FPO

Doxylamine Succinate and Pyridoxine Hydrochloride
Delayed-Release Tablets
Revised: May 2015
Rx Only

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use doxylamine succinate and pyridoxine hydrochloride delayed-release tablets safely and effectively. See full prescribing information for doxylamine succinate and pyridoxine hydrochloride delayed-release tablets.

DOXYLAMINE succinate and PYRIDOXINE hydrochloride delayed-release tablets, for oral use.

Initial U.S. Approval: 1976

----------INDICATIONS AND USAGE ----------

Doxylamine succinate and pyridoxine hydrochloride delayed-release tablets 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 ----------

- Activities requiring mental alertness: Avoid engaging in activities requiring complete mental alertness, such as driving or operating heavy machinery, while using doxylamine succinate and pyridoxine hydrochloride delayed-release tablets until cleared to do so by a healthcare provider (5.1)
- 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 doxylamine succinate and pyridoxine hydrochloride delayed-release tablets (5 percent and exceeding the rate in placebo) is somnolence. (6)

To report SUSPECTED ADVERSE REACTIONS, contact Actavis at 1-800-272-5525 or www.actavis.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. Doxylamine succinate and pyridoxine hydrochloride delayed-release tablets is intended for use in pregnant women. (8.1)

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

Revised: 05/2015

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

Doxylamine succinate and pyridoxine hydrochloride delayed-release tablets are indicated for the treatment of nausea and vomiting of pregnancy in women who do not respond to conservative management.

Limitations of Use

Doxylamine succinate and pyridoxine hydrochloride delayed-release tablets have not been studied in women with hyperemesis gravidarum.

2 DOSAGE AND ADMINISTRATION

2.1 Dosage Information

Initially, take two doxylamine succinate and pyridoxine hydrochloride delayed-release tablets 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 doxylamine succinate and pyridoxine hydrochloride delayed-release tablets.

Take as a daily prescription and not on an as needed basis. Reassess the woman for continued need for doxylamine succinate and pyridoxine hydrochloride delayed-release tablets as her pregnancy progresses.

3 DOSAGE FORMS AND STRENGTHS

Doxylamine succinate and pyridoxine hydrochloride delayed-release tablets are white to off white, round, biconvex film coated tablets, plain on both sides containing 10 mg doxylamine succinate and 10 mg pyridoxine hydrochloride. The tablets are printed with **"2132"** on one side with black ink and plain on the other.

4 CONTRAINDICATIONS

Doxylamine succinate and pyridoxine hydrochloride delayed-release tablets are 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 doxylamine succinate and pyridoxine hydrochloride delayed-release tablets *[see Drug Interactions (7.1)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Activities Requiring Mental Alertness

Doxylamine succinate and pyridoxine hydrochloride delayed-release tablets 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 doxylamine succinate and pyridoxine hydrochloride delayed-release tablets until cleared to do so by their healthcare provider.

Doxylamine succinate and pyridoxine hydrochloride delayed-release tablets 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

Doxylamine succinate and pyridoxine hydrochloride delayed-release tablets have 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 doxylamine succinate and pyridoxine hydrochloride delayed-release tablets 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 doxylamine succinate and pyridoxine hydrochloride delayed-release tablets 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 doxylamine succinate and pyridoxine hydrochloride delayed-release tablets 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 Doxylamine Succinate and Pyridoxine Hydrochloride Delayed-release Tablets (Only Those Adverse Reactions Occurring at an Incidence ≥ 5 Percent and at a Higher Incidence with DICLEGIS than Placebo are Shown)

	Doxylamine Succinate and Pyridoxine Hydrochloride Delayed-release Tablets (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 doxylamine succinate and pyridoxine hydrochloride delayed-release tablets 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 doxylamine succinate and pyridoxine hydrochloride delayed-release tablets is not recommended.

7.2 Drug-Food Interactions

A food-effect study demonstrated that the delay in the onset of action of doxylamine succinate and pyridoxine hydrochloride delayed-release tablets 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, doxylamine succinate and pyridoxine hydrochloride delayed-release tablets 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

Doxylamine succinate and pyridoxine hydrochloride delayed-release tablets are 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 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 doxylamine succinate and pyridoxine hydrochloride delayed-release tablets.

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 doxylamine succinate and pyridoxine hydrochloride delayed-release tablets 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 doxylamine succinate and pyridoxine hydrochloride delayed-release tablets 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

Doxylamine succinate and pyridoxine hydrochloride delayed-release tablets 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**).

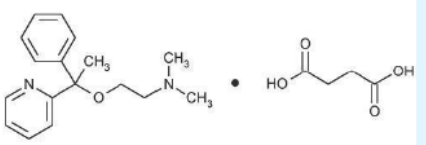
11 DESCRIPTION

Doxylamine succinate and pyridoxine hydrochloride delayed-release tablets are round, white to off white, biconvex film-coated, delayed-release tablets containing 10 mg of doxylamine succinate and 10 mg of pyridoxine hydrochloride. Tablets are printed with **"2132"** on one side with black ink and plain on the other.

Inactive ingredients are as follows: colloidal silicon dioxide, croscarmellose sodium, hypromellose, iron oxide black, magnesium stearate, magnesium trisilicate, methacrylic acid and ethyl acrylate copolymer, microcrystalline cellulose, polyethylene glycol, polysorbate, propylene glycol, talc, titanium dioxide.

Doxylamine Succinate

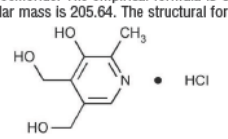
Doxylamine succinate is classified as an antihistamine. The chemical name for doxylamine succinate is ethanamine, N,N-dimethyl-2-[1-phenyl-1-(2-pyridinyl)ethoxy]-, butanedioate (1:1). The empirical formula is $C_{17}H_{22}N_2O \cdot C_4H_6O_4$ and the molecular mass is 388.46. The structural formula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



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:[4]



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

[1]The structural formulas for Doxylamine succinate and pyridoxine hydrochloride were included as per the Agency's request.

Patient Information

Doxylamine Succinate (doks-ILL-ah-meen sux-sin-ate) and Pyridoxine (peer-ih-DOX-een) Hydrochloride Delayed-release Tablets

What are doxylamine succinate and pyridoxine hydrochloride delayed-release tablets?

- Doxylamine succinate and pyridoxine hydrochloride delayed-release tablets are 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 doxylamine succinate and pyridoxine hydrochloride delayed-release tablets are safe and effective in children under 18 years of age.

Who should not take doxylamine succinate and pyridoxine hydrochloride delayed-release tablets?

Do not take doxylamine succinate and pyridoxine hydrochloride delayed-release tablets if you:

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

Before taking doxylamine succinate and pyridoxine hydrochloride delayed-release tablets, tell your healthcare provider about all of your medical conditions, including;

- **if you are breastfeeding or plan to breastfeed.** Doxylamine succinate and pyridoxine hydrochloride delayed-release tablets can pass into your breast milk and may harm your baby. You should not breastfeed while using doxylamine succinate and pyridoxine hydrochloride delayed-release tablets.

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 doxylamine succinate and pyridoxine hydrochloride delayed-release tablets?

- Talk to your healthcare provider about how much doxylamine succinate and pyridoxine hydrochloride delayed-release tablets to take and when to take it.
- Take doxylamine succinate and pyridoxine hydrochloride delayed-release tablets everyday as prescribed by your healthcare provider. Do not stop taking doxylamine succinate and pyridoxine hydrochloride delayed-release tablets without talking to your healthcare provider first.
- **See the following schedule for the usual way you should start taking doxylamine succinate and pyridoxine hydrochloride delayed-release tablets:**
  - 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 doxylamine succinate and pyridoxine hydrochloride delayed-release tablets on an empty stomach with a glass of water.
- Take doxylamine succinate and pyridoxine hydrochloride delayed-release tablets whole. Do not crush, chew, or break doxylamine succinate and pyridoxine hydrochloride delayed-release tablets before swallowing. If you cannot swallow doxylamine succinate and pyridoxine hydrochloride delayed-release tablets whole, tell your healthcare provider.
- If you take too much doxylamine succinate and pyridoxine hydrochloride delayed-release tablets (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 doxylamine succinate and pyridoxine hydrochloride delayed-release tablets, 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 doxylamine succinate and pyridoxine hydrochloride delayed-release tablets?

Doxylamine succinate and pyridoxine hydrochloride delayed-release tablets 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 doxylamine succinate and pyridoxine hydrochloride delayed-release tablets. Severe drowsiness can happen or become worse causing falls or accidents.

These are not all the possible side effects of doxylamine succinate and pyridoxine hydrochloride delayed-release tablets.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA1088.

How should I store doxylamine succinate and pyridoxine hydrochloride delayed-release tablets?

- Store doxylamine succinate and pyridoxine hydrochloride delayed-release tablets between 68°F to 77°F (20°C to 25°C).
- Keep doxylamine succinate and pyridoxine hydrochloride delayed-release 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 doxylamine succinate and pyridoxine hydrochloride delayed-release tablets and all medicines out of the reach of children.

General information about the safe and effective use of doxylamine succinate and pyridoxine hydrochloride delayed-release tablets.

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 doxylamine succinate and pyridoxine hydrochloride delayed-release tablets that is written for health professionals. Do not use doxylamine succinate and pyridoxine hydrochloride delayed-release tablets for a condition for which it was not prescribed. Do not give doxylamine succinate and pyridoxine hydrochloride delayed-release tablets to other people, even if they have the same symptoms that you have. It may harm them.

What are the ingredients in doxylamine succinate and pyridoxine hydrochloride delayed-release tablets?

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

Inactive ingredients: colloidal silicon dioxide, croscarmellose sodium, hypromellose, iron oxide black, magnesium stearate, magnesium trisilicate, methacrylic acid and ethyl acrylate copolymer, microcrystalline cellulose, polyethylene glycol, polysorbate, propylene glycol, talc, titanium dioxide.

Manufactured by:
Actavis Laboratories FL, Inc..
Fort Lauderdale, FL. 33314 USA

Distributed by:
Actavis Pharma Inc.
Parsippany, NJ 07054 USA

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

Revised: May 2015 Label Code

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

The mechanism of action of doxylamine succinate and pyridoxine hydrochloride delayed-release tablets is unknown.

12.3 Pharmacokinetics

The pharmacokinetics of doxylamine succinate and pyridoxine hydrochloride delayed-release tablets 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 doxylamine succinate and pyridoxine hydrochloride delayed-release tablets 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 Doxylamine Succinate and Pyridoxine Hydrochloride Delayed-release Tablets in Healthy Non-Pregnant Adult Women

	Single Dose		
	$AUC_{0\text{-}Inf}$ (ng•h/mL)	C_{max} (ng/mL)	T_{max} (h)
Doxylamine	1280.9 ±369.3	83.3 ± 20.6	7.2 ± 1.9
Pyridoxine	43.4 ± 16.5	32.6 ± 15.0	5.7 ± 1.5
Pyridoxal	211.6 ± 46.1	74.3 ± 21.8	6.5 ± 1.4
Pyridoxal 5'Phosphate	1536.4 ± 721.5	30.0 ± 10.0	11.7 ± 5.3
Pyridoxamine	4.1 ± 2.7	0.5 ± 0.7	5.9 ± 2.1
Pyridoxamine 5'-phosphate	5.2 ± 3.8	0.7 ± 0.5	14.8 ± 6.6
	Multiple Dose		
	$AUC_{0\text{-}Inf}$ (ng•h/mL)	C_{max} (ng/mL)	T_{max} (h)
Doxylamine	3721.5 ± 1318.5	168.6 ± 38.5	7.8 ± 1.6
Pyridoxine	64.5 ± 36.4	46.1 ± 28.3	5.6 ± 1.3
Pyridoxal	1587.2 ± 550.0	210.0 ± 54.4	6.8 ± 1.2
Pyridoxal 5'Phosphate	6099.7 ± 1383.7	84.9 ± 16.9	6.3 ± 6.6
Pyridoxamine	2.6 ± 0.8	0.5 ± 0.2	6.6 ± 1.4
Pyridoxamine 5'-phosphate	94.5 ± 58.0	2.3 ± 1.7	12.4 ± 11.2

Multiple-dose administration of doxylamine succinate and pyridoxine hydrochloride delayed-release tablets results in increased concentrations of doxylamine as well as increases in doxylamine C_{max} and $AUC_{0\text{-}last}$ 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 doxylamine succinate and pyridoxine hydrochloride delayed-release tablets. 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 Doxylamine Succinate and Pyridoxine Hydrochloride Delayed-release Tablets to Healthy Non-Pregnant Adult Women

		$AUC_{0\text{-}last}$ (ng•h/mL)	$AUC_{0\text{-}Inf}$ (ng•h/mL)	
Doxylamine Mean±SD N=18	**Single**	911.4 ± 205.6	1280.9 ± 369.3	
	Multiple	3661.3 ± 1279.2	3721.5 ± 1318.5	
Pyridoxine Mean±SD N=18	**Single**	39.3 ± 16.5	43.4 ± 16.5	
	Multiple	59.3 ± 33.9	64.5 ± 36.4	
		C_{max} (ng/mL)	T_{max} (h)	$T_{1/2el}$ (h)
Doxylamine Mean±SD N=18	**Single**	83.3 ± 20.6	7.2 ± 1.9	10.1 ± 2.1
	Multiple	168.6 ± 38.5	7.8 ± 1.6	11.9 ± 3.3
Pyridoxine Mean±SD N=18	**Single**	32.6 ± 15.0	5.7 ± 1.5	0.5 ± 0.2
	Multiple	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 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 Doxylamine Succinate and Pyridoxine Hydrochloride Delayed-release Tablets Under Fed and Fasted Conditions in Healthy Non-Pregnant Adult Women

		$AUC_{0\text{-}t}$ (ng•h/mL)	$AUC_{0\text{-}Inf}$ (ng•h/mL)	
Doxylamine Mean±SD N=42	**Fasted**	1407.2 ± 336.9	1447.9 ± 332.2	
	Fed	1488.0 ± 463.2	1579.0 ± 422.7[a]	
Pyridoxine Mean±SD N=42	**Fasted**	33.8 ± 13.7	39.5 ± 12.9[c]	
	Fed	18.3 ± 14.5	24.2 ± 14.0[b]	
		C_{max} (ng/mL)	T_{max} (h)	$T_{1/2el}$ (h)
Doxylamine Mean±SD N=42	**Fasted**	94.9 ± 18.4	5.1 ± 3.4	12.6 ± 3.4
	Fed	75.7 ± 16.6	14.9 ± 7.4	12.5 ± 2.9[a]
Pyridoxine Mean±SD N=42	**Fasted**	35.5 ± 21.4	2.5 ± 0.9	0.4 ± 0.2[c]
	Fed	13.7 ± 10.8	9.3 ± 4.0	0.5 ± 0.2[b]

[a] N=37; [b] N=18; [c] 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-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 (T1/2el) for Doxylamine Succinate and Pyridoxine Hydrochloride Delayed-release Tablets Administered as a Single Dose of Two Tablets under Fasting Conditions in Healthy Non-Pregnant Adult Women

	T1/2el (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 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 doxylamine succinate and pyridoxine hydrochloride delayed-release tablets 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 doxylamine succinate and pyridoxine hydrochloride delayed-release tablets or placebo. Two tablets of doxylamine succinate and pyridoxine hydrochloride delayed-release tablets 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 doxylamine succinate and pyridoxine hydrochloride delayed-release tablets-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 doxylamine succinate and pyridoxine hydrochloride delayed-release tablets 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 doxylamine succinate and pyridoxine hydrochloride delayed-release tablets 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

Doxylamine succinate and pyridoxine hydrochloride delayed-release tablets 100 and 300 bottle counts are supplied in a high-density polyethylene bottle with a polypropylene child-resistant cap and a silica gel desiccant canister. The 1000 bottle count is supplied in a high-density polyethylene bottle with a polypropylene cap and a silica gel desiccant canister. Each white to off white, round, biconvex film-coated, delayed-release tablet contains 10 mg doxylamine succinate and 10 mg pyridoxine hydrochloride, and is printed with "**2132**" on one side with black ink and plain on the other. Doxylamine succinate and pyridoxine hydrochloride delayed-release tablets are provided as follows:

NDC 00591-2132-01 Bottles of 100

NDC 00591-2132-03 Bottles of 300

NDC 00591-2132-10 Bottles of 1000

16.2 Storage and Handling

Store at 20°C to 25°C (68°F to 77°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 doxylamine succinate and pyridoxine hydrochloride delayed-release tablets until cleared to do so.

Inform women of the importance of not taking doxylamine succinate and pyridoxine hydrochloride delayed-release tablets 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.

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Fort Lauderdale, FL. 33314 USA

Distributed by:
Actavis Pharma, Inc.
Parsippany, NJ 07054 USA

Revised: May 2015