CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

209661Orig1s000

PHARMACOLOGY REVIEW(S)

PHARMACOLOGY/TOXICOLOGY REVIEW

Date: October 11, 2016

IND #/SS#/date: NDA 209661, SD 467, October 7, 2015
Reviewer: Kimberly Hatfield, PhD
Sponsor: Duchesnay, Inc.
950, boul. Michèle-Bohec, Blainville PQ, Canada J7C 5E2
Drug: Diclegis (b) (4) (doxylamine succinate and pyridoxine hydrochloride)
Indication: Treatment of nausea and vominting pregnancy in women who do not respond to conservative management.

RE: Labeling review for NDA 209661 (originally NDA 21876 Supplement 10)

Background: A prior approval supplement was submitted for a new formulation of Diclegis (proposed tradename still under review, submitted as Diclegis (b) (4)), (b) (4) Diclegis (10 mg doxylamine succinate, 10 mg pyridoxine hydrochloride). The new formulation represents a new product strength; Diclegis (b) (4) is a (b) (4) tablet containing 20 mg doxylamine succinate, 20 mg pyridoxine hydrochloride. The core of the tablet is delayed-release 10 mg doxylamine succinate, 10 mg pyridoxine hydrochloride, with an immediate-release (b) (4) coating of 10 mg doxylamine succinate, 10 mg pyridoxine hydrochloride. The original Diclegis had a maximum daily recommended dose of 4 tablets per day. Diclegis (b) (4) has a recommended dose of 2 tablets per day (one in morning, one at night), but the same total daily dose as Diclegis. The new formulation reduces the number of tablets to be taken by the patient per day. The delayed action and immediate release of Diclegis (b) (4) are proposed to allow for the bedtime dose to be effective immediately and also help control symptoms throughout the day.

No nonclinical studies were submitted for this supplement. The primary nonclinical review documented that this supplement is approvable. The following is a labeling review to document proposed nonclinical changes.

Nonclinical issues relative to clinical use:
Upon initial approval of Diclegis in 2013, the label was written 'in the spirit of' PLLR, and included a subsection in Section 8.1 entitled Animal Data. In the proposed label for this supplement, the sponsor edited Section 8 to conform to the new PLLR policies and added proposed wording for a Risk Summary. (b) (4)

The Risk Summary as proposed by the sponsor (b) (4)

However, this reviewer also suggests (b) (4) . Diclegis (b) (4) is indicated for use in

pregnant women, and the human data subsection of the label documents epidemiologic studies that 1) show no increased risk for malformation from first trimester exposures to doxylamine succinate and pyridoxine hydrochloride, with or without dicyclomine hydrochloride; and 2) report 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. In light of this, this reviewer feels that (b) (4)

The following are the proposed nonclinical changes to Section 8.1. I have not proposed changes to portions of this labeling that are of a clinical nature. There are also no proposed changes (from a nonclinical standpoint) to Section 8.2 (Lactation). The sponsor also did not propose any changes to Section 13 Nonclinical Toxicology. Proposed additions are underlined and deletions are ~~strikethrough~~.

8. USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

(b) (4) TRADENAME is intended for (b) (4) women.

(b) (4) epidemiologic studies in pregnant women (b) (4) no increased risk for (b) (4) malformations (b) (4)

(b) (4)

(b) (4) the estimated background risk in the U.S. general population for major birth defects and miscarriage in clinically-recognized pregnancies (b) (4) 2% to 4% and 15% to 20%, respectively. (b) (4)

(b) (4)

Data

Human Data

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.

(b) (4)

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/s/

KIMBERLY P HATFIELD
10/28/2016

MUKESH SUMMAN
10/28/2016
Nonclinical supports approval

PHARMACOLOGY/TOXICOLOGY REVIEW

Date: June 16, 2016

NDA #/SS#/date: NDA 21876, Supplement 10 / SD# 467, eCTD# 050 / 10-7-2015
SD# 476, eCTD# 053 / 11-20-2015
SD# 478, eCTD# 054 / 12-21-2015
SD# 489, eCTD# 056 / 2-26-2016
SD# 490, eCTD# 057 / 3-11-2016
SD# 491, eCTD# 058 / 3-24-2016
SD# 524, eCTD# 064 / 5-31-2016

Reviewer: Kimberly Hatfield, PhD
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U.S. Agent: Mapi USA, Attn : John J.F. Killackey, PhD
2343 Alexandria Drive, Suite 100, Lexington, KY 40504
Drug: Diclegis (b) (4) (doxylamine succinate and pyridoxine hydrochloride)
Indication: Treatment of nausea and vomiting of pregnancy in patients who do not respond to conservative management.

RE: Prior approval supplement – new strength

Background:
This prior approval supplement has been submitted to obtain approval for a new formulation of Diclegis (proposed name (b) (4)), (b) (4) Diclegis (10 mg doxylamine succinate, 10 mg pyridoxine hydrochloride). The new formulation represents a new product strength; (b) (4) is a (b) (4) tablet containing 20 mg doxylamine succinate, 20 mg pyridoxine hydrochloride. The core of the tablet is delayed-release 10 mg doxylamine succinate, 10 mg pyridoxine hydrochloride, with an immediate-release (b) (4) coating of 10 mg doxylamine succinate, 10 mg pyridoxine hydrochloride. The original Diclegis had a maximum daily recommended dose of 4 tablets per day. (b) (4) has a recommended dose of 2 tablets per day (one in morning, one at night), but the same total daily dose as Diclegis. The new formulation reduces the number of tablets to be taken by the patient per day. The delayed action and immediate release of (b) (4) are proposed to allow for the bedtime dose to be effective immediately and also help control symptoms throughout the day.

Nonclinical issues relative to clinical use:
There were no nonclinical studies submitted with this supplement.

The proposed new strength of (b) (4) contains twice the amount of drug substances than the current Diclegis formulation in order to reduce the number of

tablets to be taken per day, and ease patient burden. There are no nonclinical concerns for this new strength and regimen.

The new tablet design of a delayed release core and immediate release outer layer prompted changes to the formulation (see Table 1 at the end of the review). Section 2.3.P.2 of the Quality Overall Summary describes the Drug Product as follows:

> [redacted] *core formulation with 10 mg of each of the drug substances. The rest of the drug substances, 10 mg of each, is added in the coating of the tablets."*
>
> *"The proposed new strength* [redacted] "

The coating solutions of [redacted] We defer to CMC for the acceptability of the new differences in the [redacted] components. The change in [redacted] occurred in Supplement 2, and was deemed acceptable. The color of the tablets also changed from white to pink.

A clinical bioequivalence study was submitted to support the new formulation of [redacted]. The bioequivalence study compares [redacted] to the original Diclegis formulation and not the currently approved formulation from Supplement 2 with [redacted]. The sponsor notes this in the Quality Overall Summary in section 2.3.P. In Supplement 2, the Sponsor changed [redacted] the Diclegis tablet because the [redacted] formulation were determined to be acceptable. Supplement 2 Diclegis and the Original Diclegis were found to have comparable dissolution profiles and bioequivalence.

Labeling:
Labeling will be conducted under separate review.

Conclusion:
There are no nonclinical studies submitted. Changes to the formulation to create the delayed action core and immediate release outer layer of [redacted] are acceptable. From a nonclinical perspective, this supplement is approvable.

Table 1: Composition of [redacted] (Doxylamine Succinate, Pyridoxine HCl; 20 mg, 20 mg) [redacted] Tablets (Section 3.2.P.1)

Component and Quality Standard (and Grade, if applicable)	Function	Strength (label claim) 20 mg/20 mg [redacted] Tablets		
		Quantity per unit (mg)	% of [redacted]	% of overall Tablet Total
[redacted]				
Doxylamine Succinate, USP	API			
Pyridoxine HCl, USP	API			
Microcrystalline Cellulose [redacted] 102, NF				
Magnesium Trisilicate, USP				
[redacted]				
Croscarmellose Sodium, NF				
Magnesium Stearate, NF [redacted]				
Colloidal Silicone Dioxide, NF [redacted]				
[redacted]				
Triethyl Citrate, NF				
Simethicone [redacted]				
[redacted]				

(b) (4)

Carnauba Wax Powder, NF				(b) (4)
				(b) (4)
(b) (4) Pink, In-house	Printing ink	Printing ink	0	trace
OVERALL TABLET TOTAL		*232.6*	*100%*	*100%*

Table 2: Composition of original Diclegis (initial approval April 2013)

Component and Quality Standard	Function	Quantity per unit (mg)	% of (b) (4)	% of Overall Tablet Total
(b) (4)				
Doxylamine Succinate, USP	API			(b) (4)
Pyridoxine HCl, USP	API			
Microcrystalline Cellulose (b) (4) 102, NF				(b) (4)
Magnesium Trisilicate, USP				
Croscarmellose Sodium, NF				
Magnesium Stearate, NF (b) (4)				
Colloidal Silicon Dioxide, NF (b) (4				
Methacrylic Copolymer Acid, NF (b) (4) (b) (4				
Polyethylene Glycol 400, NF (b) (4				
Talc, USP (b) (4				
Carnauba Wax Powder, NF (b) (4)				
	Printing ink	Printing ink	0	Trace
Propylene Glycol, USP (b) (4				(b) (4)
OVERALL TABLET TOTAL		***169.46 mg***	**--**	***100.0%***

#: Manufacturer's specification

*: (b) (4)

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/s/

KIMBERLY P HATFIELD
06/17/2016

MUKESH SUMMAN
06/17/2016
Nonclinical supports AP