Alex Murphy

The Ohio State University College of Pharmacy
Drug Monograph Assignment

Diclegis - doxylamine and pyridoxine
Duchesnay USA

AHFS THERAPEUTIC CLASS: 56:22.08 – Antihistamines *(previously 56:22.92 - Antiemetics, Miscellaneous)*

MECHANISM OF ACTION: The mechanism of action of Diclegis is unknown. Mechanism of individual components: doxylamine: first generation antihistamine; pyridoxine: water-soluble vitamin.

FDA APPROVED INDICATION: treatment of nausea and vomiting of pregnancy (NVP) in women who do not respond to conservative management. Limitations of use: has not been evaluated in patients with hyperemesis gravidarum.

CLINICAL EFFICACY: A double-blind, randomized, placebo-controlled study was conducted to support the safety and efficacy of Diclegis. Adult women ≥18yo and 7 to 14 weeks gestation with NVP were randomized to 14 days of Diclegis or placebo. Diclegis was administered according to the dosing schedule, including dose titration from days 2-4 for persistent symptoms. Over the treatment period, 19% remained on initial dosing (2 tablets daily), 21% received 3 tablets daily, and 60% received 4 tablets daily. The primary endpoint was the change from baseline at Day 15 in the Pregnancy Unique-Quantification of Emesis (PUQE) score, which incorporates number of daily vomiting episodes and heaves, and length of daily nausea in hours, for an overall score of symptoms rated 3 (no symptoms) to 15 (most severe). At baseline, the mean PUQE score was 9, and at Day 15 there was a 0.7 (95% CI, 0.2-1.2, P=0.006) mean decrease in the Diclegis group compared to placebo (-4.8 vs. -3.9).

PHARMACOKINETICS
Absorption: GI tract (jejunum); time to peak of doxylamine and pyridoxine are 7.5 and 5.5 hours, respectively.
Food effect: doxylamine and pyridoxine associated with delayed absorption; both have decreases in Cmax.
Distribution: pyridoxine is highly protein bound (albumin) and its active metabolite.
Metabolism: doxylamine: hepatic by N-dealkylation to metabolites; pyridoxine: prodrug, metabolized by liver to active PLP.
Elimination: both excreted by kidney as urine as metabolites. Half-life: doxylamine 12.5 hours; pyridoxine 0.5 hours (PLP ~80 hours).

ADVERSE REACTIONS: Somnolence (14%), drowsiness, dizziness, constipation, xerostomia, urinary retention, palpitations.

SAFETY CONSIDERATIONS
- Sound-alike/look-alike issues: doxylamine may be confused with doxycycline.
- Contraindications: Concomitant use with MAOIs. Hypersensitivity to doxylamine, pyridoxine, ethanolamine-derivative antihistamines, or any inactive ingredient.
- Precautions:
  - Activities requiring mental alertness: falls/accidents resulting from combining with CNS depressants or alcohol.
  - Comorbid conditions: asthma, increased intraocular pressure, narrow angle glaucoma, others.
  - Interference with urine screen: false positive reports for methadone, opiates, and PCP.
- No Boxed Warnings, Sentinel Events Advisory, Hazardous Risk Category, or REMS program.

SPECIAL POPULATIONS
- Pregnancy: Diclegis is intended for use in pregnant women. Studies have shown no increased risk of fetal abnormalities.
- Lactation: doxylamine and pyridoxine found in breast milk; breastfeeding not recommended by manufacturer.
- Geriatrics: doxylamine: avoid use (Beer's Criteria); pyridoxine has other uses.
- Pediatrics: safety and effectiveness <18 years old have not been established; either alone have other uses.
- Hepatic/Renal Impairment: no dosage adjustments provided in labeling.

DRUG INTERACTIONS: Concomitant use with MAOIs is contraindicated. Concurrent use with CNS depressants is not recommended.

DOSAGE FORMS AVAILABLE: Delayed release, film-coated tablets: doxylamine succinate 10mg and pyridoxine hydrochloride 10mg.

DOSING: Initial: 2 tablets at bedtime on day 1 and 2; if symptoms persist, take 1 tablet in morning and 2 tablets at bedtime on day 3; if symptoms persist, may increase to 1 tablet in morning, 1 tablet mid-afternoon, and 2 tablets at bedtime on day 4 (maximum: doxylamine 40mg/pyridoxine 40mg (4 tablets) per day).

ADMINISTRATION: Take on empty stomach with a glass of water. Do not crush/chew/split. Taken as scheduled, not as needed.

COST COMPARISON:

Drug	Dosing	Unit Cost	Daily Cost	14-Day Cost
Diclegis 10mg/10mg	see dosing; max 4/day	$5.20	$20.80	$250 ^
doxylamine 25mg	0.5 q6-8h prn	$0.20	$0.36	$5
pyridoxine 25mg	0.5-1 q6-8h prn	$0.05	$0.22	$3
dimenhydrinate, diphenhydramine	25-50mg q4-6h prn	$0.20	$2.15	$30

^Day 4-14 dosing, per study: 19% take 2 tabs/day ($145), 21% take 3 tabs/day ($208), 60% take 4 tabs/day ($265)

MONITORING PARAMETERS: Daily episodes of vomiting, heaves, and length; assess need for therapy as pregnancy progresses.

CONCLUSION:

- Arguments supporting addition
  - Well tolerated; relatively mild side effect profile compared to 2nd-line interventions
- Arguments against addition
  - Expensive; cheaper substitutes available OTC with similar dosing
  - May not provide significant relief of symptoms

RECOMMENDATION: Add with restrictions.

Diclegis has shown to be modestly effective in treating NVP and has a mild side effect profile. Diclegis should be reserved for those who have failed conservative management and lifestyle efforts, and who have failed a trial of the cheaper individual components available OTC (doxylamine 12.5mg and pyridoxine 25mg q6-8h). Furthermore, the efficacy of Diclegis should be apparent within four days of treatment; therefore, if no relief of symptoms is experienced with Diclegis in the first four days, therapy should be stopped and 2nd-line agents such as dimenhydrinate or diphenhydramine should be initiated. In conclusion, Diclegis is a costly combination medication that can provide modest relief of symptoms of NVP but should be reserved for those who do not respond to conservative treatment.

REFERENCES:

Barss VA. Nausea and vomiting of pregnancy: Treatment and outcome. In: UpToDate, Post TW (Ed), UpToDate, Waltham, MA. [Updated May 4, 2021; Accessed on August 4, 2021]. https://www.uptodate.com/contents/nausea-and-vomiting-of-pregnancy-treatment-and-outcome

Data.medicaid.gov. https://data.medicaid.gov/Drug-Pricing-and-Payment/NADAC-National-Average-Drug-Acquisition-Cost-/a4y5-998d/data. [Updated August 4, 2021; Accessed August 5, 2021].

Diclegis [package insert]. Bryn Mawr, PA. Duchesnay USA, Inc; Initial approval 1976. https://www.accessdata.fda.gov/drugsatfda_docs/label/2013/021876s002lbl.pdf. Accessed August 3, 2021.

Lexicomp, Doxylamine and Pyridoxine. Lex-Drugs. Lexicomp. Wolters Kluwer. Hudson, OH. [Updated July 19, 2021; Accessed August 3, 2021]. https://online.lexi.com/lco/action/doc/retrieve/docid/patch_f/6794.

Lexicomp, Doxylamine. Lex-Drugs. Lexicomp. Wolters Kluwer. Hudson, OH. [Updated July 19, 2021; Accessed August 3, 2021]. https://online.lexi.com/lco/action/doc/retrieve/docid/patch_f/296483.

Lexicomp, Pyridoxine. Lex-Drugs. Lexicomp. Wolters Kluwer. Hudson, OH. [Updated July 19, 2021; Accessed August 3, 2021]. https://online.lexi.com/lco/action/doc/retrieve/docid/patch_f/7594.