Medicines Adverse Reactions Committee

Meeting date	12/03/2020	Agenda item	3.2.2
Title	**Ondansetron exposure *in utero* and risk of cleft palate**		
Submitted by	Medsafe Pharmacovigilance Team	Paper type	For advice
Active ingredient	**Product name**		**Sponsor**
Ondansetron	Apo-Ondansetron Film coated tablet, 4 & 8 mg Ondansetron Kabi Solution for injection, 2 mg/mL Ondansetron ODT-DRLA Film coated tablet, 4 & 8 mg Ondansetron ODT-DRLA Orodispersible tablet, 4 & 8 mg Ondansetron-Baxter Solution for injection, 2 mg/mL Onrex Film coated tablet, 4 & 8 mg (not available)		Apotex NZ Ltd Fresenius Kabi NZ Ltd Dr Reddy's NZ Ltd Dr Reddy's NZ Ltd Baxter Healthcare Ltd REX Medical Ltd
PHARMAC funding and Hospital Medicines List (HML)	Tablet 4 mg and 8 mg Tablet dispersible 4 mg and 8mg Injection 2 mg/ml, 2 ml ampoule Injection 2 mg/ml, 4 ml ampoule	Onrex (Sole Supply from 1 April 2020) Apo-Ondansetron Ondansetron ODT-DRLA Ondansetron-Baxter Ondansetron Kabi	
Previous MARC meetings	Use of ondansetron in pregnancy not previously discussed		
International action	On 27 January 2020, the MHRA published a Drug Safety Update [1] stating: *'Recent epidemiological studies suggest exposure to ondansetron during the first trimester of pregnancy is associated with a small increased risk of the baby having a cleft lip and/or cleft palate'…* *… 'If the clinical decision is to offer ondansetron in pregnancy, women must be counselled on the potential benefits and risks of use, both to her and to her unborn baby and the final decision should be made jointly.'*		
Prescriber Update	None on use of ondansetron in pregnancy		
Classification	Prescription medicine		
Usage data	In 2018, a total of 189,699 people received a prescription for oral ondansetron (4 mg or 8 mg tablets or dispersible tablets (Pharmaceutical Data Web Tool). Information on women who received a prescription for ondansetron during pregnancy linked to the pregnancy outcomes data has been requested from National Collections. (Information not yet available).		
Advice sought	**The Committee is asked to advise:** • Whether section 4.6 of the New Zealand data sheets for ondansetron products should be updated to include information about the risk of orofacial cleft defects. If so, what information should be included? • Whether any other action, such as additional monitoring on M[2] is needed. • Whether any communication on this issue in addition to MARC's Remarks is needed.		

Table of Contents

1 PURPOSE

The purpose of this MARC report is to review the evidence for an increased risk of orofacial cleft defects associated with ondansetron exposure during the first trimester of pregnancy, and to assess whether there is a need for regulatory action in New Zealand to limit any potential risk to the fetus from exposure to ondansetron during the first trimester.

In 2019, the European Pharmacovigilance Risk Assessment Committee (PRAC) assessed the risk of birth defects following exposure to ondansetron during the first trimester of pregnancy. The assessment focused on two studies, Huybrechts *et al* 2019 [2] and Zambelli-Weiner *et al* 2018 [3], that had reported associations between *in utero* exposure to ondansetron and specific structural birth defects. (These studies are discussed below in section 3.1.1). The PRAC confirmed the safety signal for ondansetron and oral cleft defects, and recommended that the European product information for ondansetron should be updated with information on the risk of orofacial malformations when administered during the first trimester of pregnancy, including a statement that ondansetron-containing medicines should not be used in the first trimester of pregnancy. [4]. A copy of the PRAC's review is annexed to this report (see Annex 1).

In response to this recommendation, the UK National Health System's Teratology Information Service (UKTIS), in collaboration with the European Network of Teratology Information Services (ENTIS) issued a statement that they do not support the recommendations made by the PRAC [5].

The MHRA recently published a Drug Safety Update article on the risk of cleft lip and cleft palate associated with ondansetron [1].

2 BACKGROUND

2.1 Ondansetron

Ondansetron is a selective serotonin 5-hydroxytryptamine-3 (5-HT3) receptor antagonist. It is indicated for the management of nausea and vomiting induced by cytotoxic chemotherapy and radiotherapy, and for prevention of post-operative nausea and vomiting [6-9]. Ondansetron is also used off-label for symptomatic relief of moderate-severe nausea and vomiting of pregnancy (NVP) and hyperemesis gravidarum (HG) [10]. (See section 2.3). In the United States, off-label use of ondansetron in pregnancy increased from < 1% of pregnancies in 2001 to 22.2% of pregnancies in 2014 [11].

The mechanism of action of ondansetron in the management of chemotherapy- and radiotherapy-induced nausea and vomiting is probably due to antagonism of 5-HT3 receptors on afferent neurons located in both the peripheral and central nervous systems [6]. Serotonin (5-HT) is released from enterochromaffin cells in the gut wall in response to cytotoxic drugs or radiation to the abdomen. The 5-HT binds to 5-HT3 receptors on vagal afferent neurons, initiating the vomiting reflex by transmitting the signal to the 'vomiting centre' in the brain. Ondansetron is understood to block the vomiting reflex by binding to vagal 5-HT3 receptors [12]. Activation of vagal afferents may also cause release of 5-HT in the area postrema (located on the floor of the fourth ventricle), promoting emesis through a central mechanism [6].

The mechanism of action in postoperative nausea and vomiting is not known but there may be a common pathway with nausea and vomiting induced by cytotoxic medicines [6].

2.2 Cleft lip and cleft palate

Orofacial clefts (OFCs) are among the most common birth defects in all populations worldwide [13]. A study of national prevalence estimates for major birth defects in the United States indicates that approximately 1:600 infants is born with cleft lip and cleft palate, 1:2800 is born with cleft lip without cleft palate, and 1:1700 is born with cleft palate alone [14]

Lip and palate development occur very early in embryogenesis: formation of the lip is complete by week 6 and the palate by week 13. In normal development:

- By week 4: the frontonasal prominence, paired maxillary processes, and paired mandibular processes surround the oral cavity
- By week 5, the nasal pits have fused to form the paired medial and lateral nasal processes.
- By end of week 6: the medial nasal processes have merged with the maxillary processes to form the upper lip and primary palate.
- During week 6, bilateral outgrowths from the maxillary processes grow down on either side of the tongue to become the palatal shelves.
- By week 12, the tongue has dropped down and the palatal shelves have elevated to above the tongue and have fused to form the palate.

All human embryos have clefts of the lip and palate that must fuse to form the normal structures. Disruptions during the relevant developmental process can prevent fusion, resulting in an OFC at birth. Cleft lip with or without cleft palate (CL/P) and cleft palate alone (CP) are considered separate aetiologic entities due to the developmental origins of the structures and the epidemiology and familial patterns of the two groups of malformation. CP is more likely to be syndromic than CL/P.

Risk factors for cleft lip and palate have been identified, including genetic factors [13], smoking [15], diabetes [16] and use of certain medicines, including topiramate [17] and valproic acid [18]. Corticosteroids have also been associated with cleft palate when administered to pregnant women before ten weeks gestation [19].

Management of cleft lip and cleft palate involves initial feeding support, surgical treatment (usually within the first year), and ongoing orthodontic and speech therapy may be needed (https://www.starship.org.nz/guidelines/cleft-lip-and-palate/).

2.3 Management of nausea and vomiting in pregnancy

The Society of Obstetric Medicine of Australia and New Zealand (SOMANZ) uses the following definitions for nausea and vomiting associated with pregnancy [10]:

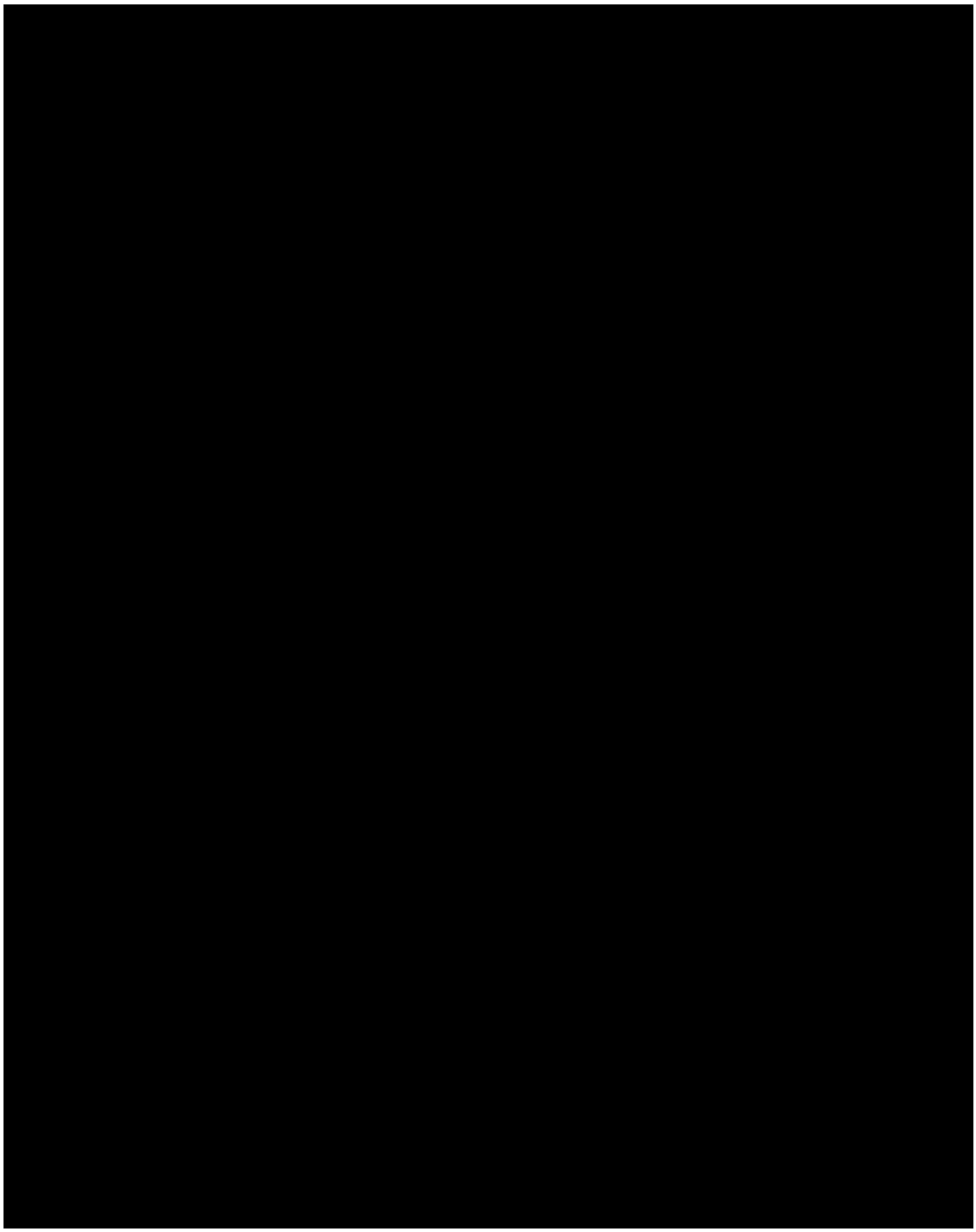
- **Nausea and vomiting of pregnancy (NVD)**: Nausea, vomiting and/or dry retching caused by pregnancy, with symptoms commencing in the first trimester, without an alternate diagnosis. NVP severity is assessed using the Motherisk Pregnancy-Unique Quantification of Emesis and Nausea (PUQE-24) scoring index (Table 1).
- **Hyperemesis gravidarum (HG)**: Nausea and/or vomiting caused by pregnancy leading to significant reduction of oral intake and weight loss of at least 5% compared with pre-pregnancy, with or without dehydration and/or electrolyte abnormalities. This condition is considered severe.

The management of NVP and HG requires appropriate assessment, relevant investigations and a holistic approach to treatment that includes:

- Interventions to reduce nausea, retching and vomiting
- Management of associated gastric dysmotility (ie, gastroesophageal reflux and constipation)

- Maintenance of hydration, fluid and electrolyte replacement
- Maintenance of adequate nutrition, including vitamin supplements if required
- Psychological monitoring and support
- Monitoring and prevention of side effects, and adverse pregnancy and fetal outcomes.

The choice of antiemetic should be individualised, based on the woman's symptoms, previous response to treatment and potential adverse effects, but none is considered more effective than others [10] (Figure 1, Table 2).



Comment:

SOMANZ recommends ondansetron as one of several antiemetic options for moderate NVP, and as the first-line antiemetic for severe and refractory NVP.

2.4 Data sheets

2.4.1 New Zealand

Section 4.6 of the New Zealand data sheets for ondansetron-containing products state:

> *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.* [6-9]

2.4.2 European Union

In July 2019, the PRAC recommended that all MAHs of ondansetron-containing medicinal products should update Section 4.6 (Fertility, pregnancy and lactation) of the Summary of Product Characteristics as follows:

> *Women of childbearing potential*
>
> *Women of childbearing potential should consider the use of contraception.*
>
> *Pregnancy*
>
> *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.

Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity.

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

2.5 Usage

National Collections information on ondansetron usage in pregnancy has been requested. This information will be tabled at the MARC meeting if available in time.

3 SCIENTIFIC INFORMATION

3.1 Published literature

3.1.1 Studies triggering PRAC advice

3.1.1.1 Zambelli-Weiner et al, 2019 (Reproductive Toxicology)

First trimester ondansetron exposure and risk of structural birth defects [3]

This nested case-control study examined the association between ondansetron exposure during the first trimester and specific structural birth defects using a large US administrative claims database (Truven Health MarketScan Commercial Database).

The study was designed to address two key limitations identified in earlier studies: small sample size with inadequate power for subgroup analyses, and bias from exposure misclassification due to reliance on filled prescriptions as a surrogate for exposure.

Methods: The source population included mother-child pairs resulting from all live births during the period 2000-2014 who had one year of follow-up for the infant. Mothers were eligible if they had been continuously enrolled for 16 months prior to delivery and were 15-49 years old on date of delivery.

Mother-child pairs were excluded if there was an increased baseline risk of congenital malformation[1] or exposure to an antiemetic other than ondansetron anytime during pregnancy. Those with ondansetron exposure exclusively outside the first trimester were also excluded to minimise exposure misclassification.

Ondansetron exposure was defined as a filled prescription or medical administration in the clinical (hospital or office) setting during the first trimester. To avoid the risk of exposure misclassification with prescription claim data (ie, due to prescriptions issued for 'as needed' use), the primary analysis examined only medical administration of ondansetron. Secondary analyses used all ondansetron exposures (prescription claims and medical administration). Mother-child pairs were considered unexposed if they had no exposure to any antiemetic anytime during the pregnancy.

Outcomes were 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. Primary outcomes of interest were cardiac defects (ICD-9 745.xx) and orofacial cleft defects (ICD-9 749.xx). Secondary outcomes included specific cardiac and orofacial cleft defects. A negative control group was identified, containing all birth defects with ICD-9 codes 740.xx – 759.xx, excluding the *a priori* birth defects of interest.

Covariates identified and available in the database included: maternal age at birth, infant year of birth, infant sex, US region of birth, maternal medical history (obesity, diabetes mellitus, epilepsy, hypertension, cancer), and medicines

[1] Increased baseline risk of congenital malformation was defined as: previous child with chromosomal birth defect or exposure to known teratogens, including recently recorded maternal diagnosis in the 16 month pre-birth period of chromosomal anomalies (ICD-9 758.xx), TORCH infections [toxoplasmosis, syphilis, varicella-zoster, parvovirus B19, rubella, cytomegalovirus, herpes simplex], or a prescription for thalidomide or isotretinoin in the pre-birth period.

taken in the first trimester (eg, acid-reducing medicines, psychotropics, prescription folic acid, macrolide antibiotics, corticosteroids, and anticonvulsants. Low birth weight, multiple gestation, high risk pregnancy diagnosis, prior preterm delivery, family history of birth defects and prior diagnosis of NVP or HG were also collected, but the data was incomplete.

Statistical analyses: Characteristics of mother-child pairs were compared by birth outcome using chi-square test or Fisher's exact test for categorical variables and Student's *t*-test for continuous variables. Logistic regression models were used to test for a statistical association between first trimester ondansetron use and risk of (1) cardiac defects and orofacial cleft defects, (2) specific cardiac, orofacial and other structural birth defects, and (3) a negative control of 'other birth defects'. Prevalence odds ratios and 95% confidence intervals were calculated.

Sensitivity analyses included: restricting the control (unexposed) group to only mother-child pairs with a diagnosis of NVP or HG to minimise confounding by indication, and stratifying results into periods before and after the release of key information on the safety of ondansetron (2000-2006, 2007-2011, and 2011-2014) to account for possible ascertainment bias.

Results: After exclusions, 864,083 mother-child pairs were identified. Early exposure to ondansetron occurred in 76,330 mother-child pairs (8.8%), including exposure to medical administration of ondansetron in 5557 mother-child pairs (0.64%). There were 802,253 infants with no birth defects, 32,100 infants diagnosed with cardiovascular birth defects, and 1590 infants diagnosed with orofacial cleft defects. Due to the large sample size, the small differences in covariate distributions between birth defect cohorts were statistically significant, but none reached the predetermined threshold of significance when added to the base exposure-outcome model.

The association of first trimester exposure to ondansetron with any cardiac defects and any orofacial cleft defects is shown in Table 3.

The primary analysis of first trimester medical administration of ondansetron showed a statistically significantly increased risk for all cardiac defects (OR: 1.52, 95% CI: 1.35‑1.70). Statistical significance remained when adjusted for maternal age at birth, infant sex and year of birth (AOR: 1.43, 95% CI: 1.28-1.61).

An increase in orofacial cleft defects was noted with first trimester ondansetron exposure but it was not statistically significant (OR: 1.32, [0.76‑2.28]; AOR 1.30 [0.75-2.25]). Similarly, in the secondary analysis, both the adjusted and unadjusted ORs were elevated for cleft lip (CL), CP, and CL/P, but none were statistically significant (Table 3).

Ondansetron exposure was also associated with a significantly increased risk of all specific cardiac birth defects, with highest risk estimates for atrial septal defect (OR 1.62 [1.43-1.84]) and atrioventricular septal defects (2.68 [1.61-4.47]). Table 3.

Limitations: The authors discussed the possibility that medical administration of ondansetron was a surrogate for more severe cases of NVP or HG, thereby resulting in confounding by indication. They note that studies have shown a protective effect of NVP/HG on the fetus. A sensitivity analysis compared mother-child pairs exposed to ondansetron to a subgroup of unexposed mother-child pairs with a specific diagnosis of NVP or HG. Controlling for indication increased risk estimates across the board, most significantly in adjusted analyses, supporting the notion that NVP/HG may exert protective effects.

Ascertainment bias is discussed. Publicity about possible risks associated with ondansetron in 2006 and 2012 may have led to more diagnostic testing for malformations. A sensitivity analysis looked at differences in congenital abnormalities across time periods corresponding to the publicity. Potential detection bias was also addressed by following infants in the study for one year post-delivery to allow latent diagnosis of birth defects.

Conclusion: The study showed a statistically significant association between first trimester exposure to ondansetron and specific structural birth defects in the infant.

Medsafe comments:

This large nested case-control study based on data from a US health claims database aimed to address the issue of exposure misclassification by including a separate analysis for women who had received ondansetron in the clinical setting (a more reliable indication of actual exposure than prescription dispensing data).

The primary analysis showed a statistically significant increase in the adjusted OR for cardiac defects in infants exposed to ondansetron *in utero* during the first trimester, but there was no statistically significant increase in orofacial clefts as a group or separately.

The secondary analysis looked at specific cardiac and oral cleft abnormalities. The adjusted OR was significantly increased for cardiac septal defects overall and for specific septal defects (atrial, ventricular and atrioventricular). Increases in the adjust OR for CP, CL and CL/P were not statistically significant.

The strengths and limitations of this study are discussed in detail in the PRAC report (Annex 1).

3.1.1.2 Huybrechts et al, 2018 (JAMA)

Association of maternal first-trimester ondansetron use with cardiac malformations and oral clefts in offspring [2]

This retrospective cohort study from the United States used the pregnancy cohort nested in the nationwide Medicaid Analytic eXtract (MAX) for the period 2000-2013. This dataset has been used extensively to study the safety of medicines during pregnancy. MAX data include demographic and insurance enrolment information, medical visits and hospital admissions, diagnoses, inpatient and outpatient procedures and prescriptions.

Inclusion criteria: Women were included in the cohort if they were aged 12-55 years and had Medicaid coverage from 3 months before the date of the last menstrual period (LMP) to 1 month after delivery. Infants were included if they had Medicaid coverage for the first 3 months of life, unless they died before reaching 3 months of age.

Exclusion criteria: Pregnancies with exposure to a known teratogenic medication (ie, warfarin, antineoplastic agents, lithium, isotretinoin, misoprostol, thalidomide) during the first trimester (n = 3562) and pregnancies with a chromosomal abnormality (n = 3156) were excluded.

Exposure: The exposed group comprised women who had at least 1 prescription for ondansetron filled during the first 3 months of pregnancy. The unexposed group comprised women who did not fill a prescription for ondansetron during the 3 months before the start of pregnancy through until the end of the first trimester. Women who filled a prescription for ondansetron during the 3 months prior to pregnancy were excluded as they may still have had ondansetron available to use during the first trimester of pregnancy. Additional reference groups comprised women who filled a prescription during the first 90 days of pregnancy for (a) pyridoxine (with or without doxylamine), (b) promethazine, (c) metoclopramide, or (d) any of these medicines.

Outcome measures: The presence of congenital malformations was defined using algorithms based on in patient or outpatient diagnoses and procedure codes in the maternal (first month after delivery) or infant (first 3 months after date of birth) record. The primary outcomes were cardiac malformations and oral clefts. Secondary analyses looked at specific subgroups of cardiac malformations and oral clefts, and congenital malformations overall.

Covariates: potential confounders included in the sensitivity analyses included indication (NVD or HG) 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 (eg obstetric comorbidity index, number of distinct prescriptions for medicines other than antiemetics, number of distinct diagnoses, outpatient visits, hospitalisations and emergency department visits).

Analyses: Absolute risks for each of the outcomes and unadjusted relative risks and risk differences were calculated. Adjusted analyses addressed (1) possible confounding by indication (NVD, HG, use of other antiemetics), and (2) all potential confounding variables. Propensity scores, estimated using logistic regression, were used to adjust for covariates. High-dimensional propensity score analyses that included 200 empirically defined covariates, in addition to the prespecified covariates, were conducted to account for potential residual confounding.

Sensitivity analyses included:

- Changing the reference group to women who filled a prescription for a different antiemetic during the first trimester (instead of women who were never treated with antiemetic agents during pregnancy).
- Redefining exposure to 2 or more filled prescriptions for ondansetron during the first trimester (to minimise the potential for exposure misclassification)
- Narrowing the exposure window to 6-12 weeks after the LMP date (the period of greatest sensitivity to teratogens for oral clefts).

Results: The cohort consisted of 1,816,414 pregnancies (1,502,895 women), of which 88,467 (4.9%) were exposed to ondansetron during the first trimester. Use of ondansetron increased from 0.01% in 2000 to 12% in 2013. The cohort included 251,679 (16.7%) women who contributed more than one pregnancy to the cohort during the period of the data extract.

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 medicines used to treat NVP (metoclopramide, promethazine, pyridoxine), psychotropic medicines, corticosteroids, and for suspected teratogens. Most markers of comorbid illness and disease severity were also elevated among ondansetron-exposed compared with unexposed women.

The absolute risk of congenital malformations in infants exposed to antiemetics in utero is shown in Table 4.

Cardiac malformations occurred in 94.4 (95% CI, 88.0-100.8) per 10,000 ondansetron-exposed pregnancies and 84.4 (95% CI, 83.0-85.7) per 10,000 unexposed pregnancies (based on 124 exposed and 1912 unexposed cases), with an unadjusted relative risk (RR) of 1.12 (95% CI, 1.04-1.20) and an unadjusted risk difference (RD) of 10.0 (95%CI, 3.5-16.5) per 10 000 births.

Oral cleft defects occurred in 14.0 (95% CI, 11.6-16.5) per 10,000 vs 11.1 (95%CI, 10.6-11.6) per 10,000 unexposed pregnancies, with an RR of 1.26 (95%CI, 1.05-1.51) and an RD of 2.9 (95%CI,0.4-5.4) per 10,000 births (Table 4 and Table 5).

The increase in risk of cardiac malformations associated with ondansetron in the unadjusted analyses was related to ventricular septal defects (400 exposed and 6826 unexposed cases; RR, 1.14; 95% CI, 1.04 to 1.27; RD, 5.7; 1.2 to 10.2 per 10 000) and secundum atrial septal defects (216 exposed and 3080 unexposed cases; RR, 1.37; 95% CI, 1.19 to 1.57; RD, 6.6; 95% CI, 3.3 to 9.9 per 10,000).

The increased risk for oral clefts was attributable to cleft palate (65 exposed; 988 unexposed cases; RR, 1.29; 95% CI, 1.00 to 1.65; RD, 1.6; −0.2 to 3.5 per 10,000). There was no evidence of an increased risk for cleft lip (33 exposed; 620 unexposed cases; RR, 1.04; 95% CI, 0.73 to 1.48; RD, 0.1; 95% CI, −1.2 to 1.4 per 10,000) or cleft lip with cleft palate (48 exposed vs 925 unexposed cases; RR, 1.01; 0.76 to 1.35; RD, 0.1, 95% CI, −1.5 to 1.6 per 10,000) in unadjusted analyses.

After stratification by propensity score, all measured patient characteristics were balanced between the ondansetron-exposed and -unexposed groups. Adjusting for indication and associated factors (propensity score level 1) did not substantially change the crude risk estimates. Adjusting for all prespecified potential confounding variables (propensity score level 2) resulted in a null point estimate for cardiac malformations (RR 0.99, 95% CI 0.93-1.06; RD -0.8, 95% CI, -7.3-5.7 per 10,000 births) and for congenital malformations overall (RR 1.01, 95% CI 0.98-1.05; RD 5.4, 95% CI -7.3-18.2 per 10,000 births). However, a statistically significant RR of 1.24 (95% CI 1.03-1.48) remained for oral clefts, corresponding to an RD of 2.7 (95% CI 0.2-5.2) per 10,000 births. (Table 5)

The sensitivity analysis gave consistent results. Requiring 2 or more prescriptions to be filled during the first trimester did not strengthen the association for oral clefts (adjusted RR 1.15, 95% CI 0.85-1.56).

[redacted]

The PRAC summarised the study results in a table, as follows (Table 6) [4]

Table 6. PRAC summary of results from Huybrechts et al Medicaid retrospective cohort study

	Unadjusted rates per 10,000 births (95% CI)		Unadjusted RR	Propensity Score Adjusted
	Ondansetron Exposed 1st 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)

Limitations: Filling a prescription does not mean that the medicine was consumed, which could bias the results toward the null. Sensitivity analysis in the subgroup of women who had at least 2 prescriptions filled during the first trimester (increasing the likelihood that the medicine had been consumed) did not strengthen the association.

Similarly, absence of a recorded diagnosis does not confirm absence of the disease. Misclassification due to incomplete documentation in the source data cannot be excluded. The authors endeavoured to minimise the effect of residual confounding using high-dimensional propensity scores, alternate reference groups and a negative control analysis.

The cohort was restricted to live births so severe congenital malformations that result in pregnancy loss or termination will be missed.

The study used Medicaid data. Medicaid insurance covers the medical expenses for approximately 50% of all pregnancies in the US. The cohort inclusion criteria resulted in a more disadvantaged sub-population within Medicaid, but the results were considered generalisable because the biological relations studied were not expected to be affected.

Conclusions: There was no association between exposure to ondansetron during the first trimester of pregnancy and increased risk of cardiac malformations or congenital malformations overall, after accounting for potentially confounding conditions. There was a small increase in the risk of oral clefts associated with ondansetron exposure, with the upper bound of the 95% CI of the adjusted RR at 1.48, corresponding to 5 additional cases per 10,000 prenatally exposed livebirths. The findings were consistent across a broad range of sensitivity analyses.

Medsafe comments:

This study was based on US Medicaid data from 2000-2013. There were over 1.8 million pregnancies in the cohort, of which 88,467 pregnancies had been exposed to ondansetron in the first trimester. The remaining 1,727,947 pregnancies formed the unexposed control group in the main analysis.

Analyses were also performed using pregnancies that were exposed to other antiemetics including pyridoxine (with or without doxylamine), promethazine, metoclopramide, or any of these antiemetics.

After adjustment for potential confounders, there was a statistically significant increase in the risk of oral clefts in infants exposed to ondansetron in the first trimester compared to no ondansetron exposure. The increase in risk amounted to 3 additional cases per 10,000 infants exposed to ondansetron *in utero*.

Increases in cardiac malformation and congenital malformations overall were observed in the unadjusted analyses, but the increases were not preserved when adjusted for a large number of covariates.

The use of prescription data as a proxy for drug exposure in this study may not reflect actual exposure, as women may have been dispensed ondansetron to take 'if needed' but not actually taken it. The authors addressed the possibility of misclassification in a sensitivity analysis that restricted exposure to only those women who had received at least two ondansetron prescriptions. The results of the sensitivity analysis were consistent with the main analysis.

The study only captured outcomes that were diagnosed by 3 months after birth. This restricted period of follow-up is likely to have more of an effect on the ascertainment for cardiac abnormalities (which may not be immediately obvious at birth), than for orofacial clefts.

3.1.2 Additional observational studies

Some of the studies discussed in this section are included in the Systematic Reviews discussed section 3.1.3.

3.1.2.1 Parker et al, 2018 (Obstetrics and Gynaecology)

Ondansetron for treatment of nausea and vomiting of pregnancy and the risk of specific birth defects [20].

This study used data from two large non-overlapping case-control studies to examine possible associations between ondansetron and birth defects:

- National Birth Defects Prevention Study (NBDPS): a U.S. multisite population-based case-control study that aims to identify risk factors associated with birth defects through maternal interviews. Cases are live births, stillbirths, and elective terminations with selected major birth defects that are identified through surveillance programmes in the participating centres. Controls are selected from vital records (birth registration) or from birth hospital records. Interviews were conducted up to 24 months after delivery.

- Slone Birth Defects Study (BDS): collected data on live births, still births and elective terminations with any major birth defect over the period 1976-2014. Participants in the case group were identified by review of discharge records or registry data at participating hospitals or birth defect registries. Controls were liveborn neonates without malformations identified from study hospitals and birth certificates in the same catchment areas as the case participants. Mothers were contacted within 6 months of delivery to complete a computer-assisted telephone interview. Participants in the case group with chromosomal abnormalities and single-gene disorders were excluded. Multiple gestations and terminations were also excluded.

Methods: The study included NBDPS data for infants with estimated delivery date (EDD) from 1997-2011, and BDS data from 1997-2014. NBDPS data for infants with EDD from 1997-2004 had had previously been analysed for oral cleft defects, neural tube defects and hypospadias (see Anderka *et al*, section 3.1.2.6). Parker *et al* restricted the analysis of these defects to infants with an EDD from 2005-2011. Due to differences in case ascertainment and control selection, data from each study were analysed separately. Both studies had used standardised interviews to capture treatments with prescription and non-prescription medicines, herbal products and supplements. Both studies used the same terminology (Slone Drug Dictionary) to code and classify all exposures. Women were classified into hierarchical first-trimester treatment categories:

(1) ondansetron (with or without other prescription antiemetics)
(2) other prescription antiemetic drugs or intravenous fluids
(3) no treatment for NVP with any medicine (including prescription Rx, IV fluids, OTC medicines, herbal remedies and supplements)

Women were excluded from the aetiologic analyses if they used ondansetron or other prescription antiemetic drugs or IV fluids only outside the first trimester, or if they used only OTC medicines, herbal products or supplements for treatment of NVP. Multiple gestations and terminations were also excluded.

In each dataset, specific birth defects or defect groups were included in the analysis if there were a minimum of 100 cases in total and a minimum of four ondansetron-exposed cases. Cases with chromosomal abnormalities and single-gene disorders were excluded.

Outcomes of interest were:

- Birth defects previously studied in the NBDPS: neural tube defects, oral cleft defects (assessed as CP and CL/P) and hypospadias
- Birth defects reported in other studies: septal defects and renal collecting system anomalies
- Previously unreported associations.

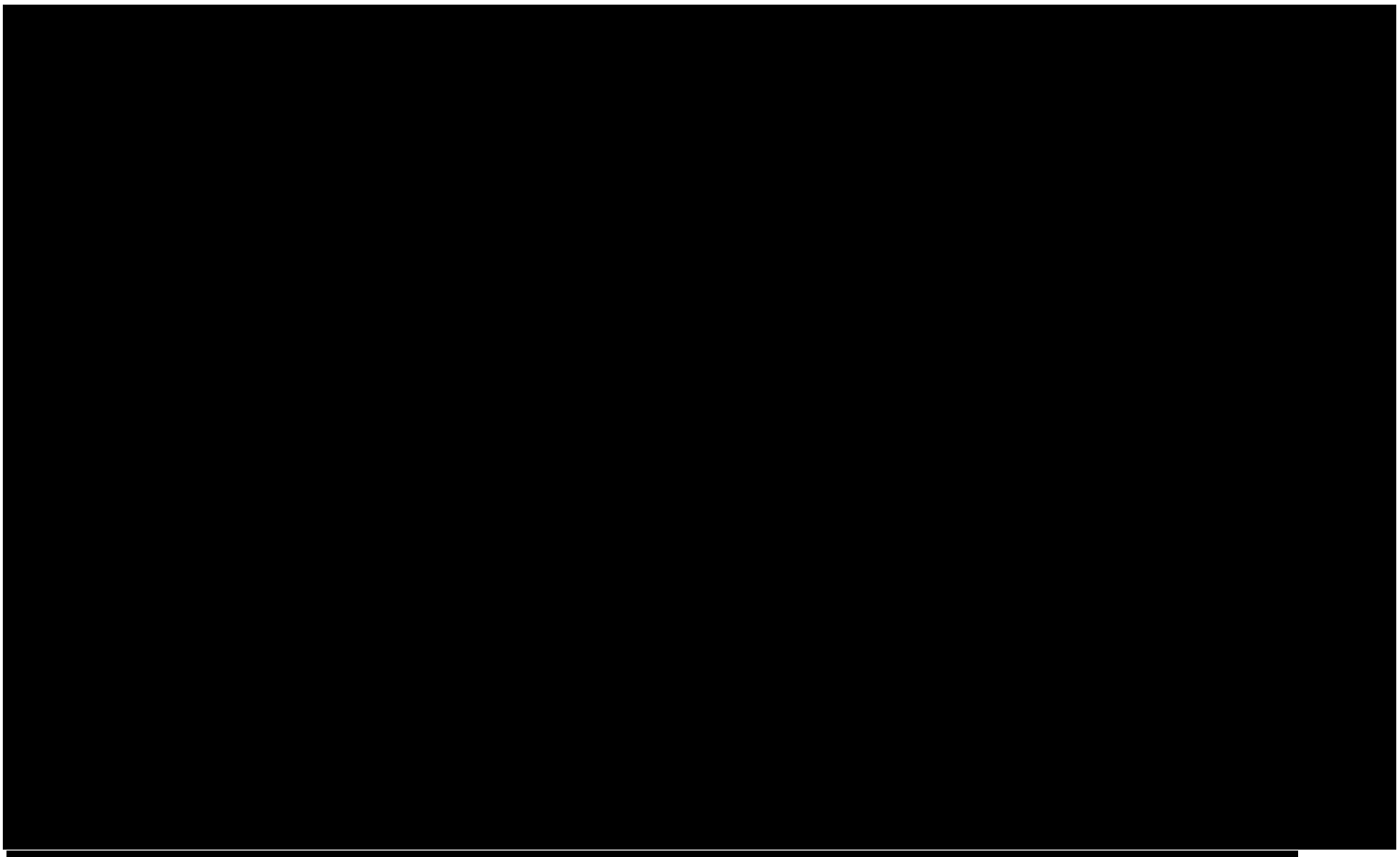
When numbers permitted, specific defects instead of an aggregated category were considered separately (eg, atrial septal defects and ventricular septal defects, instead of septal defects overall).

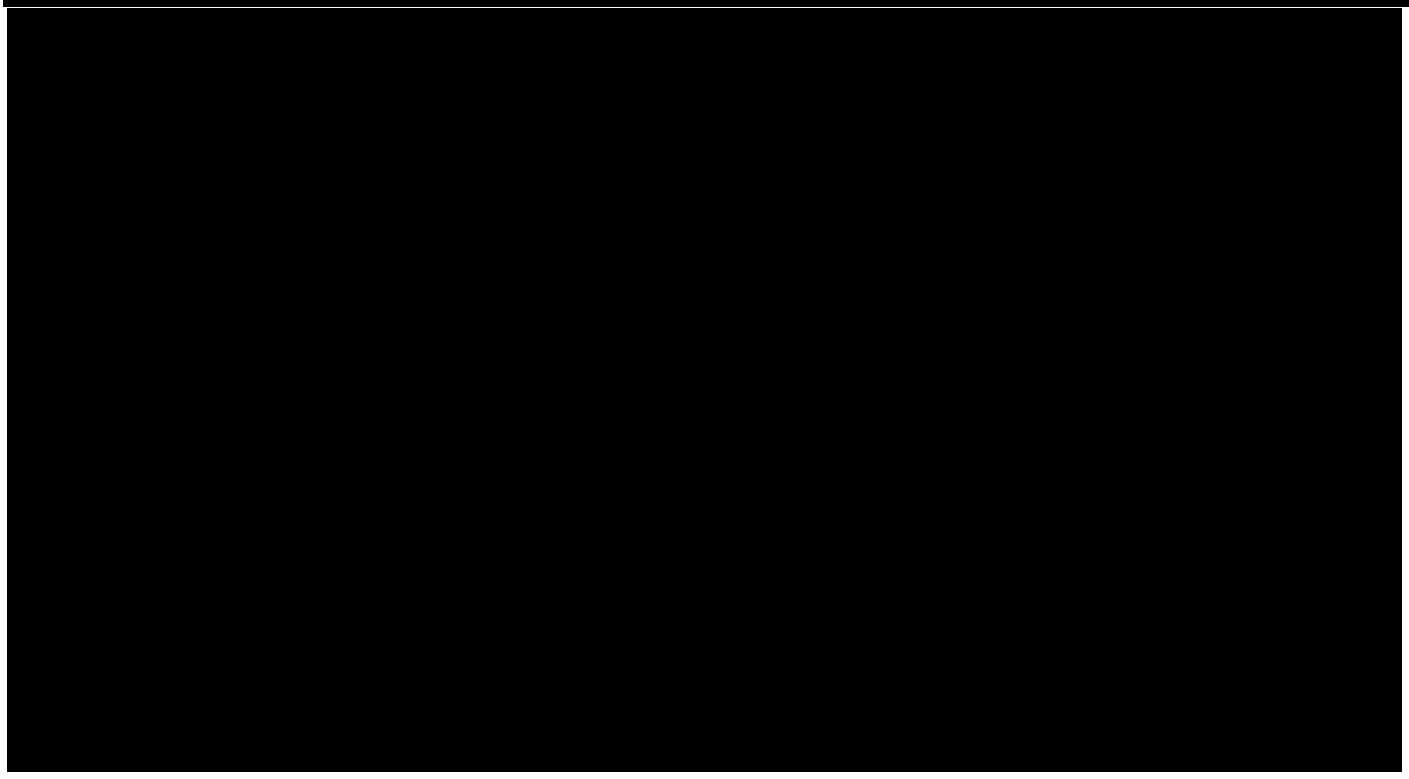
Logistic regression models were used to calculate adjusted odds ratios. Covariates included: maternal age, education, folic acid use, study year, and study site.

Results: There were 11 471 and 10 701 'control' mothers in the NBDPS (1997-2011) and BDS (1997-2014) studies, respectively, of which 70% (n=8,034) and 62% (n=6,619), respectively, experienced first-trimester NVP.

Table 7 shows the number of cases and controls included from each of the studies (NBDPS and BDS) after exclusions.

Demographic data for each of the exposure groups were reported for the control groups from each of the studies (Table 8), but this information was not reported for the cases.





There was a statistically significant increase in CP in ondansetron-exposed infants in the NBDPS dataset, (AOR 1.6; 95% CI 1.1-2.3) but not in the BDS dataset (AOR 0.5, 95% CI 0.3-1.0). For CL/P, there was no statistically significant increase in ondansetron-exposed infants compared to unexposed infants in either dataset (NBDPS AOR 1.1, 95% CI 0.8-1.5; BDS AOR 0.8, 95% CI 0.5-1.2). Table 9.

[redacted]

Medsafe comments:

The NBDPS is a large population-based multicentre case-control study of major birth defects in the United States. Data collection took place from 1998 - 2013 on pregnancies ending between October 1997 and December 2011. Cases could be live born, stillborn or induced terminations, and were identified from birth defects surveillance programs in Arkansas, California, Georgia, Iowa, Massachusetts, New Jersey, New York, North Carolina, Texas and Utah. Controls were live born infants without major birth defects identified from the same geographical regions and time periods as cases via vital records or birth hospitals. Computer-assisted telephone interviews were completed with women between 6 weeks and 24 months after the estimated date of delivery. There were 47,832 eligible cases and 18,272 eligible controls. Among these, 32,187 (67%) and 11,814 (65%) respectively, provided interview information about their pregnancies. [21]

The Slone Epidemiology Centre (Boston University) Birth Defects Study (also called the Pregnancy Health Interview Study) is a multicentre case-control study that was conducted in the areas surrounding Philadelphia, Nashville, and San Diego, and the states of Massachusetts and Rhode Island, Southern New Hampshire, and parts of New York State. Infants with birth defects and a sample of healthy infants without birth defects were identified through state birth defect registries and hospital records. Mothers of these infants were invited to take part in a telephone interview. The interview collected information on medical history, previous pregnancies, nutrition, occupation, health behaviours, smoking, use of medicines and vaccines received in the period prior to conception and throughout the pregnancy. Over 51,000 women were interviewed. [22]

Both studies were limited by a lack of objective exposure data. Exposure data was based on the mother's recall of medicines taken during the first trimester. Mothers of infants with a birth defect are more likely to have considered possible exposures during pregnancy that may have caused the birth defect, contributing to recall bias. The mean time interval between the first trimester and the interview was more than one year (and was longer for cases than controls), which may have further contributed to recall bias as, without reason to previously consider pregnancy exposures, mothers of controls may be less likely to recall the details of possible early pregnancy exposures.

The study reported the characteristics of women in the NBDPS (1997-2011) and BDS (1997-2014) control groups for each of the exposures (ondansetron, other antiemetics and no treatment); but this information was not reported for the cases. A comparison between cases and controls for each exposure would have been useful to determine how well the cases and controls were matched. It is not clear why this information was not provided in the published report.

The number of controls was much lower than the number of cases in both the NBDPS and BDS studies. It is unusual for a case-control study to have fewer controls than cases.

The number of infants exposed to ondansetron and other prescription antiemetics in each study is small. In the NBDPS (2005-2011):

- Controls (n=3267): 212 ondansetron, 209 other prescription antiemetics.
- CP (n=418): 40 ondansetron, 31 other prescription antiemetics.
- CL/P (n=828): 56 ondansetron, 49 other prescription antiemetics.

The study showed a statistically significant increase in CP in ondansetron-exposed infants in the NBDPS dataset, (AOR 1.6; 95% CI 1.1-2.3) but not in the BDS dataset (AOR 0.5, 95% CI 0.3-1.0). For CL/P, there was no statistically significant increase in ondansetron-exposed infants compared to unexposed infants in either dataset (NBDPS AOR 1.1, 95% CI 0.8-1.5; BDS AOR 0.8, 95% CI 0.5-1.2).

The findings were consistent with the earlier study by Anderaka *et al* [23], which had previously examined these outcomes in the NBDPS data for the period 1997-2004.

3.1.2.2 Fezjo et al, 2016 (Reproductive Toxicology)

Ondansetron in pregnancy and risk of adverse fetal outcomes in the United States

Method: This retrospective cohort study was part of a larger investigation evaluating the genetics of HG. Women were recruited into the study through advertisements on the Hyperemesis Education and Research Foundation website during the period 2007-2014. Inclusion criteria were a diagnosis of HG in a singleton pregnancy and treatment with IV fluids and/or total parenteral nutrition/nasogastric feeding tube. Participants with a history of HG were asked to submit their medical records. Each woman with a history of at least one pregnancy affected with HG and treated with IV fluids was asked to recruit one acquaintance with at least 2 pregnancies lasting beyond 27 weeks to participate as a control. Controls were eligible if they experienced either no NVP or NVP that did not interfere with their daily routine, no weight loss due to nausea/vomiting and no medical attention in any pregnancy due to nausea.

Participants completed an online survey about symptoms, treatments (including ondansetron) and outcomes (including birth defects). Most participants joined the study while still pregnant, and were prompted to complete the survey on fetal outcome after their due date. Participants were prompted every six months to update the survey (including information about subsequent pregnancies that occurred during the study period).

Respondents were categorised according to their exposure to ondansetron and responses to variables. Fisher's exact test was used for categorical variables and unpaired t-test was used for numerical variables. Odds ratios were estimated using logistic regression.

Results: There were 772 women with a history of HG who reported a total of 1070 pregnancies exposed to ondansetron (HG/ondansetron), and 771 pregnancies that were not exposed to ondansetron (HG/no ondansetron). An

additional 563 women who did not have HG in any pregnancy (controls) reported on 1555 pregnancies that were not exposed to ondansetron or any other antiemetic/treatment for NVP. Table 10

The authors concluded that the overall results do not support evidence of teratogenicity of ondansetron.

[redacted]

Medsafe comments:

The study design involves selection of controls by the cases themselves. This is an unusual approach and is likely to be subject to bias through association. For example, the controls may be related to the cases.

Data is subject to recall bias, and it is not clear whether ondansetron exposure was exclusive of other antiemetics.

The proportion of live births in the HG/no ondansetron group was only 57.2% compared to 89.0% and 82.7% in the HG/ondansetron and control groups, respectively. This low proportion of live births may be due to a much higher proportion of first trimester terminations and miscarriages in the HG/no ondansetron group (12.84% and 30.61%, respectively) compared to the other two groups. This significant difference in the proportion of live births between the two groups limits the validity of further outcome comparisons.

3.1.2.3 Danielsson et al, 2014 (Reproductive Toxicology)

Use of ondansetron during pregnancy and congenital malformations in the infant [24][2]

Data from the Swedish Medical Birth Register combined with the Swedish Register of Prescribed Drugs for the period 1998-2012 were used to study teratogenic risks with ondansetron.

The cohort included 1,501,434 infants of which 1349 were exposed to ondansetron in early pregnancy. Congenital malformations were identified using three national health registers.

The primary analysis assessed the risk for 'any malformation'. Secondary analyses assessed the risk for specific malformations.

In a Mantel-Haenszel analysis adjustment was made for year of delivery, maternal age, parity, smoking in early pregnancy and pre-pregnancy body mass index. Risks were expressed as odds or risk ratios with 95% confidence intervals.

Results: In the primary analysis, there was no statistically significant increase in major malformation in infants exposed to ondansetron *in utero*. The secondary analysis showed a statistically significant increase in 'cardiovascular defect'

[2] The full article was not available at the time of writing this report. Information about this study was compiled from the Abstract and the review by Levecchia *et al*, which included this study.

(adjusted OR = 1.62, 95% CI 1.04–2.54) and 'cardiac septum defect' (adjusted OR 2.05, 95% CI 1.19–3.28) in exposed infants. There were no infants with a CP and only one infant with a CL/P.

The study concluded that the teratogenic risk with ondansetron is low but an increased risk for a cardiac septum defect is likely.

Medsafe comments:

This study used the same Swedish data sources as the study by Asker *et al* [25].

The full report was not available for this review, and the details of the study are not clear from the Abstract. The study is described further in the review by Levacchia *et al* [26].

The study found a statistically significant increase in cardiovascular defects (aggregated) and cardiac septum defects in infants exposed to ondansetron. However, the prescription was filled at/after 56 days gestation (ie, after cardiac development was complete) in 779/939 (83%) infants for which this information was available (of the 1349 infants exposed in total) [26].

The information on the timing of the exposure in more than 50% of the exposed infants casts doubt on the study findings.

3.1.2.4 Pasternak et al, 2013 (NEJM)

Ondansetron in pregnancy and risk of adverse fetal outcomes [27]

Methods: This registry based retrospective cohort study used information from the Danish Medical Birth Registry and the National Patient Register, to identify all pregnancies that ended in singleton live birth, still birth, termination or miscarriage during the period 1 January 2004 – 31 March 2011. Pregnancy onset was defined as the first day of the last menstrual period (LMP) and was estimated by subtracting the gestational age from the date of birth or abortive outcome. Pregnancies were excluded if information on gestational age was missing or implausible, there were multiple records on overlapping dates, or if the pregnancy ended within the first 6 weeks of gestation.

Ondansetron exposure was identified from the Danish National Prescription Registry. For birth defects, the exposure window of interest was the first trimester (12 completed weeks from the LMP). The timing of exposure was defined by the date the prescription was filled. Women who did not receive ondansetron throughout the exposure time window were categorised as unexposed. Women who had filled an ondansetron prescription within 1 month before the LMP were excluded.

Major birth defects were identified using data from the National Patient Register (1-year follow-up after birth). Major defects were defined according to the European Surveillance of Congenital Anomalies (EUROCAT) classification, with some exclusions (chromosomal abnormalities and birth defects with known causes such as fetal alcohol syndrome).

Statistical analysis of birth defects was based on live births only. Logistic regression was used to estimate prevalence odds ratios. To account for potential confounders, logistic regression was also used to estimate propensity scores as the probability of exposure to ondansetron given baseline characteristics at pregnancy onset.

Sensitivity analyses for the birth defect outcome included:

- Restricting the definition of exposure to the period of maximal susceptibility to teratogenic agents (gestational weeks 4 to 10, or 2 to 8 weeks after the estimated time of conception).
- Including birth defects detected among induced abortions and stillbirths
- comparing exposure to ondansetron with exposure to antiemetic antihistamines considered safe in pregnancy (promethazine, cyclizine, or meclizine), using a 1:1 ratio in a propensity score-matched analysis).
- categorizing women according to whether they filled one prescription or two or more prescriptions (women who have filled a prescription more than once are more likely to have used the medicine.

Results: A total of 620,448 pregnancies were identified in the two source registries, of which 442,748 ended in live birth. Among the live births, 1233 were exposed to ondansetron during the first trimester and 440,278 were

unexposed. Following propensity score estimation and 1:4 matching, 435,346 pregnancies were excluded (no match), leaving 4932 propensity-score-matched unexposed pregnancies for the analysis of any major birth defect.

Baseline characteristics were mostly well balanced between the propensity-score-matched groups for the analysis of birth defects. However, use of antiemetics other than ondansetron was significantly higher in the ondansetron-exposed group (500/1233; 40.6%) compared to the unexposed group (209/4932; 4.2%). Hospitalisation for HG or NVD was also much higher in the exposed group (50.9%) compared to the unexposed group (0.7%).

Table 11 shows the propensity-score-matched analyses of adverse fetal outcomes associated with exposure to ondansetron in pregnancy, with and without adjustment for hospitalization for HG or NVD and the use of other antiemetics. There was no statistically significant difference in pregnancies with 'any major birth defect' between ondansetron exposed and unexposed groups (adjusted OR 1.12; 95% CI 0.69-1.82). No statistically significant difference was observed in any of the sensitivity analyses for the birth defect outcome.

Among 1233 women who were exposed to ondansetron in the first trimester (first prescription at a median of 63 gestational days; interquartile range, 54 to 73), 36 infants (2.9%) were registered as having a major birth defect during the first year of life, as compared with 141 of 4932 infants (2.9%) born to women who were not exposed (adjusted prevalence odds ratio 1.12, 95% CI 0.69-1.82). There were no cases of cleft palate in the group exposed to ondansetron.

[redacted]

Medsafe comments:

This study examined the risk of birth defects in aggregate. It did not examine whether there were differences between exposed and unexposed groups in the risk of specific congenital abnormalities such as oral cleft defects or cardiac abnormalities, or indeed subtypes of these abnormalities. However, the number

of exposed women in the cohort (1233) was too small to detect an increase in the occurrence of orofacial cleft defect, which are estimated to occur in approximately 1:600 to 1:2800 pregnancies (section 2.2).

3.1.2.5 Colvin et al, 2013 (Biomed Res Int)

Off label use of ondansetron in pregnancy in Western Australia [28]

This study from Western Australia used linkable state health administrative data from the Western Australia Data Linkage System (WADLS): Hospital Morbidity Data System (HMDS), the Midwives' Notification System (MNS), the Registry of Births and Deaths, and the WA Birth Defects Registry (now called the WA Register of Developmental Anomalies – WARDA), and the Australian Pharmaceutical Benefits Scheme (PBS). The WARDA is a comprehensive source of information on birth defects in WA, with a high level of ascertainment.

Exposed pregnancies were all births in Western Australia during the period 2002-2005 for which the mother was dispensed ondansetron under the PBS. The comparison group was all other births during the same period.

During the study period, there were 96,968 pregnancies resulting in a birth in WA. Ondansetron was dispensed to 251 pregnant women (263 infants exposed *in utero*).

Major birth defects were registered in 10/211 (4.7%) infants who were exposed to ondansetron during the first trimester and in 3975/98,062 (4.1%) unexposed infants (OR 1.2, 95% CI 0.6-2.2). There was a non-significant increase in the number of major congenital malformations.

Medsafe comments:

This study did not examine specific birth defects, but was too small to detect a difference.

3.1.2.6 Anderaka et al, 2012 (Birth Defects Res A Clin Mol Teratol)

Medications used to treat nausea and vomiting of pregnancy and the risk of selected birth defects [23]

This CDC funded study used data from the NBDPS, the same database that was later used by Parker *et al* [20] (described in section 3.1.2.1). The study aimed to assess whether NVP or its treatment was associated with the most common non-cardiac defects in the NBDPS: orofacial clefts (assessed as non-syndromic CL/P, and CP alone), neural tube defects, and hypospadias.

Methods: The study included subjects from the NBDPS with expected dates of delivery between 24 September 1997 and 31 December 2004. Interview participation rates were 76% for CL/P, 75% for CP, and 69% for controls. Of subjects for whom complete interview data were available, 1546 had CL/P, 821 had CP, and there were 5859 control infants. The mean interval between birth and interview was 10.4 months for CL/P, 10.9 months for CP, and 8.9 months for controls.

Of 22,381 women participating in the NBDPS during the study period, 75 different medicines and some herbal products were reported as treatment for NVP. Medicine exposures were grouped into categories based on their therapeutic and pharmacologic class. Medicine groups were included if they were reported by more than 15 of the selected birth defect case and control women and at least 20% reported their use for the treatment of first trimester NVP. Medicine groups meeting these criteria were: antihistamine antiemetics, other antihistamines, antihistamine antiemetic plus B6 combinations, phenothiazines (other than promethazine), prokinetics, 5HT3 antagonists, emetrol/coke syrup, bismuth subsalicylate, antacids, histamine H2-receptor antagonists (H2 blockers), proton pump inhibitors, pyroxidine (vitamin B6), steroids and herbal/natural products. Categories that did not meet the criteria and were excluded were cannabinoids, antispasmodics, antidiarrheals, laxatives, analgesics and muscle relaxants.

The main comparison was between women with NVP who used NVP medicines in the first trimester vs those who did not (regardless of indication). Measures of association were calculated for medicine categories and individual medicines or herbal products with at least four exposed cases.

Potential confounders for the adjusted analyses included maternal age, race-ethnicity, education, parity, smoking in the month before conception through the first trimester, plurality, previous miscarriage, infant sex, use of multivitamin

with folic acid anytime between the month before conception through the first trimester, body mass index (BMI), study site, and year of expected date of delivery. Adjusted odds ratios were estimated using unconditional logistic regression. Subjects with a parent, sibling or half sibling with the same birth defect were excluded because their birth defects may be etiologically different from subjects without such a family history.

Where an association was observed between first trimester medicine use and a birth defect, medicine exposure was further examined according to month of pregnancy and the intensity of nausea and vomiting (average frequency of NVP in months 1, 2 and 3 of pregnancy).

Results: None of the medicines were associated with a statistically significant increase in the risk of CL/P. (Table 12)

Ondansetron was associated with a statistically significant increase in the risk of CP (AOR 2.37; 95% CI 1.18-4.76). There was also a higher OR among women exposed to proton pump inhibitors in the crude analysis, but the increase was not statistically significant in the adjusted analysis (AOR 2.59; 95% CI 0.88-7.63). (Table 13).

[redacted]

Medsafe comments:

This study used data from the NMDPS for the period September 1997 to December 2004. Parker *et al* used data from the same source, but for the period 2005-2011. The later study was consistent with the earlier study as it also found an association between ondansetron and CP (AOR 1.6, 95% CI 1.1-2.4), but not with CL/P. Both studies are subject to the same limitations of recall bias and lack of objective exposure data.

3.1.2.7 Asker et al, 2005 (Eur J Clin Pharmacol)

Use of antiemetic drugs during pregnancy in Sweden [25][3]

In this prospective cohort study, Asker *et al* obtained information on antiemetic use during pregnancy from the Swedish Medical Birth Register for the period 1 July 1995 to 2002. Information was also obtained from the Registry of Congenital Malformations and the Hospital Discharge Registry.

[3] A copy of the full paper was not available for this review. Information on this study was obtained from the Abstract.

The study compared birth outcomes (preterm birth, low birth weight, small for gestational age, and congenital malformations) in women who were exposed to specific antiemetics (antiemetic antihistamines, dopamine modulators, and ondansetron) *vs.* no antiemetic during pregnancy.

There were 676 198 women in the cohort. Only 65 women were exposed to ondansetron during pregnancy, including 21 women who were exposed during the first trimester.

There were no reported cases of congenital malformations in women exposed to ondansetron, nor was there an association with preterm birth, low birth weight, or small for gestational age. The small number of women exposed to each antiemetic made it difficult to infer any conclusions regarding teratogenic risk.

Medsafe comments:

Off-label use of ondansetron has increased significantly since the period covered by this study. The authors reported that 4.5% of pregnant women in the cohort used an antiemetic medicine during pregnancy, of which 86% used the antiemetic before the first antenatal visit at 10-12 weeks. Use of ondansetron ranked lowest, behind meclozine and other antihistamines, which together accounted for 68% of the drugs reported, and dopamine antagonists.

Only 21 women were exposed to ondansetron in the first trimester, which is not a large enough sample to detect a difference in the frequency of orofacial cleft defects, which occur in approximately 1:600 to 1:2800 pregnancies (as discussed in section 2.2).

3.1.2.8 Einarson et al, 2004 (BJOG)

The safety of ondansetron for nausea and vomiting of pregnancy: a prospective comparative study [29]

This prospective observational cohort study aimed to determine whether the use of ondansetron during pregnancy is associated with an increased risk for major malformations by following up callers to the Motherisk Programme (Toronto, Canada) or the Mothersafe Program (Sydney, Australia) helplines. Motherisk and Mothersafe provide information to pregnant and breast-feeding women and their healthcare professionals on the safety/risk of drugs, chemicals, radiation and infectious diseases.

Methods: The study enrolled women who called the service who were taking ondansetron and were less than three months pregnant at the time of the call. Enrolment took place over a two-year period. Women who were exposed to 'other antiemetics' (Diclectin [controlled release doxylamine + vitamin B6], metoclopramide, phenothiazines, or ginger) and 'non-teratogens' (other drugs considered safe to use in pregnancy or no medicine use) were enrolled into comparator groups. Women were interviewed using a standardised intake form, which collected information on: severity of NVP (PUQE scoring system), concurrent antiemetic use and other medicines. The women were contacted 4-6 months after delivery to obtain outcome data using a standardised follow-up form. The information on the baby's health was verified with the woman's physician.

The groups were compared for age, smoking, alcohol consumption, gestational age at time of call, and birth outcomes, including live birth, miscarriage, therapeutic abortion, stillbirth and major malformations.

Results: Follow-up information was available for 176 women in each group. 188 women were enrolled in the ondansetron group, but 12 were lost to follow-up. The total number enrolled, and number lost to follow-up for each of the comparator groups is not reported. A comparison of baseline characteristics is shown in Table 14.

[redacted]

In the ondansetron group, there were six major malformations: three cases of hypospadias, double urinary collecting system in kidney, mild pulmonary stenosis and a duodenal atresia. In the 'other antiemetics' group, there were three major malformations (hydrocephalus, kidney anomaly and aortic stenosis), and in the 'non-teratogen' group there were also three malformations (one case of hypospadias and two congenital heart defects). There were no statistically significant differences between the three groups for live births, miscarriages, stillbirths, therapeutic abortions, birthweight or gestational age. Table 15

[redacted]

Medsafe comments:

No cases of cleft palate were reported in this study. However, study size, methodological issues and inadequate study reporting limit the value of this study.

There were 176 women with complete information in each of the study groups. The authors reported that 188 women were enrolled in the ondansetron group but 12 were lost to follow-up. Information on the total number of women enrolled in each of the comparison groups and the number lost to follow-up is not reported.

The authors reported *'There were no significant differences between the exposed and comparison groups, their ages were similar and very few smoked cigarettes or drank alcohol during pregnancy'*. However, Table 14 indicates that there was a significant difference in the proportion of women who smoked (0.5%, 2.8% and 8.5 % for the ondansetron, other antiemetic and non-teratogen groups, respectively).

In Table 15, it is not clear which comparison group was used to ascertain the p value.

3.1.3 Systematic Reviews

3.1.3.1 Kaplan et al, 2019 (Reproductive Toxicology)

Use of ondansetron during pregnancy and the risk of major congenital malformations: A systematic review and meta-analysis [30]

This systematic review aimed to investigate whether ondansetron use during pregnancy is associated with increased rates of congenital malformations.

Methods: The literature search used PubMed/MEDLINE, Cochrane Central Register of Controlled Trials and Reprotox databases from inception to 21 September 2016. Search terms were: ondansetron, pregnancy, congenital malformations, congenital abnormalities, birth defects, cardiovascular malformations and heart defects. Reference lists of previous systematic reviews were also searched. The meta-analysis included observational cohort and case-control studies investigating major congenital malformations after maternal use of ondansetron in pregnancy. Inclusion criteria were:

1. exposure to ondansetron during pregnancy was reported
2. healthy or disease-matched (NVD or HG) control group was included that was not exposed to ondansetron, but may have been exposed to non-teratogenic drugs or other antiemetics
3. total number of exposure and outcome events or point estimates were reported
4. data reported did not overlap with another study (if overlap detected, study with higher quality score was included, and a sensitivity analysis including each overlapping study was conducted).

Exclusion criteria were case reports and case series, animal studies, editorials and reviews.

The search strategy is illustrated in Figure 2.

[redacted]

The main outcome of interest was overall major congenital malformations. Secondary outcomes were heart defects, orofacial clefts, isolated cleft palate, genitourinary malformations and hypospadias.

Results: Eight studies were included in the meta-analysis:

- six cohort studies
  - Einarson *et al*, 2004 [29]
  - Asker *et al*, 2005 [25]
  - Colvin *et al*, 2013 [28]
  - Pasternak *et al*, 2013 [27]
  - Andersen *et al*, 2013 (unpublished abstract)
  - Danielsson *et al*, 2014 [24]
  - Fezjo *et al*, 2016 [31]
- two case-control studies
  - Anderka *et al*, 2012 [23]
  - Van Bennekom *et al*, 2016 [20, 32]

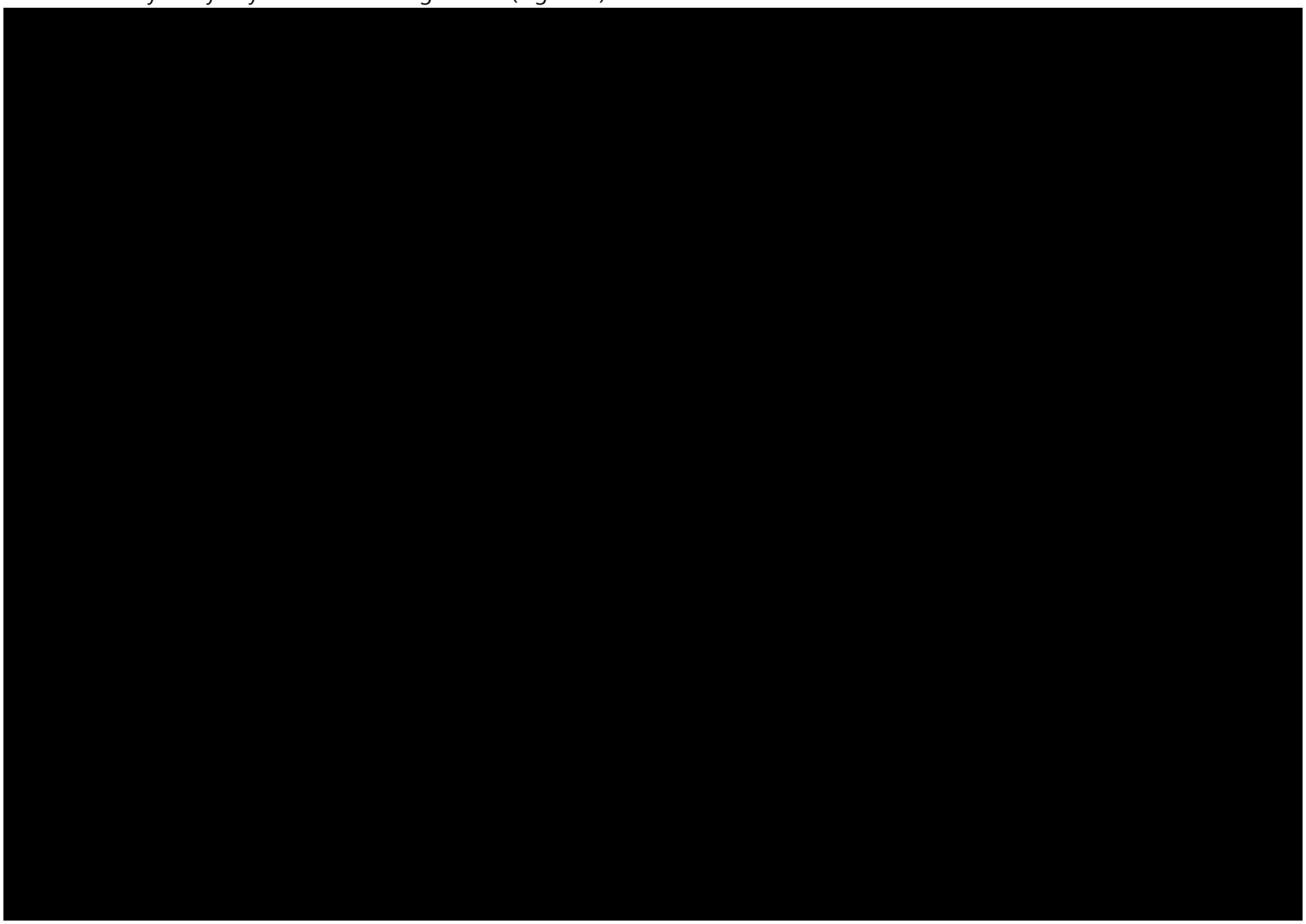
The studies by Pasternak *et al* [27] and Andersen *et al* (unpublished, abstract only) investigated largely overlapping data and yielded conflicting results. As the Andersen *et al* study was only available as an abstract (resulting in a lower methodological quality score), the study by Pasternak *et al* was included in the primary analysis instead. (The Anderson *et al* study was included in the sensitivity analysis).

The studies by study by Danielsson *et al* [24] and Asker *et al* [25] also investigated overlapping data. Asker *et al* was excluded from the primary analysis because it did not report details of the control group and had a less recent data set compared to the Danielsson *et al* study (1995–2002 vs 1995–2012, respectively).

The primary analysis looked at major congenital malformations overall. After exclusion of the Andersen *et al* study, there were 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, in the sensitivity analysis where Andersen *et al* was substituted for Pasternak *et al*, the point estimate was slightly increased, and the result became statistically significant (OR 1.23; 95% CI 1.02-1.48). No significant heterogeneity was identified for either of the analyses. (Figure 3).

Three studies were eligible for analysis of orofacial cleft defects [27, 28, 31]. No significant increase in the rates of orofacial clefts were observed following use of ondansetron during pregnancy (OR 0.89; 95% CI 0.32-2.50). No significant heterogeneity was detected between the studies. (Table 16).

Isolated cleft palate was investigated using only the two case-control studies [23, 32], as the cohort studies did not report specific numbers of infants with isolated cleft palate. Van Bennekom *et al* reported two different risk estimates from two separate datasets (National Birth Defects Prevention Study dataset [NBDPS 1997–2009] and Slone Birth Defects Study dataset [BDS 1997–2013]), which were used for the sensitivity analysis. In the primary analysis, maternal use of ondansetron was not significantly associated with isolated cleft palate (OR 1.13; 95% CI 0.43–2.97). However, the sensitivity analysis yielded conflicting results (Figure 4).



Medsafe comments:

In the primary analysis, the point estimate for overall congenital malformation increased slightly and became statistically significant only when results from the unpublished abstract by Andersen *et al* replaced the published (peer-reviewed) study results by Pasternak *et al* in the sensitivity analysis. Given the lack of information available in the abstract and that it has not been published in a peer-reviewed journal, it does not seem reasonable to put much weight on the Andersen study. The analysis using the Pasternak *et al* study, which did not find a statistically significant increase in overall congenital malformation, is more rigorous.

The analysis of orofacial cleft defect (secondary analysis) was based on two case-control studies [23, 32].

- The study by Anderka *et al* used data from the National birth Defects Prevention Study (NBDPS), a U.S. multi-site population-based case-control study designed to identify risk factors associated with birth defects. Each year, the 10 sites individually contribute maternal interviews of approximately

300 case subjects with birth defects (identified from birth defect surveillance systems in the participating states) and 100 control subjects without birth defects (randomly selected from birth certificates or selected from birth hospitals using a random sampling design). All infants with study-eligible birth defects and controls are invited to participate in the NBDPS. Mothers are contacted up to 24 months after delivery to complete a standardised computer-assisted telephone interview. Anderka *et al* included subjects from the NBDPS with expected dates of delivery between 24 September 1997 and 31 December 2004. The interview participation rates were 76% for cleft lip and palate, 75% for cleft palate, and 69% for controls. The mean interval between birth and interview was 10.4 months for cleft lip and palate, 10.9 months for cleft palate, and 8.9 months for controls. [23]

- The second case-control study was published as a conference abstract in 2015 [32]. The full paper was subsequently published in 2018 [20]. The study used data from two sources: NBDPS and the Slone Birth Defects Study (BDS). The NBDPS data for infants with expected delivery dates from 1997-2004 had already been studied by Anderka *et al* (as described above), so only infants with delivery dates from 2005-2011 were included in this study. The BDS collected data on live births, still births and elective terminations with any major birth defect over the period 1976-2014. This analysis used data from 1997-2014. Participants in the case group were identified by review of discharge records or registry data at participating hospitals or birth defect registries. Controls were liveborn neonates without malformations identified from study hospitals and birth certificates in the same catchment areas as the case participants. Mothers were contacted within 6 months of delivery to complete a computer-assisted telephone interview. Participants in the case group with chromosomal abnormalities and single-gene disorders were excluded. Multiple gestations and terminations were also excluded. Due to differences in case ascertainment and control selection data from each study were analysed separately.

  The adjusted OR for CL/P in ondansetron-exposed infants was not significantly increased in either dataset (NBDPS 1.1 [95% CI 0.8-1.5] and BDS 0.8 [0.5-1.2]). For CP only, there was a statistically significant increase in the adjusted OR in the NBDPS dataset (1.6 [1.1-2.3]) but not in the BDS dataset (0.5 [0.3-1.0]).

Both studies were limited by a lack of objective exposure data. The difference in participation between cases and controls in the NMBDS suggests a form of volunteer bias. Mothers whose infant has a congenital malformation may be more interested to take part in the study than mothers of infants without a malformation. Exposure data was based on the mother's recall of medicines taken during the first trimester. Mothers with an infant who has a birth defect are more likely to have already considered possible exposures during pregnancy. The mean time interval between the first trimester and the interview was more than one year (and was longer for cases than controls), which may have further contributed to recall bias.

Kaplan *et al* noted that they became aware of the two more recent studies (Zambelli-Weiner *et al* and Huybrechts *et al*) after submission of the manuscript for publication. They acknowledged that inclusion of these newer studies could have suggested a small but statistically significant increased risk of orofacial cleft following maternal first trimester ondansetron use. However, they considered that their conclusion would remain the same: *'ondansetron should not be considered as a first-choice treatment for NVP in the first trimester; however, since the absolute risks seem low, its use may remain justifiable on a case-by-case basis where first choice medications have failed to control the maternal symptoms'*.

3.1.3.2 Levecchia, et al, 2018 (Journal of Obstetrics and Gynaecology Canada)

Ondansetron in pregnancy and the risk of congenital malformations: a systematic review [26]

The aim of this study was to systematically review epidemiological evidence on the potential association of prenatal exposure to ondansetron and congenital malformations.

Methods: The literature search was performed using Medline, Embase, EBMALL, Proquest Dissertations & Theses Global, CINAHL (EBSCO), and Scopus from inception to June 2017. Search terms were related to the concepts: 'ondansetron', 'birth defects and early labour' and not 'post-operative vomiting and nausea', and strategies were adjusted for each database. Clinicaltrials.gov, Prospero, and Google Scholar (2011-2017) were also searched. Studies were included for review if they were in English, reported human data, presented outcomes relating to birth defects following antenatal exposure to ondansetron, and described original research. Case reports, abstracts without corresponding manuscripts, and studies evaluating pre-medication with ondansetron prior to Caesarean delivery were excluded. Data were abstracted from each study using a standard data collection form, which included the following details: study design, data sources, number of pregnancies exposed to ondansetron, details of ondansetron exposure (dose, duration, trimester at start, indication), and outcomes (risk of congenital malformation and any other reported secondary outcomes). The results were tabulated, but due to the heterogeneity of the design and reporting, no attempt was made to combine the results of the studies.

Results: Ten studies met the inclusion criteria, of which only three (Anderka *et al* [23], Pasternak *et al* [27] and Danielsson *et al* [24]) were large population-based cohort studies designed to specifically evaluate the risk of ondansetron exposure and congenital malformations.

None of the 10 studies found an overall increased risk of congenital malformations in women exposed to ondansetron in pregnancy. The studies did not provide evidence of an association between ondansetron and overall risk of birth defects; however, evidence for an increased risk of specific defects, such as cardiovascular defects and cleft palate, was conflicting.

Medsafe comments:

This systematic review identified and summarised studies of ondansetron exposure in pregnancy and risk of congenital malformations that were published up until June 2017. The 10 included studies are described in the review, but a meta-analysis of the results was not performed due to heterogeneity between the studies.

Only a few of the studies included information on oral cleft defects. These studies are discussed individually above

3.2 CARM data

The CARM database was searched for reports that include ondansetron as either a suspect or concomitant medicine, and meet at least one of the following criteria:

- Administration during pregnancy
- Route of administration recorded as 'intra-uterine'
- Reaction term indicated fetal abnormality
- Gestation indicated in the report
- Seriousness category was 'congenital abnormality'

As at 31 December 2019, the CARM database contained 393 reports for ondansetron. Of these,123 reports listed ondansetron as a suspect medicine and the remaining 270 reports listed ondansetron as concomitant. Four reports met the search criteria for exposure during pregnancy. Two reports were for cardiac malformations. There were no reports of orofacial defects. Table 17

Table 17. CARM case reports

Report ID	Age	Sex	Year	Reactions	Drugs
094234	6m	F	2011	Precocious puberty	Cyclizine Ondansetron
099608	36	PF	2012	Congenital anomaly NOS	Ondansetron Cyclizine Metamucil Metoclopramide Microlax
121456	39	PF	2016	Ventricular septal defect Drug exposure in pregnancy	Ondansetron
125469	Birth	F	2017	Total anomalous pulmonary venous return (TAPVR) malformation Atrial septal defect	Ondansetron

4 DISCUSSION AND CONCLUSIONS

Ondansetron is a 5-HT3 receptor antagonist indicated for the management of nausea and vomiting induced by cytotoxic chemotherapy and radiotherapy, and for prevention of post-operative nausea and vomiting. Ondansetron is not approved for NVP/HG in New Zealand (or in the US or the EU).

The SOMANZ guidelines for the management of NVP/HG recommend ondansetron as one of several antiemetic options for moderate NVP and as the first-line antiemetic for severe or refractory NVP/HG [10].

Off-label use of ondansetron for NVP/HG has increased since the early 2000s. Huybrechts *et al* reported use of ondansetron in the U.S. Medicaid cohort increased from 0.01% of pregnancies in 2000 to 12% in 2013 [2]. A study of the Mini Sentinel Distributed Database in the U.S., which included over 2.3 million pregnancies, reported ondansetron use had increased from < 1% of pregnancies in 2001 to 22.2% in 2014 [11].

In 2006, concerns were raised about the safety of ondansetron use in pregnancy when Siu *et al* demonstrated that ondansetron crosses the placenta [33].

Information on the risk of congenital malformations associated with first trimester exposure to ondansetron has been limited and conflicting. Studies by Einarson *et al* [29], Asker *et al* [25], Colvin *et al* [28], and Pasternak *et al* [27] found no statistically significant increased risk of major birth defects. Danielsson *et al* [24] found increased risks of cardiac defects, specifically cardiac septal defects. Anderka *et al* [23] and Parker *et al* [20] found an increased risk of CP (but not CL/P).

These studies were limited by small sample size, exposure misclassification due to reliance on filled prescriptions or recall, confounding by indication or other variables, and an exposure period that goes beyond the period of organogenesis.

The systematic review by Kaplan *et al* looked at the risk of major congenital malformations overall and specific malformations including orofacial clefts and heart defects [30]. The review included the six cohort studies and two case control studies discussed individually in section 3.1.2. Among the cohort studies, there was no significant increase in the risk of overall major congenital malformation following ondansetron use during pregnancy (OR 1.16; 95% CI 0.92-1.45). Meta-analysis of the three included studies that examined orofacial clefts [27, 28, 31] did not identify an increase in risk with exposure to ondansetron (OR 0.89; 95% CI 0.32-2.50). Analysis of the two case-control studies [23, 32], indicated that maternal use of ondansetron was not significantly associated with isolated cleft palate (OR 1.13; 95% CI 0.43–2.97), but the sensitivity analysis yielded conflicting results.

Two recent studies investigated the risk of orofacial cleft defects in infants exposed to ondansetron *in utero* [2, 3]. These studies, which were performed using data from large administrative claims databases, aimed to address key limitations of the previous studies: small sample size and exposure misclassification.

Zambelli-Weiner *et al* showed a statistically significant increase in the adjusted OR for cardiac defects in infants exposed to ondansetron *in utero* during the first trimester (adjusted OR 1.43, 95% CI 1.28-1.61), but there was no statistically significant increase in orofacial clefts as a group or separately. In the secondary analysis, the adjusted OR was significantly increased for cardiac septal defects overall and for specific septal defects (atrial, ventricular and atrioventricular). Increases in the adjusted OR for orofacial cleft defects as a group (adjusted OR 1.30, 95% CI 0.75-2.25) and individually for CP, CL and CL/P were not statistically significant. [3]

Huybrechts *et al* showed a statistically significant increase in the risk of oral clefts in infants exposed to ondansetron in the first trimester compared to no ondansetron exposure (adjusted RR 1.24, 95% CI 1.03-1.48). The increase in risk amounted to 3 additional cases per 10,000 infants exposed to ondansetron *in utero*. The study did not examine oral cleft defect subtypes. Increases in cardiac malformation and congenital malformations overall were observed in the unadjusted analyses, but the increases were not preserved when adjusted for covariates (cardiac malformation adjusted RR 0.99, 95% CI 0.93-1.06; congenital malformations overall adjusted RR 1.01, 95% CI 0.98-1.05). [2]

The PRAC reviewed the risk of first trimester ondansetron exposure following publication of the recent studies by Zambelli-Weiner *et al* and Hubrechts *et al*. The PRAC noted that these studies suggest an increased risk for specific structural birth defects in infants exposed to ondansetron in the first trimester of pregnancy, although the data is somewhat conflicting, and the effect estimates are relatively low.

The PRAC recommended that Section 4.6 of the Summary of Product Characteristics should be updated to include the recent epidemiological information, and a statement that ondansetron should not be used during the first trimester of pregnancy.

In response to this recommendation, the UK National Health System's Teratology Information Service (UKTIS), in collaboration with the European Network of Teratology Information Services (ENTIS) issued a statement that they do not support the recommendations made by the PRAC [5]. The statement noted that the background risk for orofacial cleft is 11 per 10,000 pregnancies, which increases to 14 per 10,000 in pregnancies exposed to ondansetron. The UKTIS recommended that ondansetron should be reserved as a second line agent for the treatment of NVP (as is currently recommended in Royal College of Obstetrics and Gynaecology guidelines) and that patients should be adequately counselled about the small increase in risk of orofacial cleft defects that may exist. [34]

In summary, there may be a small increase in the risk of oral cleft defects associated with first-trimester exposure to ondansetron (currently estimated as an additional 3 cases per 10,000 pregnancies). Ondansetron is not approved for the treatment of NVP/HG, but it is recommended in clinical guidelines for treatment of moderate to severe NVP and HG.

The current New Zealand data sheets for ondansetron do not include information from human epidemiological studies on the risk of exposure in pregnancy.

5 ADVICE SOUGHT

The Committee is asked to advise:

- Whether section 4.6 of the New Zealand data sheets for ondansetron products should be updated to include information about the risk of orofacial cleft defects. If so, what information should be included?
- Whether any other action, such as additional monitoring on M^2 is needed.
- Whether any communication on this issue in addition to MARC's Remarks is needed.

6 ANNEXES

1) PRAC Report: *Updated Signal assessment report on birth defects following in-utero exposure during the first trimester of pregnancy arising from recent publications with ondansetron*. 4 July 2019
2) MHRA Medicines Safety Update: *Ondansetron: small increased risk of oral clefts following use in the first 12 weeks of pregnancy.* 27 January 2020
3) Zambelli-Weiner *et al* 2019
4) Huybrechts *et al* 2018
5) UKTIS. *Official Response Statement.* September 2019

7 REFERENCES

1. Medicines and Healthcare products Regulatory Agency (MHRA). 2020. Ondansetron: small increased risk of oral clefts following use in the first 12 weeks of pregnancy. *Drug Safety Update* 13(6): 2. https://www.gov.uk/drug-safety-update/ondansetron-small-increased-risk-of-oral-clefts-following-use-in-the-first-12-weeks-of-pregnancy. (accessed 29 January 2020).
2. Huybrechts KF, Hernández-Díaz S, Straub L, et al. 2018. Association of Maternal First-Trimester Ondansetron Use With Cardiac Malformations and Oral Clefts in Offspring. *JAMA* 320(23): 2429-2437. 10.1001/jama.2018.18307 (1/28/2020).
3. Zambelli-Weiner A, Via C, Yuen M, et al. 2019. First trimester ondansetron exposure and risk of structural birth defects. *Reproductive Toxicology* 83(14-20. https://doi.org/10.1016/j.reprotox.2018.10.010
4. Pharmacovigilance Risk Assessment Committee (PRAC) of the European Medicines Agency (EMA). 2019. *Updated Signal assessment report on birth defects following in-utero exposure during the first trimester of pregnancy arising from recent publications with ondansetron* 4 July 2019. www.ema.europa.eu/en/documents/prac-recommendation/updated-signal-assessment-report-birth-defects-following-utero-exposure-during-first-trimester_en.pdf (accessed 4 February 2020).
5. UK Medicines Information (NHS). 2019. *Ondansetron in pregnancy - updated UK Teratology Information Service (UKTIS) healthcare professional monograph and patient information leaflet* September 2019. www.medicinesresources.nhs.uk/en/Medicines-Awareness/Safety-Alerts/Safety-alerts/Ondansetron-in-pregnancy--updated-UK-Teratology-Information-Service-UKTIS-healthcare-professional-monograph-and-patient-information-leaflet/ (accessed 25 February 2020).
6. Apotex NZ Ltd. 2016. *APO-ONDANSETRON data sheet* 7 December 2016. https://www.medsafe.govt.nz/profs/Datasheet/a/apo-ondansetrontab.pdf (accessed 29 January 2020).
7. Baxter Healthcare Ltd. 2019. *Ondansetron-Baxter* 30 April 2019. https://www.medsafe.govt.nz/profs/Datasheet/o/ondansetronclarisinj.pdf (29 January 2020).
8. Dr Reddy's New Zealand Limited. 2018. *Ondansetron-DRLA tablets and Ondansetron ODT-DRLA tablets* 10 October 2018. https://www.medsafe.govt.nz/profs/Datasheet/o/ondansetronODT-DRLAtab.pdf (accessed 29 January 2020).
9. Fresenius Kabi New Zealand Limited. 2014. *Ondansetron Kabi* 17 January 2014. https://www.medsafe.govt.nz/profs/Datasheet/o/ondansetronkabisol.pdf (29 January 2020).
10. Lowe SA, Bowyer L, Beech A, et al. 2019. *SOMANZ Guideline for the management of nausea and vomiting in pregnancy and hyperemesis gravidarum.* 2019. www.somanz.org/downloads/NVPGUIDELINEFinal.pdf

(accessed 11 February 2020).
11. Taylor LG, Bird ST, Sahin L, et al. 2017. Antiemetic use among pregnant women in the United States: the escalating use of ondansetron. *Pharmacoepidemiology and Drug Safety* 26(5): 592-596. 10.1002/pds.4185
12. IBM Micromedex Corporation. 2020. Ondansetron. In: IBM Micromedex 2020. www.micromedexsolutions.com/home/dispatch (accessed 11 February 2020).
13. Marazita ML. 2012. The Evolution of Human Genetic Studies of Cleft Lip and Cleft Palate. *Annual Review of Genomics and Human Genetics* 13(1): 263-283. 10.1146/annurev-genom-090711-163729
14. Mai CT, Isenburg JL, Canfield MA, et al. 2019. National population-based estimates for major birth defects, 2010-2014. *Birth Defects Res* 111(18): 1420-1435. 10.1002/bdr2.1589

15. Little J, Cardy A and Munger RG. 2004. Tobacco smoking and oral clefts: a meta-analysis. *Bull World Health Organ* 82(3): 213-8.
16. Correa A, Gilboa SM, Besser LM, et al. 2008. Diabetes mellitus and birth defects. *Am J Obstet Gynecol* 199(3): 237 e1-9. 10.1016/j.ajog.2008.06.028
17. Margulis AV, Mitchell AA, Gilboa SM, et al. 2012. Use of topiramate in pregnancy and risk of oral clefts. *Am J Obstet Gynecol* 207(5): 405 e1-7. 10.1016/j.ajog.2012.07.008
18. New Zealand Formulary. 2020. *Sodium valproate* 1 February 2020. https://nzf.org.nz/nzf_2214 (accessed 24 February 2020).
19. Park-Wyllie L, Mazzotta P, Pastuszak A, et al. 2000. Birth defects after maternal exposure to corticosteroids: prospective cohort study and meta-analysis of epidemiological studies. *Teratology* 62(6): 385-92. 10.1002/1096-9926(200012)62:6<385::aid-tera5>3.0.co;2-z
20. Parker SE, Van Bennekom C, Anderka M, et al. 2018. Ondansetron for Treatment of Nausea and Vomiting of Pregnancy and the Risk of Specific Birth Defects. *Obstet Gynecol* 132(2): 385-394. 10.1097/aog.0000000000002679
21. Reefhuis J, Gilboa SM, Anderka M, et al. 2015. The National Birth Defects Prevention Study: A review of the methods. *Birth defects research. Part A, Clinical and molecular teratology* 103(8): 656-669. 10.1002/bdra.23384
22. Slone Epidemiology Centre. *Pregnancy Health Interview Study (Birth Defects Study)* http://www.bu.edu/slone/research/news/ (accessed 20 February 2020).
23. Anderka M, Mitchell AA, Louik C, et al. 2012. Medications used to treat nausea and vomiting of pregnancy and the risk of selected birth defects. *Birth Defects Res A Clin Mol Teratol* 94(1): 22-30. 10.1002/bdra.22865
24. Danielsson B, Wikner BN and Källén B. 2014. Use of ondansetron during pregnancy and congenital malformations in the infant. *Reproductive Toxicology* 50(134-137. https://doi.org/10.1016/j.reprotox.2014.10.017
25. Asker C, Norstedt Wikner B and Kallen B. 2005. Use of antiemetic drugs during pregnancy in Sweden. *Eur J Clin Pharmacol* 61(12): 899-906. 10.1007/s00228-005-0055-1
26. Lavecchia M, Chari R, Campbell S, et al. 2018. Ondansetron in Pregnancy and the Risk of Congenital Malformations: A Systematic Review. *Journal of Obstetrics and Gynaecology Canada* 40(7): 910-918. https://doi.org/10.1016/j.jogc.2017.10.024
27. Pasternak B, Svanström H and Hviid A. 2013. Ondansetron in Pregnancy and Risk of Adverse Fetal Outcomes. *New England Journal of Medicine* 368(9): 814-823. 10.1056/NEJMoa1211035
28. Colvin L, Gill AW, Slack-Smith L, et al. 2013. Off-label use of ondansetron in pregnancy in Western Australia. *Biomed Res Int* 2013(909860. 10.1155/2013/909860
29. Einarson A, Maltepe C, Navioz Y, et al. 2004. The safety of ondansetron for nausea and vomiting of pregnancy: a prospective comparative study. *BJOG* 111(9): 940-3. 10.1111/j.1471-0528.2004.00236.x
30. Kaplan YC, Richardson JL, Keskin-Arslan E, et al. 2019. Use of ondansetron during pregnancy and the risk of major congenital malformations: A systematic review and meta-analysis. *Reproductive Toxicology* 86(1-13. https://doi.org/10.1016/j.reprotox.2019.03.001
31. Fejzo MS, MacGibbon KW and Mullin PM. 2016. Ondansetron in pregnancy and risk of adverse fetal outcomes in the United States. *Reprod Toxicol* 62(87-91. 10.1016/j.reprotox.2016.04.027
32. Van Bennekom CM, Parker SE, Anderka M, et al. 2015. 705. Ondansetron for the treatment of nausea and vomiting of pregnancy and the risk of birth defects. *Pharmacoepidemiol Drug Saf* 24(S1): 401-402. https://onlinelibrary.wiley.com/toc/10991557/2015/24/S1
33. Siu S-SN, Chan MTV and Lau T-K. 2006. Placental Transfer of Ondansetron during Early Human Pregnancy. *Clinical Pharmacokinetics* 45(4): 419-423. 10.2165/00003088-200645040-00006
34. UK Teratology Information Service. 2019. *Official Response Statement* September 2019. www.uktis.org/docs/Ondansetron%20UKTIS%20Response%20Statement.pdf (accessed 25 February 2020).