New Medicine Assessment
Doxylamine succinate and pyridoxine hydrochloride 10 mg/10 mg gastro-resistant tablets (Xonvea®) for the treatment of nausea and vomiting of pregnancy in women who do not respond to conservative management.

Recommendation: Green

Appropriate for initiation and ongoing prescribing in both primary and secondary care.

Summary of supporting evidence

- The results of the DESI study appear to show sufficient evidence to support the clinical contributions of each of the monocomponents in the fixed dose combination
- In the DIC-301 study a greater improvement of 0.8-11 PUQE units for Xonvea compared to placebo was demonstrated for days 3, 4, 5, 10 and 15. These statistically significant differences, based on the PUQE scale, represent improvements that are clinically meaningful for pregnant women suffering from NVP.
- The product was previously available but was withdrawn from the market in 1983 due to litigation burdens and adverse publicity affecting the product.
- The current formulation has been on the Canadian market since 1979 and on the US market since 2013

Details of Review

Name of medicine (generic & brand name): Doxylamine succinate and pyridoxine hydrochloride (Xonvea®)
Strengths and forms: 10 mg/10 mg gastro-resistant tablets
Dose and administration: The recommended starting dose is two tablets at bedtime (Day 1). If this dose adequately controls symptoms the next day, the patient can continue taking two tablets at bedtime. However, if symptoms persist into the afternoon of Day 2, the patient should continue the usual dose of two tablets at bedtime (Day 2) and on Day 3 take three tablets (one tablet in the morning and two tablets at bedtime). If these three tablets do not adequately control symptoms on Day 3, the patient can take four tablets starting on Day 4 (one tablet in the morning, one tablet mid-afternoon and two tablets at bedtime). The maximum recommended daily dose is four tablets (one in the morning, one in the mid-afternoon and two at bedtime). Xonvea should be taken as a daily prescription and not on an as needed basis. Continued need for Xonvea should be reassessed as the pregnancy progresses.
BNF therapeutic class / mode of action: Antiemetics and antinauseants
Licensed indication(s):

Xonvea is indicated for the treatment of nausea and vomiting of pregnancy in women who do not respond to conservative management.

Proposed use: As per licensed indication

Course and cost:

The NHS list price for 20 tablets is £28.50, this equates to 5-10 days treatment depending on dose. Xonvea should be taken as a daily prescription and not on an as needed basis. Continued need for Xonvea should be reassessed as the pregnancy progresses.

Current standard of care/comparator therapies:

There are no drugs currently licensed for NVP but there is some experience with their off-label use in clinical practice, usually at doses consistent with their licensed use. These drugs include cyclizine, promethazine, prochlorperazine, metoclopramide and ondansetron.

Using NHS list price (Drug Tariff : October 2018) the most expensive of these would cost £3.84 for 10 days treatment (Ondansetron 8mg)

Relevant NICE and other guidance:

- Antenatal care for uncomplicated pregnancies Clinical guideline [CG62] Published date: March 2008 Last updated: January 2017
- Xonvea is on the SMC timetable for review (SMC 2140). Date: TBC
- Doxylamine / pyridoxine is first line treatment for NVP in Clinical practice guideline – hyperemesis and nausea / vomiting in pregnancy; Institute of Obstetricians and Gynaecologists, Royal College of Physicians of Ireland and the Clinical Strategy and Programmes Division, Health Service Executive.

Disease Background

Nausea and vomiting are common symptoms in pregnancy which may be caused by human chorionic gonadotropin (HCG) hormone produced by the placenta.[1,2,3,4] Symptoms usually begin at around gestational weeks 3 to 8 and peak between weeks 7 to 12, when HCG levels are at their highest, before subsiding at around week 16.[(1-6)] Some women continue to experience symptoms up to or beyond week 20. Although it is often referred to as 'morning sickness', nausea and vomiting in pregnancy (NVP) can occur any time of the day.[7] Uncomplicated NVP does not have harmful effects on the pregnancy but the pregnant woman's quality of life can be severely affected.[1]

The delayed release, fixed dose combination of doxylamine succinate and pyridoxine hydrochloride, as a treatment for NVP, has a long history, being first introduced to the UK in a product marketed by Merrell Dow in 1958 as Debendox, a triple active delayed release combination combining 10mg of each of doxylamine succinate, pyridoxine hydrochloride and dicyclomine hydrochloride. The product was reformulated in 1976 and dicyclomine hydrochloride was removed as it was found not to contribute to the anti-emetic properties of the drug combination. In 1983, Merrell Dow voluntarily withdrew the product from market for non medical reasons, citing litigation burdens and adverse publicity affecting the product.

The current delayed release formulation has been on the Canadian market since 1979 and on the US market since 2013.

Current treatment options

Xonvea is the first drug to be licensed for use specifically for the treatment of nausea and vomiting of pregnancy in women. The delayed action of Xonvea permits the night time dose to be effective in the following morning hours, when the patient needs it most.

To date both non-pharmacological and pharmacological measures have been used to treat NVP.

Because NVP occurs primarily in the first trimester, when organogenesis is taking place, teratogenic effects of drug treatments are of concern.[7,8] If pharmacological treatment for NVP is used, the drugs should be taken regularly to achieve adequate blood concentrations but at their lowest effective dose and for the shortest possible time. If oral preparations cannot be tolerated, then other administration routes can be used. The choice of drug will be based on its efficacy for NVP as well as pregnancy outcomes and its adverse effect profile. Patient preference and available routes of administration are also relevant. The drugs can be taken in combination but data on their combined use in pregnancy are limited. There is limited evidence regarding the safety and efficacy of most drug therapies, including anti-emetics, during pregnancy, but available studies as well as clinical experience support the efficacy, safety and rationale for their use in clinical practice. In general, drugs may be prescribed in pregnancy when the potential benefit justifies the potential foetal risk, without evidence of harm.[3,9]

Non pharmacological measures

There are a number of non-pharmacological measures that may help manage NVP initially, these include rest, good hydration, dietary habit, multivitamin supplementation - though there is little published evidence regarding the efficacy of dietary changes. Wrist (P6) acupressure is a non-invasive method of treating nausea. A recent Cochrane Review, which included six studies (cumulatively n=511), compared the effectiveness of P6 acupressure with placebo on symptoms of NVP. Pooled data suggests there is no significant benefit overall, although some of the studies included reported positive results.[3,10] The RCOG and NICE state that P6 acupressure may reduce symptoms of NVP. RCOG also advise that women may be reassured of its safety in pregnancy.[3,7]

Current drug treatments

A number of drugs can be used to treat NVP, such as cyclizine, promethazine, prochlorperazine, metoclopramide, ondansetron and complementary medicines such as ginger and pyridoxine. None are specifically licensed for NVP but there is some experience with their (off-label) use in clinical practice, usually at doses consistent with their licensed use.[3] A recent Cochrane review found only limited evidence to support the use of any drugs to relieve mild or moderate NVP. There were a lack of high quality studies reporting relevant outcomes and heterogeneity between studies meant that data could not be pooled.[10,11]

Summary of efficacy data in proposed use:

Results – Efficacy

Study DIC – 301:[12] a double blind, multicentre, randomised, placebo controlled trial of the efficacy of Xonvea for nausea and vomiting of pregnancy.

The primary objective of this study was to compare the efficacy of Xonvea to placebo in the treatment of NVP using the Pregnancy Unique Quantification of Emesis (PUQE) assessment tool to assess efficacy.

The intent to treat efficacy population (ITT-E) contained 256 subjects. Subjects were pregnant women, at least 18 years of age, with a gestational age of 7-14 weeks, suffering from NVP, with a (PUQE) score of ≥ 6 and not responding to conservative management consisting of dietary / lifestyle advice. The ITT-E population consisted of any subject who took at least one dose of study medication and had at least one post baseline PUQE measurement.

The minimum assigned study medication was 2 tablets daily at bedtime, increasing when indicated to the maximum dosage of 4 tablets per day. Over the treatment period, 19% of Xonvea-treated patients remained on two tablets daily, 21% three tablets daily, and 60% received four tablets daily. The study had a 15 day period consisting of 14 dosing days.

Results

The mean PUQE scores were comparable at baseline in the two treatment groups. Both treatment groups showed negative mean changes from baseline in PUQE score at day 15 (± 1 day), indicating improvement in NVP symptoms. The mean (SD) change in the Xonvea group was -4.8 (2.7) and the mean change in the placebo group was -3.9 (2.6). The difference between these two mean changes was statistically significant (P=0.006), indicating statistically significantly greater improvement in the Xonvea group.

When the primary endpoint results were reanalysed using the all randomised population carrying baseline observations forward for those with no post baseline measurements, the reanalysis of the data showed a statistically significant result in the all randomised population consistent with the primary analysis i.e. -4.5 (2.7) vs -3.5 (2.8).

A post hoc analysis was conducted to evaluate the change from baseline in PUQE score to days 3,4,5 and 10. The objective of this additional analysis was to assess the efficacy at an earlier stage in the trial to minimise the impact of any natural course of NVP improvement (days 3, 4 and 5) and also to provide data several days after the maximum dose has been reached by the patient (day 10) since the maximum possible dosage is reached on day 4 (as per study protocol).

A greater improvement of 0.8-11 PUQE units for Xonvea compared to placebo was demonstrated for days 3, 4, 5, 10 and 15. These statistically significant differences, based on the PUQE scale, represent improvements that are clinically meaningful for pregnant women suffering from NVP.

FDA Drug Efficacy Study Implementation programme (DESI) 1975: an 8 way, randomised, double blind, placebo controlled, multi-centre trial, involving patients who had NVP.

The DESI study compared doxylamine, pyridoxine and dicyclomine hydrochloride, alone or in various combinations with placebo in an 8 way study design in a total of 2,308 patients. This included the comparison of the combination product doxylamine / pyridoxine to doxylamine alone and pyridoxine alone.

The patients in the study were randomised to receive 2 of the allocated tablets at bedtime for 7 nights and if necessary 1 additional tablet in the morning and mid-afternoon. The combination of doxylamine and pyridoxine showed statistically significant improvements in symptoms as evaluated by both physicians and patients compared to placebo.

Safety

The safety profile of doxylamine 10mg / pyridoxine 10mg fixed dose combination is well established. No new or unexpected safety concerns arose from the trials.

No study subject deaths occurred in any of the clinical studies.

Two meta-analyses have found no association between first trimester use and foetal malformations.[13]

Study DIC – 301[12] There were 9 subjects with serious adverse events and 7 additional subjects that discontinued the study drug due to treatment emergent adverse events (TEAE) that were not serious. Serious adverse events were collected from the time of the first dose until 30 days after the subject had either discontinued study medication or started on compassionate medication. 9 serious adverse events were reported in this study with 3% (4/133) in the Xonvea group and 3.9% (5/128) in the placebo treatment group.

Reported serious adverse events reported were: bile duct stone (1), missed abortion (2), spontaneous abortion (3), foetal disorder (1), intrauterine death (1) and premature rupture of membranes (1). Rates of foetal death were the same in both arms and in all 8 cases the event was considered unrelated to the study drug.

The conclusion was that Doxylamine succinate–pyridoxine hydrochloride delayed release combination is safe and well tolerated by pregnant women when used in the recommended dose of up to 4 tablets daily in treating nausea and vomiting of pregnancy.

Overall conclusions on the clinical efficacy

The combination of doxylamine and pyridoxine showed statistically significant improvements in symptoms as evaluated by both physicians and patients compared to placebo.

Summary of safety data

Table of Adverse events for Xonvea 10 mg/10 mg gastro-resistant tablets

Incidence of Event	Adverse Event
Very Common (≥1/10)	Somnolence
Common (≥1/100 to <1/10)	Dizziness, dry mouth, fatigue

The following events have been identified during post-approval use of the combination of 10 mg doxylamine succinate and 10 mg pyridoxine hydrochloride. As these reactions are reported voluntarily from population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

- **Immune system disorders:** hypersensitivity
- **Psychiatric disorders:** anxiety, disorientation, insomnia, nightmares
- **Nervous system disorders:** dizziness, headache, migraines, paraesthesia, psychomotor hyperactivity
- **Eye disorders:** vision blurred, visual disturbances
- **Ear and labyrinth disorders:** vertigo
- **Cardiac disorders:** dyspnoea, palpitation, tachycardia
- **Gastrointestinal disorders:** abdominal distention, abdominal pain, constipation, diarrhoea
- **Skin and subcutaneous tissue disorders:** hyperhidrosis, pruritus, rash, rash maculo-papular
- **Renal and urinary disorders:** dysuria, urinary retention
- **General disorders and administration site conditions:** chest discomfort, fatigue, irritability, malaise

Strengths and limitations of the evidence:

Strengths:

- Double blind, multicentre, randomised trials
- Reasonably large cohort of trial patients
- Trials placebo controlled
- Xonvea offers a licensed product where unlicensed products are currently used.
- Product used historically however license withdrawn

Limitations:

- No currently prescribed comparator arm(s)
- Short duration trials (although this could be argued to mirror the condition)
- Some historic trials data supports the licensing of the product

Prescribing and risk management issues:

Overdose - Xonvea is a delayed-release formulation; therefore, signs and symptoms may not be apparent immediately. Signs and symptoms of overdosage may include restlessness, dryness of mouth, dilated pupils, sleepiness, vertigo, mental confusion and tachycardia.

At toxic doses, doxylamine exhibits anticholinergic effects, including seizures, rhabdomyolysis, acute renal failure and death.

Commissioning considerations:

Anticipated patient numbers and net budget impact

In 2016, there were 774,835 live births in the UK (about 1,200 per 100,000). NVP affects up to 80% of all pregnant women and about 35% have clinically significant symptoms (336 per 100,000 people). Up to 20% continue to have symptoms throughout pregnancy. In 2016-17, there were 33,071 admissions for NVP, resulting in 36,171 bed days and 34,545 finished consultant episodes.[13]

Total population of Lancashire and South Cumbria: 1,675,000 (Office for National Statistics). Therefore, in this region 5,628 pregnant women would be expected to have clinically significant symptoms (35%) with 3,216 continuing to have symptoms of NVP throughout pregnancy (20%).

Associated additional costs or available discounts:

Xonvea is significantly more expensive than the currently prescribed unlicensed medications.

Xonvea costs £28.50 for 20 tablets.[14] Assuming doxylamine/pyridoxine is used instead of off-label cyclizine or promethazine (costing £8 to £25 for a 2-month course) for 20% of women with clinically significant symptoms (67 per 100,000), and a course costs £200, then the additional cost is estimated to be about £13,400 per 100,000 people.[13]

For Lancashire and South Cumbria (population 1,675,000) the estimated additional cost would be 1,122.25 x £200 = £224,450.

However, this additional cost may be offset slightly by a reduction in number of prescriptions issued for the unlicensed medications and potential for decrease in hospital admissions due to NVP.

Productivity, service delivery, implementation:

N/A

Innovation, need, equity:

Xonvea is the first drug to be licensed for use specifically for the treatment of nausea and vomiting of pregnancy in women.

Grading of evidence (based on SORT criteria):

Levels	Criteria	Notes
Level 1	Patient-oriented evidence from: high quality randomised controlled trials (RCTs) with low risk of bias systematic reviews or meta-analyses of RCTs with consistent findings	High quality individual RCT= allocation concealed, blinding if possible, intention-to-treat analysis, adequate statistical power, adequate follow-up (greater than 80%)
Level 2	Patient-oriented evidence from: clinical trials at moderate or high risk of bias systematic reviews or meta-analyses of such clinical trials or with inconsistent findings cohort studies case-control studies	
Level 3	Disease-oriented evidence, or evidence from: consensus guidelines expert opinion case series	Any trial with disease-oriented evidence is Level 3, irrespective of quality

Midlands and Lancashire Commissioning Support Unit,
Jubilee House, Lancashire Business Park, Leyland, PR26 6TR

References

1. Jarvis S, Nelson-Piercy C. Management of nausea and vomiting in pregnancy. Br Med J 2011; 342:doi: 10.1136/bmj.d3606.
2. Pasternak B, Svanström H, Hviid A. Ondansetron in pregnancy and risk of adverse fetal outcomes. N Engl J Med 2013; 368(9):814-823, doi:10.1056/NEJMoa1211035.
3. The management of nausea and vomiting of pregnancy and hyperemesis gravidarum: Green-top Guideline RCOG. No 69. June 2016. Available at https://www.rcog.org.uk/globalassets/documents/guidelines/green-top-guidelines/gtg69-hyperemesis.pdf
4. Treatment of nausea and vomiting in pregnancy. May 2015. Version 1.4. UK Teratology Information Service (UKTIS). Available via www.toxbase.org
5. Ebrahimi N, Maltepe C, Einarson A. Optimal management of nausea and vomiting of pregnancy. International Journal of Women's Health 2010; 2(241):248.
6. Niebyl JR, Briggs GG. The pharmacologic management of nausea and vomiting of pregnancy. Journal of Family Practice 2014; 63(2):S31-S37.
7. NICE Clinical Guideline: Antenatal care: routine care for the healthy pregnant woman (CG62) 2008 (Updated January 2017). National Institute for Clinical Excellence. Available via www.nice.org.uk
8. Heitmann K, Nordeng H, Holst L. Safety of ginger use in pregnancy: results from a large population-based cohort study. Eur J Clin Pharmacol 2013; 69:269-277.
9. Badell ML, Ramin SM, Smith JA. Treatment options for nausea and vomiting during pregnancy. Pharmacotherapy 2006; 26(9):1273-1287.
10. Matthews A, Haas A, O'Mathuna DP. Interventions for nausea and vomiting in early pregnancy (Cochrane Review). The Cochrane Collaboration 2015; Issue 9:Art No.: CD007575.
11. Goldstein LH, Berkovitch M. Antiemetics. In: Schaefer C, Peters P, Miller RK, editors. Drugs during pregnancy and lactation. Treatment options and risk assessment. Third Edition, 2015: 78-93.
12. Koren G et al: 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 (2015) https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4391332/
13. SPS - Prescribing Outlook 2018 – combined chapters October 2018 https://www.sps.nhs.uk/articles/prescribing-outlook-2018-combined-chapters/
14. MIMS online [Accessed online 22 October 2018: https://www.mims.co.uk/drugs/central-nervous-system/nausea-vomiting/xonvea]

