertaken in the United States. NBDPS has made key contributions toward understanding the risk of having a baby with a birth defect when specific medications were used just before and during pregnancy. The Slone Pregnancy Health Interview Study (Birth Defects Study) was a study of factors in pregnancy that may be related to the health of newborns focusing on the safety and risks of a wide range of environmental exposures (primarily medications) in pregnancy.

animal studies does not indicate direct or indirect harmful effects with respect to the development of the embryo, or foetus, the course of gestation and peri- and post-natal

development. However, as animal studies are not always predictive of human response the use of ondansetron in pregnancy is not recommended.

Ondansetron should not be used during first trimester of pregnancy.

Woman of childbearing potential should consider the use of contraception.

The first study found no increased risk for cardiac abnormalities after adjustment for confounders. There was no increase in cardiac abnormalities among women with first trimester ondansetron exposure in the second study; however, the second study found a statistically significant increase in cardiac abnormalities (mainly septal defects) in infants born to exposed mothers treated in the medical office or hospital setting (adjusted odds ratio (OR) of 1.43 (95% CI 1.28-1.61) after adjustment for maternal age, infant year of birth and sex of infant). No increase in risk of septal defects was reported by any of the three studies when first trimester exposure to ondansetron was considered, suggesting that the increase in septal defects reported in the mothers treated in the medical office or hospital setting could be a result of a potential selection bias stemming from the subgroup definition.

Evaluation of experimental animal studies does not indicate direct or indirect harmful effects with respect to the development of the embryo, or foetus, the course of gestation and peri- and post-natal development. However, as animal

In addition, we suggest to provide in the label further details regarding various exposure definitions used in the epidemiological studies in order to enable clearer comparisons of the results across comparable exposures. This is needed as the exposure definitions in the primary analyses in the two largest studies are not directly comparable, but alternative definitions used in secondary analyses may be closer to one another.

Effective contraception recommendation

The assessor has following recommendation for contraception, "Women of child-bearing potential should consider the use of effective contraception".

~~studies are not always predictive of human response the use of ondansetron in pregnancy is not recommended.~~

~~Ondansetron should not be used during first trimester of pregnancy.~~

~~Woman of childbearing potential should consider the use of contraception.~~

Pregnancy status should be verified for females of reproductive potential prior to starting the treatment with Zofran. Sexually active females of reproductive potential are recommended to use effective contraception (methods that result in less than 1 % pregnancy rates) when using Zofran during the treatment and for two days after stopping treatment with Zofran.

Novartis would like to highlight that there is some known off-label use of ondansetron in US and EU, partly driven by recommendation in national treatment practice guidelines. Use of the language “consider use of effective contraception” instead of a strict requirement to use contraception may potentially result in continued off-label use. Also as per Appendix 1 and 3 of the CHMP guidance “ Risk assessment of medicinal product on human reproduction and lactation: from data to labelling”, effective contraception is recommended in this scenario (Labelling option 3 as there is suspected human teratogenicity and no effects from non-clinical data)

Hence, Novartis proposes to amend recommendation for women of child bearing potential for pregnancy testing and effective contraception use.

Recommendation

In case the product information is amended as proposed a communication to inform prescribers of the new evidence of the risk of congenital malformation as a basis for their decision regarding use in pregnancy is considered warranted

Agree. However, to provide the risk mitigation plan to healthcare professionals, Novartis proposes to reconsider recommendation on contraception as discussed above.

PRAC Rapporteur's comment:

Novartis agrees with the proposals and finds them overall consistent with the outcome of Novartis assessment. Further comments on the proposed SmPC wording are acknowledged. Novartis agrees with the communication.

We appreciate Novartis agreement and comments. Novartis proposed amendments to the wording in 4.6, including the data from the third large observational study, Parker et al. 2018.

In light of proposed amendments to product information, the proposal of the majority of Member States that commented PAR is to shorten the wording to ensure that the main message does not get lost among detailed study data and to increase the readability, therefore, the amendments to product information are not supported.

With regard to the recommendation on the use of contraception in woman of childbearing potential, we believe that instead of requiring strict contraception during the use of ondansetron according to the Guideline on risk assessment of medicinal products on Human reproduction and lactation: from data to labelling (EMA/CHMP/203927/2005), the proposed wording seems more appropriate with respect to the available data, a risk-proportionate approach and indication of the medicinal product and no further recommendations on the contraception measures in women of childbearing potential is warranted. In addition, we do not agree with the amended wording proposed by Novartis regarding contraception measures as a risk mitigation plan.

3.5. Updated rapporteur's proposed recommendation

Updates of product information

Based on the totality of evidence from epidemiological studies assessed and due to the seriousness of potential congenital malformations, it is recommended that the nationally authorized products containing ondansetron should be updated in sections 4.4 and 4.6 of the SmPC (and respective sections of the PL) in line with the Guideline on risk assessment of medicinal products on Human reproduction and lactation: from data to labelling (EMA/CHMP/203927/2005), to reflect the new evidence of the risk of congenital malformations (new text underlined, text to be removed ~~struck-through~~).

Summary of Product Characteristics

- **Section 4.4 Special warnings and precautions for use**

Woman of childbearing potential should consider the use of contraception (see section 4.6).

- **Section 4.6 Fertility, pregnancy and lactation**

~~The safety of ondansetron for use in human pregnancy has not been established.~~

Based on human experience from epidemiological studies, ondansetron is suspected to cause orofacial cleft malformations when administered during the first trimester of pregnancy.

One observational study, 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)). The increased risk was due mainly to a greater number of babies born with cleft palate.

A second observational study, based on 864,083 mother-child pairs including 5,557 pregnant women who received ondansetron during the first trimester, found an adjusted odds ratio (OR) of 1.30 (95% CI 0.75-2.25) for orofacial clefting.

The available epidemiological studies on cardiac malformations show inconclusive results.

~~Evaluation of experimental Animal studies does not indicate direct or indirect harmful effects with respect to reproductive toxicity, the development of the embryo, or foetus, the course of gestation and peri- and post-natal development. However, as animal studies are not always predictive of human response the use of ondansetron in pregnancy is not recommended.~~

Ondansetron should not be used during pregnancy, especially during the first trimester.

Woman of childbearing potential should consider the use of contraception (see section 4.4).

Package leaflet, section 2:

Pregnancy and breast-feeding

~~It is not known if <product name> is safe during pregnancy. You should not use <product name> if you are pregnant, especially during the first trimester or might become pregnant. This is because <product name> can cause harm to an unborn baby.~~

~~If you are already pregnant, think you might be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking <product name>.~~

Communication

Communication in the form of a DHPC or any other type of communication (e.g. it could lead to update national guidelines on treatment of NVP/HG regarding new evidence of the risk of congenital malformations with ondansetron) should be considered at national level by Member States. It should target obstetricians/gynaecologists and others as applicable.

The following key messages could be considered for this communication:

Recommendation/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 information:

- 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 study¹, 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 study², 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).

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.

Pharmacologically and chemically related substances

The appointed lead Member States for PSURs of pharmacologically and chemically related substances (other serotonin 5HT3 antagonists) should evaluate the risk of birth defects at the next regulatory opportunity, e.g. in the upcoming PSURs.

3.6. Adopted PRAC recommendation

Having considered the available information, including the responses from study authors (Zambelli and Huybrechts) and from innovator MAH of ondansetron (Novartis) to the PRAC list of questions and also considering the methodological quality of the studies, the PRAC has agreed the following:

1. Update of product information

All MAHs of ondansetron-containing medicinal products should submit a variation within 2 months of the publication date of the PRAC recommendation, to amend the product information as described below (new text underlined/text to be removed with ~~strikethrough~~).

Summary of Product Characteristics

Section 4.6 – Fertility, pregnancy and lactation

Women of childbearing potential

Women of childbearing potential should consider the use of contraception.

Pregnancy

~~The safety of ondansetron for use in human pregnancy has not been established. Based on human experience from epidemiological studies, ondansetron is suspected to cause orofacial malformations when administered during the first trimester of pregnancy.~~

In one cohort study including 1.8 million pregnancies, first trimester ondansetron use was associated with an increased risk of oral clefts (3 additional cases per 10 000 women treated; adjusted relative risk, 1.24, (95% CI 1.03-1.48)).

The available epidemiological studies on cardiac malformations show conflicting results.

~~Evaluation of experimental Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity. the development of the embryo, or foetus, the course of gestation and peri- and post-natal development. However, as animal studies are not always predictive of human response the use of ondansetron in pregnancy is not recommended.~~

Ondansetron should not be used during the first trimester of pregnancy.

Package Leaflet

Section 2 – What you need to know before you take <product name>

Pregnancy and breast-feeding

It is not known if <product name> is safe during pregnancy. You should not use <product name> during the first trimester of pregnancy. This is because <product name> can slightly increase the risk of a baby being born with cleft lip and/or cleft palate (openings or splits in the upper lip and/or the roof of the mouth). If you are already pregnant, think you might be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking <product name>. If you are a woman of childbearing potential you may be advised to use effective contraception.

2. Communication at national level

Communication in the form of a DHPC or any other type should be considered at national level by Member States. It should target obstetricians/gynecologists and others as applicable.

The following key messages could be considered for this communication:

Recommendation/Summary:

- Based on human experience from epidemiological studies, ondansetron is suspected to cause orofacial malformations when administered during the first trimester of pregnancy. In one cohort study including 1.8 million pregnancies, first trimester ondansetron use was associated with an increased risk of oral clefts (3 additional cases per 10 000 women treated; adjusted relative risk, 1.24, (95% CI 1.03-1.48)).
- The available epidemiological studies on cardiac malformations show conflicting results.
- Ondansetron should not be used during the first trimester of pregnancy.
- Women of childbearing potential should consider the use of contraception.

The innovator MAH for ondansetron (Novartis) should contact the National Competent Authorities in all Member States where ondansetron-containing medicinal products are marketed, in order to agree on the National Competent Authority's preferred way of communication on ondansetron.

3. Request for supplementary information

The PRAC agreed that the MAHs of the following 5-HT₃ receptor antagonists should submit a cumulative review on birth defects following in-utero exposure in their upcoming PSURs: palonosetron DLP 24 July 2019; netupitant / palonosetron DLP 10 October 2019; granisetron (transdermal patch) DLP 19 October 2019; granisetron (other formulations except for transdermal patch) DLP 18 February 2021. The MAHs of the tropisetron should follow the national PSUR cycle and liaise with National Competent Authorities.

This cumulative review should include a review of published literature, epidemiological studies and post marketing cases.

4. References

1. Czeizel et al. Folic acid in pregnant women associated with reduced prevalence of severe congenital heart defects in their children: a national population-based case-control study. *Eur J Obstet Gynecol Reprod Biol.* 2015; 193:34-9.
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Annex 1

1) Full description of publication by Zambelli et al. (2019)¹³ (UK NCA)

Study overview

A recently published US observational study assessed the association between ondansetron exposure during the first trimester and specific structural birth defects, and orofacial cleft defects, using a large US administrative claims database. A nested-case control design was used to compare the risk of these specific birth defects among pregnancies exposed to ondansetron in the first trimester and those not exposed to any antiemetic during pregnancy. Mother-child pairs, with a live-birth, identified between 2000 and 2014 were included if the mother had at least 16 months of data prior to delivery and if the infant was followed up to at least 1 year of age. Exclusion criteria were prior sibling with chromosomal birth defects or exposure to known teratogens during pregnancy (including a maternal diagnosis of chromosomal anomalies, toxoplasmosis, syphilis, varicella-zoster, parvovirus B19, rubella, cytomegalovirus, and herpes (TORCH) infections, or a prescription for thalidomide or isotretinoin). Mothers with exposure to an antiemetic other than ondansetron during pregnancy or to ondansetron in the second/third trimester of pregnancy were also excluded.

For the primary analysis exposure was defined as medical administration of ondansetron in the medical office or hospital setting between the estimated date of conception and the following 91 days. For the secondary analyses ondansetron exposure was determined as prescription claims or medical administration in the same gestation period. Outcome of interests were selected *a priori* based on prior studies and were identified via ICD-codes in the year following birth. Primary outcomes included cardiac defects and orofacial clefts, secondary outcomes included other types of congenital heart anomalies; hypoplastic left heart syndrome; congenital anomalies of the circulatory system; anomalies of the larynx, trachea, and bronchus; anencephalus; spina bifida without anencephaly; limb reduction defects; craniosynostosis; congenital diaphragmatic hernia; and renal collecting system anomalies.

Potential confounding factors were identified through expert knowledge and literature review. Potential confounders were assessed and only included in the final model if they changed the effect estimates by 10% or more. Logistic regression models were used to assess the association between first trimester ondansetron use and risk of birth defects of interest.

A few additional/sensitivity analyses were carried out to explore the robustness of the primary analysis:

- Exposure misclassification: since there is a high risk of exposure misclassification using prescription/claims data for antiemetic use in pregnancy which are used on an “as needed” basis, an additional analysis using exposure defined by prescription claims + medically administered ondansetron in the first trimester was carried out.
- To explore potential confounding by indication a sensitivity analysis restricting unexposed comparison to women with diagnosis of nausea and vomiting in pregnancy (NVP) or hyperemesis gravidarum (HG) and no antiemetic treatment.
- To evaluate detection bias, a sensitivity analysis stratified by year to account for the potential impact of awareness around the risk of birth defects associated with ondansetron.
- To explore potential for residual confounding, a sensitivity analysis assessed the association of ondansetron 1st trimester exposure and all birth defects excluding the pre-specified defects of interest as a negative control

There was a total of 864,083 eligible mother-child pairs. There were 802,253 infants with no birth defects, 32,100 infants were diagnosed with cardiovascular birth defects, and 1,590 infants were diagnosed with orofacial cleft defects.

The results are shown in table 2 below (original table from manuscript). The study showed that first trimester ondansetron exposure (defined as medically administered) was associated with statistically significantly increased risk for all cardiac defects (OR:1.52, 95% CI: 1.35-1.70) and with a (non-statistically significant) increased risk of orofacial cleft defects (OR: 1.32, 95% CI: 0.76-2.28). Analyses of secondary defects of interest showed effect estimates above one but few were statistically significant except for septal defects, other circulatory defects and diaphragmatic hernia (see table 2).

The authors report that none of the a-priori defined confounding factors affected the effect estimates by 10% or more but, for comparability with previous studies, adjusted estimates accounted for infant year of birth, infant gender, and mother's age at infant birth.

The sensitivity analyses suggest little influence of confounding by NVP/HG diagnoses nor any temporal effect associated with increased awareness of potential for teratogenic effect of ondansetron.

The authors concluded that "evidence that first trimester ondansetron exposure is associated with increased risk of various structural birth defects and sheds important light on the magnitude of exposure misclassification that may have obscured this association in prior studies using prescription data."

Table 2. Association of Ondansetron Exposure with Structural Birth Defects							
Outcome (no. %)	Unexposed in During Pregnancy n=787,753	Exposed in First Trimester (Med Only) n=5,557	Exposed in First Trimester (Rx or Med) n=76,330	Prevalence Odds Ratio (95% CI) Medical Administration Only		Prevalence Odds Ratio (95% CI) Prescription or Medical Administration	
				Unadjusted	Adjusted ^a	Unadjusted	Adjusted ^a
<i>Primary Analysis</i>							
Cardiac defects	29,001 (3.67)	303 (5.45)	3,099 (4.06)	1.52 (1.35-1.70)	1.43 (1.28-1.61)	1.11 (1.07-1.16)	1.04 (1.00-1.08)
Orofacial clefting	1,433 (0.18)	13 (0.23)	157 (0.21)	1.32 (0.76-2.28)	1.30 (0.75-2.25)	1.14 (0.97-1.35)	1.12 (0.95-1.33)
<i>Secondary Analysis</i>							
Septal defects	28,666 (3.63)	301 (5.42)	3,069 (4.02)	1.53 (1.36-1.71)	1.44 (1.28-1.62)	1.12 (1.08-1.16)	1.04 (1.00-1.08)
Ventricular septal defect	9,058 (1.15)	81 (1.46)	883 (1.16)	1.30 (1.04-1.62)	1.29 (1.03-1.61)	1.02 (0.95-1.09)	1.00 (0.93-1.07)
Atrial septal defect	23,903 (3.03)	267 (4.81)	2,633 (3.45)	1.62 (1.43-1.84)	1.49 (1.32-1.69)	1.15 (1.10-1.20)	1.04 (0.99-1.08)
Atrioventricular septal defect	813 (0.10)	15 (0.27)	97 (0.13)	2.68 (1.61-4.47)	2.71 (1.62-4.52)	1.24 (1.01-1.54)	1.24 (1.00-1.53)
Hypoplastic Left Heart Syndrome	343 (0.04)	5 (0.09)	43 (0.06)	2.12 (0.88-5.12)	2.12 (0.87-5.13)	1.31 (0.95-1.80)	1.31 (0.95-1.81)
Other circulatory defects	6,044 (0.77)	76 (1.37)	678 (0.89)	1.83 (1.45-2.29)	1.75 (1.39-2.20)	1.17 (1.08-1.27)	1.11 (1.02-1.20)
Orofacial clefting	1,433 (0.18)	13 (0.23)	157 (0.21)	1.32 (0.76-2.28)	1.30 (0.75-2.25)	1.14 (0.97-1.35)	1.12 (0.95-1.33)
Cleft palate	1,068 (0.14)	11 (0.20)	112 (0.15)	1.49 (0.53-2.71)	1.46 (0.81-2.65)	1.09 (0.90-1.33)	1.06 (0.87-1.30)
Cleft lip	638 (0.08)	5 (0.09)	74 (0.10)	1.14 (0.47-2.74)	1.16 (0.48-2.81)	1.21 (0.95-1.54)	1.22 (0.96-1.56)
Cleft lip with or without palate	696 (0.09)	8 (0.14)	71 (0.09)	1.67 (0.83-3.35)	1.69 (0.84-3.40)	1.06 (0.83-1.36)	1.07 (0.84-1.38)
Laryngeal cleft	6,295 (0.80)	56 (1.01)	808 (1.06)	1.29 (0.99-1.68)	1.16 (0.89-1.51)	1.34 (1.24-1.44)	1.18 (1.09-1.27)
Craniosynostosis	11,7559 (1.49)	94 (1.69)	1,329 (1.74)	1.16 (0.95-1.43)	1.11 (0.90-1.36)	1.18 (1.11-1.25)	1.12 (1.05-1.18)
Diaphragmatic hernia	409 (0.05)	7 (0.13)	55 (0.07)	2.49 (1.18-5.25)	2.51 (1.19-5.31)	1.40 (1.06-1.86)	1.40 (1.05-1.87)
Renal collecting system anomalies	7,803 (0.99)	69 (1.24)	835 (1.09)	1.28 (1.01-1.63)	1.24 (0.98-1.58)	1.34 (1.24-1.44)	1.07 (1.00-1.16)
Limb reduction defects	557 (0.07)	4 (0.07)	49 (0.06)	1.04 (0.39-2.79)	1.03 (0.38-2.75)	0.92 (0.69-1.23)	0.91 (0.67-1.22)
Other defects (negative control)	113,106 (0.14)	878 (0.16)	12,216 (0.16)	1.10 (1.03-1.18)	1.02 (0.95-1.10)	1.12 (1.09-1.14)	1.02 (1.00-1.04)

a. Odds ratios are adjusted for: mother's age, infant year of birth, and infant gender.

UK Comment on study strengths and limitations

Overall this is a well-designed observational study addressing several limitations of previous studies assessing the fetal safety of ondansetron which included statistical power to assess specific birth defects and exposure misclassification associated with dispensing data for this type of medicine used on as-needed basis.

Its strengths include the use of a large sample size (n=864,083 mother-infant pairs) which enabled assessment of pre-specified congenital defects of interest (as opposed to assessing the risk of all congenital anomalies grouped together) and the ability to restrict the primary analysis to ondansetron administered by a clinician to minimise exposure misclassification bias. The robustness of the primary analysis was assessed in a series of sensitivity analyses including: the use of a negative control (defined as any birth defects other than the primary and secondary endpoints) to explore the potential for unmeasured confounding; restricting unexposed comparison to women with diagnosis of NVP/HG and no antiemetic treatment to explore potential confounding by indication; an analysis stratified by time period related to release of key information on the safety of ondansetron in pregnancy was performed to evaluate potential detection bias. Furthermore, only mother-infant pairs with at least 1 year follow up post birth were included which maximises identification of cases with a cardiac defect.

There are however limitations that may have biased the results:

1. Residual confounding:

The author report they used a thorough process, using DAG, for identifying potential confounders but then used a rather crude approach to determine which covariate to include in the final adjusted model (focusing on an arbitrary 10% change in the effect estimate and disregarding any impact on precision). It would have been helpful to see the effect of inclusion of all pre-specified confounding factors on the effect estimates.

Furthermore, due to the nature of the data source, the study was not able to account adequately for some important confounding factors such as folic acid intake, use of fertility treatment as well as lifestyle factors including diet, smoking, alcohol consumption or over the counter drug use, which were not accounted for in the analyses. Furthermore, only selected teratogens were assessed.

Confounding by indication cannot be totally ruled out. The authors argue that NVP/HG may exert protective effects on adverse neonatal outcomes including congenital anomalies, but the reverse should also be considered. Could there be a potential for women with more severe NVP/HG (requiring treatment and particularly medically administered treatment) to have some nutritional deficiencies that could affect the risk of birth defects? The link between folic acid intake and orofacial cleft is well established and some studies suggests that folic acid intake is also associated with reduced risk of cardiac defects¹. The results of the sensitivity analyses restricted to women with a diagnosis of NVP/HG seem consistent with the primary analysis however it is likely that the unexposed comparison without antiemetic treatment would have less severe disease. While confounding by disease severity could lead to an over-estimate of the risk, the impact of residual confounding for other factors is unknown.

The authors present the result of a sensitivity analysis on the risk of all birth defects excluding specific defects of interest which was used as a negative control. The results of this analysis were reassuring showing no association for the adjusted estimates suggesting confounding by factors that would affect all birth defects is unlikely. However, this cannot rule out potential residual confounding particularly for factors affecting the association with cardiovascular defects.

Results of a sensitivity analysis assessing the impact of external adjustment for smoking are presented in supplementary data. The authors argue that the effect estimates for the most likely scenario (scenario D based on an OR of 1.01 for cardiovascular defect and smoking and OR 1.06 for

ondansetron and smoking) is the same as for the unadjusted estimate for the primary analysis (OR=1.52). The OR for smoking and risk of birth defects is based on estimate for all birth defects combined rather than estimate specific for cardiovascular defects (Hackshaw et al² report OR 1.09 95%CI: 1.02- 1.17). However varying scenarios are presented all with limited impact on the effect estimates. Confidence intervals are not provided which would have been useful to assess impact on precision. This sensitivity analysis only provides limited reassurance on the potential for residual confounding and a quantitative bias analysis assessing the impact of multiple unmeasured confounders would have been more useful.

2. Outcome ascertainment:

Pregnancy loss and termination due to in-utero diagnosis of congenital anomalies, or infants that died before 1 year of age were not considered in the analyses which could mask cases with serious/fatal anomalies and could lead to selection bias. A sensitivity analysis assessing the impact of including infants who died in the first year of life would have been useful. Furthermore, the authors caution that the use of claims data for ascertainment of cardiac defects could lead to false positives when certain ICD codes are used to justify diagnostic procedure rather than confirm a diagnosis of a cardiac defect. If such outcome misclassification is unaffected by ondansetron exposure, this would lead to underestimation of risk.

3. Detection bias:

The authors address detection bias (whereby ondansetron users would be more likely to be screened and diagnosed with certain birth defects than non-exposed due to concerns around potential teratogenicity) in a sensitivity analysis stratifying by years prior and after publication of safety related concerns with ondansetron. The results overall do not suggest an increase in effect estimates following release of key information on the safety of ondansetron. However, the interpretation of stratified estimates is limited by wide confidence intervals and zero counts for orofacial clefts particularly for 2000-2006. The data from the two other strata suggest slightly higher risk after the ondansetron related publications in 2012. Detection bias cannot be totally discounted (particularly in situation where the ICD codes used for case ascertainment reflect diagnostic procedures rather than diagnosis as discussed above), and this could inflate effect estimates.

4. Potential for exposure misclassification:

Gestational age estimation was crude and derived from delivery date rather than any gestational age measurement at delivery or during pregnancy. This could lead to misclassification of exposure with a proportion of exposures likely occurring outside the key developmental window. Furthermore, it would have been useful to explore effect when further restricting exposure to cardiovascular developmental period postulated to prior to 56 days. If such misclassification is unidirectional for cases and controls, the effect estimates would be biased towards the null and underestimate the relative risk.

Consistency with other studies

A recent meta-analysis¹² published in 2018, summarises the findings of 10 observational studies reporting the association between ondansetron exposure in pregnancy and birth defects which showed conflicting results. There was no evidence of increased risk for overall birth defects; and the evidence for cardiovascular defects and cleft palate, were conflicting. As highlighted by Zambelli et al. (2019)¹³, a Swedish study based on national register data showed an increased risk of cardiovascular defects³ (OR 1.62, 95% CI: 1.04–2.14) and septal defects (OR 2.05, 95% CI: 1.19–3.28) and a US case control study reported an increased risk of cleft palate⁴ (OR 2.37, 95% CI: 1.18–4.76). However, this study looked at range of non-cardiac congenital anomalies and is susceptible to recall bias.

Such associations were not observed in much smaller studies looking at these specific defects^{5,7}. An abstract regarding a Danish registry study⁸ (which was not included in the meta-analysis), also report an association between 1st trimester ondansetron exposure and all congenital anomalies and specifically with cardiac defects (OR 2.0, 95% CI: 1.3–3.1). Although it is not possible to assess the validity of this study due to the lack of details on methodology available from the abstract.

Conclusion

This study had several strengths and overall was well-designed to address the study objective and dealt with several limitations which affected previous studies¹⁰. The study suggests a potential increase in risk of cardiovascular defect with first trimester exposure to ondansetron, but uncertainties affect causal inference. The effect estimates are relatively low and residual confounding could potentially explain the observed association despite the authors attempt to address this. Limitations regarding outcome and exposure misclassifications would most likely lead to underestimation of the risk estimates. Previous studies showed conflicting results, and these are also affected by similar and additional limitations which future studies are unlikely to be able to address entirely.

2) Brief comment on more recently published Huybrechts study

At the time of writing this signal paper, another US study was published (Huybrechts KF et al. JAMA December 18, 2018 Volume 320, Number 23). This was another large retrospective cohort study using US Medicaid data spanning 2000 – 2013, consisting of 88,467 pregnancies exposed to ondansetron in the first trimester and 1,727,947 unexposed pregnancies. Results from unadjusted regression models suggested ondansetron exposure was associated with a small increased risk of cardiac malformations, oral clefts and congenital malformations overall. However, after adjustment by propensity score stratification to control for treatment indication and other measured confounders, exposure to ondansetron was found to be associated with a small increased risk of oral clefts, but not cardiac malformations or congenital malformations overall (Table 1).

Table 1 Summary of results from Huybrechts KF et al 2018 Medicaid retrospective cohort study

	Unadjusted rates per 10,000 births (95% CI)		Unadjusted RR	Propensity Score Adjusted
	Ondansetron Exposed 1 st trimester	Unexposed	Unadjusted Relative Risk (95% CI)	PS Adjusted Relative Risk (95% CI)
Cardiac Malformations	94.4 (88.0 to 100.8)	84.4 (83.0 to 85.7)	1.12 (1.04 to 1.20)	0.99 (0.93 to 1.06)
Oral Clefts	14.0 (11.6 to 16.5)	11.1 (10.6 to 11.6)	1.26 (1.05 to 1.51)	1.24 (1.03 to 1.48)
Any Congenital Malformation	370.4 (358 to 382.9)	313.5 (310.9 to 316.1)	1.18 (1.14 to 1.22)	1.01 (0.98 to 1.05)

After a brief high-level review, the study and analyses appear thorough, and in contrast to the Zambelli et al. (2019)¹³ study, several measured confounders (including treatment indication, maternal conditions and concomitant medications) are adjusted for in a propensity score analysis. However, exposure is defined by prescription record data with potential for exposure misclassification in case the women doesn't take the prescribed medicine which could lead to underestimating a true effect. The authors assessed the impact of such misclassification in a sensitivity analysis restricting exposure to women who filled at least 2 prescriptions of ondansetron in the first trimester which showed results consistent to the primary analysis. Furthermore, this study only captured outcomes diagnosed in the three months after birth (rather than 1 year in Zambelli et al. (2019)¹³) which could lead to underascertainment of congenital anomalies and particularly relevant for cardiac defects which may not be detected until later.

Overall, while there is a contrasting finding with regards to risk of cardiovascular malformations, the Huybrechts et al. (2018)¹⁴ study appears to support the oral cleft risk suggested in the Zambelli et al. (2019)¹³ study. It appears a robust study and merits full appraisal.

Annex 2 - Excerpts from EU and US product information

EU SmPC 4.6:

Pregnancy

The safety of ondansetron for use in human pregnancy has not been established. Evaluation of experimental animal studies does not indicate direct or indirect harmful effects with respect to the development of the embryo, or foetus, the course of gestation and peri- and post-natal development. However, as animal studies are not always predictive of human response the use of ondansetron in pregnancy is not recommended.

US Highlights of Prescribing (Oct 2017) part extract from Pregnancy, Human data section:

Human Data

Methodological limitations of the epidemiology studies preclude a reliable evaluation of the potential risk of adverse fetal outcomes with the use of ondansetron in pregnancy. Two large retrospective cohort studies of ondansetron use in pregnancy have been published. In one study with 1,349 infants born to women who reported the use of ondansetron or received an ondansetron prescription in the first trimester, no increased risk for major congenital malformations was seen in aggregate analysis. In this same study, however, a sub-analysis for specific malformations reported an association between ondansetron exposure and cardiovascular defect (odds ratio (OR) 1.62 [95% CI (1.04, 2.14)]) and cardiac septal defect (OR 2.05 [95% CI (1.19, 3.28)]). The second study examined 1970 women who received ondansetron prescription during pregnancy and reported no association between ondansetron exposure and major congenital malformations, miscarriage or stillbirth, and infants of low-birth weight or small for gestational age. Important methodological limitations with these studies include the uncertainty of whether women who filled a prescription actually took the medication, the concomitant use of other medications or treatments, and other unadjusted confounders that may account for the study findings.

A case-control study evaluating associations between several common non-cardiac malformations and multiple antiemetic drugs reported an association between maternal use of ondansetron and isolated cleft palate (reported adjusted OR = 2.37 [95% CI (1.18, 4.76)]). However, this association could be a chance finding, given the large number of drugs-birth defect comparisons in this study. It is unknown whether ondansetron exposure in utero in the cases of cleft palate occurred during the time of palate formation (the palate is formed between the 6th and 9th weeks of pregnancy) or whether mothers of infants with cleft palate used other medications or had other risk factors for cleft palate in the offspring. In addition, no cases of isolated cleft palate were identified in the aforementioned 2 large retrospective cohort studies. At this time, there is no clear evidence that ondansetron exposure in early pregnancy can cause cleft palate.

Annex 3 - Short overview of prior studies

The first cohort study, from Canada (Einarson et al. (2004)¹⁵), followed the outcomes of 176 women exposed to ondansetron in the first trimester of pregnancy and compared them to two other similarly sized groups of women who were not exposed to ondansetron during pregnancy, but taking other antiemetics or taking other drugs considered safe in pregnancy (non-teratogen) or no drugs. There were no statistical differences found between groups with respect to the incidence of miscarriages, stillbirths, major malformations gestational age at birth, and mean birth weights. However, given the small sample size, this study was only powered to detect a 5-fold increased risk of major malformations.

The second study, from Sweden (Asker et al. (2005)¹⁶), was a cohort study examining data from the Swedish Medical Birth Registry. A total of 65 women were exposed to ondansetron during pregnancy. No increased risk of malformations was found in fetuses exposed to ondansetron.

The first larger cohort study (Anderka et al. (2012)⁴), was a review of data from the National Birth Defects Prevention Study in the United States. A total of 4524 cases and 5859 controls were examined, and the authors looked specifically at 3 birth defect categories: orofacial clefts, neural tube defects, and hypospadias. No increased risk of neural tube defects or hypospadias was found. However, the authors found an increased risk (roughly two times) of cleft palate in infants exposed to ondansetron (aOR 2.37, 95%CI 1.18-4.76). A total of 11 cases of cleft palate were noted in infants who had been exposed to ondansetron, while a total of 514 cases were noted in unexposed offspring. The results are limited by the relatively small sample size, and the increased risk for cleft palate reported in this study has not been replicated in other studies.

Another study was done by Pasternak et al. (2013)⁶. The authors, from Denmark, performed a nationwide cohort study of more than 600,000 pregnancies using data from the Medical Birth Registry and the National Patient Register from the years 2004-2011. They examined women exposed to ondansetron during the first trimester of pregnancy (through week 12) and studied the incidence of major birth defects as defined by EUROCAT. They excluded chromosomal aberrations (such as Down's syndrome) and known other causes of birth defects (such as fetal alcohol syndrome). The authors used logistic regression to estimate propensity scores as the probability of exposure to ondansetron and then matched each woman exposed to ondansetron to unexposed women in a 1:4 ratio. The models were adjusted for hospitalization for hyperemesis gravidarum or nausea and vomiting as a proxy measure of severity and exposure to other antiemetics during pregnancy. No association was found between ondansetron exposure and the incidence of major birth defects (OR 1.12, 95%CI 0.69-1.82), preterm delivery (OR 0.90, 95%CI 0.66-1.25), low birth weight (OR 0.76, 95%CI 0.51-1.13), or SGA (OR 1.13, 95%CI 0.89-1.44).

A third larger study was published in 2013 in abstract form, Andersen et al. (2013)⁸. The authors used data from the same database as Pasternak's study and looked at the years 1997-2010. Out of 897,018 total births, 1248 women redeemed a prescription for ondansetron. There were 58 congenital malformations (4.7%) in the ondansetron-exposed group, and 31357 malformations (3.5%) in the control group. The authors found an odds ratio of 1.3 (95%CI 1.0-1.7) for major malformations, most of which was due to an increased prevalence of heart defects (OR 2.0, 95%CI 1.3-3.1). However, there are several concerns. The results from this study have, curiously, only been published in abstract form and therefore it is not possible to determine their exact study methods, unlike the Pasternak study.

In 2014, another Swedish cohort study was published that evaluated approximately 1.5 million births and examined 1349 infants reported to have been exposed to ondansetron in utero (Danielsson et al. (2014)³). No significantly increased risk was found for either total malformations (OR 0.95, 95%CI

0.72-1.26) or "relatively severe" malformations (OR 1.11, 95%CI 0.81-1.53). However, when the authors looked specifically at cardiac malformations, they found a slightly increased risk compared with meclizine (OR 1.62, 95%CI 1.04-2.14). The majority of cardiac defects reported in this study were septal defects (17 of 19 total; OR 2.05, 95%CI 1.19-3.28).

In retrospective cohort study by Fejzo et al. (2016)⁷ U.S. data on outcome were collected on 1070 pregnancies exposed to ondansetron and compared to outcomes in two control groups: 771 pregnancies in women with a history of HG with no ondansetron exposure and 1555 pregnancies with neither a history of HG nor ondansetron exposure. Ventricular septal defects were reported in 2/952 of infants in the HG/Ondansetron-exposure group and 4/1286 in the No HG/No Ondansetron-exposure group. Cleft palate was reported in 1/952 live births in the HG/Ondansetron and 2/1286 in the No HG/No Ondansetron-exposure groups. These results do not support a teratogenic risk for ondansetron. However, it was noted that this study was unable to investigate the role of dose, duration and timing of ondansetron administration as this was a patient self-reporting survey.

Most of the published studies on ondansetron exposure in early pregnancy suggest that the risk of birth defect is low. One study suggested a slight increase in risk of development of cleft palate and two other studies suggested a very slight increase in risk of development of cardiac defects.

Study/Authors	Data Source	Type of study	N exposed (or N cases)	Total N (or N controls)	Outcome	RR (95% CI)	Comments
Einarson, 2004	Teratogen Information Services	Prospective cohort	176	176	Major birth defects	RR not reported: 6 cases among exposed (3.5%), 3 cases among exposed to other antiemetics (1.8%), 3 cases among non-teratogen controls (1.8%)	Difference not significant, but study underpowered
Asker, 2005	Swedish Medical Birth Registry, 1995-2002	Registry review	65: - 21 exposed 1 st trim - 12 exposed 1 st -3 rd trim - 12 exposed 2 nd -3 rd trim	31,130	No birth defects	RR not reported	Small number of exposed neonates
Anderka, 2012	National Birth Defects Prevention Study, 1997-2004	Case-control study	4524 birth defect cases (11 exposed cases)	5859	Cleft palate	2.37 (1.18-4.76)	Exposure based on maternal recall; possible chance findings; no information on cardiac defects
Pasternak, 2013	Danish registries, 2004-2011	Registry review	1233	4932	Major birth defects Heart defects - septal defect	1.12 (0.69-1.82) 1.04 (0.52-1.95) - 1.22 (0.56-2.47)	No cleft palate among exposed Estimated from Supplementary Table to the published paper Not designed or powered to study specific malformations; exposure to ondansetron obtained from national prescribing data
Colvin, 2013	Administrative data Western Australia, 2002-2005	Registry review	251 exposed (263 offspring)	96,968 births (98,062 offspring)	Major birth defects	1.2 (0.6-2.2)	No confounding adjustment; overall risk of birth defects not significantly increased and wide CI; no details about specific malformations; exposure to ondansetron obtained from national prescribing data
Andersen, 2013	Danish registries, 1997-2010	Registry review	1248 1368 1800	897,018 903,207 966,372	Major birth defects Heart defects Major birth defects Heart defects Major birth defects Heart defects	1.3 (1.0-1.7) 2.0 (1.3-3.1) 1.2 (0.9-1.5) 1.6 (1.1-1.3) 1.11 (0.85-1.44) 1.55 (1.02-2.37)	Published as abstract only (lack of information on methodology and patient details); different data in different abstracts and presentation
Danielsson, 2014	Swedish registries, 1998-2012	Registry review	1349	1,501,434	Major birth defects Heart defects - septal defects	0.95 (0.72-1.26) 1.62 (1.04-2.14) - 2.05 (1.19-3.28)	Exposure to ondansetron identified by midwife interview (435 cases) and 914 from prescription register (less accurate data on actual ingestion, dose and gestational timing)
Fejzo, 2016	U.S. data on outcome	Retrospective cohort study	1070	771 (history of HG with no ondansetron) 1555 (neither a history of HG nor ondansetron exposure)	Ventricular septal defects Cleft palate	RR not reported: 2/952 (exp.group) 4/1286 (nonexp) 1/952 2/1286	Patient self-reporting survey
Parker, 2018	National Birth Defects Prevention Study (NBDPS, 1997-2011) and Slone Birth Defects Study (BDS, 1997-2014)	Case-control study	Cases: 418 (NBDPS) 287 (BDS) Cases: 1,345 (NBDPS) 1,327 (BDS) Cases: 1,205 (NBDPS) 364 (BDS)	Controls: 3,267 (NBDPS) 5,873 (BDS) Controls: 6,751 (NBDPS) 5,873 (BDS) Controls: 6,751 (NBDPS) 5,873 (BDS)	Oral clefts Ventricular septal defect Ventricular septal defect	1.6 (1.1-2.3) (NBDPS) 0.5 (0.3-1.0) (BDS) 0.9 (0.6-1.3) (NBDPS) 1.1 (0.9-1.4) (BDS) 0.9 (0.6-1.3) (NBDPS) 0.8 (0.5-1.2) (BDS)	NBDPS based on data from 2005- 2011 only, as earlier years were included in the paper by Anderka et al. Includes results for a total of 51 malformation groups; positive association is also reported for renal agenesis-dysgenesis in BDS (OR=1.8, 1.1-3.0)