


DEPARTMENT OF HEALTH AND HUMAN SERVICES  
OFFICE OF DIRECTOR

ACTION REFERRAL

TO <i>Giese/Williams</i>	DATE <i>5-7-13</i>
-----------------------------	-----------------------

DIRECTOR'S USE ONLY	ACTION REQUESTED
1. LOG NUMBER <i>000341</i>	<input type="checkbox"/> Prepare reply for the Director's signature DATE DUE _____
2. DATE SIGNED BY DIRECTOR <i>cc: Mr. Speck</i> 	<input type="checkbox"/> Prepare reply for appropriate signature DATE DUE _____
	<input type="checkbox"/> FOIA DATE DUE _____
	<input checked="" type="checkbox"/> Necessary Action

APPROVALS (Only when prepared for director's signature)	APPROVE	* DISAPPROVE (Note reason for disapproval and return to preparer.)	COMMENT
1.			
2.			
3.			
4.			

120000

**DEPARTMENT OF HEALTH AND HUMAN SERVICES**  
**OFFICE OF DIRECTOR**

**ACTION REFERRAL**

TO	DATE
----	------

DIRECTOR'S USE ONLY	ACTION REQUESTED
1. LOG NUMBER <div style="text-align: right; font-family: monospace; font-size: 1.2em;">000342</div>	<input type="checkbox"/> Prepare reply for the Director's signature <div style="text-align: right;">DATE DUE _____</div>
2. DATE SIGNED BY DIRECTOR _____	<input type="checkbox"/> Prepare reply for appropriate signature <div style="text-align: right;">DATE DUE _____</div> <input type="checkbox"/> FOIA <div style="text-align: right;">DATE DUE _____</div> <input type="checkbox"/> Necessary Action

APPROVALS <small>(Only when prepared for director's signature)</small>	APPROVE	* DISAPPROVE <small>(Note reason for disapproval and return to preparer.)</small>	COMMENT
1.			
2.			
3.			
4.			

00032



RECEIVED

APR 26 2013

Department of Health & Human Services  
OFFICE OF THE DIRECTOR

April 24, 2013

Director  
Tony Keck  
South Carolina Department of Health & Human Services  
1801 Main Street, PO Box 8206  
Columbia, South Carolina 29201-8206

RE: Request for Immediate Medicaid Coverage of Diclegis® (Doxylamine Succinate and Pyridoxine Hydrochloride) Delayed-Release Tablets, 10 mg/10 mg; NDC 55494-100-10

Dear Tony Keck:

Duchesnay, Inc. and its U.S. distributor Duchesnay USA, Inc. are very pleased to announce that we have received final FDA approval of Diclegis – the only FDA-approved treatment for nausea and vomiting of pregnancy (“NVP”) for use in women who do not respond to conservative management, such as dietary and lifestyle modification.

Duchesnay USA will make Diclegis available to wholesalers on or about May 3, 2013. We expect South Carolina pharmacies will stock and dispense Diclegis very soon thereafter.

Duchesnay USA’s Medicaid Drug Rebate Agreement was fully executed on April 12, 2013. The mandatory Medicaid coverage date for Diclegis, therefore, is July 1, 2013. See 42 U.S.C. § 1396r-8(a)(1). In light of the important benefits of this therapy to pregnant women in the Medicaid population, however, we ask that you exercise your option to make South Carolina Medicaid coverage effective immediately upon Diclegis’s entry into the market. See id.

A copy of FDA’s news release about this important new drug approval is attached. The prescribing labeling describing the parameters for use and associated side effects of Diclegis also is attached. The FDA has granted Diclegis Pregnancy Category A status, which means the results of controlled studies have not shown an increased risk to an unborn baby during pregnancy. We hope that you will permit South Carolina Medicaid beneficiaries to have access to Diclegis as soon as possible.

If you have any questions about the timing of Medicaid coverage of Diclegis, please do not hesitate to contact me at 484-380-2641 or [ggodin@duchesnayusa.com](mailto:ggodin@duchesnayusa.com), or Eugene Kelly, Duchesnay USA’s Director of Scientific Affairs at 484-380-2641 or [gkelly@duchesnayusa.com](mailto:gkelly@duchesnayusa.com).

Sincerely,

Gilbert Godin  
Chief Executive Officer  
Duchesnay USA, Inc.

Enclosures



**U.S. Food and Drug Administration**

Protecting and Promoting Your Health

[Home](#) [News & Events](#) [Newsroom](#) [Press Announcements](#)**News & Events****FDA NEWS RELEASE****For Immediate Release:** April 8, 2013**Media Inquiries:** Andrea Fischer, 301-796-0393, [andrea.fischer@fda.hhs.gov](mailto:andrea.fischer@fda.hhs.gov) or Stephanie Yao, 301-796-0394, [stephanie.yao@fda.hhs.gov](mailto:stephanie.yao@fda.hhs.gov)**Consumer Inquiries:** 888-INFO-FDA

En Español

**FDA approves Diclegis for pregnant women experiencing nausea and vomiting**

The U.S. Food and Drug Administration today approved Diclegis (doxylamine succinate and pyridoxine hydrochloride) to treat pregnant women experiencing nausea and vomiting.

Diclegis is a delayed-release tablet intended for women who have not adequately responded to conservative management of nausea and vomiting during pregnancy, such as dietary and lifestyle modifications. These modifications include eating several small meals instead of three large meals, eating bland foods that are low in fat and easy to digest and avoiding smells that can trigger nausea.

"Many women experience nausea and vomiting during pregnancy, and sometimes these symptoms are not adequately managed through recommended changes in diet and lifestyle," said Hylton V. Joffe, M.D., M.M.Sc., director of the Division of Reproductive and Urologic Products in the FDA's Center for Drug Evaluation and Research. "Diclegis is now the only FDA-approved treatment for nausea and vomiting due to pregnancy, providing a therapeutic option for pregnant women seeking relief from these symptoms."

Diclegis was studied in 261 women experiencing nausea and vomiting due to pregnancy. Study participants in the clinical trial were at least 18 years old and had been pregnant for at least 7 weeks and up to 14 weeks. Women were randomly assigned to receive two weeks of treatment with Diclegis or a placebo. The study results showed that women taking Diclegis experienced greater improvement in nausea and vomiting than those taking placebo. Additionally, observational (epidemiological) studies have shown that the combination of active ingredients in Diclegis does not pose an increased risk of harm to the fetus.

Diclegis is taken daily. Tablets must be taken whole on an empty stomach. The recommended starting dose is two tablets taken 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).

Nausea and vomiting due to pregnancy usually improve after the first trimester. Health care professionals should reassess their patients for continued need for Diclegis as pregnancy progresses.

Drowsiness or sleepiness, which can be severe, is the most common side effect reported by women taking Diclegis. Women should avoid using Diclegis when engaging in activities requiring mental alertness, such as driving or operating heavy machinery, until cleared to do so by their health care provider.

Diclegis is marketed by Duchesnay Inc., based in Blainville, Québec, Canada.

For more information:

- FDA Approved Drugs: Questions and Answers<sup>2</sup>
- FDA: For Women<sup>3</sup>
- HHS Office on Women's Health: Pregnancy<sup>4</sup>

FDA, an agency within the U.S. Department of Health and Human Services, protects the public health by assuring the safety, effectiveness, and security of human and veterinary drugs, vaccines and other biological products for human use, and

medical devices. The agency also is responsible for the safety and security of our nation's food supply, cosmetics, dietary supplements, products that give off electronic radiation, and for regulating tobacco products.

# # #

Read our Blog: [FDA Voice](#)<sup>5</sup>

Visit the FDA on [Facebook](#)<sup>6</sup>, [Flickr](#)<sup>7</sup>, [YouTube](#)<sup>8</sup> and [Twitter](#)<sup>9</sup><sup>10</sup>

RSS Feed for [FDA News Releases](#)<sup>11</sup>

Page Last Updated: 04/09/2013

Note: If you need help accessing information in different file formats, see [Instructions for Downloading Viewers and Players](#).

[Accessibility](#) [Contact](#) [FDA Careers](#) [FDA Basics](#) [FOIA](#) [No Fear Act](#) [Site Map](#) [Transparency](#) [Website Policies](#)

U.S. Food and Drug Administration  
10903 New Hampshire Avenue  
Silver Spring, MD 20993  
Ph. 1-888-INFO-FDA (1-888-463-6332)  
Email FDA



For Government For Press

[Combination Products](#) [Advisory Committees](#) [Science & Research](#) [Regulatory Information](#) [Safety](#)  
[Emergency Preparedness](#) [International Programs](#) [News & Events](#) [Training and Continuing Education](#)  
[Inspections/Compliance](#) [State & Local Officials](#) [Consumers](#) [Industry](#) [Health Professionals](#) [FDA Archive](#)



U.S. Department of Health & Human Services

### Links on this page:

1. [/NewsEvents/Newsroom/PressAnnouncements/ucm347109.htm](#)
2. [/Drugs/ResourcesForYou/Consumers/ucm054420.htm](#)
3. <http://www.fda.gov/ForConsumers/ByAudience/ForWomen/default.htm>
4. <http://www.womenshealth.gov/pregnancy/index.html>
5. <https://blogs.fda.gov/fdavoice/>
6. <http://www.facebook.com/FDA>
7. <http://www.flickr.com/photos/fdaphotos/>
8. <http://www.youtube.com/user/USFoodandDrugAdmin?blend=23&ob=5>
9. [http://twitter.com/us\\_fda](http://twitter.com/us_fda)
10. <http://www.fda.gov/AboutFDA/AboutThisWebsite/WebsitePolicies/Disclaimers/default.htm>
11. <http://www.fda.gov/AboutFDA/ContactFDA/StayInformed/RSSFeeds/PressReleases/rss.xml>



**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.

**DICLEGIS (doxylamine succinate and pyridoxine hydrochloride) delayed-release tablets, for oral use.**  
Labeled 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)

**DOSEAGE 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)

**FULL PRESCRIBING INFORMATION CONTENTS\***

- 1 INDICATIONS AND USAGE
- 2 DOSAGE AND ADMINISTRATION
- 3 DOSAGE FORMS AND STRENGTHS
- 4 CONTRAINDICATIONS
- 5 WARNINGS AND PRECAUTIONS
- 6 USE IN SPECIFIC POPULATIONS
- 7 DRUG INTERACTIONS
- 8 USE IN SPECIFIC POPULATIONS
- 9 Pregnancy
- 10 Nursing Mothers
- 11 Pediatric Use

**WARNINGS AND PRECAUTIONS**

- 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. (3.1)
- Central nervous system (CNS) depression: Concurrent use with alcohol or other CNS depressants is not recommended. (3.1)
- Anticholinergic effects: Use with caution in patients with asthma, increased intraocular pressure, narrow angle glaucoma, stenosing peptic ulcer, pyloroduodenal obstruction and urinary bladder-neck obstruction. (3.2)

**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 Doaksway Inc. at 1-888-722-7744 or [medwatch@doaksway.com](mailto:medwatch@doaksway.com) or FDA at 1-800-FDA-1088 or [www.fda.gov/medwatch](http://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: 9/2013

**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* (1.4)]. Adverse reactions for DICLEGIS that occurred at an incidence  $\geq 5$  percent and exceeded the incidence for placebo are summarized in Table 1.

Table 1: Number (Percent) of Subjects with  $\geq 5$  Percent Adverse Reactions in a 15-Day Placebo-Controlled Study of DICLEGIS (Only Those Adverse Reactions Occurring at an Incidence  $\geq 5$  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 distention, 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 dicyclanone hydrochloride. A second meta-analysis of 12 cohort and 5 case-control studies published between 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 dicyclanone 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 (1-800-272-1222).

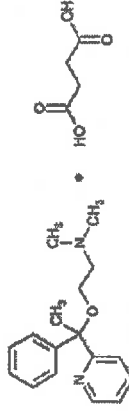
## 11 DESCRIPTION

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 400, PEG 8000, polysorbate 80, propylene glycol, shellac glaze, simethicone, talc, titanium dioxide.

### Doxylamine Succinate

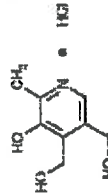
Doxylamine succinate is classified as an antihistamine. The chemical name for doxylamine succinate is ethanamine, N,N-dimethyl-2-[1-phenyl-1-(2-pyridinyl)ethoxy]-, butanedioate (1:1). The empirical formula is  $C_{17}H_{22}N_2O \cdot C_4H_4O_4$  and the molecular mass is 388.46. The structural formula 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

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		
	$AUC_{0-24}$ (ng·h/mL)	$C_{max}$ (ng/mL)	$T_{max}$ (h)	$AUC_{0-24}$ (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	1556.4 ± 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	0.3 ± 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  $AUC_{0-24}$  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

	Single			Multiple		
	$AUC_{0-24}$ (ng·h/mL)	$C_{max}$ (ng/mL)	$T_{max}$ (h)	$AUC_{0-24}$ (ng·h/mL)	$C_{max}$ (ng/mL)	$T_{max}$ (h)
Doxylamine	911.4 ± 205.6	83.3 ± 20.6	7.2 ± 1.9	1280.9 ± 369.3	168.6 ± 38.5	10.1 ± 2.1
Pyridoxine	3661.3 ± 1279.2	3721.5 ± 1318.5	7.8 ± 1.6	3721.5 ± 1318.5	38.5 ± 3.3	11.9 ± 3.3
Pyridoxine Mean-SD	39.3 ± 16.5	32.6 ± 15.0	5.7 ± 1.5	43.4 ± 16.5	46.1 ± 28.3	0.5 ± 0.2
Pyridoxine Mean-SD	59.3 ± 33.9	64.5 ± 36.4	5.6 ± 1.3	64.5 ± 36.4	28.3 ± 0.1	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  $C_{max}$  and AUC by approximately 50% compared to fasting conditions. Similarly, food significantly reduces pyridoxal AUC and reduces its  $C_{max}$  by 50% compared to fasting conditions. In contrast,

food slightly increases pyridoxal 5'-phosphate  $C_{max}$  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**

		AUC <sub>0-4</sub> (ng·h/mL)	AUC <sub>0-12</sub> (ng·h/mL)	C <sub>max</sub> (ng/mL)	T <sub>max</sub> (h)	T <sub>1/2α</sub> (h)
Doxylamine Means±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 <sup>a</sup>	75.7 ± 16.6	14.9 ± 7.4	12.5 ± 2.9 <sup>a</sup>
Pyridoxine Means±SD N=42	Fasted	33.8 ± 13.7	39.5 ± 12.9 <sup>a</sup>	35.5 ± 21.4	2.5 ± 0.9	0.4 ± 0.2 <sup>a</sup>
	Fed	18.3 ± 14.5	24.2 ± 14.0 <sup>b</sup>	13.7 ± 10.8	9.3 ± 4.0	0.5 ± 0.2 <sup>b</sup>

<sup>a</sup> N=37; <sup>b</sup> N=18; <sup>c</sup> N=31

#### 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-didesmethyl-doxylamine.

Pyridoxine is a prodrug primarily metabolized in the liver.

#### Excretion

The principle metabolites of doxylamine, N-desmethyl-doxylamine and N, N-didesmethyl-doxylamine, 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<sub>1/2α</sub>) for DICLEGIS Administered as a Single Dose of Two Tablets under Fasting Conditions in Healthy Non-Pregnant Adult Women**

	T <sub>1/2α</sub> (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 and 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  
Tel: 1-855-722-7734