

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

Evidence summary

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Key messages

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

Xonvea (Alliance Pharmaceuticals) is a delayed-release tablet containing doxylamine succinate 10 mg (an antihistamine) and pyridoxine hydrochloride 10 mg (vitamin B6). In July 2018, it was granted a marketing authorisation for treating nausea and vomiting of pregnancy in women (aged 18 years or older) who do not respond to conservative management. Doxylamine/pyridoxine is taken every day and not on an as needed basis.

Evidence was from 2 randomised, double-blind, placebo-controlled multicentre trials in the US (Koren et al. 2010 and the DESI study, which was undertaken in 1975 and reported by Zhang et al. 2017). In the key licensing study by Koren et al. (2010), symptoms of nausea and vomiting were evaluated using the Pregnancy unique quantification of emesis (PUQE) score. Small but statistically significant improvements in PUQE scores were seen with doxylamine/pyridoxine compared with placebo at days 3, 4, 5 and 15. The MHRA concluded that the improvements are clinically important for women suffering from nausea and vomiting of pregnancy. The supporting study (the DESI study reported by Zhang et al. 2017) also found that, overall, doxylamine/pyridoxine improved symptoms of nausea and vomiting compared with placebo.

Extensive data suggest that doxylamine/pyridoxine is safe for pregnant women to use, and that it is

relatively well tolerated. The results of epidemiological studies designed to detect possible teratogenicity show no association with fetal abnormalities ([UK public assessment report](#)).

Likely place in therapy

NICE's guideline on [antenatal care for uncomplicated pregnancies](#) and the Royal College of Obstetricians and Gynaecologists' (RCOG) guideline on [the management of nausea and vomiting of pregnancy](#) (which predate the availability of doxylamine/pyridoxine in the UK) recommend antihistamines or phenothiazines as first-line medicines. Doxylamine/pyridoxine offers a specifically licensed, but more costly option (on a per tablet basis) for women with symptoms that have not responded to conservative management (for example, ginger, acupuncture, and dietary and lifestyle advice). However, there is no evidence to show how the safety and efficacy of doxylamine/pyridoxine compares with current first-line treatment options such as antihistamines and phenothiazines.

The MHRA has advised (personal communication: February 2019) that use of antihistamines or phenothiazines for nausea and vomiting of pregnancy is not off-label because they are not explicitly contraindicated in pregnancy (although their use is cautioned). The exception to this is Buccastem M, which is contraindicated in pregnancy. The MHRA also noted that, because of prescribing hierarchy, the use of other medicines that do not have a specific licence for nausea and vomiting of pregnancy over doxylamine/pyridoxine, which does, would need to be justified.

Although antihistamines and phenothiazines are not specifically licensed for treating nausea and vomiting of pregnancy, their use is established in clinical practice and most have been used in pregnancy without any known adverse effects on the developing baby (UK Teratology Information Service, [Treating nausea and vomiting of pregnancy](#)). Product literature for many of these medicines advises caution in pregnancy, which should be discussed with pregnant women before they are prescribed. Some prescribers and women may prefer doxylamine/pyridoxine because it is specifically licensed for use in pregnant women.

Factors for decision making

Effectiveness

Symptoms of nausea and vomiting

At day 15, Koren et al. (2010) found a small but statistically significant improvement in the mean [Pregnancy unique quantification of emesis](#) (PUQE) symptom score (a measure of the severity of

nausea and vomiting) in the doxylamine/pyridoxine group compared with the placebo group (-4.8 compared with -3.9 respectively, $p=0.006$). Post hoc analyses obtained similar results at days 3, 4 and 5 (all differences around -1.0 point on a scale from 3 to 15 points, all $p\leq 0.002$). The differences between the groups are small but are considered clinically important by the MHRA (UK public assessment report).

The DESI study was undertaken in 1975 but not published because it was an FDA regulatory study for which publication was not routine at that time. Zhang et al. obtained the data and published their report in 2017. Over 7 days, statistically significant improvements (classed as moderate or excellent) were seen with doxylamine/pyridoxine compared with placebo in doctors' evaluations of effectiveness (78% compared with 57%, $p<0.01$) and improvement in nausea (75% compared with 52%, $p<0.001$) but not in improvement in vomiting (73% compared with 66%, $p=0.17$, not statistically significant).

Global assessment of wellbeing

Koren et al. (2010) also found a small statistically significant improvement in the global assessment of wellbeing score at 15 days (a second primary outcome) with doxylamine/pyridoxine compared with placebo (2.8 compared with 1.8, difference 1.0 point on a scale from 0 to 10 points, $p=0.005$).

Other outcomes

In the study by Koren et al. (2010), significantly fewer women taking doxylamine/pyridoxine used alternative therapies compared with women taking placebo (23.7% compared with 36.8% respectively, $p=0.04$). Also, significantly more women taking doxylamine/pyridoxine asked to continue compassionate use of their medication after the study (48.9% compared with 32.8%, $p=0.009$).

Safety

The safety profile of doxylamine/pyridoxine is relatively well established. The most common adverse reactions (incidence at least 1 in 100) are somnolence, dizziness, dry mouth and fatigue ([summary of product characteristics](#)).

In the study by Koren et al. (2010), there were no statistically significant differences between doxylamine/pyridoxine and placebo in the rates of any adverse events. Adverse events also appeared to be similar between the groups in the DESI study reported by Zhang et al. (2017), although statistical analyses were not undertaken.

The [UK public assessment report](#) states that there are extensive post-marketing and clinical data suggesting that doxylamine/pyridoxine is safe for pregnant women to use, and that it is well tolerated. Also, doxylamine/pyridoxine has been the subject of many epidemiological studies designed to detect possible teratogenicity, and the results from these studies show no association with fetal abnormalities.

Limitations of the evidence

The study by Koren et al. (2010) has some limitations. For example, the study duration was 15 days only, although nausea and vomiting of pregnancy can last longer than this. Also, the PUQE symptom and wellbeing scores are subjective, based on women's records in daily diaries, and it is unclear how large improvements would need to be to be considered clinically meaningful. Women with mild symptoms of nausea and vomiting of pregnancy were excluded from the study, as were those aged under 18 years.

The DESI study reported by Zhang et al. 2017 predated trial reporting guidelines and has important limitations. For example, the study lasted 7 days only, final results of the study were not published, data from only two thirds of participants were analysed (the per protocol population), and few details about baseline information, outcome determination or statistical analyses were available. The study predated the PUQE score and, therefore, used doctors' and women's subjective assessments rather than a validated scale to assess nausea and vomiting.

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

The included studies do not provide any data on subgroups of women with different severities of nausea and vomiting of pregnancy (including hyperemesis gravidarum), or women who experienced the condition in a previous pregnancy. Most women in the study by Koren et al. (2010) had moderate symptoms of nausea and vomiting of pregnancy at baseline.

Person-related factors

Some antihistamines and phenothiazines are licensed for treating nausea and vomiting. However, they are not specifically licensed for treating nausea and vomiting of pregnancy and carry warnings about use in pregnancy that may alarm some women if they have not been counselled. NICE and RCOG guidelines recommend antihistamines and phenothiazines for treating nausea and vomiting

of pregnancy, and there is extensive clinical experience of their use. However, some women may prefer to take doxylamine/pyridoxine because it is specifically licensed for use in pregnant women.

It is not known whether doxylamine/pyridoxine is more effective than an antihistamine alone or a phenothiazine, and some women may prefer to try a single treatment before they try a combination of 2 treatments. Almost two thirds of people in the study by Koren et al. (2010) took the maximum dosage of doxylamine/pyridoxine (4 tablets daily). Some women might prefer to take a tablet that only needs taking once or twice daily, or which can be used on an as needed basis.

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

Resource implications

The cost of 20 doxylamine/pyridoxine tablets is £28.50 (BNF, February 2019). A pack of 20 tablets would be expected to last 5 to 10 days depending on the dosage needed (2 to 4 tablets daily) to manage the woman's nausea and vomiting. Treatment for 6 to 8 weeks would cost about £240 to £320 if 4 tablets were taken each day.

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

See the [full evidence review](#) for more information.

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