February 2016

Horizon Scanning Research & Intelligence Centre

Diclectin (doxylamine succinate and pyridoxine hydrochloride) for the treatment of nausea and vomiting in pregnancy

LAY SUMMARY

Nausea and vomiting in pregnancy, also known as morning sickness, is very common in early pregnancy. It is unpleasant, but usually stops by weeks 16 to 20 of pregnancy. Some women get a very severe form of nausea and vomiting called hyperemesis gravidarum, which can be very serious and needs specialist treatment in hospital.

There are currently no medications that are specifically licensed to treat nausea and vomiting in pregnancy, although medications licensed for other diseases can be used. Diclectin is a new drug that is designed to specifically treat nausea and vomiting in pregnancy.

Diclectin is being studied to see whether it improves nausea and vomiting in pregnancy and that it is safe to use for pregnant women. If diclectin is licensed for use in the UK, it could provide a new treatment for this unpleasant condition where other non-medical remedies have not worked.

NIHR HSRIC ID: 8800

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This briefing presents independent research funded by the National Institute for Health Research (NIHR). The views expressed are those of the author and not necessarily those of the NHS, the NIHR or the Department of Health.

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NHS National Institute for Health Research

TARGET GROUP

Treatment of nausea and vomiting in pregnancy (NVP) – women who have not adequately responded to conservative management.

TECHNOLOGY

DESCRIPTION

Diclectin (formerly known as Benedectin in the USA, Debendox in the UK, and Lenotan or Merbental in other countries) is a combination preparation of doxylamine succinate and pyridoxine hydrochloride. Doxylamine succinate is an antihistamine (histamine H1 receptor antagonist) and pyridoxine is vitamin B6. This combination of agents provides anti-nauseant and anti-emetic activity, and is intended for use in pregnant women who have not adequately responded to conservative management. Diclectin is administered orally as 2-4 10mg tablets per day.

Diclectin does not currently have a Marketing Authorisation in the EU for any indication; however this combination of agents was previously marketed in the UK as Debendox and withdrawn by the manufacturer in 1983, due to the burden of litigation and not due to reasons of safety or efficacy.

INNOVATION and/or ADVANTAGES

If licensed, diclectin will offer an additional treatment option for pregnant women with nausea and vomiting.

DEVELOPER

Duchesnay Inc.

AVAILABILITY, LAUNCH OR MARKETING

In phase III trials.

PATIENT GROUP

BACKGROUND

NVP is the most common medical condition of pregnancy[1]. Symptoms may vary among women from a slight feeling of nausea in the morning to more severe nausea and vomiting and/or retching that continue throughout the day[2]. NVP usually begins between 4 and 9 weeks gestation[2]. The aetiology of NVP has yet to be clearly defined. NVP is best conceived of as a syndrome in which a product or products of the placenta directly stimulate the vomiting centre and lower the threshold for vomiting by the classic pathways (e.g., vestibular, gastrointestinal, or via the area postrema). The leading candidates for the fundamental stimulus for NVP are human chorionic gonadotrophin (hCG) (or one of its isoforms) and oestradiol[2].

Hyperemesis gravidarum is a more severe form of NVP, affecting less than 1% of pregnant women[3]. The features of this include: intractable vomiting associated with weight loss of more than 5% of pre-pregnancy weight, dehydration, electrolyte imbalances, and ketosis; it typically requires admission to hospital[4]. Guidance recommends that all women who present with severe NVP should be carefully assessed and treated to avoid the need for hospital admission; however in hyperemesis gravidarum, admission may be necessary to avoid serious maternal and foetal morbidity[4]. Maternal complications of severe hyperemesis gravidarum include Wernicke's encephalopathy, as a result of thiamine deficiency[5], and foetal complications, such as foetal growth restriction[6,7].

NHS or GOVERNMENT PRIORITY AREA

None identified.

CLINICAL NEED and BURDEN OF DISEASE

NVP affects up to 80% of all pregnant women to some degree. In most cases, it subsides by the 16th week of pregnancy, although up to 20% of women continue to have symptoms throughout pregnancy[1]. The severity of NVP can range from mild to severe; 50-55% of pregnant women have daily episodes of vomiting at some point in their pregnancy, with 87% of those affected by NVP experiencing nausea more than five times or constantly throughout the day[2]. Hyperemesis gravidarum affects less than 1% of pregnant women[3].

In England and Wales in 2013, there were 690,820 maternities[8]. In 2014-2015, there were 32,929 admissions for NVP (ICD10 O21.0-21.9), resulting in 40,326 bed days and 31,668 finished consultant episodes[9].

The population likely to be eligible to receive diclectin could not easily be estimated from available routine published sources.

PATIENT PATHWAY

RELEVANT GUIDANCE

NICE Guidance

- NICE clinical guideline. Antenatal care for uncomplicated pregnancies (CG62). March 2008.

Other Guidance

- NHS Clinical Knowledge Summary. Antenatal care - uncomplicated pregnancy. 2011[10].

CURRENT TREATMENT OPTIONS

Guidelines recommend that women should be informed that most cases of nausea and vomiting in pregnancy will resolve spontaneously within 16 to 20 weeks and that nausea and vomiting are not usually associated with a poor pregnancy outcome[11]. Women should be advised to avoid exposure to triggers such as specific odours and particular foods, and told

that symptoms may be reduced by eating dry bland foods, little and often, and ensuring adequate hydration[4].

Following conservative management, guidelines recommend that if a woman requests or would like to consider treatment, the following interventions appear to be effective in reducing symptoms[11]:

- Ginger (non-pharmacological).
- P6 (wrist) acupressure (non-pharmacological).
- Antihistamines (pharmacological).

Pharmacological treatment options, following intravenous (IV) fluid and electrolyte replacement, for the treatment of hyperemesis gravidarum include[4]:

- Cyclizine, 50mg three times daily, IV (unlicensed for this indication).
- Metoclopramide, 10mg three times daily, IV (unlicensed for this indication).
- Prochlorperazine, 5mg oral three times daily, 12.5mg three times daily, IV or intramuscular (IM) (unlicensed for this indication).
- Chlorpromazine, 10-25mg three times daily, oral, or 25mg three times daily, IM.
- Ondansetron, 4-8mg two-three times daily, IM or IV (unlicensed for this indication).
- Hydrocortisone, 100mg twice daily, oral (unlicensed for this indication).
- Prednisolone, 40-50mg each day in divided doses, oral (unlicensed for this indication).

EFFICACY and SAFETY

Trial	NCT00614445, DIC-301; pregnant females aged 18 years and over; Diclectin vs placebo; phase III.
Sponsor	Duchesnay Inc.
Status	Published.
Source of information	Publication[12], trial registery[13].
Location	USA.
Design	Randomised, double-blind, placebo-controlled.
Participants	n=280; aged over 18 years; females; pregnant; foetal gestational age 7-14 weeks; NVP; Pregnancy Unique Quantification of Emesis (PUQE) score ≥6[a].
Schedule	Randomised to doxylamine succinate 10mg/pyridoxine hydrochloride 10mg (Diclectin) 2-4 tablets daily; or placebo 2-4 tablets daily.
Follow-up	Active treatment for 14 days, follow up 30 days.
Primary outcome/s	Change in 2 domains (symptom domain and quality of life domain) of PUQE score from baseline.
Secondary outcome/s	Mean area under the curve of the change in PUQE from baseline as measured day-by-day, time loss from employment, number of women in each arm who continued with (blinded) compassionate use of her medication, number of patients reporting concurrent use of alternate therapy for NVP.
Key results	For Diclectin vs placebo, respectively: improvement in NVP symptoms (PUQE score), −4.8 ± 2.7 vs −3.9 ± 2.6 (p=0.006); mean area under the curve of the change in PUQE from baseline as measured day-by-day, 61.5 ± 36.9 vs 53.5 ± 37.5 (p<0.0001).

[a] The PUQE score measured hours of nausea, number of times vomiting, and number of times retching for a total overall score of symptoms on a scale rated from 3 (no symptoms) to 15 (most severe).

Adverse effects (AEs)	The use of Diclectin was not associated with an increased risk of any adverse effects (AEs) when compared with placebo. Secondary analysis of these data reported specifically on maternal safety: for Diclectin vs placebo, respectively: one or more AEs, 56.5% vs 51.2%; serious treatment-emergent AEs, 3.1% vs 3.1%. For Diclectin vs placebo, respectively: one or more AEs, 56.5% vs 51.2%; serious treatment-emergent AEs, 3.1% vs 3.1%.

ESTIMATED COST and IMPACT

COST

The company estimates that diclectin will cost between £100-£1,000 per patient per episode.

IMPACT - SPECULATIVE

Impact on Patients and Carers

- ☐ Reduced mortality/increased length of survival
- ☑ Reduced symptoms or disability
- ☐ Other
- ☐ No impact identified

Impact on Health and Social Care Services

- ☐ Increased use of existing services
- ☐ Decreased use of existing services
- ☐ Re-organisation of existing services
- ☐ Need for new services
- ☐ Other
- ☑ None identified

Impact on Costs and Other Resource Use

- ☑ Increased drug treatment costs
- ☐ Reduced drug treatment costs
- ☐ Other increase in costs
- ☐ Other reduction in costs
- ☐ Other
- ☐ None identified

Other Issues

- ☐ Clinical uncertainty or other research question identified
- ☑ None identified

REFERENCES

1 Einarson A, Maltepe C, Boskovic R, *et al*. Treatment of nausea and vomiting in pregnancy. An updated algorithm. Canadian Family Physician 2007;53:2109–2111.

2 Association of Professors of Gynecology and Obstetrics. Nausea and vomiting of pregnancy. www.apgo.org/education/women/nausea-and-vomiting-of-pregnancy.html Accessed 21 January 2016.

3 Niebyl JR. Nausea and vomiting in pregnancy. New England Journal of Medicine 2010;363:1544-55.

4 Jarvis S and Nelson-Piercy C. Management of nausea and vomiting in pregnancy. BMJ 2011;342:d3606.

5 Chiossi G, Neri I, Cavazzuti M *et al*. Hyperemesis gravidarum complicated by Wernicke encephalopathy: background, case report, and review of the literature. Obstetrical and Gynecological Survey 2006;61:255-68.

6 Fejzo MS, Poursharif B, Korst LM *et al*. Symptoms and pregnancy outcomes associated with extreme weight loss among women with hyperemesis gravidarum. Journal of Womens Health (Larchmt) 2009;18:1981-7.
7 Van Oppenraaij RH, Jauniaux E, Christiansen OB *et al*. ESHRE Special Interest Group for Early Pregnancy (SIGEP). Predicting adverse obstetric outcome after early pregnancy events and complications: a review. Human Reproduction Update 2009;15:409-21.
8 Office for National Statistics. Birth summary tables England and Wales 2013.. www.ons.gov.uk
9 Health & Social Care Information Centre. Hospital Episode Statistics for England. Inpatient statistics, 2014-15. www.hscic.gov.uk
10 NHS Clinical Knowledge Summary. Antenatal care – uncomplicated pregnancy. March 2011. http://cks.nice.org.uk/antenatal-care-uncomplicated-pregnancy Accessed 21 January 2016.
11 National Institute for Health and Clinical Excellence. Clinical guidelines. Antenatal care for uncomplicated pregnancies (CG62). March 2008.
12 Koren G, Clark S, Hankins G *et al*. Effectiveness of delayed-release doxylamine and pyridoxine for nausea and vomiting of pregnancy: a randomized placebo controlled trial. American Journal of Obstetrics and Gynecology 2010;203(6):571.e1-571.e7.
13 ClinicalTrials.gov. The efficacy of diclectin for nausea and vomiting of pregnancy. https://clinicaltrials.gov/ct2/show/NCT00614445 Accessed 21 January 2016.