# CENTER FOR DRUG EVALUATION AND RESEARCH

**APPLICATION NUMBER:** 

# 021876Orig1s000

# **PHARMACOLOGY REVIEW(S)**

### MEMO

### Division of Reproductive and Urologic Products Center for Drug Evaluation and Research

From: Kimberly Hatfield, Ph.D. Toxicologist

To: NDA 21876

Subject: Changes to nonclinical scientific bridge and labeling for NDA 21876 (Diclegis)

### Scientific bridge:

NDA 21876 has been submitted as a 505(b)(2) application for the drug product Diclegis (combination of doxylamine succinate and pyridoxine hydrochloride), with nonclinical evidence supporting the safety of Diclegis being based on the Agency's determination of safety for the Reference Listed Drug (RLD), Bendectin® (NDA 10-598). The nonclinical scientific bridge between Diclegis and the RLD Bendectin® has been revised since submission of the initial nonclinical NDA review. It now states:

The bridge for reliance on the nonclinical data generated with Bendectin (10 mg doxylamine succinate and 10 mg pyridoxine hydrochloride) to support the NDA for Diclegis (10 mg doxylamine succinate and 10 mg pyridoxine hydrochloride) is based on: 1) in vivo delayed release, 2) similar pharmacodynamic characteristics, and 3) in vitro dissolution based on Diclectin (a Canadian approved drug product containing 10 mg doxylamine succinate and 10 mg pyridoxine hydrochloride) manufactured at

pyridoxine hydrochloride defined in the US Pharmacopeia e.g., composition, structure, molecular weight and chemical characteristics.

Refer also to the clinical pharmacology memo further elaborating on the scientific bridge submitted by CAPT E. Dennis Bashaw, PharmD.

### Labeling changes:

During label negotiations, a change in Section 13 Carcinogenesis, Mutagenesis and Impairment of Fertility was made. The statement initially read:

Two-year carcinogenicity studies in rats and mice have been conducted with doxylamine succinate.

Doxylamine succinate is not likely to have human carcinogenic potential.

This has been changed to:

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.

Other changes made during label negotiation to Section 8.1 are appropriate and reflect minor edits. I concur with the label submitted by the Sponsor on 4-4-2013.

## This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

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/s/

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KIMBERLY P HATFIELD 04/05/2013

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ALEXANDER W JORDAN 04/05/2013

### DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION CENTER FOR DRUG EVALUATION AND RESEARCH

### PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION

Application number:	NDA 21876
Supporting document/s:	SD# 5, eCTD# 0000
Applicant's letter date:	June 8, 2012
CDER stamp date:	June 8, 2012
Product:	Doxylamine succinate and pyridoxine hydrochloride (10 mg / 10 mg) delayed release tablets
Indication:	Treatment of nausea and vomiting of pregnancy in patients who do not respond to conservative management
Applicant:	Duchesnay, Inc. 950, boul. Michèle-Bohec, Blainville, PQ J7C 5E2, Canada
Review Division:	Division of Reproductive and Urologic Products
Reviewer:	Kimberly Hatfield, PhD
Supervisor/Team Leader:	Alexander Jordan, PhD
Division Director:	Hylton Joffe, MD, MMSc
Project Manager:	George Lyght

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## **1 Executive Summary**

### 1.1 Recommendations

### 1.1.1 Approvability

Nonclinical data support approval of Diclegis (combination of doxylamine succinate and pyridoxine hydrochloride) for the treatment of nausea and vomiting of pregnancy in patients who do not respond to conservative management.

### 1.1.2 Additional Non Clinical Recommendations

No additional nonclinical studies are recommended.

### 1.1.3 Labeling

The Sponsor submitted labeling based on the Canadian monograph, which is very different in content and structure from the FDA's Physicians Labeling. Content was significantly edited. This reviewer did not edit Section 8 since it is highly clinical in nature. Diclegis will be used during pregnancy, and there is significant clinical use already in other countries. The only addition to Section 8 was a section entitled "Animal Data" in order to help conform to the style of the future Pregnancy and Lactation Labeling Rule.

(b) (4)

Of note, neither the doxylamine nor the pyridoxine components have an already established pharmacologic class. Based on the pharmacology presented in this review, we are proposing an established class with this label (doxylamine = antihistamine; pyridoxine = Vitamin B6 analog). Annotated labeling can be found at the end of this review. If it is determined that nonclinical information is necessary to be included in labeling, the suggested edits are found below: deletions are strikethrough and insertions are <u>underlined</u>. The following represents the proposed final labeling for nonclinical content.

### INDICATIONS AND USAGE

DICLEGIS is a combination product of doxylamine succinate, an antihistamine, and pyridoxine hydrochloride, a Vitamin B6 analog, indicated for the treatment of nausea and vomiting of pregnancy in patients who do not respond to conservative management. (1.1)

(b) (4)

### 8. USE IN SPECIFIC POPULATIONS 8.1 Pregnancy Pregnancy Category A

### 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 (VSD) were observed in the preterm (GD 100) fetuses. Doses were 0.5 to 20 times higher than the clinical dose based on body surface area, <sup>(b) (4)</sup>. There was no incidence of VSD in infant monkeys at term. No defects were observed at GD100 in cynomolgus monkeys administered the combination of doxylamine succinate and pyridoxine hydrochloride for 4-day periods between 22 and 41 days of gestation.

### 13. NONCLINICAL TOXICOLOGY

### 13.1 Carcinogenesis, Mutagenesis and Impairment of Fertility

Two-year carcinogenicity studies in rats and mice have been conducted with doxylamine succinate.

doxylamine succinate is not likely to have human carcinogenic potential.

### 1.2 Brief Discussion of Nonclinical Findings

The submitted nonclinical evidence supporting the combination of doxylamine succinate and pyridoxine hydrochloride safety in Diclegis is based on the Agency's determination of the safety of the RLD, Bendectin (NDA 10598), according to section 505(b)(2) of the Federal Food, Drug and Cosmetic Act. Relevant literature was also submitted, and reviewed, regarding the nonclinical assessment of doxylamine and pyridoxine, alone and in combination. Repeat dose toxicity studies were carried out for doxylamine and pyridoxine individually in mice, rat and dog. Toxicity of doxylamine in the rodent was observed as decreased body weights, organ weight changes, and liver histopathology, but occurred at doses 91-1536X the proposed clinical dose of doxylamine in Diclegis. The NOAELs in mice and rat were 325 mg/kg (39X) and 1012 mg/kg (246X), respectively. The toxicity of pyridoxine in the dog was neuromuscular (ataxia) and occurred at a dose 121X the proposed clinical dose of pyridoxine in Diclegis. Genotoxicity studies with doxylamine were negative, and doxylamine is not considered to have carcinogenic potential. Based on the high safety margins, and lack of mutagenicity/carcinogenicity, there is no concern for the safety of the individual components of Diclegis.

Reproductive toxicity studies were carried out with the original Bendectin product (doxylamine succinate and pyridoxine hydrochloride) approved in the 1970s. In rats, a maternal and fetal NOAEL was established at a 24X dose multiple, with fetal toxicity (reduced fetal weight, reduced fetal ossification of limbs, increased resorptions, and increased malformations (short 13<sup>th</sup> rib)) occurring mainly due to maternal toxicity (reduced maternal body weight and food consumption, 17% mortality at high dose) at doses of 500 and 800 mg/kg (61-97X). In monkeys, ventral septum defects in the heart were noted at doses of 20-82 mg/kg (5-20X). Ventral septal defects were noted in early sacrifice animals but not in full-term infants, indicating a potential delay in closure rather than lack of closure. A second study in monkeys with 1.3-13.3 mg/kg doses (0.3-3.2X) showed no teratogenic effects, and no embryo-, fetal- or maternal toxicity.

Pharmacokinetic data in animals was not available for the combination of doxylamine and pyridoxine. As such, we cannot compare AUC values of clinical use. Drug products similar to Diclegis are approved in other countries, and through the vast amount of human exposure data (millions of pregnant women), the potential risks due to treatment with Diclegis are very low. Both components of Diclegis are also individually available in over-the-counter products, and the proposed clinical dose of each component of Diclegis is within the range of over-the-counter use of each compound individually. Therefore, based on the safety margins of the NOAELs for the Diclegis combination (as Bendectin) or the individual components, and the observation of some toxicity at very high dose multiples, there is little concern for toxicity with Diclegis.

## 2 Drug Information

### 2.1 Drug

### 2.1.1 CAS Registry Number

Doxylamine succinate: 562-10-7 Pyridoxine hydrochloride: 58-56-0

### 2.1.2 Generic Name

Doxylamine succinate Pyridoxine hydrochloride

### 2.1.3 Nonproprietary Name(s)

Doxylamine succinate: Doxylamine; N,N-dimethyl-2-(1-phenyl-1-pyridin-2-ylethoxy) ethanamine (1:1)

Pyridoxine hydrochloride: Pyridoxine HCl; Vitamin B6; VB6; VB<sub>6</sub>

### 2.1.4 Chemical Name

Doxylamine succinate: Ethanamine, N,N-dimethyl-2-[1-phenyl-1-(2-pyridinyl)ethoxy]-, butanedioate (1:1)

Pyridoxine hydrochloride: 3,4-Pyridinedimethanol, 5-hydroxy-6-methyl-, hydrochloride

### 2.1.5 Molecular Formula/Molecular Weight

Doxylamine succinate: C<sub>17</sub>H<sub>22</sub>N<sub>2</sub>O•C<sub>4</sub>H<sub>6</sub>O<sub>4</sub>; 388.46 g/mol Pyridoxine hydrochloride: C<sub>8</sub>H<sub>11</sub>NO<sub>3</sub>•HCl; 205.64 g/mol

### 2.1.6 Structure



Doxylamine succinate

Pyridoxine hydrochloride

### 2.1.7 Pharmacologic class

Neither doxylamine succinate nor pyridoxine hydrochloride has an already established pharmacologic class. Based on the pharmacology presented in this review, we are proposing an established class with this label (doxylamine = antihistamine; pyridoxine = Vitamin B6 analog).

### 2.2 Relevant IND/s, NDA/s, and DMF/s

NDA 010598: Bendectin (oral tablet containing dicyclomine hydrochloride (10 mg), doxylamine succinate (10 mg), pyridoxine hydrochloride (10 mg))

- originally approved in 1956 for nausea and vomiting of pregnancy

### 2.3 Clinical Formulation

### 2.3.1 Drug Formulation

Diclegis delayed release tablets are composed of

(b) (4)

### Table 1: Composition of Diclegis Delayed Release Tablets

Component and Quality Standard	Function	Quantity per unit (mg)	<sup>(b) (4)</sup> % of Overall Tablet Total
(b) (4)			
Doxylamine Succinate, USP	API	10.0	(b) (4)
Pyridoxine HCI, USP	API	10.0	
Microcrystalline Cellulose PH 102, NF			(b) (4)
Magnesium Trisilicate, USP			
Croscarmellose Sodium, NF			
Magnesium Stearate, NF			
Colloidal Silicon Dioxide, NF			
			(b) (4)
(b) (4)		<u>.</u>	
			(b) (4)
•			
(b) (·			(b) (4)
Methacrylic Copolymer Acid, NE			
	)		
Polyethylene Glycol 400 NF			
(b) (4	)		
Talc USP			
(b) (4)			
(b) (4)	-		(b) (4)
Carnauba Wax Powder, NF			
			(b) (4)
(b) (d)		_	
(b) (4)	1		(b) (4)
Propylene Glycol, USP			
n-Butyl Alcohol, NF			
			(D) (4)
OVERALL TABL	ET TOTAL	169.46 mg	100.0%

#### 2.3.2 **Comments on Novel Excipients**

There are no novel excipients.

### 2.3.3 Comments on Impurities/Degradants of Concern

<sup>(b) (4)</sup> The FDA Inactive The proposed amount of Ingredient database indicates that the highest approved amount in an oral tablet is (b) (4) After consultation with the CMC reviewer, he had the following comments. The <sup>(b) (4)</sup> is acceptable. higher amount of (b) (4)

#### Proposed Clinical Population and Dosing Regimen 2.4

Diclegis is a delayed release tablet containing 10 mg doxylamine succinate (an antihistamine) and 10 mg of pyridoxine hydrochloride (Vitamin B6), and provides antinauseant and anti-emetic activity. As such, Diclegis is indicated for the treatment of nausea and vomiting of pregnancy in those patients who do not respond to conservative management. The Sponsor notes that the delayed release formulation works optimally when given prior to the anticipated onset of symptoms. For example, the delayed action of Diclegis permits the nighttime dose to be effective in the morning hours, when the patient needs it most.

According to the proposed labeling, two Diclegis delayed release tablets are taken at bedtime to control nausea and vomiting occurring in the morning. Additionally, one delayed release tablet to be taken in the morning and one delayed release tablet to be taken mid-afternoon to control symptoms throughout the day. This equals 4 tablets per day, for a total dose of 40 mg doxylamine succinate per day, and 40 mg pyridoxine hydrochloride per day (80 mg Diclegis total).

#### 2.5 **Regulatory Background**

### Brief History of the product

Doxylamine succinate and pyridoxine hydrochloride were original components of the drug product Bendectin (treatment of nausea and vomiting of pregnancy not responsive to conservative measures), which was approved by the FDA in 1956 (NDA 10-598). Bendectin was originally comprised of 3 active ingredients: doxylamine succinate, pyridoxine hydrochloride and dicyclomine hydrochloride. However, in 1976, it was reformulated to remove dicyclomine hydrochloride since this compound was found to be ineffective in treating nausea and vomiting of pregnancy through the FDA DESI (Drug Efficacy Study Implementation) program. As such, Bendectin then only contained 10 mg doxylamine succinate and 10 mg pyridoxine hydrochloride.

Questions regarding the possible teratogenicity (limb deformities in newborns) of Bendectin led to litigation and adverse publicity. Therefore, in 1983, the product Sponsor for Bendectin, Merrell Dow, decided to cease manufacture of Bendectin for non-medical reasons. In response to a submitted citizen petition, the FDA made a determination under CFR §314.161 that Bendectin was not withdrawn from the market for reasons of safety and effectiveness (August 1999), and published this in the Federal Register (Federal Register, Volume 64, No 152, Monday, August 9, 1999, p 43190). It was noted in a previous medical officer's review that "Prospective US and foreign data on limb deformities in newborns and an independent FDA review of safety for Bendectin have all failed to support the alleged association between Bendectin use and limb deformities." Though not marketed in the U.S. since 1983, product versions of Bendectin are marketed in other parts of the world (Canada, Western Europe, Australia, etc). The current Sponsor for Diclegis, Duchesnay, markets a pyridoxine hydrochloride (10 mg) and doxylamine succinate (10 mg) tablet in Canada, under the name Diclectin. The original two-tablet formulation (Bendectin) is no longer manufactured commercially nor available for comparative testing purposes to either the Canadian drug product (b) (4) Diclectin, or the proposed US product for this NDA, Diclegis. The tradename was proposed for this current NDA, but denied in early review stages.

### NDA 21876 Regulatory Background

NDA 21876 was initially submitted as a 505(b)(2) application by Duchesnay in April 2005, and the Division submitted a Refuse To File action based on 1) insufficient data to link the product (originally proposed as Bendectin), and 2) (<sup>(b) (4)</sup> indication (<sup>(b) (4)</sup>) to the reference listed drug (RLD; Bendectin), and 2) (<sup>(b) (4)</sup>) indication (<sup>(b) (4)</sup>) A pre-NDA meeting was then held in August 2005 to discuss the basis of the Division's refuse to file, and to obtain an understanding of what information would be necessary to support a NDA filing. At that time, Duchesnay chose to conduct an additional efficacy trial to support a future NDA filing, and a Special Protocol Assessment was reviewed by the Division under IND 72300.

### Current Application and 505(b)(2) Support

The Sponsor has submitted a 505(b)(2) application where:

"The nonclinical evidence supporting the combination of doxylamine succinate and pyridoxine hydrochloride safety in Diclectin *(Diclegis)* for this application, is based on the Agency's determination of the safety of the Reference Listed Drug (RLD), Bendectin® (NDA 10-598) according to section 505(b)(2) of the Federal Food Drug and Cosmetic Act. To further support this determination, a search of the literature was conducted for publications that relate to the safety of doxylamine succinate and pyridoxine hydrochloride individually and in combination." *(Documented from Nonclinical Overview, eCTD 0000(5), Module 2.4, 6/8/2012).* 

There are nonclinical literature studies submitted to support this application that reference the product-specific use of Bendectin. The established bridge between Diclegis and Bendectin, is that they contain the same active ingredients (doxylamine succinate and pyridoxine hydrochloride), in the same amounts (10 mg each), and for the same study population (adult pregnant females). The literature is relevant in that the

study by Tyl et al (Section 9, Embryofetal development) used Bendectin obtained from <sup>(b) (4)</sup> (original source: Merrell Dow Pharmaceuticals, Inc., Cincinnati, OH, lot #M072682, batch No. 1) (Merrell-Dow was the original Sponsor for Bendectin). The studies by Hendrickx et al. (Section 9 Embryofetal development) used pulverized Bendectin tablets each containing 10 mg doxylamine succinate and 10 mg pyridoxine hydrochloride.

### 2.6 General Product Information

The drug product Diclegis is a combination of doxylamine succinate (10 mg) and pyridoxine hydrochloride (10 mg). The proposed clinical dosing is 4 tablets per day, for a total dose of 40 mg doxylamine succinate per day, and 40 mg pyridoxine hydrochloride per day. Both components of Diclegis are individually available in over-the-counter products, and in doses higher than those proposed, depending on the population to be treated.

Doxylamine succinate (or simply, doxylamine) is an antihistamine and is used over-thecounter to treat both insomnia, and to treat symptoms of allergies or the common cold, such as sneezing, itching, watery eyes and runny nose. It is found as the sole ingredient in Unisom Sleep Tabs (25 mg; once daily), and is found as part of a multi-ingredient formulation in the following products: Nyquil liquid (12.5 mg; max daily dose 50 mg), Vicks Nyquil Cold & Flu Nighttime Relief (6.25 mg; max daily dose 50 mg), Delsym Night Time Cough & Cold (6.25 mg; max daily dose 50 mg), Tylenol Cold Multi-Symptom Nighttime Liquid (6.25 mg/tbsp; max daily dose 75 mg), Zicam Multi-Symptom Cold and Flu Nighttime (6.25 mg/tbsp; max daily dose 75 mg), among others. Labeling for these products recommends that women who are pregnant or nursing consult a health professional before using these products.

Pyridoxine hydrochloride (or simply, pyridoxine), is also known as Vitamin B6, and is important in the breakdown of protein, fats and carbohydrates from food into products needed by the body.<sup>1</sup> Pyridoxine is used to treat or prevent Vitamin B6 deficiency, to treat anemia, and to treat some types of seizures in babies.<sup>1</sup> It is readily available over-the-counter as a supplement and as a component of multi-vitamins. The Institute of Medicine has published the Recommended Daily Allowance of Vitamin B6 as 1.9 mg/day during pregnancy, with an upper limit of 100 mg/day.<sup>2</sup> Vitamin B6 supplements can be purchased over-the-counter in strengths of 25-500 mg.<sup>3</sup> The 2010 Physicians Desk Reference notes that most prenatal vitamins contain 25 mg Vitamin B6, to be taken once daily, and a product called Animi-3, which is a nutritional supplement containing 12.5 mg Vitamin B6 to be taken 1-4 times daily (50 mg max dose).<sup>4</sup>

<sup>&</sup>lt;sup>1</sup> Drugs.com: http://www.drugs.com/mtm/pyridoxine.html

<sup>&</sup>lt;sup>2</sup> http://www.iom.edu/~/media/Files/Activity%20Files/Nutrition/DRIs/DRI\_Vitamins.ashx

<sup>&</sup>lt;sup>3</sup> http://online.factsandcomparisons.com/MonoDisp.aspx?monoID=fandc-

hcp12748&quick=762539|5&search=762539|5&isstemmed=True&fromTop=true#firstMatch

<sup>&</sup>lt;sup>4</sup> Physicians Desk Reference, 64<sup>th</sup> edition (2010). PDR Network, LLC, Montvale NJ.

## 3 Studies Submitted

### 3.1 Studies Reviewed

There were no nonclinical studies submitted with this NDA. The Sponsor has submitted a 505(b)(2) application where:

The nonclinical evidence supporting the combination of doxylamine succinate and pyridoxine hydrochloride safety in Diclectin *(Diclegis)* for this application is based on the Agency's determination of the safety of the Reference Listed Drug (RLD), Bendectin® (NDA 10-598) according to section 505(b)(2) of the Federal Food Drug and Cosmetic Act. To further support this determination, a search of the literature was conducted for publications that relate to the safety of doxylamine succinate and pyridoxine hydrochloride individually and in combination. *(documented from Nonclinical Overview, eCTD 0000(5), Module 2.4, 6/8/2012)* 

The following literature submitted by the Sponsor was reviewed and/or referenced in this review:

- Budroe JD, Shaddock JG, Casciano DA (1984). A study of the potential genotoxicity of methapyrilene and related antihistamines using the hepatocyte/DNA repair assay. Mutat. Res., 135(2):131-7.
- Gibson JP, Staples RE, Larson EJ, Kuhn WL, Holtkamp DE and Newberne JW (1968). Teratology and reproduction studies with an antinauseant. Toxicol Appl Pharmacol., 13:439-47.
- Hendrickx AG, Cukierski M, Prahalada S, Janos G and Rowland J (1985a). Evaluation of Bendectin embryotoxicity in nonhuman primates: I. Ventricular septal defects in prenatal macaques and baboon. Teratology, 32:179 89.
- Hendrickx AG, Cukierski M, Prahalada S, Janos G, Booher S and Nyland T (1985b). Evaluation of Bendectin embryotoxicity in nonhuman primates: II Double blind study in term cynomolgus monkeys. Teratology, 32:191-4.
- Holder CL, Siitonen PH, Slikker W Jr, Branscomb CJ, Korfmacher WA, Thompson HC Jr, Cerniglia CE, Gosnell AB, Lay JO Jr (1990). Metabolism of doxylamine succinate in Fischer 344 rats. Part III: Conjugated urinary and fecal metabolites. J Anal Toxicol., 14(4):247-51.
- Holder CL, Thompson HC Jr, Gosnell AB, Siitonen PH, Korfmacher WA, Cerniglia CE, Miller DW, Casciano DA, Slikker W Jr (1987). Metabolism of doxylamine succinate in Fischer 344 rats. Part II: Nonconjugated urinary and fecal metabolites. J Anal Toxicol., 11(3):113-21.
- Hoover DM, Carlton WW, Henrikson CK (1981a). Ultrastructural lesions of pyridoxine toxicity in beagle dogs. Vet Pathol., 18(6):769-77.
- Hoover DM and Carlton WW (1981b). The subacute neurotoxicity of excess pyridoxine HCI and clioquinol (5-chloro-7-iodo-8-hydroxyquinoline) in beagle dogs I. Clinical Disease Vet Pathol., 18(6):745-56.

- Hoover DM and Carlton WW (1981c). The subacute neurotoxicity of excess pyridoxine HCl and clioquinol (5-chloro-7-iodo-8-hydroxyquinoline) in beagle dogs II. Pathology. Vet Pathol., 18(6): 757-68.
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- Jackson CD and Blackwell BN (1988b). Subchronic studies of doxylamine in Fischer 344 rats. Fundam. Appl. Toxicol., 10(2): 243-53.
- Müller L, Korte A, Madle S (1989). Mutagenicity testing of doxylamine succinate, an antinauseant drug. Toxicol Lett.,49(1):79-86.
- Pelser A, Müller DG, du Plessis J, du Preez JL, Goosen C (2002). Comparative pharmacokinetics of single doses of doxylamine succinate following intranasal, oral and intravenous administration in rats. Biopharm Drug Dispos., 23 (6):239-44.
- Skare JA, Murphy VA, Bookstaff RC, Thompson GA, Heise MA, Horowitz ZD, Powell JH, Parkinson A, St. Peter JV (1995). Safety Assessment of OTC Drugs: Doxylamine Succinate. Arch Toxicol., Suppl.17:326-40.
- Slikker Jr W, Holder CL, Lipe GW, Bailey JR, Young JF (1989). Pharmacokinetics of doxylamine, a component of Bendectin, in the rhesus monkey. Reprod Toxicol., 3(3):187-96.
- Thompson HC Jr, Gosnell AB, Holder CL, Siitonen PH, Rowland KL, Cmarik JL (1986). Metabolism of doxylamine succinate in Fischer 344 rats. Part I: Distribution and excretion. J Anal Toxicol., 10(1):18-23.
- Tyl RW, Price CJ, Marr MC, Kimmel CA (1988). Developmental toxicity evaluation of Bendectin in CD rats. Teratology, 37:539-552.
- Vitamin B6 Fact Sheet. Office of dietary Supplements, National Institute of Health Review September 15, 2011, <u>http://ods.od.nih.gov/pdf/factsheets/vitaminb6.pdf</u>

### 3.2 Studies Not Reviewed

Other literature references submitted by the Sponsor either documented information on doxylamine or pyridoxine alone, or were not relevant to approval of this NDA, and were not included.

### 3.3 Previous Reviews Referenced

The Sponsor obtained many documents involved in the review of Bendectin (NDA 10598) via the Freedom of Information Act. Those were submitted with the electronic application and can be found in the electronic document room.

## 4 Pharmacology

### 4.1 **Primary Pharmacology**

Published literature was submitted by the Sponsor to support the pharmacology of doxylamine succinate and pyridoxine hydrochloride. However, this information is based on the individual compounds, not their use as a combination product. Additional information was located by this reviewer in the public literature, Micromedex databases, PubChem databases and NIH Dietary Supplement Fact Sheets (Pyridoxine as Vitamin B6) to document the following information on the pharmacology and mechanism of action of doxylamine succinate and pyridoxine hydrochloride.

### Doxylamine:

- Doxylamine is listed as a histamine H1 antagonist.<sup>5</sup>
- Histamine H1 antagonists selectively bind to but do not activate histamine H1 receptors, thereby blocking the actions of endogenous histamine.<sup>5</sup> H1 antagonists can also antagonize the muscarinic acetylcholine receptor M1.<sup>5</sup>

### **Pyridoxine:**

- Pyridoxine is the 4-methanol form of Vitamin B6.<sup>6</sup>
- Vitamin B6 is the generic name for six compounds (vitamers) with vitamin B6 activity: pyridoxine, pyridoxal, and pyridoxamine, and their respective 5'-phosphate esters.<sup>7,8,9,10,11</sup>
  - Pyridoxine is converted to pyridoxal phosphate, a coenzyme for synthesis of amino acids, neurotransmitters, sphingolipids and aminolevulinic acid.<sup>6</sup>
  - Pyridoxine and Vitamin B6 are frequently used as synonyms, but this practice is erroneous and sometimes misleading.<sup>11</sup>
  - Pyridoxal 5' phosphate (PLP) and pyridoxamine 5' phosphate (PMP) are the active coenzyme forms of vitamin B6. Plasma PLP is the most common measure of vitamin B6 status.<sup>8,9,10</sup>
- Vitamin B6 is involved in more than 50 enzyme reactions involved in the metabolism of amino acids.<sup>7</sup>

<sup>6</sup> NCBI PubChem Compound Database

<sup>&</sup>lt;sup>5</sup> NCBI PubChem Compound Database

http://pubchem.ncbi.nlm.nih.gov/summary/summary.cgi?cid=3162#x94

http://pubchem.ncbi.nlm.nih.gov/summary/summary.cgi?cid=6019&loc=ec\_rcs#x94

<sup>&</sup>lt;sup>7</sup> Shideler CE (1983) Vitamin B6: An overview. Am J Med Technol, 49:17-22.

<sup>&</sup>lt;sup>8</sup> Institute of Medicine. Food and Nutrition Board. Dietary Reference Intakes: Thiamin, Riboflavin, Niacin, Vitamin B6, Folate, Vitamin B12, Pantothenic Acid, Biotin, and Choline. Washington, DC: National Academy Press; 1998.

<sup>&</sup>lt;sup>9</sup> McCormick D. Vitamin B6. In: Bowman B, Russell R, eds. Present Knowledge in Nutrition. 9th ed. Washington, DC: International Life Sciences Institute; 2006

<sup>&</sup>lt;sup>10</sup> NIH Vitamin B6 Fact Sheet, http://ods.od.nih.gov/factsheets/VitaminB6-HealthProfessional/

<sup>&</sup>lt;sup>11</sup> Snell, EE (1990). Vitamin B6 and decarboxylation of histidine. Ann. N.Y. Acad. Sci., 585:1-12.

- Vitamin B6 also plays a role in cognitive development through the biosynthesis of neurotransmitters and in maintaining normal levels of homocysteine, an amino acid in the blood <sup>10,12</sup>
- Vitamin B6 is involved in gluconeogenesis and glycogenolysis, immune function (for example, it promotes lymphocyte and interleukin-2 production), and hemoglobin formation. <sup>10,12</sup>
- Vitamin B6 is found in a large variety of foods, and is also available in multivitamin supplements.<sup>10</sup>

## 5 Pharmacokinetics/ADME/Toxicokinetics

### 5.1 PK/ADME

Published literature was submitted by the Sponsor to detail the PK/ADME of doxylamine succinate and pyridoxine hydrochloride, individually and in combination. Additional information was located by this reviewer in the public literature, PubChem database and Micromedex database.

Doxylamine and Pyridoxine in combination:

- When Bendectin (the originally approved Diclegis product) was administered to pregnant rhesus monkeys (gestational day (GD) 22-50), there was no significant change in AUC or clearance of the doxylamine component in pregnant monkeys versus previously collected data in nonpregnant rhesus monkeys (no difference in PK as a consequence of pregnancy).<sup>13</sup>
- Doxylamine PK (AUC and clearance) was not different between GD 22 and GD50 following multiple dose administration of Bendectin, in pregnant cynomolgus and rhesus monkeys.<sup>13</sup>
  - Cynomolgus monkey AUC = 36-38 μg\*min/mL; Clearance = 170-193 mL/min/kg.
  - $\circ~$  Rhesus monkey AUC = 40-49  $\mu g^{*}min/mL;$  Clearance = 192-329 mL/min/kg.
- Following oral administration of Bendectin in rhesus monkeys, the plasma elimination profile of doxylamine was best described by second-order PK models.<sup>14</sup>
  - Clearance of doxylamine decreased as the dose of Bendectin was increased.
  - Linear extrapolation of doxylamine plasma AUC values from low doses of Bendectin (10 times the human equivalent dose) would result in an

<sup>&</sup>lt;sup>12</sup> Mackey A, Davis S, Gregory J. (2005) Vitamin B6. In: Modern Nutrition in Health and Disease, 10th ed. (Shils M, Shike M, Ross A, Caballero B, Cousins R, eds.). Baltimore, MD:Lippincott Williams & Wilkins

 <sup>&</sup>lt;sup>13</sup> Rowland JM, Slikker Jr. W, Holder CL, Denton R, Prahalada S, Young JF, Hendrickx AG (1989)
 Pharmacokinetics of doxylamine given as Bendectin in pregnant monkey and baboon. Reproductive Toxicology, 3: 197-202.

<sup>&</sup>lt;sup>14</sup> Slikker Jr. W, Holder CL, Lipe GW, Bailey JR, Young JF (1989) Pharmacokinetics of doxylamine, a component of Bendectin, in the rhesus monkey. Reproductive Toxicology, 3:187-196.

underestimation of plasma AUC values after higher doses (≥20 times the human equivalent dose).

### Doxylamine:

- A single 2 mg oral dose to Sprague-Dawley male rats resulted in a peak plasma concentrations (Cmax ± SD) of 281.4±24.6 ng/ml, Tmax= 1.5 h.<sup>15</sup>
- A single oral dose of 2 or 20 mg to male and female rats showed that most of the dose (approximately 70%) was eliminated in the first 24 h after dosing and 95 to 100% of the dose was recovered during the 72 h course of the experiments with both sexes and dose levels. Less than 1% of the total dose remained in the rats at the end of the test period. The urinary route of elimination was more predominant than the fecal route in both sexes given the 20 mg dose. The fecal route predominates in low-dose males whereas there is no significant difference between urinary and fecal routes of elimination in low-dose females. Preliminary characterization of urinary metabolite form using extraction techniques shows 99% of the metabolites to be in the polar conjugated form.<sup>16</sup>
- Incubation of [<sup>14</sup>C]-doxylamine succinate with human and rat intestinal microflora indicated that anaerobic bacteria were not capable of effecting the degradation of [<sup>14</sup>C]-doxylamine succinate.<sup>17</sup>
- Incubation of [<sup>14</sup>C]-doxylamine succinate with isolated rat hepatocytes generated several metabolites similar to those observed in vivo including: doxylamine Noxide, desmethyldoxylamine, didesmethyldoxylamine and ring-hydroxylated products of doxylamine and desmethyldoxylamine. <sup>17</sup>
- Following oral administration of (<sup>14</sup>C)-doxylamine succinate (13.3 and 133 mg/kg doses) to male and female Fischer 344 rats, the cumulative urinary and fecal eliminations of these conjugated doxylamine metabolites at the 13.3 mg/kg dose were 44.4 +/- 4.2% and 47.3 +/- 8.1% of the total recovered dose for male and female rats, respectively. The cumulative urinary and fecal eliminations of conjugated doxylamine metabolites at the 133 mg/kg dose were 55.2 +/- 2.6% and 47.9 +/- 2.5% of the total recovered dose for male and female rats, respectively. The conjugated doxylamine metabolites that were isolated, quantitated, and identified are doxylamine O-glucuronide, N-desmethyl-doxylamine O-glucuronide, and N,N-didesmethyldoxylamine O-glucuronide.<sup>18</sup>

<sup>&</sup>lt;sup>15</sup> Pelser A, Müller DG, du Plessis J, du Preez JL, Goosen C (2002). Comparative pharmacokinetics of single doses of doxylamine succinate following intranasal, oral and intravenous administration in rats. Biopharm Drug Dispos., 23:239-244..

<sup>&</sup>lt;sup>16</sup> Thompson HC Jr, Gosnell AB, Holder CL, Siitonen PH, Rowland KL, Cmarik JL (1986). Metabolism of doxylamine succinate in Fischer 344 rats. Part I: Distribution and excretion. J Anal Toxicol.,10:18-23.

 <sup>&</sup>lt;sup>17</sup> Holder CL, Thompson HC Jr, Gosnell AB, Siitonen PH, Korfmacher WA, Cerniglia CE, Miller DW, Casciano DA, Slikker W Jr (1987). Metabolism of doxylamine succinate in Fischer 344 rats. Part II: Nonconjugated urinary and fecal metabolites. J Anal Toxicol., 11:113-121.

<sup>&</sup>lt;sup>18</sup> Holder CL, Siitonen PH, Slikker W Jr, Branscomb CJ, Korfmacher WA, Thompson HC Jr, Cerniglia CE, Gosnell AB, Lay JO Jr (1990). Metabolism of doxylamine succinate in Fischer 344 rats. Part III: Conjugated urinary and fecal metabolites. J Anal Toxicol., 14:247-251.

Pyridoxine:

- Absorption: well absorbed orally.<sup>6</sup>
- Pyridoxine, pyridoxal, and pyridoxamine are readily absorbed in the jejunum by passive diffusion.7
- Vitamin B6 is stored primarily in the liver, with lesser amounts in muscle and brain.<sup>6</sup>
- Distribution: Extensively binds to serum albumin. Pyridoxal phosphate is the primary form of vitamin B6 in the circulation and is bound to serum albumin.<sup>8,19</sup>
- Metabolism: Following oral administration, pyridoxine undergoes significant hepatic metabolism to pyridoxal phosphate, pyridoxamine phosphate, and 4-pyridoxic acid.6,20
- Excretion: 35-63% of administered pyridoxine (up to 10 mg) is excreted via urine. Bile accounts for 2% of excretion.<sup>21</sup>
- Elimination half-life of pyridoxine: 15-20 days.<sup>6</sup>
- Vitamin B6 concentrations can be measured directly by assessing concentrations of PLP; other vitamers; or total vitamin B6 in plasma, erythrocytes, or urine. Vitamin B6 concentrations can also be measured indirectly by assessing either erythrocyte aminotransferase saturation by PLP or tryptophan metabolites. Plasma PLP is the most common measure of vitamin B6 status.<sup>8,10</sup>

#### 6 **General Toxicology**

#### 6.2 **Repeat-Dose Toxicity**

The general toxicity of doxylamine succinate alone and pyridoxine hydrochloride alone was examined in literature submitted by the Sponsor. There were no general toxicity studies submitted for the combination of doxylamine and pyridoxine. In the Physician's Desk Reference for Bendectin (1982), there were no results of general toxicity studies that were detailed.

Doxylamine succinate in rats:22

- Males and females were treated orally (via diet) with doxylamine for 14 days (0, 100, 250, 500, 1000, 2000 mg/kg) or 90 days (0, 162, 405, 1012, 2530, 6325 mg/kg).
- After 14 day administration (n=6 animals/sex/group):
  - No significant clinical observations except for a 7% decrease in final body weigh in female rats (2000 mg/kg).

 <sup>&</sup>lt;sup>19</sup> Bender DA (1989). Vitamin B6 requirements and recommendations. Eur. J. Clin. Nutr. 43:289-309.
 <sup>20</sup> Merrill AH & Henderson JM (1990). Vitamin B6 metabolism by human liver. Ann NY Acad Sci, 585:110-117.

<sup>&</sup>lt;sup>21</sup> Ink SL & Henderson LM (1984). Vitamin B6 metabolism. Ann Rev Nutr, 4:455-470.

<sup>&</sup>lt;sup>22</sup> Jackson CD and Blackwell B-N (1988). Subchronic studies of doxylamine in Fischer 344 rats. Fundamental and Applied Toxicology, 10:243-253.

- Treatment-related microscopic lesions were limited to cytoplasmic vacuolization in the liver
  - More numerous at high doses in males (500-2000 mg/kg) and only at 2000 mg/kg in females.
- The doses tested are 24, 60, 121, 243 and 486 times the highest proposed clinical dose of doxylamine in Diclegis (40 mg).
- After 90 day administration (n=12 animals/sex/group):
  - Final body weights were decreased 13% in males (6325 mg/kg) and between 5-14% in females (1012-6325 mg/kg).
  - Organ weight changes (normalized to brain weight):
    - Liver increased in all treated male groups (11-68%; not dose proportional), and in 2530 and 6325 mg/kg females (36-60%).
    - Thymus decreased in 6530 mg/kg males (-33%) and 1012-6325 mg/kg females (-12-30%).
    - Heart decreased in 6530 mg/kg males (-21%) and 2530-6325 mg/kg females (-12-22%).
    - Kidney decreased in 6530 mg/kg males only (-13%).
    - Lung decreased in 6530 mg/kg females only (-17%).
  - Treatment-related microscopic changes:
    - Cytoplasmic vacuolization in the liver (3/12 males (1012 mg/kg), 5/12 females (2530 mg/kg)) which progressed to severe hepatocellular fatty change (12/12 males at both 2530 and 6325 mg/kg (severe); 12/12 females at 6325 mg/kg (moderate))
    - Dose-related changes in parotid salivary gland (cytomegaly with basophilic and coarsely granular or vacuolated cytoplasm)
  - The doses tested are 39, 98, 246, 615, and 1536 times the highest proposed clinical dose of doxylamine in Diclegis (40 mg).

Doxylamine succinate in mice:<sup>23</sup>

- Males and females were treated orally (via diet) with doxylamine for 14 days (0, 100, 250, 500, 1000, 2000 mg/kg) or 90 days (0, 80, 162, 325, 750, 1500 mg/kg).
- After 14 day administration (n=6 animals/sex/group):
  - Final body weights were decreased 4 and 7% in 2000 mg/kg males and females, respectively.
  - Treatment-related microscopic lesions were limited to scattered small foci of hepatic necrosis in both males and females.
    - Two males (1000 mg/kg), one female (100 mg/kg), one female (2000 mg/kg).
  - The doses tested are 12, 30, 61, 121 and 243 times the highest proposed clinical dose of doxylamine in Diclegis (40 mg).
- After 90 day administration (n=12 animals/sex/group):
  - Final body weights were generally decreased from controls at doses >162 mg/kg in males, and >325 mg/kg in females, but was not doseproportional, and ranged from 5-14% decreases.

<sup>&</sup>lt;sup>23</sup> Jackson CD and Blackwell B-N (1988). Subchronic studies of doxylamine in B6C3F1 mice. Fundamental and Applied Toxicology, 10:254-261.

- Organ weight changes (normalized to brain weight):
  - Liver increased in 750 and 1500 mg/kg males (27-34%), and in 162-1500 mg/kg females (not dose proportional; 4-50%).
  - Thymus increased in 1500 mg/kg males only (16%).
  - Kidney decreased in 1500 mg/kg males and females (both -17%).
  - Lung decreased in 1500 mg/kg females only (-14%).
- o Treatment-related microscopic changes:
  - Hepatic cell cytomegaly and/or karyomegaly (mild to severe; 10-12/12 male mice (severe) at 750 and 1500 mg/kg; 11/12 female mice (severe) at 1500 mg/kg; 9/12 female mice (mild) at 750 mg/kg).
  - Hepatic cell necrosis (11/12 male mice 1500 mg/kg; 12/12 female mice 1500 mg/kg)
- The doses tested are 10, 20, 39, 91 and 182 times the highest proposed clinical dose of doxylamine in Diclegis (40 mg).

Pyridoxine hydrochloride in dogs:<sup>24,25,26</sup>

- Males and females were treated orally (via gelatin capsules) with pyridoxine at increasing doses (50 mg/kg first week, 100 mg/kg second week, 150 mg/kg 3-16 weeks).
- Anorexia and loss of body weight occurred in first weeks of trial, but stabilized to control levels at study end.
- 10/10 pyridoxine dogs developed neurologic disease (manifested by ataxia) including proprioceptive loss involving both fore- and hindquarters, characterized by stiff, spastic, dysmetric leg movements.
  - Maintained muscle tone, but lacked apparent sense of motion or position of limbs.
- Erythrocyte counts, hemoglobin concentration and packed cell volume were reduced, but considered "low normal".
- Degenerative neurologic lesions limited to the dorsal funiculus, the trigeminal nerve fibers and the spinal tracts of the trigeminal nerves.
  - Number of axons reduced and irregular/fragmented myelin.
- The dose tested (150 mg/kg) is 121 times the highest proposed clinical dose of pyridoxine in Diclegis (40 mg).

<sup>&</sup>lt;sup>24</sup> Hoover DM and Carlton WW (1981). The subacute neurotoxicity of excess pyridoxine HCl and Clioquinol (5-chloro-7-iodo-8-hydroxyquinoline) in beagle dogs. I. Clinical disease. Vet. Pathol., 18:745-756.

<sup>&</sup>lt;sup>25</sup> Hoover DM and Carlton WW (1981). The subacute neurotoxicity of excess pyridoxine HCl and Clioquinol (5-chloro-7-iodo-8-hydroxyquinoline) in beagle dogs. II. Pathology. Vet. Pathol., 18:757-758.

<sup>&</sup>lt;sup>26</sup> Hoover DM, Carlton WW, Henrikson CK (1981). Ultrastructural lesions of pyridoxine toxicity in beagle dogs. Vet. Pathol., 18:769-777.

## 7 Genetic Toxicology

The genotoxicity of doxylamine succinate alone was examined in literature submitted by the Sponsor. There were no genotoxicity studies submitted for the combination of doxylamine and pyridoxine, or pyridoxine alone.

The genotoxicity of doxylamine succinate was examined via the Ames assay, and found to be negative in *Salmonella*, with and without S-9 mix from Aroclor-treated rats and Syrian hamsters.<sup>27</sup>

The genotoxicity of doxylamine succinate was also examined using a hepatocytes/DNA repair assay.<sup>28</sup> Hepatocyte monolayer cultures were established from the livers of adult male Fischer 344 rats, and treated with 0-750  $\mu$ M of doxylamine succinate along with methyl-[<sup>3</sup>H]thymidine. Net nuclear grain counts, cytotoxicity measurements, lactate dehydrogenase release and DNA repair via [<sup>3</sup>H]thymidine incorporation into the cell genome were evaluated. Doxylamine was found to weakly induce unscheduled DNA synthesis in this test system, with a concentration-related statistically significant increase in net nuclear grains over negative controls, and increased percent of cells undergoing DNA repair at the two highest doses tested (500 and 750  $\mu$ M) (Table 2). Skare et al.<sup>29</sup> noted that this test has been repeated and the results did not show any evidence of unscheduled DNA synthesis at doses comparable to and higher than those used in this study.

A third literature article examined the mutagenicity of doxylamine with respect to transplacentally-induced mutagenic effects in mouse embryos at different stages of development, as well as for induction of sister chromatid exchanges (SCE) in human lymphocyte cultures, and presence of micronuclei in Chinese hamster bone marrow.<sup>30</sup> These experiments showed 1) no cytotoxic effects in embryos on gestation day (GD) 11 or 17 (no reduction in % of polychromatic erythrocytes); 2) small but statistically significant increase in mean chromosomal aberration rates in embryos at maternally toxic doses beyond human therapeutic doses; 3) no mutagenic potential via the SCE test with mouse embryos on GD 11; 4) no mutagenic potential via the micronucleus test with fetal blood on GD 17; and 5) negative micronucleus test on Chinese hamster bone marrow and the SCE test on human lymphocytes in vitro. Skare et al. have noted that this assay has been repeated with the results showing no evidence of unscheduled DNA synthesis at doses comparable to and higher than those used above.<sup>29</sup>

<sup>&</sup>lt;sup>27</sup> Zeiger E, Anderson B, Haworth S, Lawlor T, Mortelmans K, Speck W (1987). Salmonella mutagenicity tests. III. Result fromt eh testing of 255 chemicals. Environ. Mutagen. 9 (Suppl 9):1-109. (referenced from Müller et al., 1989)

<sup>&</sup>lt;sup>28</sup> Budroe JD, Shaddock JG and Casciano DA (1984). A study of the potential genotoxicity of methapyriline and related antihistamines using the hepatocytes/DNA repair assay. Mutation Research 135:131-137

<sup>&</sup>lt;sup>29</sup> Skare JA, Murphy VA, Bookstaff RC, Thompson GA, Heise MA, Horowitz ZD, et al. (1995). Safety Assessment of OTC Drugs: Doxylamine Succinate. Arch Toxicol. Suppl.17: 326-40.

<sup>&</sup>lt;sup>30</sup> Müller L, Korte A, Madle S (1989). Mutagenicity testing of doxylamine succinate, an antinauseant drug. Toxicology Letters 49:79-86.

Dose	Expt.	Net nuclear grains $\pm$ S.E.	Per cent in repair <sup>a</sup>
0	1	$-2.21 \pm 0.31$	3.3
10 μ <b>M</b>		$-2.01 \pm 0.29$	2
50 µ M		$-2.53 \pm 0.28$	3
100 µ M		$0.78 \pm 0.28$	7
500 μM		$1.29 \pm 0.31$	13
$1000\muM$		cytotoxic	cytotoxic
DMBA, 10 µg∕ml		> 25	100
DMSO (1%)		$-2.81\pm0.23$	0
0	11	$-1.12 \pm 0.27$	6.7
50 μM		$-0.9 \pm 0.28$	7
100 µM		$-0.67 \pm 0.26$	6
250 µM		$0.08 \pm 0.28$	9
500 µM		$1.58 \pm 0.30$	22
750 µM		$1.82 \pm -0.26$	19
DMBA, 5 µg∕ml		> 25	100
DMSO (1%)		$-3.17 \pm 0.28$	2.7

able 2 : Doxylamine-induced unscheduled DNA synthesis in the hepatocyte/DN	٩I
repair assay	

<sup>a</sup> Cells with net nuclear grain counts which are ≥ 5 are considered in repair.

#### 8 Carcinogenicity

Two-year rat and mouse bioassays were conducted by the National Center for Toxicological Research for doxylamine succinate.<sup>31,32</sup> The Sponsor provided a case study overview of the findings from Skare et al. (1995).<sup>29</sup> There does not appear to be carcinogenicity data on the combination product.

The relevance of the doxylamine rodent bioassay results for human risk assessment was deliberated by the U.S. FDA via two advisory committee meetings, according to the case review, and documentation was found in the Federal Register as an Amendment of the Final Monograph for Over-the-Counter Antihistamine Drug Products to include doxylamine succinate.<sup>29,33</sup> The conclusion was that doxylamine was safe and effective for over-the-counter use as an antihistamine, that doxylamine is not likely to have

<sup>&</sup>lt;sup>31</sup> Jackson CD and Blackwell B-N (1993). 2-year toxicity study of doxylamine succinate in the Fischer 344 rat. International Journal of Toxicology, 12:1-11. <sup>32</sup> Jackson CD and Sheldon W (1993). Two-year toxicity study of doxylamine succinate in B6C3F1 mice.

International Journal of Toxicology, 12:311-321.

<sup>&</sup>lt;sup>33</sup> US Federal Register. 21 CFR Parts 310, 341, and 369. Amendment of Final Monograph for Over-the-Counter Antihistamine Drug Products; Rule. Department of Health and Human Services, Food & Drug Administration, [Docket No. 76N-052H], RIN 0905-AA06, Volume 59, Number 19, January 28, 1994.

human carcinogenic potential, and that there be no specific statement about tumors in the labeling.

The summarized data from the bioassays, for reference, is listed below.

Rat 2-year bioassay:<sup>31</sup>

- Male and female Fischer 344 rats
- 0, 500, 1000 and 2000 ppm (mg/kg) doxylamine succinate for 65 weeks (9/group) or 2 year (48/group)
- No treatment-related differences in survival in either sex.
- Reduced body weights in males (8.4%) and females (22.8%) at 2000 mg/kg.
- Treatment-related, non-neoplastic lesions were found primarily in the liver and parotid salivary gland.
  - Liver: fatty change and degeneration (both sexes); hyperplasia (resulting from degeneration due to leukemia) and atypical cells in males; and hypertrophy, chronic inflammation and mixed cell foci in females.
  - Salivary glands: treatment-related increase in cytoplasmic alteration (both sexes)
- Increased incidence of hepatocellular adenoma and carcinoma with increasing doses (significant per the trend test) in male rats at 2000 mg/kg.
  - Increased incidence of either lesion in the 2000 mg/kg group was not significant compared to that in controls.
  - When animals with carcinoma or adenoma were combined, the trend test remained significant, and the incidence of the 2000 mg/kg group was significantly increased over that in controls.
- No treatment-related increase in neoplasms found in females.
- Marked dose-related decrease in mammary fibroadenomas.

Mouse 2-year bioassay:<sup>32</sup>

- Male and female B6C3F1 mice
- 0, 190, 375, and 750 ppm (mg/kg) for 65 weeks (12/group) or 2 year (48/group)
- No treatment-related differences in survival in either sex.
- Reduced body weights in males (3.4%) and females (8.7%) at 750 mg/kg.
- Liver lesions (hepatocellular hypertrophy, atypical hepatocytes, clear cell and mixed cell foci and necrosis) in males at 750 mg/kg.
- Significant increase in hepatocellular adenomas in males (375 and 750 mg/kg) and females (750 mg/kg).
- Thyroid follicular cell hyperplasia and thyroid follicular cell adenomas were increased in treated mice of both sexes.
- Treatment-related increase in cytoplasmic alteration of the parotid salivary gland in males.
- Increased incidence in hyperplasia of the pituitary gland in females.

## 9 **Reproductive and Developmental Toxicology**

### 9.2 Embryonic Fetal Development

Literature referenced by the Sponsor included embryofetal studies in rats, rabbits and monkeys. Some studies investigated the doxylamine and pyridoxine combination product, and are reviewed in detail below. Some only investigated doxylamine alone, and are briefly summarized. Since the doxylamine alone studies do not investigate the reproductive toxicity of the combination, they will not be referenced in the label.

Briefly, doxylamine alone was shown not to have a deleterious effect on pregnancy maintenance, litter size or fetal weight in the rabbit when pregnant dams were treated on days 9-16 of gestation with 10 or 30 mg/kg doxylamine.<sup>34</sup> When maternal toxicity was produced (100 mg/kg), reduced number of live fetuses was noted and an increase in fetal wastage, along with skeletal malformations in 3 fetuses (fused sternebrae, fused ribs). There were also increased maternal deaths at the 100 mg/kg dose. The doses used here represent dose multiples of 5, 15 and 48 times the highest proposed clinical dose of doxylamine (40 mg) for Diclegis.

Rats were dosed orally (via diet) with doxylamine alone (0, 10, 30 and 100 mg/kg) from 80 days prior to mating through two successive litters.<sup>34</sup> No maternal drug-related clinical signs were noted, as were no effects on behavior, food consumption or body weight gain. Conception rates, litter sizes and survival rates were not affected by treatment. Variations in fetal and neonatal pup weight were noted among dose groups, but not deemed significant. Decreased body weight gains in pups of the two highest dose groups were noted on birth day 22 (10-20% decrease from controls). No malformations were noted in any newborns.

Below are detailed reviews of the studies investigating doxylamine and pyridoxine in combination (as Bendectin, the reference listed drug).

Study title:	<b>Developmental toxicity</b>	evaluation of Bendectin in CD rats
	Study no:	Literature
	Study report location:	eCTD Module 4.3
Conducting	laboratory and location:	Tyl et al., Teratology 37:539-552 (1988)
		Research Triangle Institute, Research Triangle
		Park, NC and National Center for Toxicological
		Research, National Toxicology Program,
		Jefferson, AK
	Date of study initiation:	Unknown
	GLP compliance:	No
	QA statement:	No

<sup>&</sup>lt;sup>34</sup> Gibson JP, Staples RE, Larson EJ, Kuhn WL, Holtkamp DE, Newberne JW (1968). Teratology and reproduction studies with an antinauseant. Toxicology and Applied Pharmacology, 13:439-447.

Drug, lot #, and % purity:	Bendectin (1:1 ratio pyridoxine) (CAS	of doxylamine and \$#8064-77-5) ; Lot
	M072682 ; Purity	/ >98%
	Doxylamine succina	ate (CAS #562-10-7)
	Pyridoxine hydrochl	oride (CAS #058-56-0)
	Nitrofen (CAS #183	6-75-5) ; Positive control ;
	Lot 8561	<sup>(b) (4)</sup> ; Purity >94%

### **Key Study Findings**

- 17% maternal mortality at the high dose (800 mg/kg) of Bendectin.
- Reduced maternal body weights and food consumption at 500 and 800 mg/kg Bendectin during treatment, with overcompensation during post-treatment.
- Embryolethality (increased resorptions) at 800 mg/kg/d.
- Developmental toxicity (reduced fetal body weight per litter, reduced fetal ossification in anterior distal limbs) at 500 and 800 mg/kg Bendectin (noted that these are likely due to maternal toxicity).
- Increased incidence of malformations (skeletal; short 13<sup>th</sup> rib) at 800 mg/kg/d Bendectin (noted that this is likely due to maternal toxicity)
- The maternal and fetal NOAEL for Bendectin was 200 mg/kg/d, which is equivalent to 24 times the highest proposed clinical dose of Diclegis (80 mg) based on body surface area.

### Methods

Doses:	Bendectin (0, 200, 500, 800 mg/kg/d)
	Nitrofen (50 mg/kg/d)
Frequency of dosing:	Once per day, GD 6-15
Dose volume:	5 mL/kg (both Bendectin and Nitrofen)
Route of administration:	Oral gavage
Formulation/Vehicle:	Bendectin (distilled water); Nitrofen (corn oil)
Species/Strain:	Rat, CD ([COBS]Crl:CD[SD]Br)
Number/Sex/Group:	Pregnant females; 37-41 females per dose
	(Bendectin), 14 females for positive control
Satellite groups:	None
Study design:	Dosing GD6-15, sacrifice on GD20.
	The Nitrofen positive control was used to indicate the
	susceptibility of the rat strain to the induction of
	diaphragmatic hernia and cardiovascular defects, and
	the ability of personnel to detect these lesions if
	induced. These were suspect findings in some
	Bendectin animal teratology studies in rats and mice.

### **Observations and Results**

### Mortality

Seven dams in the 800 mg/kg Bendectin group died (17.1% mortality); 3 on GD8, and one each on GD11, 12, 14, 19. One dam (800 mg/kg Bendectin) aborted the entire litter on GD12 (noted by study authors as an uncommon occurrence in rodents). Three dams

(800 mg/kg) had totally resorbed litters on GD20. In the initial range finding study (not shown) there were no maternal deaths in 8 dams dosed with 800 mg/kg. The basis for the difference is unknown.

### **Clinical Signs**

Bendectin treatment showed dose-related rapid weight loss (≥5 g in 24hrs), piloerection, and lethargy. Bendectin (800 mg/kg) resulted in chromodacryorrhea, prostration, hunched posture, tremor, ataxia, convulsions. Bendectin (200 mg/kg) resulted in minimal lethargy, piloerection and discolored fur.

### **Body Weight**

Maternal body weight was significantly decreased from controls in the 500 and 800 mg/kg Bendectin groups at GD 11, 15 and 20 (8-10% for 500 mg/kg; 15-20% for 800 mg/kg). In addition, absolute, treatment (GD6-15), and gestational (GD0-20) maternal weight gain was significantly decreased from controls in the 500 and 800 mg/kg Bendectin groups. Of note, during treatment, the 800 mg/kg Bendectin group lost 21 grams, while controls gained 38 g and the 500 mg/kg group only gained 7 g.

### Table 3: Maternal parameters: CD rats treated with Bendectin or Nitrofen (GD6-15)

COPYRIGHT MATERIAL (Tyl, et al., Teratology 37:539-552 (1988)

### **Feed Consumption**

Maternal food consumption was reduced 26% from controls (500 mg/kg Bendectin) and 47% from controls (800 mg/kg Bendectin) during treatment (GD6-15). Following treatment (GD15-20), food consumption in the 500 and 800 mg/kg groups was increased over controls (8 and 15%, respectively). Maternal water consumption was only significantly decreased from controls during treatment (GD6-15) in the 800 mg/kg group (-41%), but was increased during GD15-20 (+25%)

### Necropsy

Maternal uterine weight was significantly decreased from controls at 500 and 800 mg/kg (19-36%), while relative maternal liver weights (as % body weight) were increased slightly at 500 and 800 mg/kg (8-17%) (Table 3).

### **Cesarean Section Data**

Reproductive effects of maternal exposure to Bendectin or Nitrofen are summarized in Table 4. A significant decrease in implantation sites per litter was noted at 500 mg/kg Bendectin, and a significant increase in % resorptions per litter (4-fold), % nonlive implants (resorptions plus late fetal deaths; 4-fold), % affected implants (nonlive plus malformed fetuses; 2.6-fold) were noted at 800 mg/kg Bendectin. Reduced fetal body weight per litter was observed in the 500 and 800 mg/kg Bendectin groups (12-30%).

### Offspring (Malformations, Variations, etc.)

Teratologic effects are summarized in Table 4 and Table 5. Bendectin (800 mg/kg) resulted in reduced ossification of metacarpals (forelimbs), and phalanges (forelimbs) per fetus per litter. The number of ossified caudal vertebral centra in the tail was reduced in all Bendectin treated groups from controls. The study authors note for this value that, though significant, the difference between control and high dose mean values of ossification was approximately one caudal ossification site per fetus per litter, and approximately one-third of an ossification site separated the mean for low dose and control animals.

The percentage of litters with a malformed fetus (Table 5) and the number of litters with one or more fetuses with skeletal malformations (Table 6) was significantly increased at 800 mg/kg Bendectin. The predominant skeletal malformation influencing this finding was short 13<sup>th</sup> rib (less than one-half the normal length of that rib). Of note, there was no increase in the number or percentage of malformed fetuses per litter, and fetal variations were not different across all groups except for an increase (non-significant) in incomplete ossification of the skull plates and public bones, and misaligned sternebrae).

The Nitrofen positive control was used to indicate the susceptibility of the rat strain to the induction of diaphragmatic hernia and cardiovascular defects, and the ability of personel to detect these lesions if induced. This study showed that treatment with Nitrofen caused diaphragmatic hernia and cardiovascular defects, which were not increased over controls in Bendectin treated animals.

## Table 4: Reproductive effects: maternal exposure to Bendectin (GD6-15)

COPYRIGHT MATERIAL (Tyl, et al., Teratology 37:539-552 (1988)

Table 5: Teratologic effects: maternal exposure to Bendectin (GD6-15)COPYRIGHT MATERIAL (Tyl, et al., Teratology 37:539-552 (1988)

### Table 6: Specific teratological defects: maternal exposure to Bendectin (GD6-15)

(note: the original publication was cropped on the left side and missing a portion of the left column)

COPYRIGHT MATERIAL (Tyl, et al., Teratology 37:539-552 (1988)

### Study title: Evaluation of Bendectin embryotoxicity in nonhuman primates: I. Ventricular septal defects in prenatal macaques and baboon

Study no:	Literature
Study report location:	eCTD Module 4.3
Conducting laboratory and location:	Hendrickx AG, Cukierski M, Prahalada S, Janos G and Rowland J. Teratology. 1985a; 32:179 89. California Primate Research Center and Department of Pediatrics, School of Medicine, University of California, Davis, CA
Date of study initiation:	Unknown
GLP compliance:	No
QA statement:	No
Drug, lot #, and % purity:	Bendectin (10 mg each of doxylamine succinate and pyridoxine hydrochloride) Decapryn (10 mg doxylamine succinate)

### Key Study Findings

- Cardiac abnormalities were primarily investigated in response to Bendectin treatment (GD22-50).
- Drug-related ventricular septal defects were observed in all Bendectin dose groups, but did not have a clear dose response.
- Histopathology findings on GD100 versus at birth indicate that Bendectin treatment may delay the closure of the ventricular septum.
- Doses examined in cynomolgus and rhesus monkeys represent dose multiples of 5, 10, and 20 times the highest proposed clinical dose of Diclegis (80 mg), based on body surface area. The doses in baboons represent dose multiples of 0.5 and 5 times the highest proposed clinical dose of Diclegis (80 mg), based on body surface area.

### Methods

Doses:	Bendectin (0, 20.5, 41.1, 82.2 mg/kg/d) in the cynomolgus and rhesus monkey (equivalent to 10X, 20X and 40X the HED of 0.667 mg/kg (60 kg
	woman taking 4 tablets/day))
	Bendectin (0, 1.2, 12.3 mg/kg/d) in the baboon
	(equivalent to 1X and 10X the HED)
	Decapryn (20.5 mg/kg/d) (equivalent to 10X the HED)
Frequency of dosing:	Bendectin: Once per day, GD 22±3 to 50 (all 3 species)
	Bendectin: 4 consecutive days on GD 22-25, 26-29,
	30-33, 34-37, 38-41 in the monkey
Dose volume:	Unknown
Route of administration:	Nasogastric intubation
Formulation/Vehicle:	Unknown
Species/Strain:	Cynomolgus and rhesus monkey, and baboon

Number/Sex/Group: Cynomolgus monkey, females: 9 (control), 11 (10X), 6 (20X) and 10 (40X). Rhesus monkey, females: 3 (control), 6 (10X) and 10 (40X). Baboon, females: 3 (control), 5 (1X) and 11 (10X) and 6 (10X Decapryn). Satellite groups: None Study design: Fetuses were removed by hysterotomy on GD 100±2 for all 3 species. Some macaque infants were delivered via Cesarean at GD150 for cynomolgus monkeys and GD160 for rhesus monkeys. Following physical exam at birth, infants were sacrificed. Physical and external measurements were taken, selected organs weighed, skeletons stained or radiographed, and cardiovascular evaluation was performed.

\*\*\***Reviewers note:** The dose multiples calculated by the study author are not accurate compared to the highest proposed clinical dose of Diclegis (80 mg). The doses in cynomolgus and rhesus monkeys actually represent dose multiples of 5, 10, and 20 times the highest proposed clinical dose of Diclegis, based on body surface area. The doses in baboons actually represent dose multiples of 0.5 and 5 times the highest proposed clinical dose of Diclegis, based on body

### **Observations and Results**

### Mortality

None.

### **Clinical Signs, Body Weight, Food Consumption**

No remarks listed.

### **Embryofetal loss:**

One abortion in each 10X, 20X and 40X dose group for cynomolgus monkeys (dosing GD22-50). One abortion in each control and 10X dose group for rhesus monkeys (dosing GD22-50). One abortion each in 1X Bendectin and 10X Decapryn, and 2 abortions in 10X Bendectin in baboons (dosing GD22-50).

### **Cardiac Abnormalities:**

Isolated interventricular septal defect (VSD) was the specific defect of the heart that was observed. Isolated VSD indicates an abnormal communication of the left ventricle with another heart chamber which is not accompanied by other significant malformations of the heart and vessels. Table 7 details the percent incidence of VSD following exposure to Bendectin from GD22-50, and evaluation on GD100. One cynomolgus monkey was also found to have hydropericardium. The classification of the observed VSDs involved the muscular portion of the interventricular septum (smooth or trabecular portion), with one cynomolgus monkey with an atrioventricular defect. At the postnatal exam, only 1

defect was noted in one animal (cynomolgus monkey), which was a mitral valve defect. No defects were observed in cynomolgus monkeys at term, though the number of animals evaluated at each dose was very low (Table 8). One baboon fetus dosed with 10X Bendectin from GD25-50 had many other malformations in addition to the VSD (exophthalmia, micrognathia, reduction of first and fifth digits on both hands, facial hemangioma, ambiguous genitalia and small for gestational age (cause unknown; does not correspond to any recognized pattern of malformations in primates).

# Table 7: Incidence of cardiac abnormalities in cynomolgus, rhesus and baboon exposed to Bendectin or Decapryn (GD22-50)

COPYRIGHT MATERIAL (Hendrickx AG, Čukierski M, Prahalada S, Janos G and Rowland J. Teratology 1985a; 32:179-89)

Table 8: Incidence of cardiac abnormalities in cynomolgus monkeys after short-<br/>term exposure to BendectinCOPYRIGHT MATERIAL (Hendrickx AG, Cukierski M, Prahalada S, Janos G and<br/>Rowland J. Teratology 1985a; 32:179-89)

### **Conclusion:**

Spontaneous VSDs are very low in historical controls. The VSDs observed in each monkey species appear to be drug-related, but without a clear dose response. The study authors suggest that the increased incidence of VSDs observed prenatally at GD100, versus the absence of VSDs postnatally, indicates a delay in closure of the ventricular septum and spontaneous closer of the defect by term.

### Study title: Evaluation of Bendectin embryotoxicity in nonhuman primates: II. Double-blind study in term cynomolgus monkeys

Study no:	Literature
Study report location:	eCTD Module 4.3
Conducting laboratory and location:	Hendrickx AG, Cukierski M, Prahalada S, Janos G, Booher S and Nyland T. Teratology. 1985b; 32:191-4. <i>California Primate Research Center,</i> <i>School of Medicine, and Department of</i> <i>Veterinary Medicine Radiological Sciences</i> <i>University of California, Davis, CA</i>
Date of study initiation:	Unknown
GLP compliance:	Yes
QA statement:	No
Drug, lot #, and % purity:	Bendectin (10 mg each of doxylamine succinate and pyridoxine hydrochloride)

### **Key Study Findings**

- Bendectin showed no teratogenic effects, and no embryo-, fetal- or maternal toxicity.
- The maternal and fetal NOAEL is 13.3 mg/kg (3.2X). Doses examined represent dose multiples of 0.3, 0.8 and 3.2 times the highest proposed clinical dose of Diclegis (80 mg), based on body surface area.

### Methods

Doses:	0, 2X (2/5 tablet/day), 5X (1 tablet/day) and 20X (4 tablets/day) the HED (approximately 0, 1.3, 3.3 and 13.3 mg/kg/d)
Frequency of dosing:	Once per day, GD 22±3 to 50
Dose volume:	Unknown
Route of administration:	Nasogastric intubation
Formulation/Vehicle:	Placebo test tablets were identical in composition except for exclusion of doxylamine and pyridoxine
Species/Strain:	Cynomolgus monkey
Number/Sex/Group:	Cynomolgus monkey, adult females (91 total): 21 (control), 24 (2X), 24 (5X) and 21 (20X).
Satellite groups:	None

Study design: Fetuses were delivered by cesarean section near term (GD149-154). Following physical exam at birth and radiography for skeletal evaluation, infants were sacrificed. Physical and external measurements were taken, selected organs weighed, and cardiovascular evaluation was performed. Placental examinations were performed on all available placenta.

\*\*\***Reviewers note:** The dose multiples calculated by the study author are not accurate compared to the highest proposed clinical dose of Diclegis (80 mg). The doses actually represent dose multiples of 0.3, 0.8 and 3.2 times the highest proposed clinical dose of Diclegis, based on body surface area.

### **Observations and Results**

### Mortality

None.

Clinical Signs, Body Weight, Food Consumption Not remarkable.

### Necropsy

No maternal necropsy.

### Fetal loss:

An increase in abortions in the low and mid-dose groups was observed, but was not considered statistically significant compared to the controls and high-dose groups. The study authors note that the abortions are not drug-related since the high dose incidence was comparable to controls, and that reported in non-experimental colonies. The overall abortion rate in this study was 15.5%, while the abortion rate for indoor-housed nonexperimental cynomolgus monkeys in this colony is 22.5%.

### Table 9: Embryotoxicity - cynomolgus monkeys treated with Bendectin (GD22-50)

COPYRIGHT MATERIAL (Hendrickx AG, Cukierski M, Prahalada S, Janos G and Rowland J. Teratology 1985b; 32:191-4)

### **Neonatal examination:**

Lung auscultation revealed fluid sounds, which is common in cesarean section infants. Heart auscultation was normal in all animals. No significant effects following external gross examination. Two stillborn animals (one low dose, one high dose) were small for gestational age compared to controls. There were no treatment-related abnormalities observed via internal gross examination, and no treatment-related or incidental abnormalities were detected from radiographs of the neonatal skeleton. One high-dose animal had abnormally small adrenal glands, five animals (one control, three mid-dose and one high-dose) had accessory spleens, and one control animal had an unusually shaped heart apex. The study authors note that all were within range of normal anatomic variations.

### **Cardiac Abnormalities:**

In contrast to the preceding study, there were no cardiac or extracardiac malformations in term infants. This gives weight to the hypothesis that Bendectin causes a delay in closure of the ventricular septum which spontaneously closes by term.

### **Conclusion:**

No organ weights or histopathology were remarked upon in this study. However, the authors note that the doses of Bendectin show no teratogenic effects, and no embryo-, fetal- or maternal toxicity. The authors also note that this supports the findings in human studies that Bendectin has no, or very little, teratogenic potential.

### 9.4 Historical reproductive labeling for Bendectin

The Sponsor was able to obtain historical reviews from the initial approval of Bendectin as a 3-component combination, and its subsequent approval as a 2-component (doxylamine and pyridoxine) combination via the Freedom of Information Act (FOIA). In the NDA submitted for approval of the 2-ingredient Bendectin, no additional pharmacology studies were submitted. However, reproductive toxicity studies with doxylamine and pyridoxine were later submitted and reviewed with the following label suggestions. The actual reviews were not located. These excerpts are pasted from the FOIA documents.

Recommendation: The labeling for Bendectin might be revised to include a modified category A "Usage in Pregnancy" section which would incorporate discription of the animal studies such as:

"Reproduction studies have been performed in rats and rabbits and have revealed no conclusive evidence of a teratogenic effect and only minimal evidence of a possible embryotoxic effect at doses up to 75 times the maximum human therapeutic dose. Cleft palate occurred with similar incidence in fetuses of control and treated rats. One instance of açmatia (in 1/124 rat fetus at 75 times human dosage and of anencephaly (in 1/61 rabbit fetus at 25 times human dosage) Agmathia in 1/124 rat fetus of the highest dosage group and anencephaly in 1/61 rabbit fetus of the group given 25 times the maximum human dose are attributed to sporadic occurrence as was exoncephaly in a control fetus in the rabbit study."

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A second recommendation read:

Recommendation:

I would accept as adequate the substance of the Sponsor's proposed preclinical part of the pregnancy varning with the following editorial change and the parts in parentheses deleted.

> "Studies (have been performed) in rats and rabbits (and) have revealed no suggestion (of risk) of drug-induced fetal abnormalities at doses of Bendectin up to 90 times the maximum human dose..."

if the following sentence pertaining to the results of their human epidemiology study is considered adequate and accurate by FDA review. If indeed, the clinical data clearly establish no risk potential for this drug, a detailed description of the animal findings is not particularly germane.

If the clinical data are inconclusive, however, greater emphasis on details of the equivocal animal findings will be necessary.

Followed by the following that was included in a letter to the Sponsor (Merrell-National Laboratories) on December 27, 1977:

We have completed our review of all the available data pertaining to your proposed PRECAUTIONS statement and request the following ravision:

"Studies in rats and rabbits have revealed no suggestion of druginduced fetal abnormalities at doces of Dendectin up to 50 times the maximum human dose. In addition, taveral epidemiologic studies in women who received Bendectin during pregnancy have shown that the incidence of birth defects in their offspring is no higher than in women not taking the drug during pregnancy. Nevertheless, like all drugs considered for use during pregnancy, particularly during the first trimester, Bendectin should be used only when clearly needed."



Physician's labeling from both approval cycles of Bendectin could not be located.

## 11 Integrated Summary and Safety Evaluation

The Sponsor has stated that the nonclinical evidence supporting the combination of doxylamine succinate and pyridoxine hydrochloride safety in Diclegis is based on the Agency's determination of the safety of the RLD, Bendectin (NDA 10598), according to section 505(b)(2) of the Federal Food, Drug and Cosmetic Act. Literature was also

submitted relating to the safety of doxylamine succinate and pyridoxine hydrochloride individually and in combination.

Diclegis is a combination drug containing 10 mg doxylamine succinate, an antihistamine (histamine H1 antagonist) and 10 mg pyridoxine hydrochloride, a Vitamin B6 analog. The maximum daily dose is 4 tablets, or 40 mg doxylamine and 40 mg pyridoxine, for a total of 80 mg per day. Both components of Diclegis are individually available in over-the-counter products, and in doses higher than those proposed, depending on the population to be treated. Doxylamine is found as a component of Unisom, Nyquil and Zicam (among others) at maximum daily doses between 50-75 mg, and pyridoxine can be found as a dietary Vitamin B6 supplement, or as a component in multi-vitamins at recommended daily doses of 25-50 mg, though supplements have been found with Vitamin B6 strengths of up to 500 mg per day. The Institute of Medicine has published the Recommended Daily Allowance of Vitamin B6 as 1.9 mg/day during pregnancy, with an upper limit of 100 mg/day.<sup>35</sup> As such, the proposed clinical dose of each component of Diclegis is within the range of over-the-counter use of each compound individually.

As noted, the Sponsor did not submit nonclinical studies of their own, but relevant literature regarding the nonclinical assessment of doxylamine and pyridoxine, alone and in combination, was reviewed. Repeat dose general toxicity studies were conducted in mice and rats with doxylamine only at doses 10-486 times the highest proposed clinical dose of doxylamine in Diclegis. Decreased body weights (minimal) and liver histopathology (cytoplasmic vacuolization, severe hepatocellular fatty change, hepatic cell cytomegaly/karyomegaly and hepatic cell necrosis) occurred in mice at doses 182 times the proposed clinical dose, and in rats at 243 times the proposed clinical dose. As such, the proposed dose of doxylamine in Diclegis is expected to have little toxicity in the treated population.

A repeat dose study in dogs treated with pyridoxine for up to 16 weeks showed the development of neurologic disease manifested as stiff, spastic dysmetric leg movement. However this was at a dose of 150 mg/kg which is 121 times the highest proposed dose of pyridoxine in Diclegis. No other repeat dose studies were available for pyridoxine. As such, the proposed dose of pyridoxine in Diclegis is expected to have little toxicity in the treated population.

Genetic toxicology studies were submitted for doxylamine succinate alone, not the combination product, nor for pyridoxine hydrochloride alone. The literature studies indicated that doxylamine was negative in 1) the Ames assay (with or without S9); 2) the sister chromatid exchange test with mouse embryos; 3) micronucleus test on Chinese hamster bone marrow; 4) the SCE test on human lymphocytes in vitro; 5) micronucleus test with fetal blood on GD 17; and had no cytotoxic effects in embryos on GD 11 or 17 (no reduction in % of polychromatic erythrocytes). One study showed that doxylamine weakly induced unscheduled DNA synthesis in a hepatocytes/DNA repair assay. Since mutagenicity studies were not conducted with the combination product, no information on mutagenicity will be included in labeling.

<sup>&</sup>lt;sup>35</sup> http://www.iom.edu/~/media/Files/Activity%20Files/Nutrition/DRIs/DRI\_Vitamins.ashx

In regards to carcinogenicity, the relevance of the doxylamine rodent bioassay results for human risk assessment was deliberated by the US FDA via two advisory committee meetings, and documented in the Federal Register. The conclusion was that doxylamine was safe and effective for over-the-counter use as an antihistamine, that doxylamine is not likely to have human carcinogenic potential, and that there be no specific statement about tumors in the labeling. Labeling for Diclegis will indicate the lack of carcinogenic potential.

Reproductive toxicity studies have been conducted with doxylamine alone, and also via treatment with Bendectin, and can be translated to use of Diclegis. Toxicity with doxylamine alone in rats was only apparent when maternal toxicity was reached, and at doses 48 times the highest proposed clinical dose of doxylamine in Diclegis. A NOAEL could be established at 5 and 15X dose multiples. Reproductive toxicity studies in rats with Bendectin (doxylamine and pyridoxine in combination) resulted in a maternal and fetal NOAEL at a 24X dose multiple. At higher doses (97X) reduced fetal weight, reduced fetal ossification of limbs, increased resorptions, and increased malformations (short 13<sup>th</sup> rib) were observed. Many were considered due to maternal toxicity at these doses (reduced maternal body weight and food consumption, 17% mortality at high dose). In monkeys, a less detailed study with Bendectin treatment was documented in literature. Since cardiac findings were a concern with Bendectin treatment, the study specifically looked at ventral septal defects (VSD) and found that all doses (5-20X dose multiple) resulted in VSDs, but was not a dose response. In addition, it appeared that Bendectin only delayed the closure of the ventral septum and there were no visible defects at birth. A second study with doses 0.3-3.2 times the highest proposed clinical dose of Diclegis showed no teratogenic effects, and no embryo-, fetal- or maternal toxicity.

Pharmacokinetic data in animals was not available for the combination of doxylamine and pyridoxine. As such, we cannot compare AUC values of clinical use. However, toxicity resulting from Bendectin or individual component treatment occurred at dose multiples much higher than the proposed clinical doses, and there is little concern for toxicity with Diclegis. In addition, forms of Diclegis are approved drug products in other countries, and through the vast amount of human exposure data (millions of pregnant women), the potential risks due to treatment with Diclegis are very low.

Toxicity	Drug	Species	Dose	Safety
	product		(mg/kg)	margin
No general toxicity	Doxylamine	Mouse	325	39X
(NOAEL)		Rat	1012	246X
Adult rodent:	Doxylamine	Mouse	750 - 1500	91 - 182X
(dec. body weight, liver	-	Rat	500 - 6325	121 - 1536X
histopathology)				
Neurologic disorder	Pyridoxine	Dog	150	121X
(ataxia)	-	-		
		-		
No reproductive toxicity	Bendectin	Rat	200	24X
(NOAEL)				
Maternal toxicity:	Bendectin	Rat	800	97X
(inc. mortality, dec.				
BW, food consumption)				
Fetal toxicity:	Bendectin	Rat	500 - 800	61 - 97X
(dec. weight and limb				
ossification, inc. resorptions				
and malformations (short				
13 <sup>th</sup> rib)				
No reproductive toxicity	Bendectin	Monkey	1.3 - 13.3	0.3 - 3.2X
(NOAEL)		-		
Fetal toxicity:	Bendectin	Monkey	20 - 82	5 - 20X
(inc. VSDs, delayed				
ventral septum closure)				

# Table 10: Calculated safety margins for doxylamine and pyridoxine (individually or in combination)

a: based on body surface area. Compared to the individual component in Diclegis (40 mg) or the combination product (80 mg).

### Conclusions

Based on the reviewed nonclinical scientific pharmacology and toxicology literature, Diclegis, the combination product of doxylamine succinate and pyridoxine hydrochloride, is relatively safe for clinical use. In addition, its many years of clinical use in the U.S. or internationally as either Bendectin or as Diclectin, support its use in safely treating pregnant women with nausea and vomiting. From a pharmacology/toxicology perspective, we recommend approval of Diclegis for the indicated treatment of nausea and vomiting of pregnancy in patients who do not respond to conservative management.

### Labeling

The Sponsor submitted labeling based on the Canadian monograph, which is very different in content and structure from the FDA's Physician's labeling. Content was significantly edited. Section 8 is highly clinical in nature since Diclegis will be used

(b) (4)

during pregnancy, and there is significant clinical use already in other countries. There were no edits made to Section 8, only an addition of a section entitled "Animal Data" in order to help conform to the style of the future Pregnancy and Lactation Labeling Rule. As such, much of the Sponsor's text of Section 8 was not copied here because there were no nonclinical edits made.

Of note, neither the doxylamine nor the pyridoxine components have an established pharmacologic class. Based on the pharmacology presented in this review, we are creating an established class with this label (doxylamine = antihistamine; pyridoxine = Vitamin B6 analog).

If it is determined that nonclinical information is necessary to be included in labeling, the suggested edits are found below: deletions are strikethrough and insertions are <u>underlined</u>.

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

<sup>(b) (4)</sup> <u>DICLEGIS</u> is a combination product of doxylamine succinate, an <u>antihistamine, and pyridoxine hydrochloride, a Vitamin B6 analog,</u> indicated for the treatment of nausea and vomiting of pregnancy in patients who do not respond to conservative management. (1.1)

### 8. USE IN SPECIFIC POPULATIONS

### 8.1 Pregnancy

### **Pregnancy Category A**

### <u>Animal Data</u>

The effects of doxylamine succinate and pyridoxine hydrochloride in combination 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 and 100 times the highest clinical dose based on body surface area.

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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, (<sup>b)</sup> (<sup>4)</sup>ventricular septal defects (VSD) were observed in the preterm (GD 100) fetuses. (<sup>b)</sup>

Doses were 0.5-20 times higher than the proposed clinical dose based on body surface area,

(b) (4) VSD in infant monkeys (b) (4) -at term, (b) (4) -No (b) (4) were observed <u>at GD100</u> in cynomolgus monkeys (b) (4) -administered the combination of doxylamine succinate and pyridoxine hydrochloride for 4-day periods between 22 and 41 days of gestation. (b) (4)

### 13. NONCLINICAL TOXICOLOGY

### 13.1 Carcinogenesis, Mutagenesis and Impairment of Fertility

Carcinogenicity <u>Two-year carcinogenicity studies in rats and mice have been conducted with</u> <u>doxylamine succinate.</u> doxylamine succinate is not likely to have human carcinogenic potential	(b) (4) (b) (4)
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/s/

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KIMBERLY P HATFIELD 03/04/2013

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ALEXANDER W JORDAN 03/04/2013