CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

209661Orig1s000

CHEMISTRY REVIEW(S)

Chemistry/Quality Review 2

For NDA 209661

Date: 20-Oct-2016

Reviewer: Dr. Jean Salemme

NDA 209661 Chemistry review #1 by Dr. Jean Salemme, uploaded in Panorama, shows the only pending issue was an evaluation of the manufacturing sites by the OPQ/Office of Process and Facilities. All other chemistry, manufacturing and controls were found to be acceptable.

The OPQ/Office of Process and Facilities has now, on 20-Oct-2016, issued an Approve recommendation for the manufacturing sites for NDA 209661**.**

This NDA is, therefore, acceptable from a chemistry, manufacturing and controls perspective.

Jean Salemme

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Gurpreet Gill Sangha

Digitally signed by Gurpreet Gill Sangha
Date: 10/21/2016 07 21:34AM
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Comments: Signing for David Lewis

Office of Lifecycle Drug Products
Division of Post-Marketing Activities I
Review of Chemistry, Manufacturing, and Controls

1. **NDA Supplement Number: NDA 209661 (originally 21-876 / S-010 Efficacy Supplement)**

2. **Submission Being Reviewed**:

Submission	Type	Submission Date	CDER Stamp Date	Assigned Date	PDUFA Goal Date	Review Date
209661	NDA	7-Oct-2015	7-Oct-2015	7-Oct-2015	7-Nov-2016	21-Sept-2016

3. **Provides For From Cover Letter:** a new formulation for NDA 21-876, Diclegis®, consisting of a 20 mg doxylamine succinate and 20 mg pyridoxine hydrochloride multi-layer, extended release tablet, with an immediate release portion in addition to the delayed released tablet core, indicated for the same treatment as the approved formulation, NDA 21-876, Diclegis®.

4. **Review #**: 1

5. **Clinical Review Division**: Bone, Reproductive, and Urologic Products

6. **Name and Address of Applicant**:
   Duchesnay, Inc.
   950, boul. Michèle-Bohec
   Blainville, PQ Canada

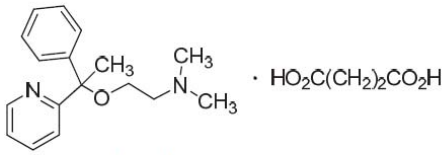
   US Agent: Mapi USA

7. **Drug Product**:

Drug Name	Dosage Form	Strength	Route of Administration	Rx or OTC	Special Product
Doxylamine Succinate and Pyridoxine Hydrochloride	Extended release tablets	20 mg/ 20 mg	oral	Rx	N/A

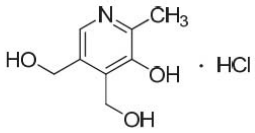
8. Name and Structure of Drug Substance:

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:



Doxylamine Succinate

Molecular Formula: $C_{17}H_{22}N_2O \cdot C_4H_6O_4$
Molecular Weight: 388.46



Pyridoxine Hydrochloride

Molecular Formula: $C_8H_{11}NO_3 \cdot HCl$
Molecular Weight: 205.64

9. Indication: Treatment of nausea and vomiting of pregnancy in patients who do not respond to conservative management

10. Supporting/Relating Documents: Chemistry review of NDA 21876 by Dr. Gene Holbert.

11. Consults:

ONDP Biopharmaceutics consult:	Approve
Office of Process and Facilities evaluation:	Approve

12. Executive Summary:

This submission was originally submitted as NDA 21-876 S-010. However, due to legal and regulatory requirements, the submission was re-classified as a new NDA, which was assigned the NDA number 209661 (a new strength and dosage form based on NDA 21-876 Diclegis). NDA 209661, originally submitted as efficacy supplement 10 to NDA 21-876, as Diclegis [redacted] (b) (4), provides for a new formulation for Diclegis which has double the amount of each of the two actives, compared to the NDA 21-876 approved tablet, and is extended-release rather than delayed release due to immediate release [redacted] (b) (4) delayed release core. The Tradename is pending.

NDA 209661 proposes the manufacture and marketing of a 20 mg doxylamine succinate and 20 mg pyridoxine hydrochloride multilayer, extended release tablet, [redacted] (b) (4) delayed release core containing 10 mg each of the two actives, coated with 10 mg of each active in immediate release [redacted] (b) (4)

The chemistry, manufacturing and control data/information provided in this submission are acceptable. The OPQ/ONDP Biopharmaceutics reviewer finds the dissolution method and acceptance criteria to be acceptable. The OPQ/Office of Process and Facilities final recommendation of the manufacturing sites is PENDING.

13. Conclusions & Recommendations:

Approve.

14. Comments/Deficiencies to be Conveyed to Applicant: None.

15. Primary Reviewer:
Jean Salemme, Ph.D., CMC reviewer, Branch 2, Division of Post-Marketing Activities I, Office of Lifecycle Drug Products, Office of Pharmaceutical Quality (OPQ)

16. Secondary Reviewer:
David Lewis, Ph.D., Acting Branch Chief, Branch 2, Division of Post-Marketing Activities I, Office of Lifecycle Drug Products, OPQ

SUMMARY

NDA 209661 was originally submitted as efficacy supplement NDA 21-876/ S-010 (Diclegis). During the review, the applicant was informed that the submission should be resubmitted as an NDA due to the proposed dosage form, a change from the NDA 21876 delayed release to the NDA 209661 extended release designation, due to the immediate release (b) (4) delayed release core. The supplement was resubmitted to NDA 209661 with the same goal dates that had been assigned to NDA 21876/ S-010.

NDA 21876 Diclegis delayed-release tablets, contains 10 mg doxylamine succinate and 10 mg pyridoxine hydrochloride. NDA 209661 proposes the manufacture of an extended release tablet containing 20 mg doxylamine succinate and 20 mg pyridoxine hydrochloride, (b) (4)

(b) (4)

. The delayed release core coated with immediate release (b) (4) results in a designation of the tablet as Extended Release, (b) (4) is a change in dosage form (b) (4), with its implication of a different mode of action. The change in dosage form and the impact on this on User Fees was not considered until, during the review of the efficacy supplement, the name for the drug was changed (b) (4). The efficacy supplement 010 then was converted to an NDA, 209661, with the same goal dates that had been assigned to the efficacy supplement 010.

Much of the NDA 21-876 approved chemistry, manufacturing and controls, including drug substance, excipients, container/closure, and specifications, methods, method validations, and container/closure are referenced to support NDA 209661.

No change is made in the drug substances. See NDA 21876, including the NDA chemistry review by Dr. Gene Holbert, for chemistry, manufacturing and controls for the drug substances. The approved and proposed tablets contain (b) (4) 10 mg of each of the drug substances. The proposed tablet has additional drug substance, 10 mg of each, added to the coating of the tablets. The actives are compatible with the new coating excipients, (b) (4)

(b) (4)

. The components of the coatings for the proposed extended release tablets are GRAS or compendial.

Stability data to 6 months at accelerated conditions are provided and support the stability of the proposed formulation.

Bioequivalence (B/E) study #150033 has been performed using production-scale batches #1315 (Reference: Diclegis 10 mg/10 mg delayed-release formulation) and #30-001V (Test: Diclegis (b) (4) 20 mg/20 mg (b) (4)). See Clinical and Clinical Biopharmaceutics reviews.

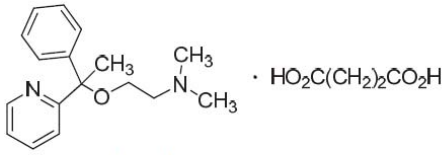
The proposed 3-stage dissolution method, acceptance criteria, and data have been evaluated by the OPQ/ONDP/Biopharmaceutics reviewer, Dr. Kalpana Paudel, and are acceptable.

The CDER Office of Process and Facilities has issued an Approve for the manufacturing sites PENDING

Information/Data Submitted to Support the Proposed Changes
Module 2 and Module 3 Drug Product are evaluated below.

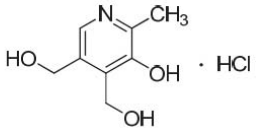
DRUG SUBSTANCES
No changes have been made in the drug substances manufacturing and controls from that approved for NDA 21876. The drug substances are doxylamine succinate USP and pyridoxine hydrochloride USP:

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:



Doxylamine Succinate

Molecular Formula: $C_{17}H_{22}N_2O \cdot C_4H_6O_4$
Molecular Weight: 388.46



Pyridoxine Hydrochloride

Molecular Formula: $C_8H_{11}NO_3 \cdot HCl$
Molecular Weight: 205.64

All chemistry, manufacturing and controls information is located in NDA 21876. As stated in the NDA 21876, Diclegis, chemistry review by Dr. Gene Holbert:

Diclectin® delayed release tablets have been marketed in Canada since 1976. The combination of doxylamine succinate and pyridoxine HCl, has been shown to be compatible based on product history, including batch analysis and stability data. In addition, drug product stability results indicate that the excipients and drug substances are compatible.

Doxylamine succinate, a white or creamy white powder, is an antihistamine with sedative and hypnotic properties. It is a component of many of the OTC cold medications purchased in the US and is also the active ingredient in certain OTC sleep aids. Doxylamine succinate is supplied by (b) (4) and is described in DMF (b) (4)

Pyridoxine HCl is a white or practically white crystalline powder or crystals. Pyridoxine is one of the compounds along with pyridoxal and pyridoxamine that are referred to as vitamin B_6. Pyridoxine HCl is used in oral vitamin supplements and injectable vitamin formulations for correction of vitamin B_6 deficiency. It is widely available over the counter as well as in prescription products. Pyridoxine HCl is water-soluble and is the salt most commonly found in vitamin B_6 nutritional supplements. Pyridoxine HCl as supplied to Duchesnay is manufactured by (b) (4)

The proposed tablet contains twice the amount of drug substances compared to the approved tablet. The suppliers of both drug substances are unchanged from those for the original NDA 21-876 application.

DRUG PRODUCT

Summary: All drug product sections have been provided. The proposed formulation has been compared to the approved formulation for NDA 21876 and shown to be qualitatively identical. The quantitative composition has been changes, with twice the amounts of actives and the (b) (4) . Analytical methods approved in NDA 21876 have been verified to be acceptable for analysis of the NDA 209661. The proposed drug product specification (b) (4) The manufacturing process consisting of the (b) (4) delayed release core coated with immediate release (b) (4) has been validated. Batch release data and stability data are provided for three batches.

The Office of Process and Facilities has issued an Approve recommendation for the manufacturing site. PENDING

The Office of New Drug Products/Biopharmaceutics reviewer, Dr. Kalpana Paudel, has found the dissolution method and acceptance criteria for the proposed tablet to be acceptable.

Manufacturers

The manufacturing sites for NDA 209661 are provided below.

2.3.P.3.1 Manufacturer(s) [Diclegis (b) (4) Tablets, Common]

Name and Address	Responsibility	FEI Inspection Date Date of Last FDA Inspection	Inspection Contact
Duchesnay Inc. 950, Michèle-Bohec boulevard Blainville, Québec Canada J7C 5E2	Fabrication, tablet printing, packaging, labeling of drug product	FEI: 3009166000 DUNS: 240538306 Last Inspection: August 2013	Guylaine Pelchat Director, Quality and Compliance Tel. 450-433-7734 ext. 146 Fax. 450-433-2211 Email: gpelchat@duchesnay.com
	Finished product storage and distribution		
(b) (4)	Release testing of drug substances and excipients prior to manufacture of drug product	(b) (4)	
	Fabrication of drug product up to core tablets		
	Release testing of drug substances and excipients prior to manufacture of drug product		
	Drug product release testing, stability testing		
	Release testing of drug substances prior to manufacture of drug product		
	Drug product release testing, stability testing		

These facilities were submitted to the Office of Process and Facilities (OPF) in order to establish a link between the facilities (and the cGMP of these facilities) and the new/re-formulated drug product.

OPQ/Office of Process and Facilities: PENDING

Comparative Composition – Diclegis (NDA 21-876) and NDA 209661

Diclegis (b) (4) tablets are composed of three separate components: tablet core, (b) (4) (b) (4) and printing ink. The composition of each component is summarized in the following table.

The proposed formulation, 20mg/20mg, is compared with the NDA 21-876, 10 mg/10 mg, in the following table:

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LABELING -

SECTION 11 - DESCRIPTION

TRADENAME extended-release tablets consist of an enteric-coated core containing 10 mg doxylamine succinate and 10 mg pyridoxine hydrochloride, and an immediate-release (b) (4) coating of 10 mg doxylamine succinate and 10 mg pyridoxine hydrochloride.

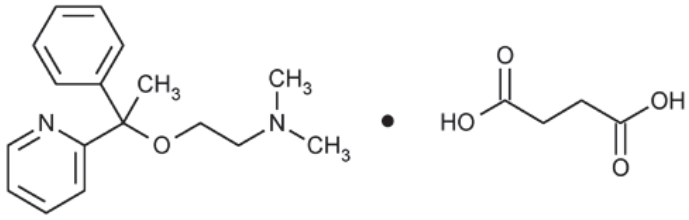
TRADENAME tablets are round, pink, film-coated, extended-release tablets containing a total of 20 mg doxylamine succinate and 20 mg pyridoxine hydrochloride. Tablets are imprinted on one side with the pink image of a pregnant woman and a "D" on the other side.

Inactive ingredients are as follows: ammonium hydroxide, n-butanol, carnauba wax powder, colloidal silicon dioxide, croscarmellose sodium, D&C Red#27 aluminum lake, denatured alcohol, ferrosoferric oxide, FD&C Blue #2 aluminum lake, hypromellose, iron oxide red, isopropyl alcohol, magnesium stearate, magnesium trisilicate, methacrylic acid copolymer, microcrystalline cellulose 102, PEG 3350, propylene glycol, shellac glaze, simethicone, sodium bicarbonate, sodium lauryl sulfate, talc, titanium dioxide, triethyl citrate.

TRADENAME is certified Kosher and Halal .

Doxylamine Succinate

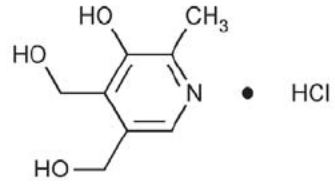
Doxylamine succinate is classified as an antihistamine. The chemical name for doxylamine succinate is ethanamine, N,N-dimethyl-2-[1-phenyl-1-(2-pyridinyl)ethoxy]-, butanedioate (1:1). The empirical formula is $C_{17}H_{22}N_2O \cdot C_4H_6O_4$ and the molecular mass is 388.46. The structural formula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



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

Pyridoxine Hydrochloride

Pyridoxine hydrochloride is a vitamin B_6 analog. The chemical name for pyridoxine hydrochloride is 3,4-pyridinedimethanol, 5-hydroxy-6-methyl-, hydrochloride. The empirical formula is $C_8H_{11}NO_3 \cdot HCl$ and the molecular mass is 205.64. The structural formula is:



`yr` `ox`ne ` y `roc` `or` `e is a white or practically white crystalline powder that is freely soluble in water, slightly soluble in alcohol and insoluble in ether.

Section 16

16.1 How supplied

TRADENAME extended -release tablets are supplied in a high-density polyethylene bottle with a polypropylene child-resistant cap and a silica gel desiccant canister. Each pink, round, film-coated, (b) (4) tablet contains 20 mg doxylamine succinate and 20 mg pyridoxine hydrochloride, and is imprinted on one side with the pink image of a pregnant woman and a "D" on the other side. (b) (4) tablets are provided as follows:

NDC 55494-120-10 Bottles of 100.

16.2 Storage and Handling

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

Evaluation: Acceptable.

Container Label

NOTE: The Tradename Diclegis (b) (4) originally proposed, is not acceptable. TRADENAME is PENDING.

Evaluation: Acceptable.

Request for Waiver from Requirements to Prepare an Environmental Assessment - Acceptable

The applicant requests the following:

> **Request for Waiver from Requirements to Prepare an Environmental Assessment**
>
> In accordance with the provisions of 21 CFR §25.15(d), the sponsor hereby requests a waiver from the requirement to submit an environmental assessment for DICLEGIS (b) (4)
>
> A waiver is justified under provisions of 21 CFR §25.31(a) because FDA action on this supplement is subject to categorical exclusion from the requirement for an environmental assessment since it will not increase the use of the active ingredients of the drug product, doxylamine succinate and pyridoxine hydrochloride, from the present amount. The currently approved product DICLEGIS (10 mg doxylamine succinate and 10 mg pyridoxine hydrochloride) with a recommended dosage of four tablets daily will be replaced by DICLEGIS (b) (4) (20 mg doxylamine succinate and 20 mg pyridoxine hydrochloride) with a maximum dosage regimen of two tablets daily.

Evaluation: Acceptable.

David Lewis

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Comments: concur; recommendation is "approve" from the standpoint of CMC pending an acceptable OPF recommendation for the manufacturing facilities.

Jean Salemme

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