

DICLEGIS- doxylamine succinate and pyridoxine hydrochloride tablet, delayed release
Duchesnay USA, Inc.

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use DICLEGIS safely and effectively. See full prescribing information for DICLEGIS.

Initial U.S. Approval: 1976

INDICATIONS AND USAGE

DICLEGIS is a fixed dose combination drug product of doxylamine succinate, an antihistamine, and pyridoxine hydrochloride, a Vitamin B6 analog, indicated for the treatment of nausea and vomiting of pregnancy in women who do not respond to conservative management. (1)

DOSAGE AND ADMINISTRATION

Take two tablets daily at bedtime. If symptoms are not adequately controlled, the dose can be increased to a maximum recommended dose of four tablets daily (one in the morning, one mid-afternoon and two at bedtime) as described in the full prescribing information. (2)

DOSAGE FORMS AND STRENGTHS

Delayed-release tablets containing 10 mg doxylamine succinate and 10 mg pyridoxine hydrochloride. (3)

CONTRAINDICATIONS

- Known hypersensitivity to doxylamine succinate, other ethanolamine derivative antihistamines, pyridoxine hydrochloride or any inactive ingredient in the formulation (4)
- Monoamine oxidase (MAO) inhibitors (4, 7)

WARNINGS AND PRECAUTIONS

- Central nervous system (CNS) depressants: Concurrent use with alcohol or other CNS depressants is not recommended (5.1)
- Anticholinergic actions: Use with caution in patients with asthma, increased intraocular pressure, narrow angle glaucoma, stenosing peptic ulcer, pyloroduodenal obstruction and urinary bladder-neck obstruction (5.2)

ADVERSE REACTIONS

The most common adverse reaction with DICLEGIS (≥ 5 percent and exceeding the rate in placebo) is somnolence. (6)

To report SUSPECTED ADVERSE REACTIONS, contact Duchesnay Inc. at 1-855-722-7734 or medicalinfo@duchesnayusa.com or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- Severe drowsiness can occur when used in combination with alcohol or other sedating medications. (7)

USE IN SPECIFIC POPULATIONS

Pregnancy Category A. DICLEGIS is intended for use in pregnant women. (8.1)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 5/2013

- Activities requiring mental alertness: Avoid engaging in activities requiring complete mental alertness, such as driving or operating heavy machinery, while using DICLEGIS until cleared to do so by a healthcare provider ([5.1](#))

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

DICLEGIS is 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.

2 DOSAGE AND ADMINISTRATION

2.1 Dosage Information

Initially, take two DICLEGIS delayed-release tablets orally at bedtime (Day 1). If this dose adequately controls symptoms the next day, continue taking two tablets daily at bedtime. However, if symptoms persist into the afternoon of Day 2, take the usual dose of two tablets at bedtime that night then 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, continue taking three tablets daily. Otherwise 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.

Take on an empty stomach with a glass of water [[see Clinical Pharmacology \(12.3\)](#)]. Swallow tablets whole. Do not crush, chew, or split DICLEGIS tablets.

Take as a daily prescription and not on an as needed basis. Reassess the woman for continued need for DICLEGIS as her pregnancy progresses.

3 DOSAGE FORMS AND STRENGTHS

DICLEGIS delayed-release tablets are white, round, film coated tablets containing 10 mg doxylamine succinate and 10 mg pyridoxine hydrochloride. The tablets are imprinted with the pink image of a pregnant woman on one side.

4 CONTRAINDICATIONS

DICLEGIS is contraindicated in women with any of the following conditions:

- Known hypersensitivity to doxylamine succinate, other ethanolamine derivative antihistamines, pyridoxine hydrochloride or any inactive

- ingredient in the formulation

- Monoamine oxidase (MAO) inhibitors intensify and prolong the adverse central nervous system effects of DICLEGIS [[see Drug Interactions \(7.1\)](#)].

5 WARNINGS AND PRECAUTIONS

5.1 Activities Requiring Mental Alertness

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.

DICLEGIS use is not recommended if a woman is concurrently using central nervous system (CNS) depressants including alcohol. The combination may result in severe drowsiness leading to falls or accidents [[see Drug Interactions \(7.1\)](#)].

5.2 Concomitant Medical Conditions

DICLEGIS has anticholinergic properties and, therefore, should be used with caution in women with: asthma, increased intraocular pressure, narrow angle glaucoma, stenosing peptic ulcer, pyloroduodenal obstruction and urinary bladder-neck obstruction.

6 ADVERSE REACTIONS

The following adverse reactions are discussed elsewhere in the labeling:

- Somnolence [[see Warnings and Precautions \(5.1\)](#)]

- Falls or other accidents resulting from the effect of the combined use of DICLEGIS with CNS depressants including alcohol [[see Warnings and Precautions \(5.1\)](#)]

6.1 Clinical Trial Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

The safety and efficacy of DICLEGIS were compared to placebo in a double-blind, randomized, multi-center trial in 261 women with nausea and vomiting of pregnancy. The mean gestational age at enrollment was 9.3 weeks, range 7 to 14 weeks gestation [[see Clinical Studies \(14\)](#)]. Adverse reactions for DICLEGIS that occurred at an incidence ≥ 5 percent and exceeded the incidence for placebo are summarized in Table 1.

Table 1: Number (Percent) of Subjects with ≥ 5 Percent Adverse Reactions in a 15 Day Placebo-Controlled Study of DICLEGIS (Only Those Adverse Reactions Occurring at an Incidence ≥ 5 Percent and at a Higher Incidence with DICLEGIS than Placebo are Shown)

| | Diclegis (N = 133) | Placebo (n = 128) |
|------------|-----------------------|----------------------|
| Somnolence | 19 (14.3%) | 15 (11.7%) |

6.2 Postmarketing Experience

The following adverse events, listed alphabetically, have been identified during post-approval use of the combination of 10 mg doxylamine succinate and 10 mg pyridoxine hydrochloride. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Cardiac disorders: dyspnea, palpitation, tachycardia

Ear and labyrinth disorders: vertigo

Eye disorders: vision blurred, visual disturbances

Gastrointestinal disorders: abdominal distension, abdominal pain, constipation, diarrhea

General disorders and administration site conditions: chest discomfort, fatigue, irritability, malaise

Immune system disorders: hypersensitivity

Nervous system disorders: dizziness, headache, migraines, paresthesia, psychomotor hyperactivity

Psychiatric disorders: anxiety, disorientation, insomnia, nightmares

Renal and urinary disorders: dysuria, urinary retention

Skin and subcutaneous tissue disorders: hyperhidrosis, pruritus, rash, rash maculo-papular

7 DRUG INTERACTIONS

7.1 Drug Interactions

Use of DICLEGIS is contraindicated in women who are taking monoamine oxidase inhibitors (MAOIs), which prolong and intensify the anticholinergic (drying) effects of antihistamines. Concurrent use of alcohol and other CNS depressants (such as hypnotic sedatives and tranquilizers) with DICLEGIS is not recommended.

7.2 Drug-Food Interactions

A food-effect study demonstrated that the delay in the onset of action of DICLEGIS may be further delayed, and a reduction in absorption may occur when tablets are taken with food [[see Dosage and Administration \(2\)](#), [Clinical Pharmacology \(12.3\)](#)]. Therefore, DICLEGIS should be taken on an empty stomach with a glass of water [[see Dosage and Administration \(2\)](#)].

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category A

DICLEGIS is intended for use in pregnant women.

The combination of doxylamine succinate and pyridoxine hydrochloride has been the subject of many epidemiological studies (cohort, case control and meta-analyses) designed to detect possible teratogenicity. A meta-analysis of 16 cohort and 11 case-control studies published between 1963 and 1991 reported no increased risk for malformations from first trimester exposures to doxylamine succinate and pyridoxine hydrochloride, with or without dicyclomine hydrochloride. A second meta-analysis of 12 cohort and 5 case-control studies published between

Reference ID: 3381709

1963 and 1985 reported no statistically significant relationships between fetal abnormalities and the first trimester use of the combination doxylamine succinate and pyridoxine hydrochloride with or without dicyclomine hydrochloride.

Animal Data

The effects of doxylamine succinate and pyridoxine hydrochloride on embryofetal development have been studied in rats and monkeys.

Once daily treatment of pregnant rats with doxylamine succinate and pyridoxine hydrochloride during organogenesis (gestational day (GD) 6-15) resulted in increased fetal resorptions, decreased fetal body weight and increased skeletal variations with reduced ossification at doses 60 to 100 times the highest clinical dose based on body surface area.

Pregnant cynomolgus monkeys were treated once daily with doxylamine succinate and pyridoxine hydrochloride during organogenesis (GD 22-50). At birth, there were no observed malformations, and no evidence of embryo, fetal or maternal toxicity at doses up to 3.2 times the highest proposed clinical dose based on body surface area. In a similarly designed study in pregnant cynomolgus and rhesus monkeys and baboons, ventricular septal defects (VSDs) were observed in the preterm (GD 100) fetuses. Doses used in this study were 0.5-20 times higher than the clinical dose based on body surface area, with no relationship between dose and incidence of VSD. There were no VSDs in infant monkeys at term. No VSDs were observed at GD 100 in cynomolgus monkeys administered the combination of doxylamine succinate and pyridoxine hydrochloride for 4-day periods between 22 and 41 days of gestation.

8.3 Nursing Mothers

Women should not breastfeed while using DICLEGIS.

The molecular weight of doxylamine succinate is low enough that passage into breast milk can be expected. 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.

Pyridoxine hydrochloride is excreted into breast milk. There have been no reports of adverse events in infants presumably exposed to pyridoxine hydrochloride through breast milk.

8.4 Pediatric Use

The safety and effectiveness of DICLEGIS in children under 18 years of age have not been established.

Fatalities have been reported from doxylamine overdose in children. The overdose cases have been characterized by coma, grand mal seizures and cardiorespiratory arrest. Children appear to be at a high risk for cardiorespiratory arrest. A toxic dose for children of more than 1.8 mg/kg has been reported. A 3 year old child died 18 hours after ingesting 1,000 mg doxylamine succinate. However, there is no correlation between the amount of doxylamine ingested, the doxylamine plasma level and clinical symptomatology.

10 OVERDOSAGE

10.1 Signs and Symptoms of Overdose

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.

At toxic doses, doxylamine exhibits anticholinergic effects, including seizures, rhabdomyolysis, acute renal failure and death.

10.2 Management of Overdose

If treatment is needed, it consists of gastric lavage or activated charcoal, whole bowel irrigation and symptomatic treatment. For additional

information about overdose treatment, call a poison control center (1 800-222-1222).

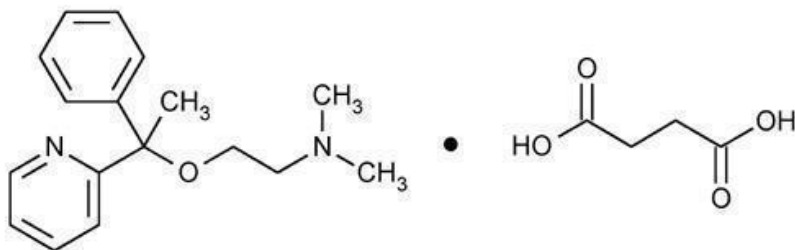
11 DESCRIPTION

DICLEGIS (doxylamine succinate and pyridoxine hydrochloride) delayed-release tablets are round, white, film-coated, delayed-release tablets containing 10 mg of doxylamine succinate and 10 mg of pyridoxine hydrochloride. Tablets are imprinted on one side with the pink image of a pregnant woman.

Inactive ingredients are as follows: ammonium hydroxide, n-butanol, carnauba wax powder, colloidal silicon dioxide, croscarmellose sodium, D&C Red#27, denatured alcohol, FD&C Blue#2, hypromellose, isopropyl alcohol, magnesium stearate, magnesium trisilicate, methacrylic acid copolymer, microcrystalline cellulose 102, PEG 8000, polysorbate 80, propylene glycol, shellac glaze, simethicone, sodium bicarbonate, sodium lauryl sulfate, talc, titanium dioxide, triethyl citrate.

Doxylamine Succinate

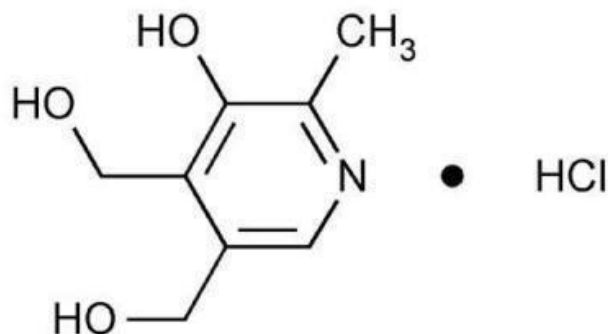
Doxylamine succinate is classified as an antihistamine. The chemical name for doxylamine succinate is ethanamine, N,N-dimethyl-2-[1-phenyl-1-(2-pyridinyl)ethoxy]-, butanedioate (1:1). The empirical formula is $C_{17}H_{22}N_2O \cdot C_4H_6O_4$ and the molecular mass is 388.46. The structural formula is:



Doxylamine succinate is a white to creamy white powder that is very soluble in water and alcohol, freely soluble in chloroform and very slightly soluble in ether and benzene.

Pyridoxine Hydrochloride

Pyridoxine hydrochloride is a vitamin B6 analog. The chemical name for pyridoxine hydrochloride is 3,4-pyridinedimethanol, 5-hydroxy-6-methyl-, hydrochloride. The empirical formula is $C_8H_{11}NO_3 \cdot HCl$ and the molecular mass is 205.64. The structural formula is:



Pyridoxine hydrochloride is a white or practically white crystalline powder that is freely soluble in water, slightly soluble in alcohol and insoluble in ether.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Reference ID: 3381709

The mechanism of action of DICLEGIS is unknown.

12.3 Pharmacokinetics

The pharmacokinetics of DICLEGIS has been characterized in healthy non-pregnant adult women. Pharmacokinetic results for doxylamine and pyridoxine, including its vitamin B6 metabolites, pyridoxal, pyridoxal 5'-phosphate, pyridoxamine and pyridoxamine 5'-phosphate, are summarized in Tables 2 to 5.

Absorption

A single-dose (two tablets) and multiple-dose (four tablets daily), open-label study was conducted to assess the safety and pharmacokinetic profile of DICLEGIS administered in healthy non-pregnant adult women. Single-doses (two tablets at bedtime) were administered on Days 1 and 2. Multiple-doses (one tablet in the morning, one tablet in the afternoon and two tablets at bedtime) were administered on Days 3-18.

Blood samples for pharmacokinetic analysis were collected pre-and post-dose on Days 2 and 18 as well as pre-dose prior to bedtime dose only (trough) on Days 9, 10, 11, 16, 17, and 18.

Doxylamine and pyridoxine are absorbed in the gastrointestinal tract, mainly in the jejunum.

The C_{max} of doxylamine and pyridoxine are achieved within 7.5 and 5.5 hours, respectively (see Table 2).

Table 2 – Single-Dose and Multiple-Dose Pharmacokinetics of DICLEGIS in Healthy Non-Pregnant Adult Women

| | Single Dose | | | Multiple Dose | | |
|---------------------------|-----------------------------------|-----------------------------|-------------------------|-----------------------------------|-----------------------------|-------------------------|
| | AUC _{0-inf} (ng•h/mL) | C _{max} (ng/mL) | T _{max} (h) | AUC _{0-inf} (ng•h/mL) | C _{max} (ng/mL) | T _{max} (h) |
| Doxylamine | 1280.9 ± 369.3 | 83.3 ± 20.6 | 7.2 ± 1.9 | 3721.5 ± 1318.5 | 168.6 ± 38.5 | 7.8 ± 1.6 |
| Pyridoxine | 43.4 ± 16.5 | 32.6 ± 15.0 | 5.7 ± 1.5 | 64.5 ± 36.4 | 46.1 ± 28.3 | 5.6 ± 1.3 |
| Pyridoxal | 211.6 ± 46.1 | 74.3 ± 21.8 | 6.5 ± 1.4 | 1587.2 ± 550.0 | 210.0 ± 54.4 | 6.8 ± 1.2 |
| Pyridoxal 5'-Phosphate | 1536.4 ± 721.5 | 30.0 ± 10.0 | 11.7 ± 5.3 | 6099.7 ± 1383.7 | 84.9 ± 16.9 | 6.3 ± 6.6 |
| Pyridoxamine | 4.1 ± 2.7 | 0.5 ± 0.7 | 5.9 ± 2.1 | 2.6 ± 0.8 | 0.5 ± 0.2 | 6.6 ± 1.4 |
| Pyridoxamine 5'-phosphate | 5.2 ± 3.8 | 0.7 ± 0.5 | 14.8 ± 6.6 | 94.5 ± 58.0 | 2.3 ± 1.7 | 12.4 ± 11.2 |

Multiple-dose administration of DICLEGIS results in increased concentrations of doxylamine as well as increases in doxylamine C_{max} and AUC_{0-last} of absorption. The time to reach the maximum concentration is not affected by multiple doses. The mean accumulation index is more than 1.0 suggesting that doxylamine accumulates following multiple dosing (see Table 3).

Although no accumulation was observed for pyridoxine, the mean accumulation index for each metabolite (pyridoxal, pyridoxal 5'-phosphate, and pyridoxamine 5'-phosphate) is more than 1.0 following multiple-dose administration of DICLEGIS. The time to reach the maximum concentration is not affected by multiple doses (see Table 2).

Table 3 – Pharmacokinetics of Doxylamine and Pyridoxine Following Single Dose and Multiple Dose

Administration of DICLEGIS to Healthy Non-Pregnant Adult Women

| | | AUC0-last (ng•h/mL) | AUC0-inf (ng•h/mL) | Cmax (ng/mL) | Tmax (h) | T1/2el (h) |
|-------------------------------|----------|------------------------|-----------------------|--------------|-----------|------------|
| Doxylamine Mean±SD N=18 | Single | 911.4 ± 205.6 | 1280.9 ± 369.3 | 83.3 ± 20.6 | 7.2 ± 1.9 | 10.1 ± 2.1 |
| | Multiple | 3661.3 ± 1279.2 | 3721.5 ± 1318.5 | 168.6 ± 38.5 | 7.8 ± 1.6 | 11.9 ± 3.3 |
| Pyridoxine Mean±SD N=18 | Single | 39.3 ± 16.5 | 43.4 ± 16.5 | 32.6 ± 15.0 | 5.7 ± 1.5 | 0.5 ± 0.2 |
| | Multiple | 59.3 ± 33.9 | 64.5 ± 36.4 | 46.1 ± 28.3 | 5.6 ± 1.3 | 0.5 ± 0.1 |

Food Effect

The administration of food delays the absorption of both doxylamine and pyridoxine. This delay is associated with a lower peak concentration of doxylamine, but the extent of absorption is not affected (see Table 4).

The effect of food on the peak concentration and the extent of absorption of the pyridoxine component is more complex because the pyridoxal, pyridoxamine, pyridoxal 5'-phosphate and pyridoxamine 5'-phosphate metabolites also contribute to the biological activity. Food significantly reduces the bioavailability of pyridoxine, lowering its Cmax and AUC by approximately 50% compared to fasting conditions. Similarly, food significantly reduces pyridoxal AUC and reduces its Cmax by 50% compared to fasting conditions. In contrast, food slightly increases pyridoxal 5'-phosphate Cmax and extent of absorption. As for pyridoxamine and pyridoxamine 5'-phosphate, the rate and extent of absorption seem to decrease under fed conditions.

Table 4 – Pharmacokinetics of Doxylamine and Pyridoxine Following Administration of DICLEGIS Under Fed and Fasted Conditions in Healthy Non-Pregnant Adult Women

| | | AUC0-t (ng•h/mL) | AUC0-inf (ng•h/mL) | Cmax (ng/mL) | Tmax (h) | T1/2el (h) |
|-------------------------------|--------|---------------------|-----------------------|--------------|------------|-------------|
| Doxylamine Mean±SD N=42 | Fasted | 1407.2 ± 336.9 | 1447.9 ± 332.2 | 94.9 ± 18.4 | 5.1 ± 3.4 | 12.6 ± 3.4 |
| | Fed | 1488.0 ± 463.2 | 1579.0 ± 422.7* | 75.7 ± 16.6 | 14.9 ± 7.4 | 12.5 ± 2.9* |
| Pyridoxine Mean±SD N=42 | Fasted | 33.8 ± 13.7 | 39.5 ± 12.9‡ | 35.5 ± 21.4 | 2.5 ± 0.9 | 0.4 ± 0.2‡ |
| | Fed | 18.3 ± 14.5 | 24.2 ± 14.0‡ | 13.7 ± 10.8 | 9.3 ± 4.0 | 0.5 ± 0.2‡ |

* N=37
‡ N=31
‡ N=18

Distribution

Pyridoxine is highly protein bound, primarily to albumin. Its main active metabolite, pyridoxal 5'-phosphate (PLP) accounts for at least 60% of circulating vitamin B6 concentrations.

Metabolism

Doxylamine is biotransformed in the liver by N-dealkylation to its principle metabolites N-desmethyl-doxylamine and N, N-didesmethyldoxylamine.

Pyridoxine is a prodrug primarily metabolized in the liver.

Excretion

The principle metabolites of doxylamine, N-desmethyl-doxylamine and N, N-didesmethyldoxylamine, are excreted by the kidney.

The terminal elimination half-life of doxylamine and pyridoxine are 12.5 hours and 0.5 hours, respectively (see Table 5).

Table 5 – Terminal Elimination Half-Life (T_{1/2el}) for DICLEGIS Administered as a Single Dose of Two Tablets under Fasting Conditions in Healthy Non-Pregnant Adult Women

| | T _{1/2el} (h) |
|---------------------------|------------------------|
| Doxylamine | 12.6 ± 3.4 |
| Pyridoxine | 0.4 ± 0.2 |
| Pyridoxal | 2.1 ± 2.2 |
| Pyridoxal 5'-Phosphate | 81.6 ± 42.2 |
| Pyridoxamine | 3.1 ± 2.5 |
| Pyridoxamine 5'-Phosphate | 66.5 ± 51.3 |

Use in Specific Populations

Race: No pharmacokinetic studies have been conducted related to race.

Hepatic Impairment: No pharmacokinetic studies have been conducted in hepatic impaired patients.

Renal Impairment: No pharmacokinetic studies have been conducted in renal impaired patients.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity

Two-year carcinogenicity studies in rats and mice have been conducted with doxylamine succinate. Doxylamine succinate is not likely to have human carcinogenic potential. The carcinogenic potential of pyridoxine hydrochloride has not been evaluated.

14 CLINICAL STUDIES

A double-blind, randomized, multi-center, placebo-controlled study was conducted to support the safety and efficacy of DICLEGIS in the treatment of nausea and vomiting of pregnancy. Adult women 18 years of age or older and 7 to 14 weeks gestation (median 9 weeks of gestation) with nausea and vomiting of pregnancy were randomized to 14 days of DICLEGIS or placebo. Two tablets of DICLEGIS were administered at bedtime on Day 1. If symptoms of nausea and vomiting persisted into the afternoon hours of Day 2, the woman was directed to take her usual dose of two tablets at bedtime that night and, beginning on Day 3, to take one tablet in the morning and two tablets at bedtime. Based upon assessment of remaining symptoms at her clinic visit on Day 4 (± 1 day), the woman may have been directed to take an additional tablet mid-afternoon. A maximum of four tablets (one in the morning, one in the mid-afternoon and two at bedtime) were taken daily.

Over the treatment period, 19% of DICLEGIS-treated 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. The PUQE score incorporates the number of daily vomiting episodes, number of daily heaves, and length of daily nausea in hours, for an overall score of symptoms rated from 3 (no symptoms) to 15 (most severe).

At baseline, the mean PUQE score was 9.0 in the DICLEGIS arm and 8.8 in the placebo arm. There was a 0.7 (95% confidence interval 0.2 to 1.2 with p-value 0.006) mean decrease (improvement in nausea and vomiting symptoms) from baseline in PUQE score at Day 15 with DICLEGIS compared to placebo (see Table 6).

Table 6 – Change from Baseline in the Primary Endpoint, Pregnancy Unique-Quantification of Emesis (PUQE) Score at Day 15. (Intent-to-Treat Population with Last-Observation Carried Forward)

| PUQE Score* | Doxylamine Succinate + Pyridoxine Hydrochloride | 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] |

*

The Pregnancy-Unique Quantification of Emesis and Nausea (PUQE) score incorporated the number of daily vomiting episodes, number of daily heaves, and length 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.

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How supplied

DICLEGIS delayed-release tablets are supplied in a high-density polyethylene bottle with a polypropylene child-resistant cap and a silica gel desiccant canister. Each white, round, film-coated, delayed-release tablet contains 10 mg doxylamine succinate and 10 mg pyridoxine hydrochloride, and is imprinted on one side with the pink image of a pregnant woman. DICLEGIS tablets are provided as follows:

NDC 55494-100-10 Bottles of 100.

16.2 Storage and Handling

Store at 20°C to 25°C (68°F to 77°F); excursions permitted between 15°C and 30°C (59°F and 86°F) [see USP Controlled Room Temperature]. Keep bottle tightly closed and protect from moisture. Do not remove desiccant canister from bottle.

17 PATIENT COUNSELING INFORMATION

See FDA-approved patient labeling (Patient Information)

17.1 Somnolence and Severe Drowsiness

Inform women to avoid engaging in activities requiring complete mental alertness, such as driving or operating heavy machinery, while using DICLEGIS until cleared to do so.

Inform women of the importance of not taking DICLEGIS with alcohol or sedating medications, including other antihistamines (present in some cough and cold medications), opiates and sleep aids because somnolence could worsen leading to falls or other accidents.

DICLEGIS® is a registered trademark of Duchesnay Inc.

U.S. Patent Nos. 6,340,695 & 7,560,122.

Distributed by:

Duchesnay USA, Inc.

Bryn Mawr, PA, 19010

Reference ID: 3381709

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Fax: 1-888-588-8508

www.duchesnayusa.com

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Patient Package Insert

Patient Information

DICLEGIS (dye-CLEE-gis)

(doxylamine succinate and pyridoxine hydrochloride) delayed-release tablets

What is DICLEGIS?

- DICLEGIS is a prescription medicine used to treat nausea and vomiting of pregnancy in women who have not improved with change in diet or other non-medicine treatments.
- It is not known if DICLEGIS is safe and effective in children under 18 years of age.

Who should not take DICLEGIS?

Do not take DICLEGIS if you:

- are allergic to doxylamine succinate, other ethanolamine derivative antihistamines, pyridoxine hydrochloride or any of the ingredients in DICLEGIS. See the end of this leaflet for a complete list of ingredients in DICLEGIS.
- take monoamine oxidase inhibitors (MAOIs) (Marplan, Nardil, Emsam, Eldepryl, Zelapar, Parnate)

Before taking DICLEGIS, tell your healthcare provider about all of your medical conditions, including;

- if you are breastfeeding or plan to breastfeed. DICLEGIS can pass into your breast milk and may harm your baby. You should not breastfeed while using DICLEGIS.

Tell your healthcare provider about all the medicines you take, including prescription or over-the-counter medicines, vitamins, or herbal supplements.

How should I take DICLEGIS?

- Talk to your healthcare provider about how much DICLEGIS to take and when to take it.
- Take DICLEGIS everyday as prescribed by your healthcare provider. Do not stop taking DICLEGIS without talking to your healthcare provider first.
- See the following schedule for the usual way you should start taking DICLEGIS:
 - Day 1- Take 2 tablets, by mouth at bedtime.
 - Day 2- Take 2 tablets at bedtime. If your nausea and vomiting is better or controlled on Day 2, continue to take 2 tablets every night at bedtime. This will be your usual dose unless your healthcare provider tells you otherwise.
 - Day 3- If you still had nausea and vomiting on Day 2, take 3 tablets on Day 3 (1 tablet in the morning and 2 tablets at bedtime).
 - Day 4- If your nausea and vomiting was better or controlled on Day 3, continue to take 3 tablets each day (1 tablet in the morning and 2 tablets at bedtime). If you still had nausea and vomiting on Day 3, start taking 4 tablets each day (1 tablet in the morning, 1 tablet in the afternoon, and 2 tablets at bedtime).
- Do not take more than 4 tablets (1 in the morning, 1 in the mid-afternoon, and 2 at bedtime) in 1 day.
- Take DICLEGIS on an empty stomach with a glass of water.

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- Take DICLEGIS tablets whole. Do not crush, chew, or break DICLEGIS tablets before swallowing. If you cannot swallow DICLEGIS tablets whole, tell your healthcare provider.
- If you take too much DICLEGIS (overdose), you may have the following symptoms: restlessness, dry mouth, the pupils of your eyes become larger (dilated), sleepiness, dizziness, confusion, fast heart rate, seizures, muscle pain or weakness, and sudden and severe kidney problems. If you have these symptoms and they are severe, they may lead to death. Stop taking DICLEGIS, call your healthcare provider or go to the nearest hospital emergency room right away. For more information about overdose treatment, call your poison control center at 1-800-222-1222.

What are the possible side effects of DICLEGIS?

DICLEGIS may cause serious side effects, including drowsiness.

- Do not drive, operate heavy machinery, or other activities that need your full attention unless your healthcare provider says that you may do so.
- Do not drink alcohol, or take other central nervous system depressants such as cough and cold medicines, certain pain medicines, and medicines that help you sleep while you take DICLEGIS. Severe drowsiness can happen or become worse causing falls or accidents.

These are not all the possible side effects of DICLEGIS.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store DICLEGIS?

- Store DICLEGIS between 68°F to 77°F (20°C to 25°C).
- Keep DICLEGIS tablets dry, in a tightly closed container, and out of the light.
- Safely throw away medicine that is out of date or no longer needed.

Keep DICLEGIS and all medicines out of the reach of children.

General information about the safe and effective use of DICLEGIS.

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. You can ask your pharmacist or healthcare provider for information about DICLEGIS that is written for health professionals. Do not use DICLEGIS for a condition for which it was not prescribed. Do not give DICLEGIS to other people, even if they have the same symptoms that you have. It may harm them.

What are the ingredients in DICLEGIS?

Active ingredient: doxylamine succinate (an antihistamine) and pyridoxine hydrochloride (vitamin B6)

Inactive ingredients: ammonium hydroxide, n-butanol, carnauba wax powder, colloidal silicon dioxide, croscarmellose sodium, D&C Red#27, denatured alcohol, FD&C Blue #2, hypromellose, isopropyl alcohol, magnesium stearate, magnesium trisilicate, methacrylic acid copolymer, microcrystalline cellulose 102, PEG 8000, polysorbate 80, propylene glycol, shellac glaze, simethicone, sodium bicarbonate, sodium lauryl sulfate, talc, titanium dioxide, triethyl citrate.

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www.duchesnayusa.com or call 1-855-722-7734.

This Patient Information has been approved by the U.S. Food and Drug Administration

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Package/Label Display Panel

Bottle Label-Outside Front Cover with Imprint Area for Lot & Expiry