Healthcare Improvement Scotland | SMC Advice on new medicines

SMC2140

doxylamine succinate 10mg and pyridoxine hydrochloride 10mg gastro-resistant tablets (Xonvea®)

Alliance Pharmaceuticals Limited

5 April 2019

The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and advises NHS Boards and Area Drug and Therapeutic Committees (ADTCs) on its use in NHSScotland. The advice is summarised as follows:

ADVICE: following a full submission

doxylamine succinate and pyridoxine hydrochloride (Xonvea®) is not recommended for use within NHSScotland.

Indication under review: the treatment of nausea and vomiting of pregnancy in women who do not respond to conservative management.

Doxylamine in combination with pyridoxine significantly improved symptoms of nausea and vomiting compared with placebo in women with nausea and vomiting of pregnancy.

The submitting company did not present a sufficiently robust clinical or economic analysis to gain acceptance by SMC.

The license holder has indicated their intention to resubmit.

Chairman
Scottish Medicines Consortium

Indication

The treatment of nausea and vomiting of pregnancy in women who do not respond to conservative management.[1]

Dosing Information

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).

Doxylamine/pyridoxine should be taken as a daily prescription and not on an as needed basis. Continued need should be reassessed as the pregnancy progresses. To prevent a sudden return of nausea and vomiting of pregnancy symptoms, a gradual tapering dose is recommended at the time of discontinuation.

Further details are included in the Summary of Product Characteristics (SPC).[1]

Product availability date

2 October 2018

Summary of evidence on comparative efficacy

Doxylamine succinate in combination with pyridoxine hydrochloride is currently the only medicine specifically licensed in the UK for the treatment of nausea and vomiting of pregnancy. Doxylamine succinate is an antihistamine that exerts an antiemetic action by selectively binding to histamine H1 receptors in the brain. Pyridoxine hydrochloride is a water soluble vitamin (vitamin B6). Xonvea® is a delayed-release formulation. The mechanism of action of the combination to treat nausea and vomiting of pregnancy is not known.[1] The submitting company has requested that SMC considers this product when positioned for use in women with nausea and vomiting of pregnancy where conservative management has failed, and who have a Pregnancy-Unique Quantification of Emesis (PUQE) score of 10 or greater. The PUQE scoring system is a validated tool that quantifies the severity of nausea and vomiting in pregnancy. The symptom domain assesses the number of daily vomiting episodes, number of daily retching episodes and length of daily nausea in hours to give an overall score between 3 (no symptoms) and 15 (most severe symptoms). The second domain is a global assessment of well-being from zero (worst possible) to ten (best possible).

Key evidence for this indication comes from study DIC-301, a phase III, randomised, double-blind, multi-centre, placebo-controlled study. Recruited patients were women (≥18 years) who were between 7 and 14 weeks pregnant and suffering from nausea and vomiting of pregnancy, with a PUQE score ≥6, that had not responded to conservative management of dietary and lifestyle advice according to the American College of Obstetrics and Gynaecology practice bulletin (2004). In utero singleton pregnancy was confirmed by ultrasound and patients had not been treated with other anti-emetics.[2]

Patients were randomly assigned to doxylamine succinate 10mg and pyridoxine hydrochloride 10mg delayed-release tablets (n=131) or placebo (n=125) for 14 days. On day 1, two tablets of doxylamine/pyridoxine or placebo were taken at bedtime. If patients still experienced nausea and vomiting in the afternoon of day 2, the dose could be increased on day 3 to one tablet in the morning in addition to the bedtime dose. The patients were assessed in clinic on day 4 and an additional tablet could be taken mid-afternoon if required to control nausea and vomiting symptoms in the evening.[2]

The primary outcome was the change from baseline to day 15 in the two domains of the PUQE score. Patients completed study diaries including PUQE score once each day in the morning before their medication. The global assessment of well-being scale of the PUQE was also completed on days 1, 8, and 14. Patients were phoned on days 2, 6, 12, and 14 to assess diary information, adverse events, concomitant medications, and compliance with study medication. Patients who received at least one dose of study medication and had PUQE assessment at baseline and day 15 were included in the efficacy analyses.[2]

The mean difference in PUQE score and global assessment of well-being from baseline to day 15 indicated improvement in both groups. The difference between groups was small but statistically significant, favouring doxylamine/pyridoxine group for both domains.[2] The primary outcome and selected secondary outcomes are included in Table 1 below. A post-hoc analysis of the study demonstrated a greater improvement with doxylamine/pyridoxine group than with placebo group in PUQE score of 0.8 to 1.1 units from baseline to days 3, 4, 5, 10 and 15.[3]

Table 1. Primary and selected secondary outcomes from study DIC-301.[2, 3]

	Doxylamine/pyridoxine (n=131)	Placebo (n=125)	p value
Mean ± SD difference in PUQE score from baseline to day 15	-4.8 ± 2.7	-3.9 ± 2.6	0.006
Mean ± SD area under the curve difference in PUQE score from baseline (day-by-day)	61.5 ± 36.9	53.5 ± 37.5	<0.001
Mean ± SD difference in global assessment of well-being from baseline to day 15	2.8 ± 2.8	1.8 ± 2.2	0.005
Mean ± SD time loss from employment (days)	0.92 ± 3.86	2.37 ± 10.23	0.06

Number of patients asking for compassionate use of study medication after day 14 (%)	64 (49%)	41 (33%)	0.009
Number of patients who reported concurrent use of non-pharmacological therapy for nausea and vomiting of pregnancy such as diet modifications, teas, aroma therapy, massage and yoga (%)	31 (24%)	46 (36%)	0.04

SD: standard deviation

The mean number of tablets taken was similar between groups (36.6 ± 13.3 in the doxylamine/pyridoxine group versus 34 ± 15.1 in the placebo group). There were no reports of hyperemesis gravidarum in either group.[3]

Pope et al 2015 was a prospective, matched-cohort study aiming to compare doxylamine/pyridoxine with pyridoxine alone for the treatment of nausea and vomiting of pregnancy. Cases were recruited from records of patients who contacted the Motherisk helpline in Toronto between 2000 and 2014 and had been taking doxylamine/pyridoxine or pyridoxine for at least 4 days prior to their call. The primary outcome, change in PUQE score over 1 week of treatment, identified a significant difference favouring the doxylamine/pyridoxine group over pyridoxine alone. Sub-group analysis identified a larger overall mean change in PUQE score in the moderate to severe group of patients (baseline PUQE score ≥ 10) who received doxylamine/pyridoxine compared with pyridoxine alone.[4]

DESI 10598 was a randomised, double-blind placebo-controlled study conducted in 1975 in women in the first 12 weeks of pregnancy experiencing nausea and vomiting of pregnancy (n=2,308). Patients were randomised to receive either doxylamine/dicyclomine/pyridoxine, doxylamine/pyridoxine, dicyclomine/doxylamine, dicyclomine/pyridoxine, doxylamine, dicyclomine, pyridoxine or placebo for 1 week. Significant improvements were observed for all combinations containing doxylamine and doxylamine alone versus placebo in symptoms of nausea and vomiting of pregnancy according to physician and patient assessment.[3, 5]

Summary of evidence on comparative safety

In the key DIC-301 study, adverse events (AEs) and concomitant medications were recorded at all visits and follow-up phone calls. A further phone call was made 30 days after the last dose to capture serious adverse events for patients completing the treatment period or early termination.

In the DIC-301 study at least one treatment-emergent AE was reported by 56% of patients in the doxylamine/pyridoxine group and 51% of patients in the placebo group. Serious treatment-emergent AEs were reported by 3.1% of patients in both groups. In the doxylamine/pyridoxine group 4.6% of patients discontinued study medication due to an adverse event and 3.1% in the placebo group.[6]

This study did not identify any significant differences between the number of AEs in the doxylamine/pyridoxine or placebo groups. The most frequently occurring treatment-emergent adverse events included nervous system disorders (32% and 29%), gastro-intestinal disorders (18% and 17%), somnolence (14% and 12%), and headache (13% and 16%).[6] Rates of foetal death were the same in both groups (8 cases in total) and all were considered unrelated to study treatment.[3]

Doxylamine and pyridoxine, either individually or as combination products, have been used extensively in North America. The Medicines and Healthcare Products Regulatory Agency (MHRA) noted that many published clinical data have demonstrated the safety and tolerability in pregnant women. In addition, results from a number of epidemiological studies have not identified an association with foetal abnormalities. A risk management plan has been submitted to address the potential safety risk of somnolence and potential interactions with monoamine oxidase inhibitors and missing information on use in breastfeeding women, those under <18 years, and in hepatic or renal impairment.[3]

Summary of clinical effectiveness issues

Nausea and vomiting of pregnancy affects up to 80% of pregnant women and although many do not require treatment, it is one of the most common reasons for hospital admission in pregnancy.[7] In a minority of women the severity of nausea experienced is similar in character and intensity to chemotherapy-associated nausea and is the symptom that most negatively affects quality of life.[3]

Women with mild nausea and vomiting of pregnancy should be managed in the community with dietary and lifestyle advice, oral anti-emetics and oral fluids. Ginger and acupressure are options for patients who prefer to avoid pharmacological therapies. There are no other medications specifically licensed for treatment of nausea and vomiting of pregnancy. Guidelines recommend that first-line pharmacological anti-emetics include anti-histamines such as cyclizine and promethazine and also prochlorperazine or chlorpromazine as there are safety and efficacy data available. Metoclopramide, ondansetron and domperidone are potential second-line treatment options. Medications from different classes should be tried if the first treatment is not effective and combinations can be considered for those who do not respond to a single medication. Ambulatory care should be used if primary care management fails and the patient's PUQE score is less than 13. This service can provide parenteral fluids, parenteral vitamins and anti-emetics. Women who have recurrent nausea and vomiting of pregnancy or hyperemesis gravidarum despite adequate ambulatory day care treatment should be managed as inpatients due to the associated complications, in particular electrolyte imbalance and nutritional deficiencies.[7]

The submitting company has requested that SMC considers this product when positioned for use in women with nausea and vomiting of pregnancy where conservative management has failed, and who have a PUQE score of ≥10. Patients recruited to the key DIC-301 study were required to have a PUQE score ≥6. There are no data from this study to estimate the magnitude of treatment effect of doxylamine/pyridoxine in patients with PUQE score ≥10. The mean PUQE score at

baseline was around 9 in both groups. PUQE score of 7 to 12 indicates moderate nausea and vomiting of pregnancy.[7] Sub-group analysis in Pope et al 2015, a prospective cohort study, identified a greater overall mean change in PUQE score in the moderate to severe group of patients (baseline PUQE score ≥10) who received doxylamine/pyridoxine compared with pyridoxine alone.[4]

In DIC-301 the mean difference in change from baseline to day 15 in PUQE score and global assessment of well-being was significantly greater in the doxylamine/pyridoxine group compared with the placebo group, indicating greater improvement in symptoms of nausea and vomiting of pregnancy. This study demonstrated a greater improvement with doxylamine/pyridoxine over placebo in PUQE score of 0.8 to 1.1 units from baseline to days 3, 4, 5, 10 and 15. These improvements are small but the MHRA concluded that they are clinically meaningful for women suffering from nausea and vomiting of pregnancy.[3]

The requirements of the Committee for Medicinal Products for Human Use (CHMP) guidelines state that clinical study data must show superiority of the fixed dose combination against each of the mono-components. The pivotal study did not include any monotherapy arms. In addition, the study should show the clinical contribution of each of the components. It was concluded by the MHRA that DESI 10598 appears to partially address this. However, the demonstration of superiority of doxylamine/pyridoxine over its mono-components was not possible from this study. The MHRA noted that although the study was conducted over 40 years ago the applicant stated that it was conducted in accordance to standards comparable to the current clinical practice.[3, 5] Based on the MHRA's conclusion and the current RCOG guidance, which does not recommend pyridoxine[7], the evidence base for pyridoxine may not be robust.

The 2 week study duration of DIC-301 was long enough to demonstrate efficacy in treatment of nausea and vomiting of pregnancy however symptoms may continue for longer than this time period. The mean gestation of patients recruited to study DIC-301 was 9.3 weeks.[2] Nausea and vomiting of pregnancy usually starts before this, between weeks 4 and 7, peaks at week 9 and resolves in 90% of patients by week 20.[7] Therefore recruited patients' symptoms could potentially have been beginning to subside during the study.

Patients were excluded if they had been treated with other anti-emetics which could potentially affect the generalisability to some patients if they had already received anti-emetic medication according to the current guidance. This may represent a group of patients who are more difficult to treat. In addition, there is no evidence available from DIC-301 in patients with the most severe condition, hyperemesis gravidarum. DIC-301 was conducted in the USA; around 40% of patients were Hispanic or Latino and almost 40% were black or African American.[6] This is not representative of the patients who would be expected to receive this medication in Scotland. However, it is unlikely that there would be any large differences in nausea and vomiting of pregnancy depending on race as it is primarily thought to be associated with rising levels of beta human chorionic gonadotrophin (hCG) hormone.[7] The study only included patients with a singleton pregnancy.

The key study compared doxylamine/pyridoxine with placebo. Cyclizine, prochlorperazine, promethazine or chlorpromazine are first-line pharmacological therapy options recommended in the RCOG guidance and although these are not licensed for use in pregnancy, safety and efficacy data are available.[7] The submitting company state that it was not possible to carry out an indirect treatment comparison due to insufficient data for doxylamine in combination with pyridoxine and the comparators which meant that they were unable to establish any networks including this treatment.

The introduction of doxylamine/pyridoxine would provide a licensed treatment option for women suffering from nausea and vomiting of pregnancy.

Summary of comparative health economic evidence

The company submitted a cost-minimisation analysis (CMA) as the primary economic analysis comparing doxylamine/pyridoxine to cyclizine, prochlorperazine, and promethazine, in treating women with nausea and vomiting of pregnancy (NVP) who do not respond to conservative management. A selective positioning was proposed by the company for treating women with NVP who have a PUQE score ≥10. The submitting company state that these patients are most likely to require hospital inpatient admission as a consequence of the NVP. The choice of comparators was based on a survey of Scottish GPs (n=70) and was generally supported by SMC clinical experts, although the comparators are noted as being used off-label.

For the CMA, equal efficacy between doxylamine/pyridoxine and cyclizine, prochlorperazine, and promethazine individually was assumed. Based on expert clinical opinion it was assumed severe NVP would occur at week 8 of pregnancy and treatment would start then with either doxylamine/pyridoxine or the comparator medicines and continue to week 12, a time period of 28 days. Medicine acquisition costs were taken into account, but as all medicines were oral no administration costs were considered. The daily dosing of doxylamine/pyridoxine was assumed to be two tablets with a daily treatment cost of £2.85.For cyclizine, prochlorperazine, or promethazine three tablets per day was assumed at a daily treatment cost of £0.19, £0.06 or £0.16 respectively. The impact of adverse events was not included in the model based on the DIC-301 study showing no significant adverse event differences between doxylamine/pyridoxine combination and placebo.

Resource use included hospital inpatient admissions, emergency calls, GP consultations, midwife consultations, ambulance service, accident and emergency (A&E) department attendance. The baseline rate of hospitalisation in patients with a PUQE score ≥10 was derived from Scottish NVP hospitalisation data and published sources and was estimated to be 29.2%, with an average length of hospital stay estimated at 1.52 days.[8, 9] Doxylamine/pyridoxine was assumed to lead to a 50% reduction in this baseline rate (to 14.6%) based on a study conducted in Canada that reported a doubling in NVP hospitalisations over the period 1988-92 when the original doxylamine/pyridoxine was withdrawn from the Canadian market in 1983.[10, 11] The baseline rates of all other health care

resources were derived from a study on NHS resource burden associated with managing NVP in the Newcastle and Gateshead clinical commissioning group (CCG) region[9], but in the base case were set equal for both doxylamine/pyridoxine combination and the comparators.

A cost-utility analysis (CUA) was also performed, which consisted of a simple decision tree design, with patients starting in a moderate or a severe NVP health state based on PUQE score with a probability of transitioning to severe, moderate or mild NVP states after 15 days. The source of clinical data was the DIC-301 study, with a greater proportion of patients receiving doxylamine/pyridoxine than placebo estimated to move to less severe NVP health states at day 15 assessment. The placebo arm of the DIC-301 study was assumed to represent the efficacy of the comparator treatments. As with the CMA the time horizon considered was 28 days, and the same medicine and resource use costs as in the CMA were applied. Utilities were derived from a number of published sources with the severe NVP state based on EQ-5D values from a previous economic evaluation[12], and the moderate and mild state values based on studies in NVP and pregnancy that had mapped the SF-36 to the EQ-5D.[13, 14] The utility values used for the severe, moderate and mild health states were 0.44, 0.62 and 0.76 respectively, and incremental QALYs were estimated for day 15-28 based on the relative movements between health states at day 15 for doxylamine/pyridoxine versus the comparator medicines. No disutilities for adverse events were included as no safety data were considered in the economic analyses.

The base case result from the CMA was an estimated net cost saving for doxylamine/pyridoxine combination versus each of the comparator medicines, as the incremental medicine acquisition costs of doxylamine/pyridoxine were more than offset by the cost savings from reduced hospital admissions estimated (table 2). In threshold analysis, it was indicated that cost neutrality would be achieved against cyclizine with a 40% reduction in hospital admissions. A number of scenario analyses were performed using alternative published sources for length of hospital stay with NVP, higher reduction in hospital admissions based on US study exploring impact of withdrawal of the original doxylamine/pyridoxine, assuming a reduction in other resource use with doxylamine/pyridoxine, as shown in Table 2. Each of these were associated with a larger cost saving than in the base case. The only scenario explored by the company that produced a positive incremental cost for doxylamine/pyridoxine versus each comparator medicine was the application of a lower baseline rate of hospital admission of 15.6% derived from the Newcastle and Gateshead CCG study[9] (Table 2).

The main results of the CUA was the same cost saving as in the CMA, but an estimated 0.00088 QALY gain for doxylamine/pyridoxine combination.

Table 2: Key results from the CMA (Total incremental costs/savings over 28 days)

Doxylamine/pyridoxine combination	Incremental cost/savings versus Cyclizine	Incremental cost/savings versus Prochlorperazine	Incremental cost/savings versus Promethazine
Base case: based on 29.2% baseline rate of hospital admission due to NVP, and 50% reduction due to doxylamine/pyridoxine combination	-£17.74	-£14.08	-£16.75
Scenario 1: 2 days hospital stay[15]	-£46.28	-£42.62	-£45.29
Scenario 2: 67% reduction in hospital admission[16]	-£49.05	-£45.40	-£48.07
Scenario 3: Assumption of a 20% reduction in resource use	-£38.88	-£35.23	-£37.90
Scenario 4: 15.6% baseline rate of hospital admission[9]	£25.23	£28.88	£26.21
Additional requested scenario: 25% reduction in hospital admission	£28.32	£31.98	£29.31

There were several weaknesses and uncertainties associated with the economic analyses:

- The estimates of reduced hospital admission and other resource use reduction are based on very limited and dated evidence from North America or by assumption, and the estimation of cost savings is sensitive to the hospital admission baseline rates applied which are uncertain. It is uncertain that doxylamine/pyridoxine would lead to any significant reduction in hospitalisation or other resource use. Additional scenario analysis requested applying a 25% reduction in hospitalisation resulted in an incremental cost for doxylamine/pyridoxine in the CMA (table 2).
- No evidence is presented supporting the equal efficacy and safety of doxylamine/pyridoxine and the comparator medicines, although this may be a reasonable assumption for the CMA. However, by assuming equal efficacy there is no mechanism by which a benefit, such as a reduction in hospitalisation, can be attained.
- Only two tablets per day have been assumed for doxylamine/pyridoxine, whereas a 3rd or 4th tablet can be added after day 3 or 4 if symptoms persist. The company was requested to perform threshold analysis to provide an estimate of the proportion of patients that would

need to receive 3 or 4 tablets for the analysis to show cost neutrality versus cyclizine. The threshold values were 47.9% of patients if three tablets were required and 24.9% of patients if 4 tablets were required. These values are below the 67.9% of patients in the DIC-301 study who received >2 tablets, indicating that there is likely to be an incremental cost associated with doxylamine/pyridoxine even with a 50% reduction in hospitalisations assumed.

- Assuming a 28-day duration of treatment over weeks 8 to 12 of pregnancy with doxylamine/pyridoxine and comparators in the economic analyses is too simplistic, and does not take account of discontinuation of treatment before or beyond 28 days. In practice as NVP can occur from weeks 4 to at least week 20 it seems likely that the patient will be monitored over a longer time period and treatment duration will vary according to need, for example if the NVP resolves then treatment could be stopped or started again in the case of recurrence. The simple design means that adequate assessment of relative costs and consequences is limited and the reliability of the results presented is uncertain.
- The CUA model has several additional flaws, including the assumption of a 28-day treatment duration not fitting the structure of the model as in the current design it appears that patients who move into the mild state would continue to receive doxylamine/pyridoxine. In addition, the patient population does not match those for the selective positioning in that it includes patients with a PUQE score between 7 and 10, the assessment of health state transition at day 15 and the health-related quality of life impact lasting 14 days is unlikely to reflect clinical practice, and the use of placebo as a proxy for comparator effectiveness is likely to overestimate the benefit of doxylamine/pyridoxine. Due to these limitations, the CUA is not sufficiently reliable to enable an assessment of the cost-effectiveness of doxylamine/pyridoxine.

Overall, the economic analyses are not sufficiently robust, hence the economic case for doxylamine/pyridoxine has not been demonstrated.

Summary of patient and carer involvement

No patient group submissions were received.

Additional information: guidelines and protocols

The Royal College of Obstetricians and Gynaecologists (RCOG) published their guideline: The Management of Nausea and Vomiting of Pregnancy and Hyperemesis Gravidarum, in 2016. This guideline states that women with mild nausea and vomiting of pregnancy should be managed in the community with oral anti-emetics, support, oral fluids and dietary advice. Ambulatory day care should be used if primary care management fails and the patient's PUQE score is less than 13. This service can provide parenteral fluids, parenteral vitamins and anti-emetics. Women who have recurrent nausea and vomiting of pregnancy or hyperemesis gravidarum despite adequate

ambulatory day care treatment should be managed as inpatients due to the associated complications, in particular electrolyte imbalance and nutritional deficiencies.

Ginger can be used for mild nausea and vomiting for patients who wish to avoid pharmacological therapies. Accupressure may help to reduce symptoms. The guideline notes that first-line anti-emetics including antihistamines (H1 receptor antagonists) and phenothiazines should be prescribed when required as there are safety and efficacy data available. In the UK first-line recommendations include cyclizine, prochlorperazine, promethazine and or chlorpromazine. Clinicians should use antiemetics with which they are familiar and should use drugs from different classes if the first drug is not effective. Combinations of different drugs should be used in women who do not respond to a single antiemetic. For women with persistent or severe HG, the parenteral or rectal route may be necessary and more effective than an oral regimen. Due to the risk of extrapyramidal effects, metoclopramide should be used as a second-line treatment option although it is considered safe and effective. Evidence is available to suggest that ondansetron is safe and effective, but because data are limited it should be used as second-line therapy. Domperidone can also be considered as a second-line treatment option. If these treatments fail, corticosteroids can be used third-line. Pyridoxine is not recommended due to a lack of consistent evidence.[7]

The NICE clinical guideline: Antenatal care for uncomplicated pregnancies, published in 2006 and updated in 2018 states that if a patient would like to consider treatment for nausea and vomiting in pregnancy, ginger, P6 (wrist) acupressure and antihistamines appear to be effective in reducing symptoms. Information about all forms of self-help and non-pharmacological treatments should be made available. The guideline also notes that patients should be informed that nausea and vomiting are not usually associated with a poor pregnancy outcome and most cases will resolve spontaneously within 16 to 20 weeks.[17]

Additional information: comparators

Cyclizine, prochlorperazine, promethazine or chlorpromazine.

Cost of relevant comparators

Medicine	Dose Regimen	Cost per two week course (£)
Doxylamine succinate and pyridoxine hydrochloride	**Initially two tablets orally at bedtime, if symptoms are not controlled this can be increased to one tablet in the morning and two tablets at bedtime and then further increased to one tablet in the morning, one tablet mid-afternoon and two tablets at bedtime.**	**40 to 80**
Chlorpromazine	10 to 25 mg 4 to 6 hourly	Up to 96
Prochlorperazine	5 to 10 mg 6 to 8 hourly	Up to 8
Promethazine	12.5–25 mg 4 to 8 hourly	Up to 7
Cyclizine	50mg orally 8 hourly	Up to 5

Doses are for general comparison and do not imply therapeutic equivalence. Costs from eVadis on 01 February 2019. Costs calculated based on a two week course as per the duration in the DIC-301 study. Dose regimen for cyclizine, prochlorperazine, promethazine and chlorpromazine taken from RCOG guideline.[7] *Costs could be higher or lower depending on the dose and duration of treatment required by individual patients.*

Additional information: budget impact

The submitting company estimated there would be 11,075 patients eligible for treatment with doxylamine/pyridoxine in each year over the first 5 years, to which confidential uptake rates were applied.

The gross impact on the medicines budget was estimated to be £88k in year 1 rising to £442k in year 5. As other medicines were assumed to be displaced, the net medicines budget impact was estimated to be £84k in year 1 rising to £421k in year 5.

*Other data were also assessed but remain confidential.**

References

1. Doxylamine/pyridoxine (Xonvea®) summary of product characteristics. Electronic Medicines Compendium. Last updated: 01.10.18, www.medicines.org.uk/emc/. [cited.
2. Koren G, Clark S, Hankins GD, Caritis SN, Miodovnik M, Umans JG, et al. Effectiveness of delayed-release doxylamine and pyridoxine for nausea and vomiting of pregnancy: a randomized placebo controlled trial. Am J Obstet Gynecol. 2010;203(6):571 e1-7.
3. Medicines and Healthcare products Regulatory Authority, UKPAR: Xonvea®, 2018.
4. Pope E, Maltepe C, Koren G. Comparing pyridoxine and doxylamine succinate-pyridoxine HCl for nausea and vomiting of pregnancy: A matched, controlled cohort study. J Clin Pharmacol. 2015;55(7):809-14.
5. Desi. Bendectin Peer Review Report, 14 March 1975. Overall Summary of '8-Way' Bendectin Study, pp1-58 (Bendectin NDA-10-598).
6. Koren G, Clark S, Hankins GD, Caritis SN, Umans JG, Miodovnik M, 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 Childbirth. 2015;15:59.
7. Royal College of Obstetricians and Gynaecologists. The Management of Nausea and Vomiting of Pregnancy and Hyperemesis Gravidarum. Green-top Guideline No. 69. 2016. Available from: https://www.rcog.org.uk/en/guidelines-research-services/guidelines/gtg69/.
8. Einarson TR, Piwko C, Koren G. Quantifying the global rates of nausea and vomiting of pregnancy: a meta analysis. J Popul Ther Clin Pharmacol. 2013;20(2):e171-83.
9. Gadsby R, Rawson V, Dziadulewicz E, Rousseau B, Collings H. Nausea and vomiting of pregnancy and resource implications: The NVP Impact Study. Accepted for print. Brit J of Gen Prac. 2018.
10. Neutel C. Variation in rates of hospitalization for excessive vomiting in pregnancy by Bendectin/Diclectin use in Canada (In: Nausea and Vomiting of Pregnancy State of the Art 2000). Available at: https://www.nvp-volumes.org/p1_9.htm (last accessed: 8 Sep 2017).
11. Neutel CI, Johansen HL. Measuring drug effectiveness by default: The case of Bendectin. Canadian Journal of Public Health. 1995;86(1):66–70.
12. Murphy A, McCarthy FP, McElroy B, Khashan AS, Spillane N, Marchocki Z, et al. Day care versus inpatient management of nausea and vomiting of pregnancy: cost utility analysis of a randomised controlled trial. Eur J Obstet Gynecol Reprod Biol. 2016;197:78-82.
13. Attard CL, Kohli MA, Coleman S, Bradley C, Hux M, Atanackovic G, et al. The burden of illness of severe nausea and vomiting of pregnancy in the United States. Am J Obstet Gynecol. 2002;186(5 Suppl Understanding):S220-7.
14. Tendais I, Figueiredo B, Mota J, Conde A. Physical activity, health-related quality of life and depression during pregnancy. Cad Saude Publica. 2011;27(2):219-28.
15. O'Donnell A, McParlin C, Robson SC, Beyer F, Maloney E, Bryant A, et al. Treatments for hyperemesis gravidarum and nausea and vomiting in pregnancy: a systematic review and economic assessment. Health Technol Assess. 2016;20(74).
16. Kutcher JS, Engle A, Firth J, Lamm SH. Bendectin and birth defects. II: Ecological analyses. Birth Defects Res A Clin Mol Teratol. 2003;67(2):88-97.
17. National Institute for Health and Care Excellence (NICE). Antenatal care for uncomplicated pregnancies. 2017 [cited 2018 Oct 05]; Available from: https://www.nice.org.uk/guidance/cg62/chapter/1-Guidance#management-of-common-symptoms-of-pregnancy.

This assessment is based on data submitted by the applicant company up to and including 15 March 2019.

**Agreement between the Association of the British Pharmaceutical Industry (ABPI) and the SMC on guidelines for the release of company data into the public domain during a health technology appraisal: http://www.scottishmedicines.org.uk/About_SMC/Policy*

Medicine prices are those available at the time the papers were issued to SMC for consideration. SMC is aware that for some hospital-only products national or local contracts may be in place for comparator products that can significantly reduce the acquisition cost to Health Boards. These contract prices are commercial in confidence and cannot be put in the public domain, including via the SMC Detailed Advice Document. Area Drug and Therapeutics Committees and NHS Boards are therefore asked to consider contract pricing when reviewing advice on medicines accepted by SMC.

Advice context:

No part of this advice may be used without the whole of the advice being quoted in full.

This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.