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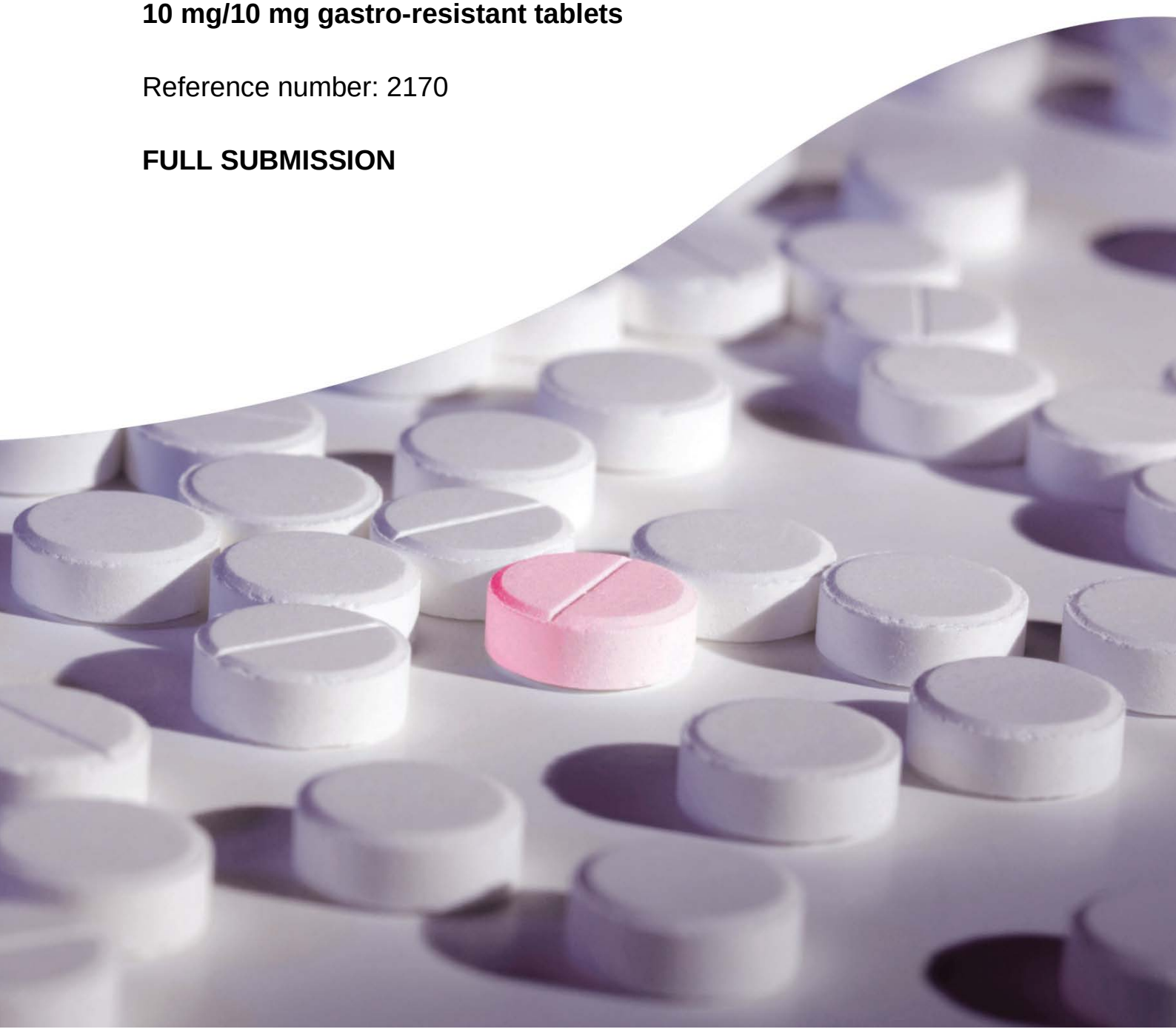
All Wales Therapeutics & Toxicology Centre
Canolfan Therapiwteg a Thocsicoleg Cymru Gyfan

AWMSG SECRETARIAT ASSESSMENT REPORT

Doxylamine succinate/pyridoxine hydrochloride (Xonvea®) 10 mg/10 mg gastro-resistant tablets

Reference number: 2170

FULL SUBMISSION



PAMS
Patient Access to Medicines Service
Mynediad Claf at Wasanaeth Meddyginiaethau

This report has been prepared by the All Wales Therapeutics & Toxicology Centre (AWTTC).

Please direct any queries to AWTTC:

All Wales Therapeutics & Toxicology Centre (AWTTC)
University Hospital Llandough
Penlan Road
Llandough
Vale of Glamorgan
CF64 2XX

awttc@wales.nhs.uk
029 2071 6900

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AWMSG Secretariat Assessment Report
Doxylamine succinate/pyridoxine hydrochloride (Xonvea®)
10 mg/10 mg gastro-resistant tablets

1.0 KEY FACTS

Assessment details	Doxylamine succinate/pyridoxine hydrochloride (Xonvea®) for the treatment of nausea and vomiting of pregnancy (NVP) in women who do not respond to conservative management. The company has focused its submission on the use of doxylamine/pyridoxine for the subpopulation of women who are at highest risk of hospitalisation and have a Pregnancy-Unique Quantification of Emesis (PUQE) score ≥ 10.
Current clinical practice	There are currently no other licensed pharmacological treatments available in the UK for the treatment of NVP. Existing treatment consists of conservative management strategies such as dietary or lifestyle modifications. First-line antiemetics, such as antihistamines and phenothiazines, may also be prescribed (off-label).
Clinical effectiveness	The company submission includes a phase III study designed to evaluate the efficacy of doxylamine/pyridoxine versus placebo. Treatment with doxylamine/pyridoxine resulted in a statistically significant improvement in symptoms compared with placebo and a trend to less time lost from employment. A prospective, post-marketing study showed that efficacy was not lost when the combination was used for longer durations.
Cost-effectiveness	A cost-utility analysis compares doxylamine/pyridoxine (10 mg/10 mg) gastro-resistant oral tablets with oral cyclizine (50 mg), promethazine (10 mg) or prochlorperazine (5 mg) in the first-line treatment of women with NVP who have a PUQE score ≥ 10 and do not respond to conservative management. The company base case suggests that doxylamine/pyridoxine dominates all comparator treatments with small cost savings and marginal utility improvements. Considering the uncertainty around the hospitalisation rate, dose, and the small utility gains, there are limitations to the economic analyses. Incremental cost-effectiveness ratios are therefore highly unstable and range from dominant to £88,361 (if no effect on hospitalisation rate is assumed) per quality-adjusted life year. AWTTC are of the opinion that the most plausible ICER is more than likely to exceed the estimate of £45,676 to £49,353 per Quality-Adjusted Life-Year gained.

Budget impact	The company estimates that 6,517 patients are eligible to receive treatment with doxylamine/pyridoxine in Wales each year in Years 1 to 5. The company base case suggests an additional cost of £49,513 in Year 1, increasing to £247,403 in Year 5. The base case also predicts NHS resource savings, resulting from a 50% reduction in hospitalisations, valued at £55,868 in Year 1, increasing to £279,168 in Year 5. AWTTC consider the most plausible budget impact (based on 3.41 tablets a day as reported in the Summary of Product Characteristics) to be between £83,193 in Year and £415,699 in Year 5. The budget impact analysis does not account for changes in birth rate, mortality rate and treatment discontinuation. The treatment cycle is limited to 28 days, and any increase in treatment duration would result in additional costs. The savings in resource use are based on a 50% reduction in hospitalisations as reported in a study published in 2000. The transferability of these data to the present indication is questionable.

This assessment report is based on evidence submitted by Alliance Pharmaceuticals Ltd[1] and an evidence search conducted by the All Wales Therapeutics and Toxicology Centre (AWTTC) on 17 December 2018.

2.0 BACKGROUND

2.1 Condition and clinical practice

Nausea and vomiting of pregnancy (NVP) affects up to 80% of pregnant women and is one of the most common indications for hospital admission among pregnant women[2]. Onset of NVP typically starts between the fourth and seventh weeks of gestation, peaks in approximately the ninth week, and resolves by week 20 in 90% of women[2].

The National Institute for Health and Care Excellence (NICE) Clinical Knowledge Summary and The Royal College of Obstetricians and Gynaecologists (RCOG) guidelines recommend off-label use of an antihistamine (cyclizine or promethazine) or a phenothiazine (prochlorperazine) as first line antiemetic pharmacotherapy[2,3]. Clinicians should use medicines from different classes if the first-line medicine is not effective; for example, metoclopramide and ondansetron[2]. The Health and Safety Executive/Royal College of Physicians of Ireland (HSE/RCPI) guidelines recommend doxylamine/pyridoxine as the first-line pharmacotherapy treatment[4]. Doxylamine/pyridoxine is recommended as first-line treatment in the US, Canada and parts of Spain under different trade names[4].

2.2 Medicine

Doxylamine succinate/pyridoxine hydrochloride (Xonvea®) is licensed for NVP in women who do not respond to conservative management (July 2018) and is a delayed-release formulation[5]. Doxylamine/pyridoxine is the antiemetic combination of the antihistamine doxylamine and vitamin B6 (pyridoxine)[4]. This combination has been available in other countries (such as Canada and USA) for decades under different trade names[6]. Doxylamine succinate exerts an anti-emetic action by selectively binding to H1 receptors in the brain. The mechanism of doxylamine/pyridoxine combination is

not well established since the etiology of NVP is not well known[7]. There are currently no other licensed pharmacological treatments available in the UK for the treatment of NVP.

Based on company-sought clinical expert opinion the applicant company has focused its submission on the use of doxylamine/pyridoxine for the subpopulation of women who have a Pregnancy-Unique Quantification of Emesis (PUQE) score ≥ 10[1]. The PUQE incorporates physical (nausea, vomiting, retching) and wellbeing aspects of NVP and is a validated index used to classify the condition's severity: a score of ≤ 6 is interpreted as mild NVP, 7–12 as moderate NVP, and 13–15 as severe NVP[2] (see Glossary). Company-sought clinical expert opinion states it is most likely that women with scores ranging from 10–15 (inclusive) would be admitted to hospital[1].

2.3 Comparators

In line with NICE and RCOG guidelines, the comparators included in the company's submission are:

- off-label cyclizine hydrochloride (Valoid®)[8]
- off-label promethazine hydrochloride (Phenergan®)[9]
- off-label prochlorperazine maleate[10]

2.4 Guidance and related advice

- NICE. Antenatal care for uncomplicated pregnancies. Clinical Guideline 62 (published March 2008, last updated December 2018)[11].
- NICE. Nausea/vomiting in pregnancy. Clinical Knowledge Summary (October 2018)[3].
- RCOG. The management of nausea and vomiting of pregnancy and hyperemesis gravidarum (Green-top Guideline no 69) (2016)[2].
- HSE/RCPI. Hyperemesis and nausea/vomiting in pregnancy (published November 2015, last updated Nov 2018)[4].

2.5 Prescribing and supply

AWTTC is of the opinion that, if recommended, doxylamine succinate/pyridoxine hydrochloride (Xonvea®) may be appropriate for prescribing by all prescribers within NHS Wales for the indication under consideration.

3.0 CLINICAL EFFECTIVENESS

The company submission includes evidence from one pivotal phase III study, designed to evaluate the efficacy of doxylamine/pyridoxine versus placebo for the treatment of NVP[6], and also results from a prospective, post-marketing study designed to evaluate the longer-term effectiveness of doxylamine/pyridoxine[12]. Two further studies provide supporting evidence. The first shows that the combination of doxylamine plus pyridoxine was significantly more effective in treating NVP than pyridoxine alone[13]. However, pyridoxine alone is not recommended for treating nausea and vomiting in pregnancy on the grounds that there is a lack of consistent evidence of effectiveness, therefore this study will not be discussed further[2,3]. The second supporting study was a dose-finding study[14]. This along with three further studies, which are older and contain alternative formulations[15-17], will also not be discussed.

3.1 Study DIC-301

DIC-301 was a double-blind, multicentre, placebo-controlled study to evaluate the efficacy of doxylamine/pyridoxine in the treatment of NVP[6]. Women with a gestational age range of 7 to 14 weeks, who had not responded to conservative management, were randomised to receive doxylamine/pyridoxine (n = 131) or placebo (n = 125) for

14 days. The minimum dose was two tablets daily taken orally at bedtime, increasing when required to the maximum dose of four tablets per day.

Treatment with any other anti-emetics was not permitted but concurrent use of alternative therapies, such as nutritional modifications, teas, aromatherapy, massage, and yoga, were permitted. The primary efficacy outcome was the change from baseline over 15 days in PUQE score and Global Assessment of Well-Being (GAWB). Secondary outcomes included the number of women who requested ongoing compassionate use (blinded) of their medication and time lost from employment[6].

Treatment with doxylamine/pyridoxine resulted in a statistically significant larger improvement from baseline in symptoms of NVP compared with placebo based on both the PUQE score (−4.8 ± 2.7 versus −3.9 ± 2.6; p = 0.006) and GAWB (2.8 ± 2.8 versus 1.8 ± 2.2; p = 0.005)[6]. From baseline to Day 15 compared with placebo the treatment difference was 0.9 PUQE score units; p = 0.006. After the trial, 64 (48.9%) treated with doxylamine/pyridoxine asked to continue compassionate use of their medication, compared with 41 (32.8%) women receiving placebo (p = 0.009). There was a trend toward more time lost from employment in the placebo group compared with the doxylamine/pyridoxine group (2.37 ± 10.23 versus 0.92 ± 3.86; p = 0.06)[6]. Over the treatment period, 19% of patients treated with doxylamine/pyridoxine remained on two tablets daily, 21% three tablets daily, and 60% received four tablets daily[5].

Secondary analysis evaluated whether the primary measure of efficacy can be demonstrated after five days of treatment[18]. The change in PUQE score between baseline and Day 15 was compared to the changes observed for Days 3, 4 and 5. The use of doxylamine/pyridoxine showed a small improved NVP symptom control compared to placebo for Days 3, 4, and 5 with mean difference in the PUQE score units of 1.0 (p = 0.002), 1.1 (p < 0.001) and 1.0 (p = 0.006) respectively[18]. A mixed model for repeated measure effects showed the treatment effect remained stable on Days 3, 4, or 5. By Day 15 the effect had however become smaller and lost statistical significance.

3.2 Bishai et al 2000

This review article by Bishai and colleagues also included the results from their prospective, post-marketing study evaluating the longer-term (12–14 weeks) efficacy of doxylamine/pyridoxine in the treatment of NVP[12]. The study involved two cohorts of women (n = 174 in total) who were counselled by the Motherisk NVP Helpline in Canada and were advised to take two tablets at bedtime, increasing when required to the maximum dose of four tablets per day. Women were first interviewed at the onset of symptoms (generally at six to eight weeks gestation) and again at 20 weeks gestation.

The first cohort of patients (n = 149) were already taking doxylamine/pyridoxine at the time they contacted the helpline[12]. The second cohort started doxylamine/pyridoxine after the counselling session. During follow-up at 20 week's gestation, 106 patients (71%) in the first cohort (n = 149) reported an improvement in their NVP symptoms, related to doxylamine/pyridoxine; 34 (23%) did not report improvement and two patients (1%) reported worsening of their symptoms[12]. Follow up for the second cohort (n = 25), found 21 (84%) reported improvement, three (12%) reported no change and one (4%) experienced a worsening of symptoms. Results suggest that doxylamine/pyridoxine does not lose efficacy when used for longer durations in a 'real world' versus controlled clinical trial setting[12].

3.3 Safety Information

The Medicines and Healthcare Products Regulatory Agency (MHRA) states that the safety profile of doxylamine/pyridoxine is well-established[7]. The combination has been marketed in Canada since 1983, in the US since 2013, and other countries under different trade names, with no reported safety concerns[7].

The adverse reactions commonly associated with the combination include somnolence dizziness, dry mouth, and fatigue[5]. No study subject deaths have occurred in any of the clinical trials[7]. Furthermore, many studies have confirmed the foetal safety of the combination[6]. Taking into account the long history of clinical use of the combination and the absence of demonstrable safety concerns, the MHRA have concluded the safety data demonstrate an acceptable safety profile for this combination product[7].

3.4 AWTTC critique

- There are no studies comparing the efficacy of doxylamine/pyridoxine with that of the main pharmacological treatment comparators used in Wales.
- The applicant company wishes to focus their submission on the subpopulation of women who are at highest risk of hospitalisation and have a PUQE score ≥ 10. However, in the pivotal study DIC-301, the median PUQE score at enrolment for doxylamine/pyridoxine-treated patients was 9 (range 6 to 15) and for placebo-treated patients was 8 (range from 5 to 15)[1]. No patients reported hyperemesis gravidarum in either treatment group.
- DIC-301 did not investigate hospitalisation rates. Other studies included in the submission providing hospitalisation data were not designed to investigate a direct causal relationship between doxylamine/pyridoxine use and hospitalisation rates. Therefore, there is a need for caution in interpreting the data provided; this includes conclusions drawn regarding potential causality between the temporary withdrawal of this medicine in the USA in the 1980s and a 50% increase in hospitalisation rates.
- Other secondary efficacy outcomes relating to healthcare resource use (i.e. telephone calls or visits) were found to be similar between groups. However, the lack of available data makes this outcome difficult to evaluate. The low number of visits and telephone calls to healthcare providers made by women taking part in the trial (in both treatment arms) may also not be representative of clinical practice outside of the trial setting.
- Limited information was provided regarding the prospective post-marketing study reported by Bishai and colleagues. The longer-term evidence was subjective, based on participants self-reporting if they were better, the same, or worse; efficacy was not evaluated using a validated index of NVP severity such as the PUQE score.
- As well as an improvement in those women taking doxylamine/pyridoxine in the pivotal study, there was also a notable improvement in the placebo group from baseline, which could be due to the fact that NVP spontaneously resolves. In addition, significantly more women receiving placebo (n = 46, 36%) than doxylamine/pyridoxine (n = 31, 23.7%) used alternative therapies concomitantly for symptoms of NVP ($p = 0.04$)[6], which could also have contributed to the observed improvement in the placebo arm.
- In Study DIC-301, the minimum assigned dose of study medication was two tablets daily at bedtime. A total of 67.9% (n = 89/131), however took more than the minimum required 28 tablets during the trial[6]. In addition, the treatment duration was 14 days. The longest treatment period found in the company's clinical study report was three weeks; however clinical expert opinion suggests that patients may need treatment for up to two months[1].
- The applicant company performed a systematic review with the view to performing an indirect treatment comparison/meta-analysis; however, due to

the scarcity of clinical data in this indication it was not possible to establish any evidence networks that included doxylamine/pyridoxine[1].
- Although it is the most common trimester for NVP, Study DIC-301 only looks at NVP in women with a gestational age range of 7 to 14 weeks.
- Study DIC-301 was conducted in the USA and only about 60% of women were Caucasian.

4.0 COST-EFFECTIVENESS

The company's submission[1] includes a cost-utility analysis (CUA) comparing doxylamine/pyridoxine 10 mg/10 mg gastro-resistant oral tablets versus three oral comparators, cyclizine (50 mg), promethazine (10 mg) or prochlorperazine (5 mg), in women with NVP who have a PUQE score of ≥ 10 and do not respond to conservative management.

A Markov model with a decision tree structure estimates the difference in treatment costs between doxylamine/pyridoxine and cyclizine, promethazine and prochlorperazine. The model adopts an NHS Wales/Personal and Social Services perspective and a nine-month time horizon, with costs and utilities relating only to the duration of NVP considered. No discounting was applied as follow-up did not exceed one year. In the model it is assumed that doxylamine/pyridoxine and the comparators are used in a first-line context after conservative management has failed.

Patients enter the model with a PUQE score of ≥ 10, in either moderate or severe NVP, based on published PUQE scores[19]. Patient distribution between the moderate and severe NVP groups are based on Crozier et al (2017)[20], and re-normalised assuming that 50% of the moderate NVP population (PUQE scores of 7 to 12) had a PUQE score of 10 to 12[21]. On Day 15 of treatment, patients' transition to one of three health states (mild, moderate and severe NVP). Transition probabilities are based on the normalised distribution of PUQE score change between baseline and Day 15 as reported in Study DIC-301[6]; with the placebo values used as proxy for the comparators. Treatment is assumed to last for 28 days after which time NVP is considered cured.

Treatment acquisition costs are sourced from the British National Formulary (BNF)[22] for the comparators (based on the recommended starting dose of three tablets per day for each comparator) and provided by the company for doxylamine/pyridoxine (based on the recommended starting dose of two tablets a day). Costs of adverse events are not included. Hospitalisation rates for the comparators are calculated using the number of NVP hospitalisations in Wales in 2016 to 2017[23], conception data for 2016[24], and published epidemiology data[20,25]. Hospitalisation rate for doxylamine/pyridoxine is assumed to be 50% lower based on published evidence that showed that the removal of doxylamine/pyridoxine (Bendectin®) from the Canadian market in 1983 coincided with a doubling in the rates of hospitalisations due to NVP between 1988 and 1992[26]. All other primary and secondary care service resource use is based on published data[27] and clinical expert opinion and assumed to be the same for doxylamine/pyridoxine and all comparators. Unit costs are obtained from a recent systematic review[28] as well as published unit costs[29,30]. An average duration per hospitalisation of 1.52 days is assumed based on company data on file[31].

Utility data for the mild, moderate and severe health states are derived from published literature identified using a systematic review[32-35] and mapped to EQ-5D values where required[36]. The model assumes that the time spent in each health state is two weeks, in line with the change in PUQE score at Day 15 observed in the pivotal study[6], and the 28-day treatment duration period.

Deterministic and probabilistic sensitivity analyses were conducted to test the influence of the uncertainty of individual parameters on the model results. The parameters tested, among others, included mean change in PUQE score, healthcare resource use and utility values. Scenario analyses also explore the use of higher doses of doxylamine/pyridoxine and a cost-minimisation analysis assuming therapeutic equivalence between doxylamine/pyridoxine and all comparators.

4.1 Results

The results of the base case are detailed in Table 1. Despite the large difference in cost between doxylamine/pyridoxine and the other comparators the assumed reduction in hospitalisations means overall there is still a large cost difference in favour of doxylamine/pyridoxine. Doxylamine/pyridoxine is therefore the dominant treatment option in this scenario when compared with cyclizine, prochlorperazine and promethazine. The incremental quality-adjusted life year (QALY) gains are predominantly driven by a larger proportion of women transitioning to the mild PUQE state after Day 15 in the doxylamine/pyridoxine arm of the model.

Table 1. Results of the base case analysis

	Doxylamine/pyridoxine	Cyclizine	Difference
Medicine acquisition costs	£79.80	£5.33	**£74.47**
Other costs*	£191.43	£277.11	**−£85.68**
Total costs	£271.23	£282.45	**−£11.22**
Total QALYs	0.04670	0.04582	**0.00088**
ICER (£/QALY gained)	Doxylamine/pyridoxine dominates		
	Doxylamine/pyridoxine	**Prochlorperazine**	**Difference**
Medicine acquisition costs	£79.80	£2.10	**£77.70**
Other costs*	£191.43	£277.11	**−£85.68**
Total costs	£271.23	£279.21	**−£7.99**
Total QALYs	0.04670	0.04582	**0.00088**
ICER (£/QALY gained)	Doxylamine/pyridoxine dominates		
	Doxylamine/pyridoxine	**Promethazine**	**Difference**
Medicine acquisition costs	£79.80	£4.44	**£75.36**
Other costs*	£191.43	£277.11	**−£85.68**
Total costs	£271.23	£281.55	**−£10.33**
Total QALYs	0.04670	0.04582	**0.00088**
ICER (£/QALY gained)	Doxylamine/pyridoxine dominates		

ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life year
*Other costs include GP visits, community midwife visits, hospitalisations, outpatient attendances, A&E attendances and emergency call-outs.

The results of the univariate sensitivity analysis show that the incremental cost-effectiveness ratios (ICERs) are most sensitive to NVP prevalence, hospitalisation rate and healthcare resource use costs. Doxylamine/pyridoxine remained dominant or cost-effective based on the usual accepted thresholds in all analyses. The results of scenario analysis are assessed in order of plausibility in Table 2.

Probabilistic sensitivity analyses indicate that doxylamine/pyridoxine has a 74.9% and 80.9% probability of being cost-effective at a threshold of £20,000 and £30,000 per QALY gained, respectively.

Table 2. Results of scenario and sensitivity analyses

Scenarios	ICER	Plausibility
Average dose of 2.47 tablets per day for doxylamine/pyridoxine	Cyclizine: £8,565 Prochlorperazine: £12,243 Promethazine: £9,582	This scenario provides a plausible alternative to the base case, given that (unpublished) real world data from the US suggests an average dosing for patients using doxylamine/pyridoxine of 2.47 tablets per day[37]. PUQE scores were not collected during this study and it is not possible to assess whether these data are representative of the moderate/severe population under consideration. However, the company argues that mild patients in clinical practice are likely to be managed by conservative measures and unlikely to be prescribed medication, and therefore it is a reasonable assumption that patients who are likely to receive doxylamine/pyridoxine in Wales are similar to the population from this study receiving an average of 2.47 tablets per day.
Average dose of 3.41 tablets per day for doxylamine/pyridoxine	Cyclizine: £45,676 Prochlorperazine: £49,353 Promethazine: £46,692	This scenario is the preferred AWTTC base case as it is specified in the SPC[5] that during the pivotal study, 19% of Xonvea®-treated patients remained on two tablets daily, 21% on three tablets daily, and 60% received four tablets daily over the treatment period. This equates to a weighted average of 3.41 tablets per day.
Cost-minimisation analysis	Cost savings range from £7.99 to £40.35	This scenario lacks plausibility given that no evidence exists to corroborate the assumption of therapeutic equivalence between doxylamine/pyridoxine and all comparators and the company claims clinical superiority in the CUA.
AWTTC: All Wales Therapeutics and Toxicology Centre; CUA: cost-utility analysis; ICER: incremental cost-effectiveness ratio; PUQE: Pregnancy-Unique Quantification of Emesis; SPC: Summary of Product Characteristics		

4.2 AWTTC critique

The submission is characterised by both strengths and limitations:

Strengths:

- The submission gives a detailed, transparent account of the methods and data sources used in the analysis.
- Extensive sensitivity and scenario analyses have been conducted to test the effect of parameter uncertainty on the model results.

Limitations:

- The lack of direct and indirect comparative data between doxylamine/pyridoxine and its comparators is a severe limitation of this analysis, introducing considerable uncertainty around the plausibility of the results.
- The 50% reduction in hospitalisation rate for doxylamine/pyridoxine is based on a study published in 2000[26] which showed that the removal of doxylamine/pyridoxine (Bendectin®) from the Canadian market in 1983 coincided with a doubling in the rates of hospitalisations due to NVP between 1988 and 1992. According to clinical expert opinion sought by AWTTC, the assumption of causality and the transferability of these data to the present analysis is questionable and introduces bias into the results. Any changes to this value will considerably affect the cost-effectiveness results, as hospitalisations are the main cost driver in the model (all other healthcare costs are assumed equal between comparators). In the most extreme case, assuming

no effect of doxylamine/pyridoxine on hospitalisations, the ICERs would increase to between £84,684 and £88,361 depending on the comparator.

- The base case assumes an average dose of two tablets per day for doxylamine/pyridoxine and three tablets per day for each of the comparators. The rationale for this dosing is unclear. The maximum dose for doxylamine/pyridoxine is four tablets per day. If three tablets per day were used in the model (including an initial period of gradual dose increase), the ICER would change from dominant to between £29,373 and £33,051 per QALY gained. Using the maximum dose for the intervention and all comparators would result in ICERs between £68,266 and £71,943 per QALY gained. According to the Summary of Product Characteristics (SPC)[5], the average dose in the pivotal trial was 3.41 tablets per day. This would result in ICERs between £45,676 and £49,353 per QALY gained which is considered the preferred AWTTC base case. Given the indication population comprises patients in the more severe population, who may be more likely to dose towards the upper end of the dosing range, a more plausible approach would be to apply a weighted average approach for tablet dosing relative to this patient population. The company argues that two tablets a day is the recommended dose for doxylamine/pyridoxine according to its SPC[5] and that the real world average dose of 2.47 tablets is likely to be a realistic estimate of dosing in the moderate/severe patient group.
- Due to the lack direct or indirect comparison data for doxylamine/pyridoxine and the selected comparators, the model uses the placebo results from the pivotal study[6] as proxy values for the comparator clinical effectiveness. This may overestimate the efficacy and cost-effectiveness of doxylamine/pyridoxine.
- Due to the short treatment duration of 28 days, utility changes are marginal. The small utility values cause the ICER to be unstable causing large differences in ICER results.
- Healthcare resource use (other than hospitalisations) was based on a health economic case study in the Newcastle and Gateshead Clinical Commissioning Group, based on data collected over a 1-year period from April 2014 to March 2015[38]. These data were then extrapolated and adjusted to estimate baseline rates of healthcare resource use for the UK, but did not take into account disease severity of the population of interest (patients with PUQE score ≥ 10). As such, baseline rates of healthcare resource use may be underestimated as they are likely to be representative of the whole NVP population, including mild patients. Due to lack of available data, all non-hospitalisation resource use is assumed to be equal for all treatment options which may not be realistic, but may be a conservative assumption.
- The analysis does not take into account treatment discontinuation and adverse events for any treatment arm. Considering that 20% of the women in the doxylamine/pyridoxine group of the pivotal study[6] discontinued treatment within the first 14 days, of which 3.6% cited adverse events as the reason for discontinuation, this will introduce bias and the effect of this omission on the results is unknown.
- While the mapping for utilities was done according to good practice, utility values are derived from different sources without consideration of heterogeneity. It is therefore unclear whether they accurately reflect patient quality of life in the different PUQE score levels.
- The mean PUQE score at baseline in the pivotal study[6] is 8.9 (9 for intervention patients and 8.8 for placebo patients). Considering that the population under review is limited to those with PUQE scores ≥ 10, the generalisability of the pivotal study results to the population under review is questionable and introduces bias into the results.

- It is unclear how generalisable the results are to the current Welsh context. The pivotal study[6] was undertaken in the United States of America, with most supporting data being dated, not specific to the doxylamine/pyridoxine preparation in question and not including Welsh patients.

4.3 Review of published evidence on cost-effectiveness

A literature review conducted by AWTTC did not identify any studies relevant to the cost-effectiveness of doxylamine/pyridoxine compared to oral cyclizine, promethazine and prochlorperazine in women with NVP who have a PUQE score of ≥ 10 and do not respond to conservative management.

5.0 BUDGET IMPACT

5.1 Context and methods

The company has estimated that there will be 22,250 pregnant women with NVP every year in Wales. This estimate is based on Office for National Statistics conception statistics for 2016[24] and a prevalence rate of 69.4%[25.] Of these women, 29.29% (6,517 women) are assumed to suffer from NVP with a PUQE score of ≥ 10[20] assuming that patients with PUQE scores 10 to 12 represent 50% of the moderate NVP population. Changes in birth rate, mortality rate and treatment discontinuation were not considered. Treatment duration is 28 days. An assumed market share of 10% in Year 1, increasing to 50% in Year 5 is applied to estimate the number of people likely to be prescribed doxylamine/pyridoxine in Wales for this indication. The company provides a breakdown of how comparator medicines are likely to be displaced based on equal proportional displacement. Basic sensitivity analysis was performed.

5.2 Results

The budget impact is presented in Table 3. The company estimates that introducing doxylamine/pyridoxine would lead to an overall cost of £49,513 in Year 1, increasing to £247,403 in Year 5. This estimate incorporates cost differences resulting from the displacement of cyclizine (50 mg), promethazine (10 mg) and prochlorperazine (5 mg). The company carried out a sensitivity analysis, changing uptake rates of doxylamine/pyridoxine by 10%; this resulted in overall costs between £44,575 and £54,449 in Year 1, increasing to between £222,729 and £272,165 in Year 5.

Table 3. Costs associated with use of doxylamine/pyridoxine in women with NVP who have a PUQE score of ≥ 10 and do not respond to conservative management

	2019	2020	2021	2022	2023
Number of eligible patients (all women with NVP)	22,250	22,250	22,250	22,250	22,250
Sub-population of eligible patients (indication under consideration; PUQE ≥ 10)	6,517	6,517	6,517	6,517	6,517
Uptake of new medicine (%)	10%	20%	30%	40%	50%
Number of patients receiving new medicine allowing for discontinuations	652	1,303	1,955	2,607	3,258
Medicine acquisition costs in a market without new medicine	£25,176	£25,176	£25,176	£25,176	£25,176
Medicine acquisition costs in a market with new medicine	£74,688	£124,122	£173,632	£223,144	£272,578
Net medicine acquisition costs	£49,513	£98,947	£148,456	£197,969	£247,403
Net supportive medicines costs	£0	£0	£0	£0	£0
Net medicine acquisition costs (savings/costs) - including supportive medicines where applicable	**£49,513**	**£98,947**	**£148,456**	**£197,969**	**£247,403**
NVP: nausea and vomiting of pregnancy; PUQE: Pregnancy-Unique Quantification of Emesis					

The company estimated that net resource implications arising from the introduction of doxylamine/pyridoxine will lead to a cost saving of £55,868 in Year 1, increasing to £279,168 in Year 5, thus more than offsetting the medicine acquisition cost. This is a consequence of reduced secondary care costs based on 50% fewer hospitalisation in the doxylamine/pyridoxine arm[26]. These resource-type savings are included for potential planning purposes but may not be realised in practice.

5.3 AWTTC critique

- The submission gives a transparent account of the methods and data sources used to estimate budget impact. However, the company has not factored changes in birth rate, treatment discontinuation and mortality into the calculations and the effect of this omission on the budget impact results is unknown.
- Budget impact is calculated based on an average dose of two tablets a day for doxylamine/pyridoxine and three tablets for all comparators. Considering that the maximum dose of doxylamine/pyridoxine is four tablets daily, this could underestimate the cost of doxylamine/pyridoxine. Assuming three tablets a day for doxylamine/pyridoxine (with gradual increase of dosage) results in a budget impact of £73,669 in Year 1, increasing to £368,112 in Year 5. Using four tablets a day would increase budget impact to and £96,897 in Year 1, increasing to £484,178 in Year 5. According to the SPC[5], the weighted average in the pivotal trial was 3.41 tablets per day which would result in a budget impact of £83,193 in Year 1 and £415,699 in Year 5. AWTTC consider this the most plausible scenario.
- The treatment cycle is limited to 28 days in the budget impact analysis. However, the company states that NVP on average persists for six weeks[27]. Considering the higher acquisition cost of doxylamine/pyridoxine, increasing treatment duration to six weeks (with two tablets per day) would result in additional costs of £74,269 in Year 1, increasing to £371,104 in Year 5.
- The savings in resource use are based on a 50% reduction in hospitalisations as reported by Neutel (2000)[26] and Kutcher et al. (2003)[39]. These studies

explored the rate of birth defects and hospitalisation with Bendectin® in Canada and the United States of America between the 1970s and 1990s, respectively. The assumptions of causality and transferability of results to the present analysis are highly questionable.

- The budget impact considerations are limited to acquisition costs and hospitalisation costs only; other resource use is not included (e.g. monitoring costs and costs associated with adverse events).
- Uptake rate estimates for doxylamine/pyridoxine are based on assumptions made by the company and might underestimate actual uptake considering the lack of licensed treatments for severe NVP. However, the company provides basic sensitivity analysis to explore the impact of 10% variability in doxylamine/pyridoxine uptake rates on the displacement of the other comparators and budget impact.

GLOSSARY

The Pregnancy Unique Quantification of Emesis (PUQE) scoring system[6]

PUQE score (select an appropriate score for each of the three items and total them)					
In the last 24 h, for how long have you felt nauseated or sick to your stomach?	Not at all (1)	≤ 1 h (2)	2–3 h (3)	4–6 h (4)	>6 h (5)
In the last 24 h, how many times have you vomited or thrown up?	None (1)	1–2 (2)	3–4 (3)	5–6 (4)	≥ 7 (5)
In the last 24 h, how many times have you had retching or dry heaves without bringing anything up?	None (1)	1–2 (2)	3–4 (3)	5–6 (4)	≥ 7 (5)
PUQE score interpretation: Mild: ≤ 6; Moderate: 7–12; Severe: 13–15					

The Global Assessment of Well-Being (GAWB) questionnaire[6]

Global Assessment of Well-Being
How many hours have you slept out of 24 h?
If this is not your normal sleep hours, why?
On a scale of 0–10, how would you rate your well-being in the last week? *Reference Scale 0 (worst possible) to 10 (the best you felt before pregnancy)*
Can you tell me what causes you to feel that way?

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