NICE National Institute for Health and Care Excellence

Evidence review

Doxylamine/pyridoxine (Xonvea) for treating nausea and vomiting of pregnancy

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This evidence review sets out the best available evidence on doxylamine/pyridoxine for treating nausea and vomiting of pregnancy. It should be read in conjunction with the evidence summary, which gives the key messages.

Disclaimer

The content of this evidence review was up-to-date in April 2019. See summaries of product characteristics (SPCs), British national formulary (BNF) or the Medicines and Healthcare products Regulatory Agency (MHRA) or NICE websites for up-to-date information.

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Background

Nausea and vomiting of pregnancy is defined as nausea or vomiting during early pregnancy without other causes. It affects up to 80% of pregnant women and is one of the most common reasons why pregnant women are admitted to hospital, typically for 3 or 4 days. Hyperemesis gravidarum is the most severe form of nausea and vomiting of pregnancy, which affects up to 3.6% of pregnant women. It is diagnosed when weight loss, dehydration and electrolyte imbalances are seen. (Royal College of Obstetricians and Gynaecologists [RCOG], the management of nausea and vomiting of pregnancy and hyperemesis gravidarum).

Nausea and vomiting are not usually associated with poor pregnancy outcomes, and most cases resolve spontaneously within 16 to 20 weeks. If a woman would like to consider treatment, the NICE guideline on antenatal care for uncomplicated pregnancies (currently being updated, publication expected December 2020) advises that ginger, wrist acupressure and antihistamines appear to be effective for reducing symptoms.

The RCOG guideline on managing nausea and vomiting of pregnancy (NICE accredited) recommends the following medicines:

- First line: antihistamines and phenothiazines (cyclizine, prochlorperazine, promethazine or chlorpromazine)
- Second line: metoclopramide, domperidone or ondansetron
- Third line: corticosteroids.

Combinations of medicines can be used in women whose symptoms do not respond to a single anti-emetic. For women with persistent or severe hyperemesis gravidarum, the parenteral or rectal route may be necessary, and more effective than an oral regimen. More information on managing nausea and vomiting of pregnancy can be found in a NICE Clinical knowledge summary and UK Teratology information service monograph on the condition.

This evidence review considers a combination product containing doxylamine and pyridoxine (Xonvea, Alliance Pharmaceuticals), which received a marketing authorisation for treating nausea and vomiting of pregnancy in July 2018.

A similar product has previously been available in the UK. Debendox, which contained doxylamine, pyridoxine and dicyclomine, was marketed by Merrell Dow in 1958. In the early 1970s, a study found that dicyclomine did not contribute to the anti-emetic properties of the combination (the DESI study reported by Zhang et al. 2017) and Debendox (marketed as Bendectin in the US) was reformulated in 1976 to contain doxylamine and pyridoxine only. Around this time, concerns were raised that Debendox might increase the risk of fetal abnormalities. The Committee on Safety of Medicines examined evidence from a large number of epidemiological studies and concluded that, although there had been some reports of congenital malformation associated with Debendox use in early pregnancy, a causal relationship was not established (Current Problems in Pharmacovigilance, July 1981). However, in 1983, Merrell Dow voluntarily withdrew the product from the market for non-medical reasons because of adverse publicity and the burden of litigation. Doxylamine/pyridoxine has not been marketed in the UK since then, although it has been available in Canada since 1979 (as Diclectin) and in the US since 2013 (as Diclegis) for managing nausea and vomiting of pregnancy (UK Public assessment report).

Product overview

Mode of action

Xonvea (Alliance Pharmaceuticals) is a gastro-resistant tablet containing doxylamine succinate 10 mg (a first generation antihistamine that selectively binds H_1 receptors in the brain) and pyridoxine hydrochloride 10 mg (vitamin B6). Its mode of action is not well established because the aetiology of nausea and vomiting of pregnancy is not well known. The delayed action of the product allows the night time dose to work the following morning, when some women may need treatment most (UK Public assessment report).

Regulatory status

Doxylamine/pyridoxine (Xonvea, Alliance Pharmaceuticals) has a marketing authorisation for treating nausea and vomiting of pregnancy in women (aged 18 years or older) who do not respond to conservative management (summary of product characteristics). This was granted in July 2018. The regulatory status of

other antihistamines used in pregnancy is discussed in the likely place in therapy section of this evidence review.

Dosing information

The recommended starting dosage of doxylamine/pyridoxine is 2 tablets (20 mg of each constituent) at bedtime. This may be increased, if needed, to the maximum recommended dosage of 4 tablets daily (1 tablet in the morning, 1 tablet mid-afternoon and 2 tablets at bedtime, total 40 mg daily of each constituent; summary of product characteristics).

Doxylamine/pyridoxine should be taken every day and not on an as needed basis. Continued need for the medicine should be reassessed as the pregnancy progresses. When it is discontinued, the dosage should be tapered gradually to prevent nausea and vomiting returning suddenly.

Effectiveness

This evidence review discusses the best available evidence for doxylamine/pyridoxine (Xonvea) for treating nausea and vomiting of pregnancy. This is:

- a 2-arm randomised, double-blind, placebo controlled trial in 3 centres in the US (DIC-301, Koren et al. 2010)
- an 8-way, randomised, double-blind, placebo controlled trial in 14 centres in the US (the DESI study, reported by Zhang et al. 2017).

Three further papers are included because they report additional data on the study by Koren et al. 2010 (Costantine et al. 2012, Koren et al. 2015 and Koren et al. 2016).

The study by Koren et al. (2010) was undertaken to support the reintroduction of doxylamine/pyridoxine to the market because no randomised controlled trials (RCTs) were undertaken for the original product when it was launched in 1958. Koren et al. (2010) included 256 pregnant women (7–14 weeks of gestation [mean 9.3 weeks], average age 25.5 years) with nausea and vomiting that had not responded to conservative management with dietary and lifestyle advice. The women were

randomised to receive delayed-release doxylamine/pyridoxine (both 10 mg) or placebo for 14 days, starting with a dosage of 2 tablets at night and increasing to a maximum dosage of 4 tablets daily according to response. Symptoms of nausea and vomiting and general wellbeing were evaluated daily using the Pregnancy unique quantification of emesis (PUQE) score and information was collected by the women in daily diaries.

The DESI study reported by Zhang et al. (2017) was undertaken in 1975 as part of the FDA's Drug Efficacy Study Implementation (DESI) program to evaluate the relative efficacy of doxylamine, pyridoxine and dicyclomine for managing nausea and vomiting of pregnancy. The study was not published because it was an FDA regulatory study for which publication was not routine at that time; therefore, Zhang et al. (2017) made freedom of information requests to obtain the data and publish the study's findings for the Restoring invisible and abandoned trials initiative. The DESI study included 2,308 pregnant women in the first 12 weeks of gestation (baseline characteristics not reported) with nausea or vomiting who were able to complete questionnaires. Women were randomised to the following groups:

- placebo
- dicyclomine 10 mg
- doxylamine 10 mg
- pyridoxine 10 mg
- dicyclomine/doxylamine (both 10 mg)
- dicyclomine/pyridoxine (both 10 mg)
- doxylamine/pyridoxine (both 10 mg)
- dicyclomine/doxylamine/pyridoxine (all 10 mg).

They were asked to take 2 tablets at bedtime and, if necessary, 1 additional tablet in the morning and mid-afternoon for 7 nights. Reported outcomes included doctors' judgements of efficacy in terms of improvement in nausea and vomiting, and frequency of nausea and vomiting recorded in participants' diaries. Results for treatment arms containing dicyclomine are not reported in this evidence review.

This evidence review considers the evidence for the combination treatment and its licensed indication, and does not include studies that considered other strengths and

dosages of doxylamine and pyridoxine (used alone or in combination) or other indications. For example, it does not consider pre-emptive use of doxylamine/pyridoxine in women who suffered nausea and vomiting in a previous pregnancy.

Appendix A summarises details of the included studies. Appendix B gives an overview of the results for clinical effectiveness. Appendix E gives details of studies identified in the literature search that were then excluded.

Improvement in PUQE symptom score

In the study by Koren et al. (2010), there were improvements from baseline in PUQE symptom scores (the primary outcome) in both groups at day 15, showing improvement in the symptoms of nausea and vomiting. The mean improvement in the doxylamine/pyridoxine group was −4.8 and the mean change in the placebo group was −3.9. The difference between the 2 groups was small but statistically significant (−0.9 point on a scale from 3 to 15 points, p=0.006). On average, symptoms were moderate in both groups at baseline (mean PUQE score about 9) and became mild with treatment (PUQE scores around 4 and 5 in the doxylamine/pyridoxine and placebo groups respectively).

Post hoc analyses (Koren et al. 2016) considered the changes from baseline in PUQE scores at days 3, 4 and 5 to assess the efficacy of doxylamine/pyridoxine compared with placebo at an earlier stage in the study and determine the impact of any natural course of improvement in nausea and vomiting of pregnancy. Doxylamine/pyridoxine improved mean symptom scores more than placebo at day 3 (difference −1.0, p=0.002), day 4 (difference −1.1, p<0.001) and day 5 (difference −1.0, p=0.006).

It is unclear how many points on the PUQE scale constitute a clinically meaningful improvement. However, according to the MHRA, the small but statistically significant differences in PUQE scores seen with doxylamine/pyridoxine compared with placebo at all time points in this study represent improvements that are clinically important for pregnant women suffering from nausea and vomiting of pregnancy (UK public assessment report).

Percentage improvement in symptoms

The DESI study reported by Zhang et al. (2017) predates the PUQE score and used doctors' and women's assessments rather than a validated scale to assess nausea and vomiting. Over 7 days, statistically significant improvements in symptoms were seen with doxylamine/pyridoxine compared with placebo in most evaluations:

- Doctors' evaluations of effectiveness (78% compared with 57%, p<0.01)
- Doctors' evaluations of improvement in nausea (75% compared with 52%, p<0.001)
- Doctors' evaluations of improvement in vomiting (73% compared with 66%, p=0.17, not statistically significant)
- Women's evaluations of reduction in nausea (64% compared 31%, p<0.01)
- Women's evaluations of at least 5 treatment days with no vomiting (48% compared with 28%, p<0.01).

Doxylamine/pyridoxine was not directly compared with doxylamine or pyridoxine alone. However, based on comparisons with placebo, doxylamine was considered to be the most effective of the active ingredients assessed for treating nausea and vomiting, and pyridoxine had an added effect on nausea. Dicyclomine was found to be ineffective for either nausea or vomiting in this study (UK public assessment report).

Improvement in global assessment of wellbeing

In Koren et al. (2010), global assessment of wellbeing (a second primary outcome) improved in both groups. Between baseline and day 15, the mean global assessment of wellbeing score increased by 2.8 with doxylamine/pyridoxine and by 1.8 with placebo. The difference between the 2 groups was small but statistically significant (1.0 point on a scale from 0 to 10 points, p=0.005).

Time lost from employment

The mean time lost from employment in Koren et al. (2010) did not differ significantly between the groups after 14 days' treatment (0.92 days with doxylamine/pyridoxine compared with 2.37 days with placebo, p=0.06). This result is of borderline statistical

significance and it is possible it would have become statistically significant if treatment outcomes had been assessed over a longer period of time.

Compassionate use of study medicine

After 14 days, in Koren et al. (2010), women were offered compassionate use of the treatment they had received in the study. Significantly more women taking doxylamine/pyridoxine asked to continue compassionate use of their medication compared with women taking placebo (48.9% compared with 32.8%, p=0.009).

Use of alternative therapies

Koren et al. (2010) recorded the number of women who also used other treatments for nausea and vomiting of pregnancy; for example, nutritional changes, teas, aromatherapy, massage and yoga. Significantly fewer women taking doxylamine/pyridoxine used alternative therapies compared with placebo (23.7% compared with 36.8% respectively, p=0.04).

Rates of hyperemesis gravidarum

No women in either treatment group in Koren et al. (2010) reported hyperemesis gravidarum during the study (UK public assessment report).

Safety

The safety profile of doxylamine/pyridoxine is considered to be reasonably well established. Based on clinical trial experience, the most common adverse reactions (at least 1 in 100) are somnolence, dizziness, dry mouth and fatigue (summary of product characteristics).

In the study by Koren et al. (2010), there were no statistically significant differences between doxylamine/pyridoxine and placebo in the rates of any adverse events. In the doxylamine/pyridoxine group, 30.5% of women experienced at least 1 treatment related adverse event compared with 25.2% of women in the placebo group (p=0.34, Koren et al. 2015). Somnolence (14.5% and 12.0% respectively, p=0.54) and headache (13.0% and 16.0% respectively, p=0.51) were the most common treatment emergent adverse events in both groups.

Overall, in the study by Koren et al. (2010), 11 women stopped their study treatment because of adverse events (6 [4.5%] taking doxylamine/pyridoxine and 5 [3.9%] taking placebo).[1] Of these, 7 non-serious events were considered treatment related, including somnolence, syncope, and dizziness in 4 women treated with doxylamine/pyridoxine, and dyspepsia, somnolence and abdominal pain for 3 women treated with placebo. The other 4 events were serious (2 in each group including missed and spontaneous abortion); however, 3 were considered unrelated to study treatment and 1 was considered unlikely to be related to study treatment (UK public assessment report).

The DESI study reported by Zhang et al. (2017) found that 8.6% of women taking doxylamine/pyridoxine experienced adverse events compared with 11.1% of women taking placebo (no statistical analysis). No serious adverse events were reported for any of the treatments used in the study. The most common adverse event with doxylamine/pyridoxine was drowsiness (5.6% compared with 3.0% for placebo, no statistical analysis).

The UK Public assessment report states that there are extensive post marketing clinical data for other brands of doxylamine/pyridoxine, and that its components have been used for treating nausea and vomiting for over 55 years in over 33 million pregnancies. The report also notes that numerous published clinical data have demonstrated the safety and tolerability of doxylamine/pyridoxine for pregnant women. In addition, this product combination has been the subject of many epidemiological studies designed to detect possible teratogenicity, and the results from these studies show no association with fetal abnormalities. The UK Teratology Information Service monograph on doxylamine/pyridoxine states that this combination of medicines has been widely studied, with no evidence of an increased risk of congenital malformations.

Appendix B gives details of the results for safety and tolerability from the included studies.

[1] These data differ slightly in Koren et al. (2015), which reported that 6 women taking doxylamine and 4 women taking placebo stopped treatment because of adverse events.

Person-related factors

Some antihistamines and phenothiazines are licensed for treating nausea and vomiting. However, they are not specifically licensed for treating nausea and vomiting of pregnancy and carry warnings about use in pregnancy that may alarm some women if they have not been counselled. NICE and RCOG guidelines recommend antihistamines and phenothiazines for treating nausea and vomiting of pregnancy, and there is extensive clinical experience of their use. However, some women may prefer to take doxylamine/pyridoxine because it is specifically licensed for use in pregnant women.

It is not known whether doxylamine/pyridoxine is more effective than an antihistamine alone or a phenothiazine, and some women may prefer to try a single treatment before they try a combination of 2 treatments.

Almost two thirds of people in the study by Koren et al. (2010) took the maximum dosage of doxylamine/pyridoxine (4 tablets daily). Some women might prefer to take a tablet that only needs taking once or twice daily. Doxylamine/pyridoxine should be taken every day, but some women may prefer a treatment that can be used on an as needed basis.

Some women with nausea and vomiting of pregnancy may be worried that they might not be able to swallow a tablet without vomiting. Doxylamine/pyridoxine is an oral delayed-release formulation that is taken at night before going to sleep and works the following morning, when some women may need treatment most (UK Public assessment report). Some other treatments are available as suppositories and injections, and are options that some women may prefer.

Evidence strengths and limitations

The study by Koren et al. (2010) has some limitations. For example, the study duration was 15 days only, although serious adverse events were checked after a further 30 days. Nausea and vomiting of pregnancy can last longer than this, and 41% of women (105/256) asked for compassionate use of their study treatment after the study period and adverse events were recorded. The PUQE symptom and

wellbeing scores are subjective, based on women's records in daily diaries, and it is unclear how large improvements need to be to be considered clinically important.

Questions have been raised about the methods and results of the study by Koren et al. (2010), suggesting that doxylamine/pyridoxine has no clinically important benefit over placebo (Persaud et al. 2018). However, during the licensing process, the MHRA asked the manufacturer to reanalyse the results for the primary outcomes using a different population and different method for handling missing data, and the results were found to be consistent with the primary analyses. The MHRA concluded that, although the difference between the groups was small, it could represent a change from 3 hours of nausea per day with placebo to only 1 hour or less with doxylamine/pyridoxine. They considered this is clinically meaningful for pregnant women with nausea and vomiting of pregnancy, and positively influences quality of life (UK Public assessment report).

The DESI study (reported by Zhang et al. 2017) was undertaken in 1975 and, therefore, predated trial reporting guidelines. Zhang et al. (2017) found information about the study was incomplete; for example, limited baseline data were available and statistical methods, including sample size calculation, were not reported. Only woman who were able to complete questionnaires were included, which may have caused selection bias. The study predated the PUQE score and, therefore, used doctors' and women's subjective assessments rather than a validated scale to assess nausea and vomiting.

The DESI study has important limitations because the final results of the study are not published; data from only two thirds of recruited individuals were analysed (the per protocol population) although the follow up period was only 1 week; and few details about outcome determination or statistical analyses are available. Zhang et al. (2017) noted that the integrity of the data is questionable because data from at least 1 investigator were subsequently excluded for reasons including 'data recording in absence of patient visits'. Although the study appears to be applicable to the medicine and population being assessed, the product used in this study is a different formulation from Xonvea. Nevertheless, the MHRA concluded that the results of the DESI study appear to show that doxylamine and pyridoxine both contribute to the clinical effects of the fixed-dose combination.

There are no studies comparing doxylamine/pyridoxine to other active treatments for nausea and vomiting of pregnancy. There is a small study comparing its components (at different dosages from those in the combination product) with ondansetron (Oliveira et al. 2014) but this was excluded because it is outside the scope of this evidence review.

The included studies do not provide any data on subgroups of women with different severities of nausea and vomiting of pregnancy (including hyperemesis gravidarum), or women who experienced the condition in a previous pregnancy. The mean PUQE score was 9 at baseline in Koren et al. (2010), which is considered moderate according to the scoring system. Women with PUQE scores of less than 6 (mild symptoms) were excluded from the study.

When they assessed doxylamine/pyridoxine, the MHRA considered that, although the results of the key study by Koren et al. (2010) were statistically significant, they were largely borderline. However, they concluded that, overall, the evidence from the clinical studies, additional analyses, literature review and current clinical use is sufficient to support the efficacy of doxylamine/pyridoxine for treating nausea and vomiting of pregnancy in women who do not respond to conservative management (UK public assessment report).

The UK public assessment report notes that no information is available on using doxylamine/pyridoxine in pregnant females aged less than 18 years, breast-feeding women, or women with hepatic or renal impairment.

Appendix C summarises the quality assessment of the included studies.

Resource impact

The cost of 20 doxylamine/pyridoxine tablets is £28.50 (BNF, February 2019). A pack of 20 tablets would be expected to last 5 to 10 days depending on the dosage needed (2–4 tablets daily) to manage the woman's nausea and vomiting.

Nausea and vomiting of pregnancy usually starts between the 4th and 7th weeks of gestation, peaks between the 9th and 16th weeks, and resolves by around the 20th week (RCOG, The management of nausea and vomiting of pregnancy and

hyperemesis gravidarum). Over the treatment period in the study by Koren et al. (2010), 19% of women took 2 tablets daily, 21% took 3 tablets daily and 60% took 4 tablets daily (summary of product characteristics). Treatment for 6 to 8 weeks would cost about £240 to £320 if 4 tablets were taken each day.

The costs per tablet of many treatments that are currently used for nausea and vomiting of pregnancy are much less; for example, cyclizine, prochlorperazine and promethazine. However, this does not take into account factors such as therapeutic equivalence. See the resource impact assessment accompanying this evidence review for a more detailed assessment of the budget impact of this medicine.

Likely place in therapy

The RCOG guideline on the management of nausea and vomiting of pregnancy and hyperemesis gravidarum states that the condition may reduce quality of life, impairing a woman's ability to function on a day-to-day basis, and negatively affecting relationships with her partner and family. Persistent nausea is the symptom that most adversely affects quality of life. Therefore, it is important to ensure it is well managed.

The NICE guideline on antenatal care for uncomplicated pregnancies advises that ginger, wrist acupressure and antihistamines may be effective for reducing symptoms of nausea and vomiting of pregnancy. The RCOG guideline also recommends phenothiazines first line.

The MHRA has advised (personal communication: February 2019) that use of antihistamines or phenothiazines for nausea and vomiting of pregnancy is not off-label because they are not contraindicated in pregnancy. (The exception to this is Buccastem M, which is contraindicated in pregnancy.) However, their summaries of product characteristics advise caution in pregnancy, which may alarm women if it is not discussed with them.

Doxylamine/pyridoxine provides another option, which is specifically licensed for treating nausea and vomiting of pregnancy that has not responded to conservative management. As well as ginger and acupressure, conservative management may include (NICE clinical knowledge summary on nausea and vomiting of pregnancy):

- rest
- avoiding foods or smells that trigger symptoms (for example, spicy or fatty foods, or hot meals)
- eating plain biscuits or crackers in the morning before getting up
- eating bland, small, frequent meals low in carbohydrate and fat but high in protein
- drinking little and often rather than large amounts.

The MHRA has advised (personal communication: February 2019) that because of prescribing hierarchy, the use of other medicines that do not have a specific licence for nausea and vomiting of pregnancy over doxylamine/pyridoxine, which does, would need to be justified. Although antihistamines and phenothiazines are not specifically licensed for treating nausea and vomiting of pregnancy, their use is established in clinical practice and most have been used in pregnancy without any known adverse effects on the developing baby (UK Teratology Information Service, Treating nausea and vomiting of pregnancy). Product literature for many of these medicines advises caution in pregnancy, which should be discussed with pregnant women before they are prescribed. Some prescribers and women may prefer doxylamine/pyridoxine because it is specifically licensed for use in pregnant women.

There is no evidence to show how the safety and efficacy of doxylamine/pyridoxine compares with current first line treatment options such as antihistamines and phenothiazines.

Second line options recommended by RCOG include metoclopramide, domperidone and ondansetron. As well as these treatments not being licensed specifically for use in nausea and vomiting of pregnancy, they should be taken for a short period only, which may not be long enough to manage this condition. The MHRA has advised that metoclopramide should be prescribed for up to 5 days only because of the risk of neurological adverse effects such as short-term extrapyramidal disorders and tardive dyskinesia. Similarly, the maximum treatment duration of domperidone should not usually exceed 1 week because of the risk of serious cardiac adverse effects. When prescribed for the licensed indications, ondansetron should be used for up to 5 days only.

Before any treatment is prescribed, the possible risks to the mother and developing baby should be discussed with the woman and balanced against the benefits. Information on medicines in pregnancy is available from the UK Teratology Information Service and the associated website BUMPS (best use of medicines in pregnancy).

Development of the evidence review

Process

The evidence summary: process guide sets out the process NICE uses for evidence summaries and details how the summaries are developed, quality assured and approved for publication.

Expert advisers and declarations of interest

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Terms used in this evidence review

Pregnancy unique quantification of emesis (PUQE) score

A scale used to evaluate the severity of nausea and vomiting of pregnancy. The symptom domain of the PUQE score incorporates the number of daily vomiting episodes, the number of daily retching episodes, and the length of daily nausea in hours, for an overall score of symptoms rated from 3 (no symptoms) to 15 (most severe symptoms). A PUQE score of 3 to 6 is considered mild, 7 to 12 is considered moderate and 13 to 15 is considered severe.

The quality of life domain of the PUQE score incorporates women's report of their present wellbeing from 0 (worst possible) to 10 (best possible).

The PUQE symptom and wellbeing scores are subjective, based on women's records in daily diaries, and it is unclear how many points on the scales constitute clinically meaningful improvements.

Appendices

Appendix A: Summary of included studies

Study	Number of participants	Population	Intervention	Comparison	Primary outcome	Major limitations
Koren et al. 2010 Double-blind RCT 3 US centres	n=256	Pregnant women aged 18 years and over (average age 25.5 years), with single pregnancies of 7–14 weeks' gestation (mean 9.3 weeks), with NVP that had not responded to conservative management with dietary and lifestyle advice and a PUQE score[a] of at least 6 (mean 8.9, moderate)	Doxylamine succinate 10 mg and pyridoxine hydrochloride 10 mg[b] (n=131)	Placebo (n=125)[b]	Change from baseline in each of the 2 domains of the PUQE score[a], which are severity of symptoms and general wellbeing	The study duration was 15 days only, although NVP can last longer than this. However, adverse events were monitored over a longer period (serious adverse events were checked after a further 30 days and some women opted for compassionate use of their study treatment after the study period and adverse events were recorded)
DESI study reported by Zhang et al. 2017 Double-blind RCT undertaken in 1975[c]	n=1,599[d]	Pregnant women[e] in the first 12 weeks of gestation with NVP and who were able to complete questionnaires	Women were randomised to 1 of the following 8 groups: • placebo (n=181) • dicyclomine 10 mg (n=203) • doxylamine 10 mg (n=209) • pyridoxine 10 mg (n=191) • dicyclomine/doxylamine (both 10 mg, n=218) • dicyclomine/pyridoxine (both 10 mg, n=195)		No outcomes were prespecified and the study protocol does not indicate which outcome was the primary outcome[g]	The study predated trial reporting guidelines. Limited baseline data were available and statistical methods, including sample size calculation were not reported. Only woman who were able to complete questionnaires were

Study	Number of participants	Population	Intervention	Comparison	Primary outcome	Major limitations
14 US centres			• doxylamine/pyridoxine (both 10 mg, n=213) • dicyclomine/doxylamine/pyridoxine (all 10 mg, n=189)[f]			included, which may have caused selection bias. The study predated the PUQE score and, therefore, used doctors' and women's subjective assessments rather than a validated scale to assess nausea and vomiting. Data from only two thirds of recruited individuals were analysed (the per protocol population) although the follow up period was only 1 week. Zhang et al. (2017) noted that the integrity of the data is questionable because data from at least 1 investigator were subsequently excluded for reasons including 'data recording in absence of patient visits'.

References:

Koren G, Clark S, Hankins GDV et al. (2010) Effectiveness of delayed-release doxylamine and pyridoxine for nausea and vomiting of pregnancy: a randomized placebo controlled trial. American Journal of Obstetrics and Gynecology 203(6): 571.e1–7

Zhang R, and Persaud N (2017) 8-way randomized controlled trial of doxylamine, pyridoxine and dicyclomine for nausea and vomiting during pregnancy: restoration of unpublished information. PloS one 12(1): e0167609

[a] See terms used in this evidence review for full definition of PUQE score

[b] Xonvea formulation. The dosage was 2 tablets at night, increasing when indicated to the maximum dosage of 4 tablets daily according to the timing, duration, severity and frequency of symptoms. Treatment was taken for 14 days

[c] The DESI study reported by Zhang et al. was undertaken in 1975 as part of the FDA's Drug Efficacy Study Implementation program to evaluate the relative efficacy of doxylamine, pyridoxine, and dicyclomine for managing nausea and vomiting of pregnancy. The study was not published at that time;

Study	Number of participants	Population	Intervention	Comparison	Primary outcome	Major limitations
therefore, Zhang et al. made freedom of information requests to obtain the data and publish the study's findings for the Restoring invisible and abandoned trials initiative [d] 2,359 women were originally randomised but 51 (2.1%) were excluded because of incomplete data, 132 (5.6%) were lost to follow up and 709 (30.0%) dropped out and were excluded from analyses (reasons included lack of efficacy, adverse effects and loss of symptoms) [e] Limited baseline data were available [f] Bendectin formulation (marketed as Debendox in the UK and withdrawn in 1983). The formulation of this product was different from the delayed-release formulation assessed by Koren et al. 2010, which is Xonvea (marketed as Diclectin in Canada). The dosage was 2 tablets at bedtime and, if necessary, 1 additional tablet in the morning and mid-afternoon. Treatment was taken for 7 nights. Results are not reported in this evidence review for treatment arms containing dicyclomine [g] Outcomes included doctors' judgements of efficacy in terms of improvement in nausea and vomiting, and frequency of nausea and vomiting recorded in participants' diaries						
Abbreviations: NVP, nausea and vomiting of pregnancy; PUQE, pregnancy unique quantification of emesis (the symptom score ranges from 3 to 15 with higher scores indicating the most severe symptoms and the general wellbeing domain ranges from 1 to 10 with higher scores indicating better general wellbeing); RCT, randomised controlled trial						

Appendix B: Results tables

Koren et al. 2010

	Doxylamine/pyridoxine	Placebo	Analysis
n	**131**	**125**	
Primary outcomes			
Mean difference in PUQE symptom score[a] from baseline to day 15 (±SD)	−4.8 (±2.7) from baseline of 9.0 (±2.1)	−3.9 (±2.6) from baseline of 8.8 (±2.1)	Doxylamine/pyridoxine was better than placebo Difference −0.9, p=0.006, statistically significant
Mean difference in PUQE global assessment of general well-being[a] from baseline to day 15 (±SD)	2.8 (±2.8) from baseline of 5.0 (±2.3)	1.8 (±2.2) from baseline of 5.4 (±2.2)	Doxylamine/pyridoxine was better than placebo Difference 1.0, p=0.005, statistically significant
Selected secondary outcomes			
Days lost from employment	0.92 (±3.86)	2.37 (±10.23)	Doxylamine/pyridoxine did not differ from placebo Difference 1.45, p=0.06, no significant difference
Number of women asking for compassionate use of study medicine after day 14	64/131 (48.9%)	41 (32.8%)	Doxylamine/pyridoxine was better than placebo Difference 23 (16.1%), p=0.009, statistically significant
Number of women using alternate therapies	31/131 (23.7%)	46/125 (36.8%)	Doxylamine/pyridoxine was better than placebo Difference 15 (13.1%), p=0.04, statistically significant
Adherence to study medication[b]	90.0% (±14.5%)	86.5% (±18.2%)	Difference 3.5%, p=0.08, no significant difference
Mean difference in PUQE symptom score[a] from baseline to day 3 (±SD)[c]	−3.1 (±2.7)	−2.1 (±2.4)	Doxylamine/pyridoxine was better than placebo Difference −1.0, p=0.002, statistically significant
Mean difference in PUQE symptom score[a] from baseline to day 4 (±SD)[c]	−3.6 (±2.5)	−2.5 (±2.2)	Doxylamine/pyridoxine was better than placebo Difference −1.1, p<0.001, statistically significant
Mean difference in PUQE symptom score[a] from baseline to day 5 (±SD)[c]	−4.0 (±2.5)	−3.0 (±2.4)	Doxylamine/pyridoxine was better than placebo Difference −1.0, p=0.006, statistically significant

	Doxylamine/pyridoxine	Placebo	Analysis
Safety and tolerability outcomes			
n	**131**	**125 or 127**[e]	
Number of women with at least 1 treatment emergent adverse event[e]	74/131 (56.5%)	65/127 (51.2%)	Doxylamine/pyridoxine did not differ from placebo p=0.40, no significant difference
Number of women with at least 1 treatment related adverse event[d]	40/131 (30.5%)	32/127 (25.2%)	Doxylamine/pyridoxine did not differ from placebo p=0.34, no significant difference
Number of women who stopped treatment because of adverse events[e]	6/131 (4.6%)	4/127 (3.1%)	Doxylamine/pyridoxine did not differ from placebo p=0.75, no significant difference
Number of women with somnolence	19/131 (14.5%)	15/125 (12.0%)	Doxylamine/pyridoxine did not differ from placebo p=0.54, no significant difference
Number of women with dry mouth	4/131 (3.0%)	1/125 (0.8%)	Doxylamine/pyridoxine did not differ from placebo p=0.37, no significant difference
Number of women with hypersensitivity	1/131 (0.8%)	0/125 (0%)	Doxylamine/pyridoxine did not differ from placebo p>0.99, no significant difference
Number of women with dizziness	8/131 (6.1%)	8/125 (6.4%)	Doxylamine/pyridoxine did not differ from placebo p=0.94, no significant difference
Number of women with headache	17/131 (13.0%)	20/125 (16.0%)	Doxylamine/pyridoxine did not differ from placebo p=0.51, no significant difference
Number of women with loss of consciousness	0/131 (0%)	1/125 (0.8%)	Doxylamine/pyridoxine did not differ from placebo p=0.49, no significant difference

[a] See terms used in this evidence review for full definition of PUQE score

[b] Prespecified analysis reported in Costantine et al. 2012. Overall adherence was calculated by counting the number of tablets remaining at day 14 compared with the number of tablets that were prescribed throughout the study

Costantine MM, Matok I, Chiossi G et al. (2012) Determinants of adherence to delayed-release doxylamine and pyridoxine in patients with nausea and vomiting of pregnancy. Therapeutic drug monitoring 34(5): 569–73

[c] Post hoc secondary analyses of PUQE scores were reported in Koren et al. 2016. Scores were not available for all women at all time points and the number of women in each analysis is less than for the full ITT population (minimum 112 women)

	Doxylamine/pyridoxine	Placebo	Analysis
Koren G, Clark S, Hankins GDV et al. (2016) Demonstration of early efficacy results of the delayed-release combination of doxylamine-pyridoxine for the treatment of nausea and vomiting of pregnancy. BMC pregnancy and childbirth 16(1): 371			
[d] Secondary analyses of adverse events were reported in Koren et al. 2015. It is unclear whether these analyses were prespecified and why the number of women in the analyses differs slightly between the papers			
Koren G, Clark S, Hankins GDV et al. (2015) Maternal safety of the delayed-release doxylamine and pyridoxine combination for nausea and vomiting of pregnancy; a randomized placebo controlled trial. BMC pregnancy and childbirth 15: 59			
Abbreviations: ITT, intention-to-treat; p, p value, PUQE, pregnancy unique quantification of emesis (the symptom score ranges from 3 to 15 with higher scores indicating the most severe symptoms and the general wellbeing domain ranges from 1 to 10 with higher score indicating better general wellbeing); SD, standard deviation			

Zhang et al. 2017

	Doxylamine/pyridoxine	Doxylamine	Pyridoxine	Placebo	Analysis
n	**213**	**209**	**191**	**181**	
Efficacy outcomes[a]					
Percentage of women in whom the effectiveness of medication was considered moderate or excellent based on doctors' evaluations	78%	77%	66%	57%	Doxylamine/pyridoxine and doxylamine alone were better than placebo Difference 21% and 20% respectively, both p<0.01, statistically significant Pyridoxine alone did not differ from placebo Difference 9%, p=0.10, no significant difference
Percentage of women whose nausea improved based on doctors' evaluations	75%	69%	68%	52%	All 3 active treatments were better than placebo Difference 23%, 17% and 16% respectively, all p<0.01, statistically significant
Percentage of women whose vomiting improved based on doctors' evaluations[b]	73%	78%	66%	66%	Doxylamine alone was better than placebo Difference 12%, p=0.01, statistically significant

	Doxylamine/pyridoxine	Doxylamine	Pyridoxine	Placebo	Analysis
					Doxylamine/pyridoxine and pyridoxine alone did not differ from placebo Difference 7% and 0% respectively, p=0.17 and p=0.36 respectively, no significant difference
Percentage reduction in nausea from baseline based on patient diaries	64%	56%	35%	31%	Doxylamine/pyridoxine and doxylamine alone were better than placebo Difference 33% and 25%, both p<0.01, statistically significant Pyridoxine alone did not differ from placebo Difference 4%, p=0.09, no significant difference
Percentage of women with no vomiting on at least 5 treatment days based on patient diaries [b]	48%	54%	29%	28%	Doxylamine/pyridoxine and doxylamine alone were better than placebo Difference 20% and 26%, both p<0.01, statistically significant Pyridoxine alone did not differ from placebo Difference 1%, p=0.37, no significant difference
Safety and tolerability outcomes					
n	**267**	**273**	**272**	**270**	
Adverse events	23/267 (8.6%)	41/273 (15.0%)	26/272 (9.6%)	30/270 (11.1%)	Not reported
Drowsiness	15/267 (5.6%)	14/273 (5.1%)	3/272 (1.1%)	8/270 (3.0%)	Not reported
Fatigue	2/267 (0.7%)	6/273 (2.2%)	1/272 (0.4%)	3/270 (1.1%)	Not reported
Headache	2/267 (0.7%)	6/273 (2.2%)	5/272 (1.8%)	4/270 (1.5%)	Not reported

[a] The study protocol does not indicate which outcome was the primary outcome. Only selected outcomes have been reported in this evidence review and results for treatment arms containing dicyclomine are not listed

[b] The analysis of vomiting includes only women with vomiting symptoms at baseline. Numbers not reported

	Doxylamine/pyridoxine	Doxylamine	Pyridoxine	Placebo	Analysis

Abbreviations: ITT, intention-to-treat; p, p value, PUQE, pregnancy unique quantification of emesis (the symptom score ranges from 3 to 15 with higher scores indicating the most severe symptoms and the general wellbeing domain ranges from 1 to 10 with higher score indicating better general wellbeing); SD, standard deviation

Appendix C: Quality assessment of included studies

Quality assessment question	Koren et al. 2010
Did the trial address a clearly focused issue?	Yes
Was the assignment of patients to treatments randomised?	Yes[a]
Were patients, health workers and study personnel blinded?	Yes[b]
Were the groups similar at the start of the trial?	Yes
Aside from the experimental intervention, were the groups treated equally?	Yes
Were all of the patients who entered the trial properly accounted for at its conclusion?	Yes
How large was the treatment effect?	See results table
How precise was the estimate of the treatment effect?	See results table
Can the results be applied in your context? (or to the local population)	Yes
Were all clinically important outcomes considered?	No[c]
Are the benefits worth the harms and costs?	See overview
[a] Study sites randomised participants using an interactive voice response system. Although not reported, it is likely that allocation was concealed	
[b] The study was reportedly double-blind; The manufacturer has confirmed that the placebo was identical to doxylamine/pyridoxine	
[c] Outcomes such as freedom from symptoms and rate of hyperemesis gravidarum were not considered, nor was teratogenicity, although this would not be possible in this type of study	
Checklist used: CASP RCT checklist	

Quality assessment question	Zhang et al. 2017
Did the trial address a clearly focused issue?	Yes
Was the assignment of patients to treatments randomised?	Yes[a]
Were patients, health workers and study personnel blinded?	Yes[b]
Were the groups similar at the start of the trial?	Unclear[c]
Aside from the experimental intervention, were the groups treated equally?	Unclear[d]
Were all of the patients who entered the trial properly accounted for at its conclusion?	Unclear[d]
How large was the treatment effect?	See results table
How precise was the estimate of the treatment effect?	See results table
Can the results be applied in your context? (or to the local population)	Unclear[e]
Were all clinically important outcomes considered?	No[f]
Are the benefits worth the harms and costs?	See overview

Quality assessment question	Zhang et al. 2017
[a] To ensure allocation concealment, a centralised service was used	
[b] Medications were identical in appearance and had the coating used for Bendectin (dicyclomine/doxylamine/pyridoxine). Participants, investigators and doctors were blinded	
[c] Little information is available for baseline characteristics, although severity of nausea and vomiting appears to have been similar across the groups	
[d] The DESI study was not published when it was undertaken because it was an FDA regulatory study for which publication was not routine at that time. Some data are incomplete. Data from only two thirds of recruited individuals were analysed (the per protocol population) although the follow up period was only 1 week	
[e] Although the study appears to be applicable to the medicine and population being assessed, the product used in this study is a different formulation of doxylamine/pyridoxine from Xonvea	
[f] Outcomes such as rate of hyperemesis gravidarum and quality of life were not considered, nor was teratogenicity, although this would not be possible in this type of study	
Checklist used: CASP RCT checklist	

Appendix D: Literature search strategy

Database search strategies

Database: Medline

Platform: Ovid
Version: Ovid MEDLINE(R) ALL <1946 to January 04, 2019>
Search date: 7th Jan 19
Number of results retrieved: 120
Search strategy:

Database: Ovid MEDLINE(R) ALL <1946 to January 04, 2019>
---
1 exp Morning Sickness/ (1687)
2 morning sick*.tw. (239)
3 (pregnan* adj5 (sick* or nause* or vomit*)).tw. (2044)
4 (emes* or emet* or hypereme*).tw. (12787)
5 Pregnancy/ (833044)
6 Pregnant Women/ (7124)
7 5 or 6 (833523)
8 nausea/ or vomiting/ (28643)
9 7 and 8 (2040)
10 or/1-4,9 (16070)
11 Doxylamine/ (369)
12 PYRIDOXINE/ (7555)
13 11 and 12 (216)
14 (doxylamine and pyridoxine).tw. (79)
15 (xonvea or diclectin or diclegis or debendox or benedectin or bendectin or lenotan or merbental).tw. (176)
16 or/13-15 (275)
17 10 and 16 (124)
18 limit 17 to english language (120)

Database: Medline in-process

Platform: Ovid
Version: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations <January 04, 2019>
Search date: 7th Jan 19
Number of results retrieved: 3
Search strategy:

Database: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations <January 04, 2019>
---
1 exp Morning Sickness/ (0)
2 morning sick*.tw. (26)
3 (pregnan* adj5 (sick* or nause* or vomit*)).tw. (202)
4 (emes* or emet* or hypereme*).tw. (1090)

5 Pregnancy/ (0)
6 Pregnant Women/ (0)
7 5 or 6 (0)
8 nausea/ or vomiting/ (0)
9 7 and 8 (0)
10 or/1-4,9 (1267)
11 Doxylamine/ (0)
12 PYRIDOXINE/ (0)
13 11 and 12 (0)
14 (doxylamine and pyridoxine).tw. (9)
15 (xonvea or diclectin or diclegis or debendox or benedectin or bendectin or lenotan or merbental).tw. (8)
16 or/13-15 (16)
17 10 and 16 (3)
18 limit 17 to english language (3)

Database: Medline epubs ahead of print

Platform: Ovid
Version: Ovid MEDLINE(R) Epub Ahead of Print <January 04, 2019>
Search date: 7th Jan 19
Number of results retrieved: 0
Search strategy:
Database: Ovid MEDLINE(R) Epub Ahead of Print <January 04, 2019>
---
1 exp Morning Sickness/ (0)
2 morning sick*.tw. (1)
3 (pregnan* adj5 (sick* or nause* or vomit*)).tw. (21)
4 (emes* or emet* or hypereme*).tw. (171)
5 Pregnancy/ (0)
6 Pregnant Women/ (0)
7 5 or 6 (0)
8 nausea/ or vomiting/ (0)
9 7 and 8 (0)
10 or/1-4,9 (188)
11 Doxylamine/ (0)
12 PYRIDOXINE/ (0)
13 11 and 12 (0)
14 (doxylamine and pyridoxine).tw. (0)
15 (xonvea or diclectin or diclegis or debendox or benedectin or bendectin or lenotan or merbental).tw. (0)
16 or/13-15 (0)
17 10 and 16 (0)
18 limit 17 to english language (0)

Database: Medline daily update

Platform: Ovid
Version: Ovid MEDLINE(R) Daily Update <January 04, 2019>
Search date: 7th Jan 19
Number of results retrieved: 0

Search strategy
Database: Ovid MEDLINE(R) Daily Update <January 04, 2019>
---
1 exp Morning Sickness/ (1)
2 morning sick*.tw. (1)
3 (pregnan* adj5 (sick* or nause* or vomit*)).tw. (0)
4 (emes* or emet* or hypereme*).tw. (7)
5 Pregnancy/ (476)
6 Pregnant Women/ (16)
7 5 or 6 (476)
8 nausea/ or vomiting/ (4)
9 7 and 8 (0)
10 or/1-4,9 (7)
11 Doxylamine/ (0)
12 PYRIDOXINE/ (0)
13 11 and 12 (0)
14 (doxylamine and pyridoxine).tw. (0)
15 (xonvea or diclectin or diclegis or debendox or benedectin or bendectin or lenotan or merbental).tw. (0)
16 or/13-15 (0)
17 10 and 16 (0)
18 limit 17 to english language (0)

Database: Embase

Platform: Ovid
Version: Embase <1974 to 2019 Week 01>
Search date: 7th Jan 19
Number of results retrieved: 189
Search strategy:
Database: Embase <1974 to 2019 Week 01>
---
1 morning sickness/ (385)
2 hyperemesis gravidarum/ (2472)
3 morning sick*.tw. (323)
4 (pregnan* adj5 (sick* or nause* or vomit*)).tw. (2297)
5 (emes* or emet* or hypereme*).tw. (17721)
6 pregnant woman/ (66494)
7 exp pregnancy/ (620329)
8 6 or 7 (651435)
9 "nausea and vomiting"/ (34660)
10 nausea/ or vomiting/ (270556)
11 9 or 10 (300205)
12 8 and 11 (8767)
13 or/1-5,12 (27941)
14 bendectin/ (389)
15 doxylamine plus pyridoxine/ (67)
16 (doxylamine and pyridoxine).tw. (116)
17 (xonvea or diclectin or diclegis or debendox or benedectin or bendectin or lenotan or merbental).tw. (358)

18 or/14-17 (532)
19 13 and 18 (240)
20 limit 19 to english language (233)
21 limit 20 to (conference abstract or conference paper or "conference review" or letter or note) (44)
22 20 not 21 (189)

Database: Cochrane Library – incorporating Cochrane Database of Systematic Reviews (CDSR) and CENTRAL

Platform: Wiley
Version:
CDSR – Issue 1 of 12, January 2019
CENTRAL – Issue 1 of 12, January 2019
Search date: 29th May 2018
Number of results retrieved: CDSR – 2; CENTRAL – 31.

#1 MeSH descriptor: [Morning Sickness] explode all trees 69
#2 morning sick* 176
#3 pregnan* near/5 (sick* or nause* or vomit*) 521
#4 emes* or emet* or hypereme* 3980
#5 MeSH descriptor: [Pregnancy] this term only 875
#6 MeSH descriptor: [Pregnant Women] this term only 185
#7 #5 or #6 1052
#8 MeSH descriptor: [Nausea] this term only 3498
#9 MeSH descriptor: [Vomiting] this term only 3220
#10 #8 or #9 4587
#11 #7 and #10 11
#12 #1 or #2 or #3 or #4 or #11 4537
#13 MeSH descriptor: [Doxylamine] this term only 36
#14 MeSH descriptor: [Pyridoxine] this term only 376
#15 #13 and #14 18
#16 doxylamine and pyridoxine 31
#17 xonvea or diclectin or diclegis or debendox or benedectin or bendectin or lenotan or merbental 24
#18 #15 or #16 or #17 33
#19 #12 and #18 33

Database: CRD databases

Platform: CRD
Version: N/A
Search date: 8th Jan 19
Number of results retrieved: 1
Search strategy:
1 MeSH DESCRIPTOR Morning Sickness EXPLODE ALL TREES 8
2 (morning sick*) 11
3 (pregnan* near (sick* or nause* or vomit*)) 27
4 (emes* or emet* or hypereme*) 183
5 MeSH DESCRIPTOR Pregnancy 2505

6 MeSH DESCRIPTOR Pregnant Women 31
7 #5 OR #6 2512
8 MeSH DESCRIPTOR nausea 155
9 MeSH DESCRIPTOR vomiting 158
10 #8 OR #9 192
11 #7 AND #10 14
12 #1 OR #2 OR #3 OR #4 OR #11 214
13 MeSH DESCRIPTOR Doxylamine 1
14 MeSH DESCRIPTOR PYRIDOXINE 12
15 #13 AND #14 1
16 (doxylamine and pyridoxine) 1
17 (xonvea or diclectin or diclegis or debendox or benedectin or bendectin or lenotan or merbental) 1
18 #15 OR #16 OR #17 1
19 #12 AND #18 1

Trials registry search strategies

Clinicaltrials.gov

Search date: 7th Jan 19
Number of results retrieved: Multiple separate keyword strategies employed so result no. is not available
Search strategy: xonvea, diclectin, diclegis, doxylamin, debendox, bendectin

Clinicaltrialsregister.eu

Search date: 7th Jan 19
Number of results retrieved: 0
Search strategy: xonvea, diclectin, diclegis, doxylamin, debendox, bendectin

Appendix E: Excluded studies

A literature search for doxylamine/pyridoxine was conducted which identified 227 references after duplicates were removed (see search strategy for full details). These references were screened using their titles and abstracts and 9 references were obtained and assessed for relevance to the doxylamine/pyridoxine (Xonvea) product.

Two randomised controlled trials identified from the search were included in this evidence review (Koren et al. 2010 and Zhang et al. 2017). Three further papers were included because they report further data on the study by Koren et al. 2010 (Costantine et al. 2012, Koren et al. 2015 and Koren et al. 2016). Four papers were excluded and are listed in the following table. A summary of the included studies is shown in appendix A.

Study reference	Reason for exclusion
O'Donnell A, McParlin C, Robson SC et al. (2016) Treatments for hyperemesis gravidarum and nausea and vomiting in pregnancy: a systematic review and economic assessment. Health technology assessment (Winchester, and England) 20(74): 1–268	Study not prioritised (not the best available evidence: narrative study results only)
Oliveira LG, Capp SM, You WB et al. (2014) Ondansetron compared with doxylamine and pyridoxine for treatment of nausea in pregnancy: a randomized controlled trial. Obstetrics and gynecology 124(4): 735–42	Poor relevance against search terms (wrong strength)
Persaud N, Meaney C, El-Emam K et al. (2018) Doxylamine-pyridoxine for nausea and vomiting of pregnancy randomized placebo controlled trial: Prespecified analyses and re-analysis. PloS one 13(1): e0189978	Study not prioritised (re-analysis of data from Koren et al. 2010)
Pope E, Maltepe C, and Koren G (2015) Comparing pyridoxine and doxylamine succinate-pyridoxine HCl for nausea and vomiting of pregnancy: A matched, controlled cohort study. Journal of clinical pharmacology 55(7): 809–14	Study not prioritised (not the best available evidence: observational study)