DUCHESNAY USA
Caring for mother and child during pregnancy

Diclegis®
(doxylamine succinate and pyridoxine hydrochloride)
delayed-release tablets 10mg/10mg

Dear Doctor,

Duchesnay USA has announced the approval of **DICLEGIS®** (doxylamine succinate and pyridoxine hydrochloride) delayed-release tablets, a fixed dose combination drug product for the treatment of nausea and vomiting of pregnancy in women who do not respond to conservative management. DICLEGIS delayed-release tablets are white, round, film-coated tablets containing 10 mg doxylamine succinate and 10 mg pyridoxine hydrochloride.

Patients should initially take two DICLEGIS delayed-release tablets orally at bedtime (Day 1). If this dose adequately controls symptoms the next day, patients should continue taking two tablets daily at bedtime. However, if symptoms persist into the afternoon of Day 2, patients should take the usual dose of two tablets at bedtime that night, and then should take three tablets starting on Day 3 (one tablet in the morning and two tablets at bedtime). If these three tablets adequately control symptoms on Day 4, patients should continue taking three tablets daily. Otherwise, patients should take four tablets starting on Day 4 (one tablet in the morning, one tablet mid-afternoon, and two tablets at bedtime).

The maximum recommended dose is four tablets (one in the morning, one in the mid-afternoon, and two at bedtime) daily. DICLEGIS is taken as a daily prescription and not on an as needed basis to help control symptoms throughout the day.

Limitations of Use

Diclegis has not been studied in women with hyperemesis gravidarum.

The efficacy of DICLEGIS for the treatment of nausea and vomiting in pregnancy has been demonstrated in a double-blind, randomized, multi-center, placebo-controlled study. Adult women age 18 and older and 7 to 14 weeks gestation (median 9 weeks) with nausea and vomiting of pregnancy were randomized to 14 days of either DICLEGIS or placebo.

Over the treatment period, 19% of DICLEGIS patients remained on 2 tablets daily, 21% received 3 tablets daily, and 60% received 4 tablets daily.

- The primary efficacy endpoint was the change from baseline at Day 15 in the Pregnancy-Unique Quantification of Emesis (PUQE) score.

Results were as follows:

Change from Baseline in the Primary Endpoint, PUQE score at Day 15. (Intent-to-Treat Population with Last-Observation Carried Forward)

PUQE Score*	DICLEGIS	Placebo	Treatment Difference (95% Confidence Interval)
Baseline	9.0 ± 2.1	8.8 ± 2.1	
Change from Baseline at Day 15	-4.8 ± 2.7	-3.9 ± 2.6	-0.7 [-1.2,-0.2]

*PUQE score incorporated the number of daily vomiting episodes, number of daily heaves, and lengths of daily nausea in hours, for an overall score of symptoms rated from 3 (no symptoms) to 15 (most severe). Baseline was defined as the PUQE score completed at the enrollment visit.

- There was a 0.7 (95% confidence interval 0.2-1.2 with p-value 0.006) mean decrease from baseline in PUQE score at Day 15 with DICLEGIS compared to placebo.

Indication

DICLEGIS® is a fixed-dose combination drug product of doxylamine succinate, an antihistamine, and pyridoxine hydrochloride, a vitamin B_6 analog, indicated for the treatment of nausea and vomiting of pregnancy in women who do not respond to conservative management.

Limitations of Use

DICLEGIS has not been studied in women with hyperemesis gravidarum.

Important Safety Information

DICLEGIS is contraindicated in women with known hypersensitivity to doxylamine succinate, other ethanolamine derivative antihistamines, pyridoxine hydrochloride, or any inactive ingredient in the formulation. DICLEGIS is also contraindicated in combination with monoamine oxidase inhibitors (MAOIs) as MAOIs intensify and prolong the adverse CNS effects of DICLEGIS. Use of MAOIs may also prolong and intensify the anticholinergic (drying) effects of antihistamines.

DICLEGIS may cause somnolence due to the anticholinergic properties of doxylamine succinate, an antihistamine. Women should avoid engaging in activities requiring complete mental alertness, such as driving or operating heavy machinery, while using DICLEGIS until cleared to do so by their healthcare provider.

Use of DICLEGIS is not recommended if a woman is concurrently using CNS depressants, such as alcohol or sedating medications, including other antihistamines (present in some cough and cold medications), opiates, and sleep aids. The combination of DICLEGIS and CNS depressants could result in severe drowsiness leading to falls or other accidents.

DICLEGIS has anticholinergic properties and should be used with caution in women who have: (1) asthma, (2) increased intraocular pressure, (3) an eye problem called narrow angle glaucoma, (4) a stomach problem called stenosing peptic ulcer, (5) pyloroduodenal obstruction, or (6) a bladder problem called bladder-neck obstruction.

Fatalities have been reported from doxylamine overdose in children. Children appear to be at a high risk for cardiorespiratory arrest. However, the safety and effectiveness of DICLEGIS in children under 18 years of age have not been established.

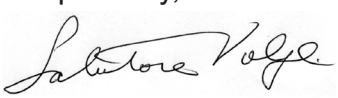
DICLEGIS is a delayed-release formulation; therefore, signs and symptoms of intoxication may not be apparent immediately. Signs and symptoms of overdose may include restlessness, dryness of mouth, dilated pupils, sleepiness, vertigo, mental confusion, and tachycardia. If you suspect an overdose or seek additional overdose information, you can contact a poison control center at 1-800-222-1222.

The FDA granted DICLEGIS Pregnancy Category A status, which means that the results of controlled studies have not shown increased risk to an unborn baby during pregnancy.

Women should not breast-feed while using DICLEGIS because the antihistamine component (doxylamine succinate) in DICLEGIS can pass into breast milk. Excitement, irritability, and sedation have been reported in nursing infants presumably exposed to doxylamine succinate through breast milk. Infants with apnea or other respiratory syndromes may be particularly vulnerable to the sedative effects of DICLEGIS resulting in worsening of their apnea or respiratory conditions.

For additional information about DICLEGIS, please refer to the full prescribing information, available at www.diclegis.com.

Respectfully,



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Physicians' Desk Reference®

Tablet(s) shown may not be actual size