

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

021876Orig1s000

CHEMISTRY REVIEW(S)

Memorandum

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

Date: 4/4/2013

From: Gene W. Holbert, Ph.D.
Senior Review Chemist, ONDQA
Division of New Drug Quality Assessment II
ONDQA

Through: Moo-Jhong Rhee, Ph.D.
Chief, Branch IV
Division of New Drug Quality Assessment II
ONDQA

To: CMC Review #1 of NDA 21876

Subject: Approval Recommendation

When CMC review #1 was filed, two issues were outstanding, Establishment Evaluation and the final package insert.

On 04/04/2013, the final package insert was submitted and the revisions are *satisfactory* from the ONDQA perspective (**Attachment 1**).

On 03/20/2013, the Office of Compliance issued an overall “**Acceptable**” recommendation for all facilities involved in manufacturing and testing of the drug substance and drug product (EER Summary Report, **Attachment 2**).

Regarding the established name of the drug for this application, CDER MaPP 5021.1 requires that an API with salt be expressed with free base form, unless any exception rule applies per the MaPP.

For this application, it is recommended that the established name be expressed as the salt form for the following reasons, which, we believe, are qualified for the exception rules as specified in the MaPP:

- Both drug substances are the subject of several USP monographs (Doxylamine Succinate, Doxylamine Succinate Syrup, Doxylamine Succinate Tablets, Pyridoxine Hydrochloride, Pyridoxine Hydrochloride Injection, and Pyridoxine Hydrochloride Tablets).
- The drug product has been formulated based on the strength of each salt (10 mg), as was the Reference Listed Drug (Bendectin, NDA 10598).
- Both ingredients are listed as the salt in several OTC products available in the US, such as the Vicks NyQuil line of cold and flu products and Unisom Sleep Tabs (doxylamine

succinate) and oral supplements such as Centrum vitamin products and injectable vitamins such as Infuvite (pyridoxine hydrochloride, vitamin B6)

Recommendation: This NDA is now recommended for **Approval** from the ONDQA perspective.

2 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS)
immediately following this page

Attachment 2: Establishment Evaluation Report

FDA CDER EES ESTABLISHMENT EVALUATION REQUEST SUMMARY REPORT

Application:	NDA 21876/000	Sponsor:	DUCHESNAY
Org. Code:	580		H7L 3W9
Priority:	5		LAVAL, QUEBEC, CANADA
Stamp Date:	20-DEC-2004	Brand Name:	(b) (4) DOXYLAMINE SUCCINATE 10MG/PYRI
PDUFA Date:	08-APR-2013	Estab. Name:	
Action Goal:		Generic Name:	DOXYLAMINE SUCCINATE 10MG/PYRIDOXINE HCL
District Goal:	09-OCT-2012	Product Number; Dosage Form; Ingredient; Strengths	001; TABLET, DELAYED ACTION; PYRIDOXINE HYDROCHLORIDE; 10MG 001; TABLET, DELAYED ACTION; DOXYLAMINE SUCCINATE; 10MG
FDA Contacts:	R. MCKNIGHT	Project Manager	3017961765
	G. HOLBERT	Review Chemist	3017961368
	D. CHRISTNER	Team Leader	3017961341

Overall Recommendation:	ACCEPTABLE	on 20-MAR-2013	by T. SHARP	()	3017963208
	PENDING	on 07-MAR-2013	by EES_PROD		
	PENDING	on 22-JUN-2012	by EES_PROD		

Establishment:	CFN:	FEI:	(b) (4)
			(b) (4)
DMF No:		AADA:	
Responsibilities:	DRUG SUBSTANCE MANUFACTURER		
Profile:	NON-STERILE API BY CHEMICAL SYNTHESIS	OAI Status:	NONE
Last Milestone:	OC RECOMMENDATION		
Milestone Date:	25-JAN-2013		
Decision:	ACCEPTABLE		
Reason:	DISTRICT RECOMMENDATION		

**FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT**

Establishment: [REDACTED] (b) (4)

DMF No: [REDACTED] **AADA:** [REDACTED]

Responsibilities: DRUG SUBSTANCE RELEASE TESTER
FINISHED DOSAGE RELEASE TESTER
FINISHED DOSAGE STABILITY TESTER

Profile: CONTROL TESTING LABORATORY **OAI Status:** NONE

Last Milestone: CC RECOMMENDATION

Milestone Date: 31-JAN-2013

Decision: ACCEPTABLE

Reason: DISTRICT RECOMMENDATION

Establishment: [REDACTED] (b) (4)

DMF No: [REDACTED] **AADA:** [REDACTED]

Responsibilities: DRUG SUBSTANCE RELEASE TESTER
FINISHED DOSAGE RELEASE TESTER

Profile: CONTROL TESTING LABORATORY **OAI Status:** NONE

Last Milestone: CC RECOMMENDATION

Milestone Date: 22-JUN-2012

Decision: ACCEPTABLE

Reason: BASED ON PROFILE

Establishment: [REDACTED] (b) (4)

DMF No: [REDACTED] **AADA:** [REDACTED]

Responsibilities: FINISHED DOSAGE LABELER
FINISHED DOSAGE MANUFACTURER
FINISHED DOSAGE PACKAGER

Profile: TABLETS, DELAYED RELEASE **OAI Status:** NONE

Last Milestone: CC RECOMMENDATION

Milestone Date: 25-JUN-2012

Decision: ACCEPTABLE

Reason: DISTRICT RECOMMENDATION

**FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT**

Establishment: [REDACTED] (b) (4)

DMF No: [REDACTED] **AADA:** [REDACTED]

Responsibilities: DRUG SUBSTANCE MANUFACTURER

Profile: NON-STERILE API BY CHEMICAL SYNTHESIS **OAI Status:** NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 01-MAR-2013

Decision: ACCEPTABLE

Reason: DISTRICT RECOMMENDATION

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

/s/

DONNA F CHRISTNER
04/04/2013

MOO JHONG RHEE
04/04/2013
Chief, Branch IV

NDA 21876

Diclegis

(doxylamine succinate and pyridoxine hydrochloride)

Duchesnay Inc.

Gene W. Holbert, Ph.D.

Senior Review Chemist

**Office of New Drug Quality Assessment
Division of New Drug Quality Assessment II
Branch IV**

CMC Review for the

Division of Reproductive and Urologic Products

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Chemistry Review Data Sheet

1. NDA 21876
2. REVIEW #: 1
3. REVIEW DATE: February 27, 2013
4. REVIEWER: Gene W. Holbert, Ph.D.
5. PREVIOUS DOCUMENTS:

Previous Documents
None

Document Date

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed
Original
Amendment
Amendment
Amendment
Amendment

Document Date
06/08/2012
12/04/2012
01/14/2013
02/26/2013
03/12/2013

7. NAME & ADDRESS OF APPLICANT:

Name: Duchesnay Inc.
Address: 950, boul. Michèle-Bohec
Blainville, PQ
J7C 5E2
Canada

Representative: John J.F. Killackey, Ph.D.
OptumInsight
131 Morristown Road
Basking Ridge, NJ 07920
Telephone: (866) 722-6734 ext. 5782

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Diclegis
b) Non-Proprietary Name (USAN): doxylamine succinate/pyridoxine hydrochloride

Chemistry Review Data Sheet

- c) Code Name/#: N/A
d) Chem. Type/Submission Priority:
- Chem. Type: 5
 - Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 505 (b)(2)

10. PHARMACOL. CATEGORY: Antihistamine/vitamin

11. DOSAGE FORM: Tablets

12. STRENGTH/POTENCY: 10 mg/10 mg

13. ROUTE OF ADMINISTRATION: Oral

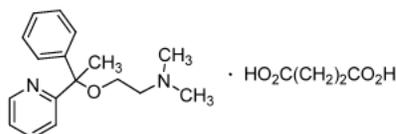
14. Rx/OTC DISPENSED: Rx OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

SPOTS product – Form Completed

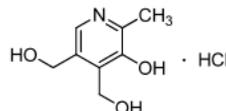
Not a SPOTS product

16. 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

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

Chemistry Review Data Sheet

DMF #	TYPE	HOLDER	ITEM REVIEWED	CODE ¹	STATUS ²	REVIEW DATE	COMMENTS
(b) (4)	II	(b) (4)	(b) (4)	3	Adequate	03/17/2010 L. Rodriguez	LOA: 04/10/2012
	III			4	Adequate	---	LOA: 08/07/2012
	III			1	Adequate	06/14/2012 G. Holbert	LOA: 10/07/2011
	III			3	Adequate	06/15/2010 G. Lunn	LOA: 11/18/2011

¹ Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 – Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

² Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
New Drug Application	NDA 10-598	Bendectin
Investigational New Drug	IND 72,300	Diclegis

18. STATUS:

ONDC:

CONSULTS/CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A		
EES	Pending		
Pharm/Tox	N/A		
Biopharm	Pending		
LNC	N/A		
Methods Validation	N/A		
OPDRA	N/A		
EA	Categorical exclusion	02/27/2013	G. Holbert
Microbiology	N/A		

The Chemistry Review for NDA 021876

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

This NDA has provided sufficient information to assure identity, strength, purity, and quality of the drug product.

However, labeling is *not* finalized, and a site recommendation from the Office of Compliance has *not* been made as of the date of this review.

Therefore, from the CMC perspective, this NDA is *not* ready for approval until all pending issues are satisfactorily resolved.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

Diclegis Delayed Release Tablets are round, white, film-coated tablets imprinted with a pink image of a pregnant woman. Each tablet contains 10 mg of Doxylamine Succinate, USP and 10 mg of Pyridoxine HCl, USP. Inactive ingredients include ammonium hydroxide, n-butanol, carnauba wax powder, colloidal silicon dioxide, croscarmellose sodium, D&C Red #27, FD&C Blue #2, hypromellose, isopropyl alcohol, magnesium stearate, magnesium trisilicate, methacrylic acid copolymer, microcrystalline cellulose 102, PEG 400, PEG 8000, polysorbate 80, propylene glycol, shellac glaze, simethicone, talc and titanium dioxide. With the exception of the film coating and printing ink, all excipients are compendial. The flavoring, film coating and ink are composed of ingredient that are compendial and/or GRAS.

The drug product is packaged in a 75-mL opaque bottle with a 38-mm child-resistant cap and a silica gel desiccant canister. The cap contains an induction inner seal consisting of a

(b) (4)

Diclegis Delayed Release Tablets are manufactured for Duchesnay by

(b) (4)

The manufacturing process consists of

(b) (4)

Executive Summary Section

The application contains 3 months of long term and accelerated stability data on three full scale registration batches manufactured by (b) (4), using pyridoxine HCl manufactured by the proposed commercial supplier (b) (4). There were no significant changes in any of the lots stored at the long term or accelerated condition. Forty-eight months of supporting stability data were also submitted for drug product manufactured by (b) (4) using pyridoxine HCl manufactured by the historical drug substance supplier (b) (4). The applicant has proposed an 24 month expiry dating period when stored at 20-25°C (68-77°F) in tightly closed containers and protected from light and moisture. Data for an additional three batches (24 months) was submitted to demonstrate the efficacy of the desiccant canister in maintaining product quality during storage.

The active drug substances are doxylamine succinate and pyridoxine HCl.

Use of a combination of these two drug substances to treat nausea and vomiting of pregnancy has a long history. In 1956, the FDA approved Bendectin tablets manufactured by Merrell National Laboratories Division of Richardson Merrill. The initial Bendectin formulation contained a third active ingredient, dicyclomine hydrochloride, which was removed from the formulation since it was determined to be ineffective for nausea and vomiting by the FDA Drug Efficacy Study Implementation (“DESI”) program. Bendectin was marketed in the USA from 1956 to 1983 when it was withdrawn for non-medical reasons (i.e. litigation costs and adverse publicity).

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).

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 B₆. Pyridoxine HCl is used in oral vitamin supplements and injectable vitamin formulations for correction of vitamin B₆ 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 B₆ nutritional supplements. Pyridoxine HCl as supplied to Duchesnay is manufactured by (b) (4).

B. Description of How the Drug Product is Intended to be Used

Two Diclegis delayed-release tablets should be taken at bedtime to control nausea and vomiting occurring in the morning. One delayed-release tablet in the morning and one

Executive Summary Section

delayed-release tablet mid-afternoon may be taken to control symptoms throughout the day.

C. Basis for Not-Approval Recommendation

21 CFR314.125(b)(13)

- An overall “Acceptable” recommendation for the manufacturing facilities has not been made from the Office of Compliance

21 CFR 314.125(b)(6)

- The label/labeling has not been finalized yet as of this review.

III. Administrative**A. Reviewer’s Signature**

Signed electronically in DARRTS

B. Endorsement Block

Gene W. Holbert, Ph.D./February 19, 2013
Moo-Jhong Rhee, Ph.D./Date

C. CC Block

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/s/

GENE W HOLBERT
03/14/2013

MOO JHONG RHEE
03/14/2013
Chief, Branch IV