

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

021876Orig1s000

OTHER REVIEW(S)

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for *each* PMR/PMC in the Action Package.

NDA/BLA # 021876
Product Name: Diclegis (doxylamine succinate and pyridoxine hydrochloride) delayed release tablets, 10 mg/10 mg

PMR/PMC Description: PMR 2033-1: An adequately powered safety and efficacy study in pregnant adolescent girls, 12 to 17 years of age, with nausea and vomiting of pregnancy who are appropriate candidates for pharmacologic therapy.

PMR/PMC Schedule Milestones: Final Protocol Submission: 01/2014
Study/Trial Completion: 01/2018
Final Report Submission: 07/2018
Other: _____

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

The efficacy and safety of Diclegis delayed release tablets for the treatment of nausea and vomiting of pregnancy in women who do not respond to conservative management has been demonstrated in the phase 3 clinical program. This randomized, double-blind, controlled safety and efficacy study will provide data in pregnant adolescent girls 12 to 17 years of age, with nausea and vomiting of pregnancy who are otherwise appropriate candidates for pharmacological therapy.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

The goal of the trial is to assess the long-term safety and efficacy of Diclegis delayed release tablets for the treatment of nausea and vomiting of pregnancy in pregnant adolescent girls 12 to 17 years of age.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

- **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?

Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

- Analysis using pharmacovigilance system?

Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?

Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

This randomized, double-blind, controlled safety and efficacy study in pregnant adolescent girls 12 to 17 years of age, with nausea and vomiting of pregnancy who are otherwise appropriate candidates for pharmacological therapy.

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- Pharmacokinetic studies or clinical trials
- Drug interaction or bioavailability studies or clinical trials
- Dosing trials

Continuation of Question 4

- Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

-
- Meta-analysis or pooled analysis of previous studies/clinical trials
 - Immunogenicity as a marker of safety
 - Other (provide explanation)
Required pediatric trial under PREA
-

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
- Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
- Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
- Dose-response study or clinical trial performed for effectiveness
- Nonclinical study, not safety-related (specify)

-
- Other
-

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

- Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

If so, does the clinical trial meet the following criteria?

- There is a significant question about the public health risks of an approved drug
- There is not enough existing information to assess these risks
- Information cannot be gained through a different kind of investigation
- The trial will be appropriately designed to answer question about a drug's efficacy and safety, and
- The trial will emphasize risk minimization for participants as the protocol is developed

PMR/PMC Development Coordinator:

This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.

(signature line for BLAs)

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

/s/

MEREDITH ALPERT
04/10/2013

SURESH KAUL
04/10/2013

505(b)(2) ASSESSMENT

Application Information		
NDA # 021876	NDA Supplement #: S-	Efficacy Supplement Type SE-
Proprietary Name: Diclegis Established/Proper Name: 10 mg doxylamine/ 10 mg pyridoxine HCL delayed release tablets		
Dosage Form: delayed release tablets Strengths:		
Applicant: Duchesnay C/O Optuminsight Life Science		
Date of Receipt: June 8, 2012 (re-submitted after refuse to file)		
PDUFA Goal Date: April 8, 2013		Action Goal Date (if different):
RPM: George Lyght, Pharm.D		
Proposed Indication(s): Treatment of nausea and vomiting of pregnancy in patients who do not respond to conservative management		

GENERAL INFORMATION

- 1) Is this application for a recombinant or biologically-derived product and/or protein or peptide product *OR* is the applicant relying on a recombinant or biologically-derived product and/or protein or peptide product to support approval of the proposed product?

YES NO

If "YES" contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.



**INFORMATION PROVIDED VIA RELIANCE
(LISTED DRUG OR LITERATURE)**

- 2) List the information essential to the approval of the proposed drug that is provided by reliance on our previous finding of safety and efficacy for a listed drug by reliance on published literature, or by reliance on a final OTC monograph. *(If not clearly identified by the applicant, this information can usually be derived from annotated labeling.)*

Source of information* (e.g., published literature, name of listed drug(s), OTC final drug monograph)	Information relied-upon (e.g., specific sections of the application or labeling)
NDA 10598 Bendectin Tablets	Nonclinical section
Published Literature	Nonclinical Section

*each source of information should be listed on separate rows, however individual literature articles should not be listed separately

- 3) Reliance on information regarding another product (whether a previously approved product or from published literature) must be scientifically appropriate. An applicant needs to provide a scientific “bridge” to demonstrate the relationship of the referenced and proposed products. Describe how the applicant bridged the proposed product to the referenced product(s). (Example: BA/BE studies)



Additional studies requested by OCP/OND for the 505(b)(2) NDA:

- A multiple dose pk trial of the to be marketed product (including parent and metabolite pk data for both entities).
- A phase 3 clinical trial.

RELIANCE ON PUBLISHED LITERATURE

- 4) (a) Regardless of whether the applicant has explicitly stated a reliance on published literature to support their application, is reliance on published literature necessary to support the approval of the proposed drug product (i.e., the application *cannot* be approved without the published literature)?

YES NO
If “NO,” proceed to question #5.

- (b) Does any of the published literature necessary to support approval identify a specific (e.g., brand name) *listed* drug product?

YES NO

If "NO", proceed to question #5.
If "YES", list the listed drug(s) identified by name and answer question #4(c).

Bendectin Tablets

(c) Are the drug product(s) listed in (b) identified by the applicant as the listed drug(s)?
 YES NO

RELIANCE ON LISTED DRUG(S)

Reliance on published literature which identifies a specific approved (listed) drug constitutes reliance on that listed drug. Please answer questions #5-9 accordingly.

5) Regardless of whether the applicant has explicitly cited reliance on listed drug(s), does the application **rely** on the finding of safety and effectiveness for one or more listed drugs (approved drugs) to support the approval of the proposed drug product (i.e., the application cannot be approved without this reliance)?
 YES NO
If "NO," proceed to question #10.

6) Name of listed drug(s) relied upon, and the NDA #(s). Please indicate if the applicant explicitly identified the product as being relied upon (see note below):

Name of Listed Drug	NDA #(s)	Did applicant specify reliance on the product? (Y/N)
Bendectin Tablets	NDA 10598	Y

Applicants should specify reliance on the 356h, in the cover letter, and/or with their patent certification/statement. If you believe there is reliance on a listed product that has not been explicitly identified as such by the applicant, please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

7) If this is a (b)(2) supplement to an original (b)(2) application, does the supplement rely upon the same listed drug(s) as the original (b)(2) application?
 N/A YES NO

If this application is a (b)(2) supplement to an original (b)(1) application or not a supplemental application, answer "N/A".

If "NO", please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

8) Were any of the listed drug(s) relied upon for this application:

a) Approved in a 505(b)(2) application?
 YES NO

If "YES", please list which drug(s).

Name of drug(s) approved in a 505(b)(2) application:

b) Approved by the DESI process?

YES NO

If "YES", please list which drug(s).

Name of drug(s) approved via the DESI process:

c) Described in a final OTC drug monograph?

YES NO

If "YES", please list which drug(s).

Name of drug(s) described in a final OTC drug monograph: doxylamine

d) Discontinued from marketing?

YES NO

If "YES", please list which drug(s) and answer question d) i. below.

If "NO", proceed to question #9.

Name of drug(s) discontinued from marketing: Bendectin Tablets

i) Were the products discontinued for reasons related to safety or effectiveness?

YES NO

(Information regarding whether a drug has been discontinued from marketing for reasons of safety or effectiveness may be available in the Orange Book. Refer to section 1.11 for an explanation, and section 6.1 for the list of discontinued drugs. If a determination of the reason for discontinuation has not been published in the Federal Register (and noted in the Orange Book), you will need to research the archive file and/or consult with the review team. Do not rely solely on any statements made by the sponsor.)

9) Describe the change from the listed drug(s) relied upon to support this (b)(2) application (for example, "This application provides for a new indication, otitis media" or "This application provides for a change in dosage form, from capsule to solution").

The application adds "in patients who do not respond to conservative management" to the indication, treatment of nausea and vomiting of pregnancy.

The purpose of the following two questions is to determine if there is an approved drug product that is equivalent or very similar to the product proposed for approval that should be referenced as a listed drug in the pending application.

*The assessment of pharmaceutical equivalence for a recombinant or biologically-derived product and/or protein or peptide product is complex. If you answered **YES to question #1**, proceed to question #12; if you answered **NO to question #1**, proceed to question #10 below. **NO***

10) (a) Is there a pharmaceutical equivalent(s) to the product proposed in the 505(b)(2) application that is already approved (via an NDA or ANDA)?

(Pharmaceutical equivalents are drug products in identical dosage forms intended for the same route of administration that: (1) contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug

ingredient over the identical dosing period; (2) do not necessarily contain the same inactive ingredients; **and** (3) meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates. (21 CFR 320.1(c), FDA's "Approved Drug Products with Therapeutic Equivalence Evaluations" (the Orange Book)).

Note that for proposed combinations of one or more previously approved drugs, a pharmaceutical equivalent must also be a combination of the same drugs.

YES NO

If "NO" to (a) proceed to question #11.
If "YES" to (a), answer (b) and (c) then proceed to question #12.

(b) Is the pharmaceutical equivalent approved for the same indication for which the 505(b)(2) application is seeking approval?

YES NO

(c) Is the listed drug(s) referenced by the application a pharmaceutical equivalent?

N/A YES NO

*If this application relies only on non product-specific published literature, answer "N/A"
If "YES" to (c) and there are no additional pharmaceutical equivalents listed, proceed to question #12.*

If "NO" or if there are additional pharmaceutical equivalents that are not referenced by the application, list the NDA pharmaceutical equivalent(s); you do not have to individually list all of the products approved as ANDAs, but please note below if approved approved generics are listed in the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

Pharmaceutical equivalent(s):

11) (a) Is there a pharmaceutical alternative(s) already approved (via an NDA or ANDA)?

(Pharmaceutical alternatives are drug products that contain the identical therapeutic moiety, or its precursor, but not necessarily in the same amount or dosage form or as the same salt or ester. Each such drug product individually meets either the identical or its own respective compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times and/or dissolution rates. (21 CFR 320.1(d)) Different dosage forms and strengths within a product line by a single manufacturer are thus pharmaceutical alternatives, as are extended-release products when compared with immediate- or standard-release formulations of the same active ingredient.)

Note that for proposed combinations of one or more previously approved drugs, a pharmaceutical alternative must also be a combination of the same drugs.

YES NO

If "NO", proceed to question #12.

(b) Is the pharmaceutical alternative approved for the same indication for which the 505(b)(2) application is seeking approval?

YES NO

(c) Is the approved pharmaceutical alternative(s) referenced as the listed drug(s)?
N/A YES NO

*If this application relies only on non product-specific published literature, answer "N/A"
If "YES" and there are no additional pharmaceutical alternatives listed, proceed to question #12.*

If "NO" or if there are additional pharmaceutical alternatives that are not referenced by the application, list the NDA pharmaceutical alternative(s); you do not have to individually list all of the products approved as ANDAs, but please note below if approved generics are listed in the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

Pharmaceutical alternative(s):

PATENT CERTIFICATION/STATEMENTS

12) List the patent numbers of all unexpired patents listed in the Orange Book for the listed drug(s) for which our finding of safety and effectiveness is relied upon to support approval of the (b)(2) product.

Listed drug/Patent number(s):

No patents listed *proceed to question #14*

13) Did the applicant address (with an appropriate certification or statement) all of the unexpired patents listed in the Orange Book for the listed drug(s) relied upon to support approval of the (b)(2) product?

YES NO

If "NO", list which patents (and which listed drugs) were not addressed by the applicant.

Listed drug/Patent number(s):

14) Which of the following patent certifications does the application contain? (*Check all that apply and identify the patents to which each type of certification was made, as appropriate.*)

- No patent certifications are required (e.g., because application is based solely on published literature that does not cite a specific innovator product)
- 21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA. (Paragraph I certification)
- 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired. (Paragraph II certification)

Patent number(s):

- 21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire. (Paragraph III certification)

Patent number(s):

Expiry date(s):

- 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted. (Paragraph IV certification). *If Paragraph IV certification was submitted, proceed to question #15.*
- 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the NDA holder/patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above). *If the applicant has a licensing agreement with the NDA holder/patent owner, proceed to question #15.*
- 21 CFR 314.50(i)(1)(ii): No relevant patents.
- 21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent as described in the corresponding use code in the Orange Book. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications. (Section viii statement)

Patent number(s):

Method(s) of Use/Code(s):

15) Complete the following checklist **ONLY** for applications containing Paragraph IV certification and/or applications in which the applicant and patent holder have a licensing agreement:

(a) Patent number(s):

(b) Did the applicant submit a signed certification stating that the NDA holder and patent owner(s) were notified that this b(2) application was filed [21 CFR 314.52(b)]?

YES NO

If "NO", please contact the applicant and request the signed certification.

(c) Did the applicant submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)]? This is generally provided in the form of a registered mail receipt.

YES NO

If "NO", please contact the applicant and request the documentation.

(d) What is/are the date(s) on the registered mail receipt(s) (i.e., the date(s) the NDA holder and patent owner(s) received notification):

Date(s):

Note, the date(s) entered should be the date the notification occurred (i.e., delivery date(s)), not the date of the submission in which proof of notification was provided

- (e) Has the applicant been sued for patent infringement within 45-days of receipt of the notification listed above?

*Note that you may need to call the applicant (after 45 days of receipt of the notification) to verify this information **UNLESS** the applicant provided a written statement from the notified patent owner(s) that it consents to an immediate effective date of approval.*

YES NO Patent owner(s) consent(s) to an immediate effective date of approval

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

/s/

GEORGE A LYGHT
04/08/2013

SEALD Director Sign-Off Review of the End-of-Cycle Prescribing Information: Outstanding Format Deficiencies

Product Title	DICLEGIS (doxylamine succinate and pyridoxine hydrochloride) delayed-release tablets, for oral use
Applicant	Duchesnay USA, Inc.
Application/Supplement Number	NDA 21876
Type of Application	Original NDA
Indication(s)	For the treatment of nausea and vomiting of pregnancy in women who do not respond to conservative management
Established Pharmacologic Class ¹	Antihistamine/Vitamin B6 Analog
Office/Division	ODE III/DRUP
Division Project Manager	George Lyght
Date FDA Received Application	June 8, 2012
Goal Date	April 8, 2013
Date PI Received by SEALD	April 4, 2013
SEALD Review Date	April 5, 2013
SEALD Labeling Reviewer	Abimbola Adebowale
SEALD Division Director	Laurie Burke

PI = prescribing information

¹ The established pharmacologic class (EPC) that appears in the final draft PI.

This Study Endpoints and Labeling Development (SEALD) Director Sign-Off review of the end-of-cycle, draft prescribing information (PI) for critical format elements reveals **outstanding labeling format deficiencies that must be corrected** before the final PI is approved. After these outstanding labeling format deficiencies are corrected, the SEALD Director will have no objection to the approval of this PI.

The critical format elements include labeling regulation (21 CFR 201.56 and 201.57), labeling guidance, and best labeling practices (see list below). This review does not include every regulation or guidance that pertains to PI format.

Guide to the Selected Requirements of Prescribing Information (SRPI) Checklist: For each SRPI item, one of the following 3 response options is selected:

- **NO**: The PI **does not meet** the requirement for this item (**deficiency**).
- **YES**: The PI **meets** the requirement for this item (**not a deficiency**).
- **N/A** (not applicable): This item does not apply to the specific PI under review.

Selected Requirements of Prescribing Information

Highlights (HL)

GENERAL FORMAT

- NO** 1. Highlights (HL) must be in two-column format, with ½ inch margins on all sides and in a minimum of 8-point font.

Comment: *Top, left and right margins are > ½ inches. Decrease to ½ inch margins.*

- YES** 2. The length of HL must be less than or equal to one-half page (the HL Boxed Warning does not count against the one-half page requirement) unless a waiver has been granted in a previous submission (i.e., the application being reviewed is an efficacy supplement).

Instructions to complete this item: If the length of the HL is less than or equal to one-half page then select “YES” in the drop-down menu because this item meets the requirement. However, if HL is longer than one-half page:

➤ **For the Filing Period (for RPMs)**

- *For efficacy supplements:* If a waiver was previously granted, select “YES” in the drop-down menu because this item meets the requirement.
- *For NDAs/BLAs and PLR conversions:* Select “NO” in the drop-down menu because this item does not meet the requirement (deficiency). The RPM notifies the Cross-Discipline Team Leader (CDTL) of the excessive HL length and the CDTL determines if this deficiency is included in the 74-day or advice letter to the applicant.

➤ **For the End-of Cycle Period (for SEALD reviewers)**

- The SEALD reviewer documents (based on information received from the RPM) that a waiver has been previously granted or will be granted by the review division in the approval letter.

Comment: *HL is longer than one-half page. DRUP will grant a waiver in the approval letter.*

- YES** 3. All headings in HL must be presented in the center of a horizontal line, in UPPER-CASE letters and **bolded**.

Comment:

- YES** 4. White space must be present before each major heading in HL.

Comment: *Do not need extra white space after each major heading.*

- YES** 5. Each summarized statement in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contains more detailed information. The preferred format is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each information summary (e.g. end of each bullet).

Comment:

- YES** 6. Section headings are presented in the following order in HL:

Section	Required/Optional
• Highlights Heading	Required
• Highlights Limitation Statement	Required
• Product Title	Required
• Initial U.S. Approval	Required
• Boxed Warning	Required if a Boxed Warning is in the FPI
• Recent Major Changes	Required for only certain changes to PI*

Selected Requirements of Prescribing Information

• Indications and Usage	Required
• Dosage and Administration	Required
• Dosage Forms and Strengths	Required
• Contraindications	Required (if no contraindications must state “None.”)
• Warnings and Precautions	Not required by regulation, but should be present
• Adverse Reactions	Required
• Drug Interactions	Optional
• Use in Specific Populations	Optional
• Patient Counseling Information Statement	Required
• Revision Date	Required

* RMC only applies to the Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions sections.

Comment:

YES

7. A horizontal line must separate HL and Table of Contents (TOC).

Comment:

HIGHLIGHTS DETAILS

Highlights Heading

YES

8. At the beginning of HL, the following heading must be **bolded** and appear in all UPPER CASE letters: “**HIGHLIGHTS OF PRESCRIBING INFORMATION**”.

Comment:

Highlights Limitation Statement

YES

9. The **bolded** HL Limitation Statement must be on the line immediately beneath the HL heading and must state: “**These highlights do not include all the information needed to use (insert name of drug product in UPPER CASE) safely and effectively. See full prescribing information for (insert name of drug product in UPPER CASE).**”

Comment:

Product Title

YES

10. Product title in HL must be **bolded**.

Comment:

Initial U.S. Approval

YES

11. Initial U.S. Approval in HL must be placed immediately beneath the product title, **bolded**, and include the verbatim statement “**Initial U.S. Approval:**” followed by the **4-digit year**.

Comment:

Boxed Warning

N/A

12. All text must be **bolded**.

Comment:

N/A

13. Must have a centered heading in UPPER-CASE, containing the word “**WARNING**” (even if more than one Warning, the term, “**WARNING**” and not “**WARNINGS**” should be used) and other words to identify the subject of the Warning (e.g., “**WARNING: SERIOUS INFECTIONS**”).

Comment:

Selected Requirements of Prescribing Information

- N/A** 14. Must always have the verbatim statement “*See full prescribing information for complete boxed warning.*” in *italics* and centered immediately beneath the heading.

Comment:

- N/A** 15. Must be limited in length to 20 lines (this does not include the heading and statement “*See full prescribing information for complete boxed warning.*”)

Comment:

- N/A** 16. Use sentence case for summary (combination of uppercase and lowercase letters typical of that used in a sentence).

Comment:

Recent Major Changes (RMC)

- N/A** 17. Pertains to only the following five sections of the FPI: Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions.

Comment:

- N/A** 18. Must be listed in the same order in HL as they appear in FPI.

Comment:

- N/A** 19. Includes heading(s) and, if appropriate, subheading(s) of labeling section(s) affected by the recent major change, together with each section’s identifying number and date (month/year format) on which the change was incorporated in the PI (supplement approval date). For example, “Dosage and Administration, Coronary Stenting (2.2) --- 3/2012”.

Comment:

- N/A** 20. Must list changes for at least one year after the supplement is approved and must be removed at the first printing subsequent to one year (e.g., no listing should be one year older than revision date).

Comment:

Indications and Usage

- YES** 21. If a product belongs to an established pharmacologic class, the following statement is required in the Indications and Usage section of HL: “(Product) is a (name of established pharmacologic class) indicated for (indication)”.

Comment:

Dosage Forms and Strengths

- N/A** 22. For a product that has several dosage forms, bulleted subheadings (e.g., capsules, tablets, injection, suspension) or tabular presentations of information is used.

Comment:

Contraindications

- YES** 23. All contraindications listed in the FPI must also be listed in HL or must include the statement “None” if no contraindications are known.

Comment:

Selected Requirements of Prescribing Information

- YES** 24. Each contraindication is bulleted when there is more than one contraindication.

Comment:

Adverse Reactions

- YES** 25. For drug products other than vaccines, the verbatim **bolded** statement must be present: “**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer’s U.S. phone number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch**”.

Comment:

Patient Counseling Information Statement

- YES** 26. Must include one of the following three **bolded** verbatim statements (without quotation marks):

If a product does not have FDA-approved patient labeling:

- “**See 17 for PATIENT COUNSELING INFORMATION**”

If a product has FDA-approved patient labeling:

- “**See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.**”
- “**See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.**”

Comment:

Revision Date

- NO** 27. **Bolded** revision date (i.e., “**Revised: MM/YYYY or Month Year**”) must be at the end of HL.

Comment: *Although the revision date is bolded and placed at the end of HL, it should read “Revised: 04/2013” not “Revision date: 04/2013.”*

Contents: Table of Contents (TOC)

GENERAL FORMAT

- YES** 28. A horizontal line must separate TOC from the FPI.

Comment:

- YES** 29. The following **bolded** heading in all UPPER CASE letters must appear at the beginning of TOC: “**FULL PRESCRIBING INFORMATION: CONTENTS**”.

Comment:

- YES** 30. The section headings and subheadings (including title of the Boxed Warning) in the TOC must match the headings and subheadings in the FPI.

Comment:

- N/A** 31. The same title for the Boxed Warning that appears in the HL and FPI must also appear at the beginning of the TOC in UPPER-CASE letters and **bolded**.

Comment:

Selected Requirements of Prescribing Information

- YES** 32. All section headings must be **bolded** and in UPPER CASE.
Comment:
- YES** 33. All subsection headings must be indented, not bolded, and in title case.
Comment:
- YES** 34. When a section or subsection is omitted, the numbering does not change.
Comment:
- YES** 35. If a section or subsection from 201.56(d)(1) is omitted from the FPI and TOC, the heading “**FULL PRESCRIBING INFORMATION: CONTENTS**” must be followed by an asterisk and the following statement must appear at the end of TOC: “*Sections or subsections omitted from the Full Prescribing Information are not listed.”
Comment:

Full Prescribing Information (FPI)

GENERAL FORMAT

- YES** 36. The following heading must appear at the beginning of the FPI in UPPER CASE and **bolded**: “**FULL PRESCRIBING INFORMATION**”.
Comment:
- YES** 37. All section and subsection headings and numbers must be **bolded**.
Comment:
- NO** 38. The **bolded** section and subsection headings must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below. If a section/subsection is omitted, the numbering does not change.

Boxed Warning
1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
6 ADVERSE REACTIONS
7 DRUG INTERACTIONS
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Labor and Delivery
8.3 Nursing Mothers
8.4 Pediatric Use
8.5 Geriatric Use
9 DRUG ABUSE AND DEPENDENCE
9.1 Controlled Substance
9.2 Abuse
9.3 Dependence
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY

Selected Requirements of Prescribing Information

12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
12.4 Microbiology (by guidance)
12.5 Pharmacogenomics (by guidance)
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology
14 CLINICAL STUDIES
15 REFERENCES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

Comment: Periods are included after the numbers for the section headings in the FPI. As per the regulations (see above), there are no periods after the numbers for the section headings in the FPI. Delete the periods.

- YES** 39. FDA-approved patient labeling (e.g., Medication Guide, Patient Information, or Instructions for Use) must not be included as a subsection under Section 17 (Patient Counseling Information). All patient labeling must appear at the end of the PI upon approval.

Comment:

- YES** 40. The preferred presentation for cross-references in the FPI is the section heading (not subsection heading) followed by the numerical identifier in italics. For example, “[see Warnings and Precautions (5.2)]”.

Comment:

- N/A** 41. If RMCs are listed in HL, the corresponding new or modified text in the FPI sections or subsections must be marked with a vertical line on the left edge.

Comment:

FULL PRESCRIBING INFORMATION DETAILS

Boxed Warning

- N/A** 42. All text is **bolded**.

Comment:

- N/A** 43. Must have a heading in UPPER-CASE, containing the word “**WARNING**” (even if more than one Warning, the term, “**WARNING**” and not “**WARNINGS**” should be used) and other words to identify the subject of the Warning (e.g., “**WARNING: SERIOUS INFECTIONS**”).

Comment:

- N/A** 44. Use sentence case (combination of uppercase and lowercase letters typical of that used in a sentence) for the information in the Boxed Warning.

Comment:

Contraindications

- N/A** 45. If no Contraindications are known, this section must state “None”.

Comment:

Adverse Reactions

Selected Requirements of Prescribing Information

- YES** 46. When clinical trials adverse reactions data is included (typically in the “Clinical Trials Experience” subsection of Adverse Reactions), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

“Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.”

Comment:

- YES** 47. When postmarketing adverse reaction data is included (typically in the “Postmarketing Experience” subsection of Adverse Reactions), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

“The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.”

Comment:

Patient Counseling Information

- YES** 48. Must reference any FDA-approved patient labeling, include the type of patient labeling, and use one of the following statements at the beginning of Section 17:

- “See FDA-approved patient labeling (Medication Guide)”
- “See FDA-approved patient labeling (Medication Guide and Instructions for Use)”
- “See FDA-approved patient labeling (Patient Information)”
- “See FDA-approved patient labeling (Instructions for Use)”
- “See FDA-approved patient labeling (Patient Information and Instructions for Use)”

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/s/

ABIMBOLA O ADEBOWALE
04/05/2013

LAURIE B BURKE
04/05/2013

**FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion**

******Pre-decisional Agency Information******

Memorandum

Date: March 29, 2013

To: George Lyght, PharmD
Regulatory Project Manager
Division of Reproductive and Urologic Products (DRUP)

From: Carrie Newcomer, PharmD
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

**Subject: NDA: 021876
DICLEGIS (doxylamine succinate and pyridoxine hydrochloride)
delayed-release tablets, for oral use (Diclegis)**

As requested in your consult dated August 17, 2012, OPDP has reviewed the draft labeling (package insert [PI], patient package insert [PPI], and carton/container labeling) for the original NDA submission for Diclegis. OPDP reviewed the proposed, substantially complete, marked-up version of the PI provided by DRUP via e-mail on March 29, 2013 and the draft carton/container labeling submitted by the applicant on March 12, 2013, available in the EDR.

OPDP notes that the Division of Medical Policy Programs (DMPP) provided comments on the draft PPI on March 28, 2013. OPDP agrees with DMPP's comments and has provided additional comments directly on DMPP's review of the PPI.

OPDP's comments on the PI and PPI are provided directly in the attached copy of the labeling.

OPDP has the following comments on the carton/container labels, also attached:

1. The carton and container labels read, "**Usual Dosage:** (b) (4)
(b) (4)
(b) (4) These instructions omit important, specific details about dosing from the draft PI, which states: (b) (4) take two

(b) (4)

We recommend that the carton and container labels contain accurate, informative dosing information that is consistent with the final PI, or that dosing information be omitted in favor of a statement referring to the PI for dosage information.

2. The inside front cover of the carton label states:

(b) (4)

We note that the majority of this language has been deleted from the Dosage and Administration section of the draft PI. We recommend deleting this language from the carton label to be consistent with the PI.

3. The carton and container labels contain

(b) (4)

4. The carton label states,

(b) (4)

5. The carton and container labeling includes the Patient Package Insert. We remind Duchesnay to update the PPI to be consistent with the final approved label.

Thank you for your consult. If you have any questions, please contact Carrie Newcomer at 6-1233, or carrie.newcomer@fda.hhs.gov.

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/s/

CARRIE A NEWCOMER
03/29/2013

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy Initiatives
Division of Medical Policy Programs**

PATIENT LABELING REVIEW

Date: March 28, 2013

To: Hylton V. Joffe, MD,
Director
Division of Reproductive and Urologic Products (DRUP)

Through: LaShawn Griffiths, MSHS-PH, BSN, RN
Associate Director for Patient Labeling
Division of Medical Policy Programs (DMPP)

Robin Duer, RN, BSN, MBA
Senior Patient Labeling Reviewer
Division of Medical Policy Programs (DMPP)

From: Sharon W. Williams, RN, BSN, MSN
Patient Labeling Reviewer
Division of Medical Policy Programs (DMPP)

Subject: DMPP Review of Patient Labeling: Patient Package Insert
(PPI)

Drug Name (established name): DICLEGIS (doxylamine succinate and pyridoxine hydrochloride)

Dosage Form and Route: Delayed-Release Tablets

Application Type/Number: NDA 21-876

Applicant: Duchesnay Inc.

1 INTRODUCTION

On June 8, 2012, Duchesnay Inc. submitted an original 505(b)(2) New Drug Application (NDA) for DICLEGIS (doxylamine succinate and pyridoxine hydrochloride) delayed-release tablets. DICLEGIS is indicated for the treatment of nausea and vomiting of pregnancy. The reference listed drug (RLD) for this application is Bendectin (doxylamine succinate and pyridoxine hydrochloride) delayed-release tablets.

This review is written in response to a request by the Division of Reproductive and Urologic Products (DRUP) for the Division of Medical Policy Programs (DMPP) to review the Applicant's proposed Patient Package Insert (PPI) for DICLEGIS (doxylamine succinate and pyridoxine hydrochloride) Delayed-Release Tablets.

2 MATERIAL REVIEWED

- Draft DICLEGIS (doxylamine succinate and pyridoxine hydrochloride) delayed-release tablets PPI received on June 8, 2012 and received by DMPP on August 20, 2012
- Draft DICLEGIS (doxylamine succinate and pyridoxine hydrochloride) delayed-release tablets Prescribing Information (PI) received June 8, 2012, revised throughout the review cycle, and received by DMPP on March 25, 2013

3 REVIEW METHODS

Our review of this PPI reflects changes to previous patient labeling practice. These changes are designed to decrease the length of patient information while maintaining consistency with the Regulations as specified in 21 CFR 208.20.

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss. We have reformatted the PPI document using the Verdana font, size 11.

In our review of the PPI we have:

- simplified wording and clarified concepts where possible
- ensured that the PPI is consistent with the prescribing information (PI)

- removed unnecessary or redundant information
- ensured that the PPI meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)
- ensured that the PPI is consistent with the approved comparator labeling where applicable

4 CONCLUSIONS

The PPI is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP on the correspondence.
- Our annotated version of the PPI is appended to this memo. Consult DMPP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the PPI.

Please let us know if you have any questions.

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/s/

SHARON W WILLIAMS
03/28/2013

ROBIN E DUER
03/28/2013

LASHAWN M GRIFFITHS
03/28/2013

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management**

Label and labeling Memo

Date: March 22, 2013

Safety Evaluator: Manizheh Siahpoushan, PharmD
Division of Medication Error Prevention and Analysis

Team Leader: Zachary Oleszczuk, PharmD
Division of Medication Error Prevention and Analysis

Drug Name: Diclegis
(Doxylamine Succinate and Pyridoxine Hydrochloride)
Delayed-release Tablets, 10 mg/10 mg

Application Type/Number: NDA 021876

Applicant/Sponsor: Duchesnay Inc.

OSE RCM #: 2012-1368-1

*** This document contains proprietary and confidential information that should not be released to the public.***

1 INTRODUCTION

This memo responds to a request from the Division of Urology and Reproductive Products (DRUP) for review of the revised container labels for Diclegis (Doxylamine Succinate and Pyridoxine Hydrochloride) submitted on March 12, 2013 in response to recommendations communicated to the Applicant by DMEPA.

2 MATERIAL REVIEWED

DMEPA reviewed the revised Diclegis container labels submitted March 12, 2013 (see Appendix A).

3 CONCLUSIONS AND RECOMMENDATIONS

Review of the revised container labels show that the Applicant implemented DMEPA's recommendations and we find the revisions acceptable. We have no additional recommendations at this time.

Please copy the Division of Medication Error Prevention and Analysis on any communication to the Applicant with regard to this review. If you have further questions or need clarifications on this review, please contact the OSE Regulatory Project Manager, Marcus Cato at 301-796-3903.

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/s/

MANIZHEH SIAHPOUSHAN
03/22/2013

ZACHARY A OLESZCZUK
03/22/2013

MEMORANDUM

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

CLINICAL INSPECTION SUMMARY

DATE: February 15, 2013

TO: Theresa H. van der Vlugt, M.D., M.P.H., Medical Reviewer
Shelley R. Slaughter, M.D., Ph.D., Medical Team Leader
George Lyght, Pharm.D., Regulatory Health Project Manager
Division of Reproductive and Urologic Products (DRUP)

FROM: Cynthia F. Kleppinger, M.D.
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

THROUGH: Janice Pohlman, M.D., M.P.H.
Team Leader
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

Susan D. Thompson, M.D.
Acting Branch Chief
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections

NDA: 21876

APPLICANT: Duchesnay Inc.

DRUG: Doxylamine succinate pyridoxine hydrochloride 10 mg/10 mg delayed
release tablets (Diclegis)

NME: No

THERAPEUTIC CLASSIFICATION: Standard Review

INDICATIONS: Treatment of nausea and vomiting of pregnancy in patients who do not

respond to conservative management.

CONSULTATION REQUEST DATE: October 1, 2012
CLINICAL INSPECTION SUMMARY DATE: February 11, 2013
DIVISION ACTION GOAL DATE: April 8, 2012
PDUFA DATE: April 8, 2013

I. BACKGROUND:

The sponsor of this application submitted one supporting Phase 3 study DIC-301 “A Double-blind, Multicenter, Randomized, Placebo-Controlled Trial of the Efficacy of Diclectin[®] for Nausea and Vomiting of Pregnancy”. Diclectin[®] (the combination of doxylamine succinate, 10 mg and pyridoxine hydrochloride, 10 mg) delayed release tablets are commercially available in Canada for the management of nausea and vomiting of pregnancy (NVP). Diclegis is the provisionally approved trade name for NDA 21876.

Subjects were pregnant women with a gestational age of 7-14 weeks, at least 18 years old, with NVP and the Pregnancy-Unique Quantification of Emesis (PUQE) score ≥ 6 who had not responded to conservative management consisting of dietary/lifestyle advice according to the 2004 American College of Obstetrics and Gynecology (ACOG) Practice Bulletin. The study had a 15 day period consisting of 14 dosing days.

The primary efficacy criterion for evaluation included change from baseline in the PUQE score at Day 15 (± 1 day). Secondary efficacy criteria included change from baseline in the 3 components of the PUQE, change from baseline in the Global Assessment of Well-Being, number of tablets taken, time loss from household tasks and/or employment, total number of visits and phone calls to health care providers, and rates of hyperemesis gravidarum.

There was compassionate dispensation of the study drug allowed after study completion.

This multi-center study was conducted at three main sites at university/hospital settings (with three satellite sites) in the United States. Five of the six sites were inspected. A total of 280 subjects were enrolled, 203 (72.5%) subjects completed and 77 (27.5%) subjects discontinued from the study.

The first subject enrolled February 7, 2008 and the last subject completed June 16, 2009.

A total of nine SAEs were reported during the study. A total of 11 subjects discontinued study drug due to AEs.

Paper case report forms (CRFs) were used with double-key data entry by the CRO (b) (4). Laboratory determinations were electronically captured.

There were 4 amendments to the original protocol dated 21 Dec 2006 (Amendment 1 [dated 20 Mar 2007], Amendment 2 [dated 07 Jun 2007], Amendment 3 [dated 13 Sep 2007], and Amendment 4 [dated 20 May 2008]).

Site #20 and Site #11 enrolled a large numbers of study participants. The Clinical Investigator (CI) Dr. Hankins (Site #11) was also the CI for Site #10 in Galveston, Texas and the CI for Site #12 in Pearland, Texas. The CI Dr. Miodovnik (Site #30) was also the CI for Site #31 at Georgetown Medical University. The ORA field investigators were told that if there were significant issues at the original site selected to contact OSI Headquarters immediately for possible expansion of the inspection to the other related site(s). It was determined immediately that there was a records issue with Site #30. Therefore, the inspection was expanded to Site #31 and also Site #10. (The review division was contacted for possible expansion of the inspection and had requested that Site #12 be inspected, but the ORA field investigator inspected Site #10).

II. RESULTS (by Site):

Name of CI/Site #	Protocol # and # of Subjects	Inspection Date	Final Classification
Stanley "Steve" Caritis, M.D. Site #20	Protocol DIC-301 Randomized: 72	12/18/2012 – 1/11/2013	Pending Preliminary classification VAI
Gary Hankins, M.D. Site #11 Added Site #10	Protocol DIC-301 Randomized: 57 Randomized: 40	1/14/2013 – 1/30/2013	Pending Preliminary classification VAI
Menachem Miodovnik, M.D. Site #30 Added Site #31	Protocol DIC-301 Randomized: 35 Protocol DIC-301 Randomized: 19	12/5/2012 – 12/13/2012	Pending Preliminary classification VAI

Key to Classifications

NAI = No deviation from regulations.

VAI = Deviation(s) from regulations.

OAI = Significant deviations from regulations. Data unreliable.

Pending = Preliminary classification based on information in 483, preliminary communication with the field, and review of EIR; final classification is pending.

1. Stanley N. Caritis, M.D.

300 Halket Street, Suite 610

Pittsburgh, PA 15213

- a. **What was inspected:** For protocol DIC-301, 31 of the 72 subject records were reviewed. Original case histories and source documents were reviewed to verify data listings provided, such as primary efficacy endpoints, secondary efficacy endpoints, adverse events, protocol deviations, subject randomization, subject discontinuations, and concomitant medications. Records were reviewed for documentation of the consent process, baseline PUQE score to ensure these subjects met the inclusion/exclusion PUQE score of > 6, all eligibility criteria, and drug accountability. The subject study records and medical records were reviewed to confirm that the subjects were not taking a prohibited medication during the study or did not have the required 48 hour wash-out period prior to the baseline blood work. Blinding/randomization procedures were reviewed. The study regulatory binder, the two site correspondence binders, and the investigator pharmacy manual were also reviewed.
- b. **General observations/commentary:** There were 80 subjects who signed informed consent, 8 screen failures, and 72 subjects enrolled in the study. Of the 72 subjects enrolled, 12 subjects were lost to follow-up, 1 subject was terminated due to treatment failure, and 2 subjects were removed; therefore, 57 subjects completed the study. Of the 57 subjects that completed the study, 36 subjects continued with compassionate use. The last subject follow-up was on 7/6/2009. The study is completed.

During the inspection, the FDA ORA field investigator encountered a delay in obtaining the subjects' medical records. The inspection was preannounced on 12/13/2012, the inspection commenced on 12/18/2012, and medical records did not become available for review until after 1/2/2013. The hospital system was transitioning between paper medical records and electronic medical records and all of the paper records were stored off-site. The medical records were provided to the FDA field investigator as the staff was receiving them from medical records. Two medical records were not provided in their entirety until the day of close-out 1/11/2013. There were also delays in finding space for the FDA ORA field investigator to review the records and in interviewing the employees.

The subjects' files consisted of both photocopy and original records. In general, the documentation of the study was organized and complete. The blind was not documented to have been broken for any of the 31 subjects reviewed. The first subject signed a consent form on 2/7/2008. There were no other records that documented the consent process in the study files.

Most records were identified with who performed the work or collected and entered the data. There were some instances in which a study physician was unavailable and a clinic physician performed the physical exam and/or ultrasound. There were instances in which the doctor performing the physical exam was not identified or the person performing the exam was not listed as

study personnel. Later a Note to File after the fact indicated that Dr. Caritis previously delegated the responsibilities of performing the physical exams to these individuals.

New England Institutional Review Board (NEIRB) was responsible for the initial and continuing review of the study. Dr. Caritis obtained IRB approval for the protocol and subsequent revisions, as well as the consent form, prior to enrollment of study subjects. The IRB required annual continuing review and conducted on-site visits. An on-site visit was conducted on 9/12/2008.

There were two unanticipated adverse events reported. The first was related to Subject 20-007 being hospitalized during the study and thus removed from the study due to “bile stones”. The other unanticipated adverse event reported was Subject 20-014 who had an intrauterine fetal death. Both SAEs were reported to the sponsor and IRB.

There were no cases of hyperemesis gravidarum during the study for any of the 31 subjects reviewed.

As noted earlier, of the 57 subjects that completed the study, 36 subjects continued with compassionate use. However, the majority of the compassionate use follow-up was not completed as directed in the protocol (patients were required to have regular follow-up visits every four weeks until the drug had been discontinued for 30 days). If follow-up occurred during the compassionate use period, it was routinely documented as 30 days post the last dose of the study drug during the initial study period not from the last dose of compassionate use. Additionally, the last dose of compassionate use study medication was not documented for the majority of these subjects. In the review of the study drug accountability log, only 4 of the 36 compassionate use subjects returned study medication. There was also no documentation to show that study staff reviewed clinic charts to identify adverse events or serious adverse events for these subjects.

At the conclusion of the inspection, a Form FDA 483, Inspectional Observations, was issued. Dr. Caritis responded to the items listed on the Form FDA 483 in a letter dated January 31, 2013 and outlined his commitment and specific actions for improving study practices to prevent such observations from occurring in future studies. Those observations noted were:

Observation 1: An investigation was not conducted in accordance with the signed statement of investigator and investigational plan.

► Specifically, in 7 of the 31 subject records reviewed, one or more of the required protocol procedures were not completed. For example,

- Subject 20-013, Day 15 final study completion visit was completed 3 days outside of the window. *PI agreed with this finding.*
- Subject 20-023, Day 1 ultrasound was performed 2 days outside of window.

PI agreed with this finding.

- Subject 20-025, Day 1 urinalysis was not completed. ***PI disagrees with this finding. The urine was collected but there was never a report and no documentation as to any follow-up.***
- Subject 20-038, Day 1 hematology was not completed. ***PI disagrees with this finding. The specimen was sent but was not suitable for testing.***
- Subject 20-052, Day 4 blood sample for pharmacokinetic measurements of pyridoxine, pyridoxal, pyridoxal 5'-phosphate and doxylamine was not taken. ***PI agrees with this finding.***
- Subject 20-062, Day 1 urinalysis was not completed and the Day 15 final study completion visit was completed outside of the window. ***PI agrees with this finding. Documentation was present that subject was unable to void; however, there was no documentation of follow-up attempt.***

► Section 15.2 of the study protocol states that the medical records or source documents for each patient shall document that informed consent was obtained prior to performance of any study specific procedures. Besides a signed and dated informed consent form, there is no documentation of the informed consent process in the medical records or on a source document for Subject 20-004. ***PI agrees with this finding. Two other subjects listed were removed from this report as the PI stated there was documentation of the process in the medical charts.***

The Site Signature Log / Authorization Log for this study identifies the individuals that were authorized to complete the study related physical examination. There were many instances in which the physical exam was not completed by authorized study personnel or under the supervision of the CI. For example, there is no documentation as to who completed the Day 1 Physical Exam for Subject 20-037 on 9/16/2008. Subject 20-032's Day 1 study physical exam was completed by a resident fellow during the time of the study who was not listed on the Site Signature Log/Authorization Log. Furthermore, there is no documentation that this exam was completed under Dr. Caritis's supervision. ***PI agrees with this finding.***

Observation 2: Failure to prepare or maintain adequate and accurate case histories with respect to observations and data pertinent to the investigation. Specifically,

- Section 9.1.5 of the protocol requires subjects to try conservative management consisting of dietary/lifestyle advice according to the 2004 ACOG Practice Bulletin prior to being enrolled in the study. Twenty-nine of the 31 study records reviewed do not document if the subject tried conservative therapies prior to enrollment. ***PI says that although it was identified and confirmed for each subject prior to enrollment and the medical record did document the presence of nausea and vomiting and advice for conservative management, he agrees that there was no documentation that subjects tried conservative therapies prior to enrollment.***

- Section 9.2.1 of the protocol requires the investigator to confirm the patient's nausea and vomiting is not of an etiology other than nausea and vomiting in pregnancy (NVT). Subjects 20-009, 20-023, 20-025, and 20-032 reported an ongoing (active) history of migraines. The study records for these subjects do not rule-out migraines as the cause of the nausea and vomiting. ***PI disagrees with this finding, stating that women with migraines causing nausea and vomiting present clinically with different symptoms than women with nausea and vomiting of pregnancy.***
- The case histories require all medications taken 30 days prior to baseline through study completion during each clinic visit, within 30 days after last day of study drug, and at any time SAEs/AEs are assessed to be documented as a prior/concomitant medication.
 - Subject 20-006 was treated with B6/Unisom for NVT on 1/30/2008. This subject was enrolled in the study on 2/28/2008. B6/unisom was not recorded as a prior medication in the case report records. ***PI agrees with this finding.***
 - Subject 20-007 was prescribed B6/Unisom to treat NVT at their OB visit on 2/26/2008 and enrolled in the study on 2/28/2008. There is no documentation to confirm that the subject did or did not take these medications. These medications would exclude this subject from the study. ***PI agrees with this finding.***
 - Subject 20-032 was prescribed B6/Unisom to treat NVT at their OB visit on 8/13/2008 and enrolled in the study on 8/14/2008. On 8/15/2008, the subject reported to have taken 1/2 tablet of Unisom. Unisom was originally developed as an anti-emetic. ***PI agrees with this finding.***
 - Subject 20-036 was prescribed Compazine, a dopamine antagonist, for NVT on 9/10/2008 and enrolled in the study on 9/12/2008. There is no documentation to confirm that the subject did or did not take these medications. This medication would exclude this subject from the study. ***PI agrees with this finding.***
 - Subject 20-071 was prescribed Reglan, an anti-emetic, on 4/27/2009. The subject was seen on 5/11/2009 for an OB visit, and the clinic notes document that the subject was still taking Reglan and was seeing improvement. The subject was enrolled into the study on 5/13/2009. The case report form that documents prior and concomitant medications indicates that no prior or concomitant medications were used for this subject. ***PI agrees with this finding.***
 - Section 9.2.11 of the protocol states a subject will be excluded if the patient has received an investigational drug within 30 days before enrollment in this study or is scheduled to receive an investigational drug during the course of this study. At least 15 of the study subjects reviewed consent to be screened for another study, ("A Randomized Trial of Thyroxine Therapy for Subclinical Hypothyroidism or Hypothyroxinemia Diagnosed During Pregnancy") at or around the

same time of enrollment into this study. There is no documentation to confirm that the subject did not complete another investigational study 30 days prior to enrollment in this study or documentation to show that the subject was not eligible for the Thyroxine Study and was enrolled in this study concurrently. ***The PI responded that he was PI for both studies. The thyroid study was a two part study. The first part was a screening study. Subjects in the screening study were also screened and enrolled into the DIC-301 research study. Subjects enrolled into the Thyroxine Treatment Study were not eligible for the DIC-301 research study. PI stated that research records were reviewed. None of the subjects in question who were screened for eligibility into the Thyroid Study signed informed consent or participated in the Thyroid and Diclectin study simultaneously.***

- c. **Assessment of data integrity:** The audit did not indicate serious deviations/findings that would impact the validity or reliability of the submitted data. However, the review division may wish to consider the impact, if any, regarding the fact that 29 of the 31 study records reviewed do not document if the subjects tried conservative therapies prior to enrollment and the impact of the potential use of B6/Unisom, Compazine and Reglan in the subjects listed above. The other deviations noted appear to be isolated in nature and are unlikely to significantly impact primary safety or efficacy analyses. In addition, it does not appear that the rights, safety, or welfare of subjects was compromised. With the exception of issues noted above, the study appears to have been conducted adequately, and the data generated by this site appear acceptable in support of the respective indication.

Note: Observations noted for this site are based on communications with the FDA field investigator, review of the Form FDA 483, review of the response from Dr. Caritis, and review of the electronic version of the Establishment Inspection Report (EIR). An inspection summary addendum will be generated if conclusions change upon receipt and review of the gathered evidence package.

2. Gary Hankins, MD

University of Texas Medical
Branch (UTMB) OB
Regional Maternal Clinic
Pasadena, TX 77502
and
UTMB Galveston
301 University Blvd
Galveston, TX 77502

According to site officials there were three locations where subjects were screened and enrolled for protocol DIC-301. This inspection provided coverage for two of the three sites

under this Investigator's control; Site #10 (Galveston, TX) and site #11 (Pasadena, TX).
NOTE: The majority of subjects were enrolled at the Pasadena site, due to Hurricane Ike hitting Galveston in the summer of 2008.

- a. **What was inspected:** For protocol DIC-301, a total of 20 subjects' charts were reviewed (7 from Galveston Site #10 and 13 from the Pasadena Site #11). The inspection included review of subjects' medical records, informed consents, laboratory results, case report forms, source documents, pharmacy logs, subject diaries, and data listings. In addition, the inspection also covered the regulatory binder and IRB correspondences.
- b. **General observations/commentary:** For the Pasadena site (#11) 57 subjects were screened, 57 subjects enrolled, and 38 subjects completed the study. For the Galveston site (#10), 40 subjects were screened, 40 subjects were enrolled and 27 subjects completed the study.

Both the Pasadena and Galveston sites had subjects that continued on the study drug/placebo for compassionate use after the completion of the study (9 subjects and 20 subjects, respectively).

The University of Texas Medical Branch (UTMB) Office of Research Subject Protections was the IRB utilized during this study. Before subjects were allowed to participate in the study, the investigator obtained IRB approval of the study protocol and all modifications to the various protocol versions, and human subject consent forms. The study underwent full review and was approved on 10/01/2007; per the IRB there was to be quarterly monitoring of the study.

The informed consent forms were in both English and Spanish. The FDA ORA field investigators were unable to determine if several subjects were consented prior to the start of any study related procedures. Two subjects out of eleven from the Pasadena site and two out of seven subjects from the Galveston site showed the consent form being signed on the same day as study procedures were initiated.

It was noted that there were several protocol deviations detected during the monitoring visits, such as Subject 11017's 30-day telephone contact was outside of the window, Subject 11007 took medication prior to the PK sample being drawn, and Subject 11011 did not complete the Global Assessment questions on Day 8 and Day 14.

There were three subjects that did not meet the inclusion/exclusion criteria:

- Subject 10023, had a history of depression and was taking the medication Celexa (citalopram) a selective serotonin reuptake inhibitor (SSRI).
- Subject 10029, at the time of enrollment was taking OTC Allegra-D, an antihistamine.
- Subject 10010 signed her consent form on 03/31/2008; her ultrasound was performed on 02/15/2008 two weeks outside of the window per the inclusion

criteria.

There were no deaths related to this study. According to the data listing report which was submitted to the Agency and run on 25 Sept 2009 on data from 27 Aug 2009, there were 4 SAE's reported. Per the site enrollment log for Galveston Site #10, in the column "Reason for screen failure or early termination" Subject 10002 is noted as having had an SAE but was not terminated early from the study. This SAE is not listed. Upon further exploration, Subject #10002 was seen on March 7, 2008 for her study termination visit. She was then allowed to continue on the study medication under the compassionate use protocol. On March 10, 2008, the subject had an ultrasound which showed a possible cystic hygroma. She underwent medical management with misoprostol and discontinued the study drug/placebo. The subject underwent a D&C on (b) (6).

At the conclusion of the inspection, a Form FDA 483, Inspectional Observations, was issued as follows:

Observation 1: Failure to obtain informed consent in accordance with 21 CFR part 50 from each human subject prior to conducting study-related tests. There was no documentation that the informed consent was signed prior to study procedures for Subject 11-001, Subject 11-017, Subject 10-001, and Subject 10-029.

Observation 2: An investigation was not conducted in accordance with the investigational plan. Specifically, the following subjects met the exclusion criteria and completed the study

- Subject 10-010's ultrasound was two weeks outside of the inclusion criteria.
- Subject 10-023 had a history of depression and was taking the medication Celexa (citalapram) a SSRI.
- Subject 10-029 at the time of enrollment was taking OTC Allegra-D, an antihistamine.

Note: According to the protocol, Section 9.2 Exclusion Criteria #4: The patient has used antihistamine or other anti-emetic therapy (anticholinergics, dopamine antagonists, serotonin antagonists, ginger, acupressure, etc.) in the previous 48 hours or plans to do so during the study. Section 9.2 Exclusion Criteria #5 states: Patients must be excluded if they meet any of the following criteria: The patient is using drugs that have anticholinergic activity (e.g., tricyclic antidepressants).

- c. **Assessment of data integrity:** Data from these two sites are acceptable. The audit did not indicate serious deviations/findings that would impact the validity or reliability of the submitted data.

Note: Observations noted for this site are based on communications with the FDA field investigator, review of the Form FDA 483, and review of the draft Establishment Inspection Report (EIR). An inspection summary addendum will be generated if conclusions change upon

receipt and review of the final EIR and the gathered evidence package.

3. Menachem Miodovnik, MD

Washington Hospital Center
110 Irving St. NW
Washington, DC 20010

and

Georgetown Medical University
Washington, DC 20057

At the announcement of the inspection, the FDA ORA field investigator was informed about destroyed files for Site #30. The OSI reviewer was alerted and asked ORA to immediately expand the inspection to Site #31. Both research departments were managed by Medstar Health Research which switched their document storage in 2011 to (b) (4)

When Medstar Health Research requested the study files, they received an e-mail Wednesday, November 28, 2012 from (b) (4) regarding records for protocol DIC-301. The e-mail reported that in (b) (4), the building's roof collapsed (b) (4)

There were approximately 80 boxes stored at (b) (4) including some hospital records.

There were 13 cartons requested and the email confirmed that 9 of the cartons were destroyed as they were in the "collapsed zone". (This was later corrected to 10 cartons destroyed). The building where the 3 cartons were stored was shut down in an effort to stabilize the structure and continue to retrieve documents. The building was released for entry to specified engineers to retrieve the cartons.

Initial review of the boxes retrieved revealed the following documents for Site #30:

- Complete records for 15 research participants
 - All IRB correspondence
 - 1572s
 - All protocols with signatures
 - All investigators CV, license, and financial disclosure forms
 - One (1) SAE report
 - Site screening and enrollment log (no identifiers)
 - Delegation log
 - Monitoring log with date and signature, but no reports
 - Laboratory normal values
- a. **What was inspected:** For protocol DIC-301, the FDA field investigator reviewed data which was retrievable from the storage facility. These included all 15 available subject records. The Sponsor also supplied a CD containing scanned copies of additional logs, and CRFs which were destroyed in the building collapse for review. Review of the informed consent and verification of source documents for screening and visit data

were done for the following: Subjects 30-001 through 30-007, Subjects 30-021 through 30-026, Subject 30-034 and Subject 30-035.

Stored records were not available for Subjects 30-008 through 30-020 and 30-027 through 30-033. Research staff used the initials of the subjects along with the date screened from the Site Enrollment Log and the birth dates from the scanned versions of the case report forms provided by the sponsor to find the name of each subject. Once the name was known, research staff used the hospital’s electronic medical records system to look up OB clinic visits to see if any matched the screening date of each subject. Some subjects had OB clinic visits which matched their Admission Visit, and some did not. Documentation of all OB visits on or near the Admission Visit was collected for review. If there were no visits but the subject had been a patient at Washington Hospital Center at some point, documentation of their existence as a patient was collected.

Documentation of the following visit dates were found in the electronic medical records system. As noted below, Subjects 30-008, 30-015, 30-028, 30-029 and 30-030 did not have any documentation for their Admission Visits within the electronic medical records system.

Subject Number	Date of Admission Visit	Nearest OB Visit Date
30-008	(b) (6)	(b) (6)
30-009		
30-010		
30-011		
30-012		
30-013		
30-014		
30-015		None. Have evidence this person was a patient at WHC.
30-016		(b) (6)
30-017		
30-018		
30-019		
30-020		
30-027		
30-028		None. Have evidence this person was a patient at WHC.
30-029		OB Visit Date (b) (6) Ultrasound date (b) (6)
30-030		

30-031	(b) (6)	
30-032		
30-033		

The site could not provide original monitoring reports as they were destroyed in the offsite storage building collapse.

It appears that all case report forms, informed consent documents and regulatory binders for Site 31 (Georgetown Medical University) were destroyed in the collapse.

- b. **General observations/commentary:** There were 35 subjects screened and 35 subjects enrolled at Site #30. It could not be confirmed how many completed. Available study documents were found to be well organized; however, some source documentation had not been included in the prepared files and had to be printed from the electronic medical record system.

The first subject signed the informed consent on 9/13/2007. The FDA ORA field investigator was unable to document the last patient out as both subjects 30-034 and 30-035 were lost to follow up. Subject 30-033 completed the study on May 19, 2009 and was provided with compassionate use drug on May 19, 2009.

The 1572s appeared to have been prepared as a single document covering both Site #30 and Site #31. They both list Washington Hospital Center and Georgetown University Medical Center as the addresses where the clinical investigations were taking place. Dr. Miodovnik was the PI for both sites. He stated that all study subjects were seen in the OB Clinic at Washington Hospital Center for study visits.

It was discovered that a Clinical Research Associate (CRA) was listed in the Authorization Log as having the authorization to perform all aspects of the clinical trial including medical exams and safety assessments. She also filled out and signed nearly 100% of the case report forms reviewed and the source documentation worksheets reviewed during the inspection. Her CV showed that she had not been trained as a nurse, nurse practitioner, or physician. The PI stated during the inspection that this CRA was not allowed to perform any tasks related to medical assessments and that the Authority Log was incorrect.

MedStar Health IRB reviewed study DIC-301 and approved all amendments and consent forms. Initial approval was 9/26/07. Review of the informed consent documents were done for the following: Subjects 30-001 through 30-007, Subjects 30-021 through 30-026, Subject 30-034 and Subject 30-035. All signed the correct IRB approved informed consent document on the day of their Admission Visit. Nearly all subjects were administered informed consent by the CRA mentioned above.

All lab results were reviewed and signed off by the CI.

Drug accountability documentation was not found for subjects whose documents were available and who participated in the compassionate use period of the study. Study visits for compassionate use were not recorded at all and drug accountability was to be recorded during these visits. In addition, the case report forms provided by the Sponsor/CRO did not include any place to document drug accountability during the compassionate use phase of the study. The Sponsor provided documentation of returned product. This did not include any compassionate use product. No product was left onsite.

At the conclusion of the inspection, a Form FDA 483, Inspectional Observations, was issued for:

Observation 1: Failure to prepare or maintain adequate case histories with respect to observations and data pertinent to the investigation.

- For at least two subjects (30-021 and 30-025) there is no source documentation by the physician or a designee for the physical examination and vital signs during the Admission Visit (Day 1). Each subject did have what the Sponsor/CRO titled "Source Document Worksheets". However, these were filled out by the CRA. All other subjects reviewed had a printed electronic medical record or notes from a physician of the medical history and physical from their Admission Visit.
- For all subject files reviewed, there is no source documentation of the physician or designee reviewing procedures, completing drug accountability, or diary review on Days 4, 8, and 15. "Source Document Worksheets" were filled out by the CRA, who did not have a medical background to perform any tasks related to medical assessments. There was no documentation that the subjects' primary provider or another study physician or nurse conducted the visits.
- For all subject files reviewed, there is no source documentation of the study phone calls performed by a person designated to perform the calls and provide medical knowledge on Days 2, 6, 12, and 14. "Source Document Worksheets" were filled out by the CRA, who did not have a medical background to perform any tasks related to medical assessments. There was no documentation that the subjects' primary provider or another study physician or nurse approved the medical instructions given by the CRA.

Observation 2: An investigation was not conducted in accordance with the investigational plan.

- An SAE was not reported to the IRB within the protocol specified time frame. Subject 30-005 entered the hospital on 6/21/08 for premature rupture of membranes. The site became aware of the SAE on 7/16/08 and did not report the event to the IRB until 10/6/08.
- Section 9.1.5 of the protocol requires subjects to try conservative management consisting of dietary/lifestyle advice according to the 2004 ACOG Practice Bulletin prior to being enrolled in the study. There was no documentation in the

source records reviewed if the subjects tried conservative therapies prior to enrollment. Site staff explained that this was documented in the record as “Nutrition: counseled”. However, documentation of previous instructions to change diet and lifestyle to attempt to negate the nausea and vomiting due to pregnancy was not observed for any subject.

- Study visits required by the compassionate use section of the protocol were not performed according to the protocol. Subjects were to be followed every 4 weeks until the drug had been discontinued for 30 days. The protocol required assessment of the patient’s condition, adverse events, drug accountability, and need for continued treatment for NVP. Subjects 30-003, 30-023, 30-025, and 30-026 received drug for compassionate use. Subsequent prenatal care visits were general care and did not have the protocol assessments documented. Final CRF data for the subjects was from when the subject would have been at the end of the subject’s use of compassionate drug and not for the additional 30 days of follow-up as required by the protocol.

- c. **Assessment of data integrity:** Unfortunately, a confirmed natural disaster made the inspection of this site extremely difficult. However, 15/35 of the subject records were recovered and could be evaluated. The audit did not indicate serious deviations/findings that would impact the validity or reliability of the submitted data. Again, as noted with the other inspections, the review division may wish to consider the impact, if any, regarding the fact that study records reviewed do not document if the subjects tried conservative therapies prior to enrollment. With the exception of issues noted above, the study appears to have been conducted adequately, and the data generated by this site appear acceptable in support of the respective indication.

Note: Observations noted for this site are based on communications with the FDA field investigator, review of the Form FDA 483, and review of the complete Establishment Inspection Report (EIR).

III. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

The inspection for this NDA consisted of four domestic clinical sites, one more than originally assigned. An attempt was made to also review the subject study records at a fifth site (#31) that was not initially chosen for inspection due to a natural disaster; however, records could not be recovered due to the same natural disaster. Study regulatory records were recovered to confirm the oversight of the study.

The four clinical sites inspected, Dr. Caritis (Site #20), Dr. Hankins (Site #11 and Site #10), and Dr. Miodovnik (Site #30) were each issued a Form FDA 483 citing inspectional observations and preliminary classifications for each of these inspections are Voluntary Action Indicated (VAI). Records could not be inspected for Site #31; however, since Dr. Miodovnik was also the PI for this site, it could be assumed that the oversight of the clinical study at this site would be similar to that for Site #30. Although regulatory violations were noted as described above for all four sites inspected, they are unlikely to significantly impact primary

safety and efficacy analyses. As noted above, the review division may wish to consider the impact, if any, regarding study records reviewed at several sites which do not document if the subjects tried conservative therapies prior to enrollment and also the impact of the potential use of B6/Unisom, Compazine, and Reglan in the subjects at Dr. Caritis Site #10. The overall data in support of this application may be considered reliable based on available information.

Observations noted above are based on communications with the FDA ORA field investigators, review of the Form FDA 483 for each site, review of the response from Dr. Caritis, and review of the Establishment Inspection Reports. An inspection summary addendum will be generated if conclusions change upon OSI final classification.

{See appended electronic signature page}

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/s/

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**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management**

Label, Labeling and Packaging Review

Date: October 18, 2012

Reviewer: Manizheh Siahpoushan, PharmD
Division of Medication Error Prevention and Analysis

Team Leader: Zachary Oleszczuk, PharmD
Division of Medication Error Prevention and Analysis

Division Director: Carol Holquist, RPh
Division of Medication Error Prevention and Analysis

Drug Name and Strength: Diclegis
(Doxylamine Succinate and Pyridoxine Hydrochloride)
Delayed-release Tablets, 10 mg/10 mg

Application Type/Number: NDA 021876

Applicant/sponsor: Duchesnay Inc.

OSE RCM #: 2012-1368

*** This document contains proprietary and confidential information that should not be released to the public.***

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1 INTRODUCTION

This review evaluates the proposed container label and insert labeling for Diclegis, NDA 021876, for areas of vulnerability that could lead to medication errors.

1.1 BACKGROUND AND REGULATORY HISTORY

This 505 (b)(2) Application was resubmitted to the FDA by Duchesnay Inc., on June 8, 2012 after Refusal to File on December 17, 2004. The Reference Listed Drug (RLD) is Bendectin. The US manufacturer of Bendectin ceased manufacturing Bendectin in 1983 and it has remained absent from the US market since that time. On August 9, 1999, FDA issued a notice of a determination under 21 CFR 314.161 that Bendectin (Doxylamine Succinate, Pyridoxine Hydrochloride) was not withdrawn from sale for safety or effectiveness reasons. Duchesnay Inc. has marketed a version of this drug product, called Diclectin, in Canada since 1975.

In response to DMEPA's request in the June 25, 2012 teleconference, the Applicant submitted container labels for the proposed product on July 16, 2012 because the original June 8, 2012 submission contained only a text presentation of the container labels and not the actual mock-up of the labels. In a subsequent submission on August 13, 2012, the Applicant submitted updated container labels with the proprietary name, Diclegis because DMEPA found the proposed proprietary name, (b) (4) unacceptable.

Additionally, the proposed proprietary name, Diclegis, submitted on August 3, 2012, will be reviewed under a separate cover in OSE Review #2012-1809.

1.2 PRODUCT INFORMATION

The following product information is provided in the August 3, 2012 proprietary name submission.

- Active Ingredient: Doxylamine Succinate and Pyridoxine Hydrochloride
- Indication of Use: Pregnancy related nausea and vomiting
- Route of Administration: Oral
- Dosage Form: Delayed-release tablets
- Strength: 10 mg/10 mg
- Dose and Frequency: The usual dosage for this product is 2 to 4 tablets. The frequency of administration is once to three times daily until symptoms of nausea and vomiting resolve, typically by week 16; thus the dosing interval is every day for at least 16 weeks. The maximum daily dose is 40 mg/40 mg.
- How Supplied: Bottle of 100 tablets
- Storage: 20°C to 25°C (68°F to 77°F); excursions permitted between 15°C and 30°C (59°F and 86°F)
- Container and Closure Systems: The packaging components in direct contact with the product help ensure its stability. The container closure system includes a

75-mL opaque bottle, a 38-mm child-resistant cap, and a silica gel desiccant canister. The cap component contains an induction inner seal consisting of a

(b) (4)

(b) (4)

2 METHODS AND MATERIALS REVIEWED

DMEPA searched the FDA AERS database for Bendectin (RLD) and Diclectin (marketed in Canada) medication error reports. We also reviewed the Diclegis container label and package insert labeling submitted by the Applicant.

2.1 SELECTION OF MEDICATION ERROR CASES

We searched the FDA Adverse Event Reporting System (AERS) database using the strategy listed in Table 1. This search strategy identified no reports of medication errors.

Table 1: AERS Search Strategy	
Date: 7/31/12	No date range
Drug Name	Trade names: Bendectin, Diclectin Verbatim term: Bendect% , Diclect%
MedDRA Search Strategy	Medication Errors (HLGT) Product Packaging Issues HLT Product Label Issues HLT Product Quality Issues (NEC) HLT

2.2 LABELS AND LABELING

Using the principals of human factors and Failure Mode and Effects Analysis,¹ along with post marketing medication error data, the Division of Medication Error Prevention and Analysis (DMEPA) evaluated the following:

- Container label submitted on August 13, 2012 (Appendix B)
- Insert Labeling submitted on June 8, 2012 (no image)

3 MEDICATION ERROR RISK ASSESSMENT

The following section describes the risk assessment of the Diclegis label and labeling.

¹ Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

3.1 INTEGRATED SUMMARY OF MEDICATION ERROR RISK ASSESSMENT

DMEPA identified deficiencies in the container label and insert labeling. These deficiencies include:

- Inadequate prominence or display of important information
- Cluttered layout and repetitive information that crowds the label or detracts from important information
- Missing important label and labeling statements such as “Swallow tablets whole. Do not crush, chew, or split the tablets.”

4 CONCLUSIONS

DMEPA concludes that the proposed container label and insert labeling can be improved to increase the readability and prominence of important information on the label to promote the safe use of the product, to mitigate any confusion, and to clarify information.

If you have further questions or need clarifications, please contact Marcus Cato, OSE project manager, at 301-796-3903.

5 RECOMMENDATIONS

Based on this review, DMEPA recommends the following be implemented prior to approval of this NDA:

A. General Comments for Container Label and Insert Labeling

We request you revise the statement (b) (4) (or variations of this statement) where it appears throughout the insert labeling (i.e. Dosage and Administration, Storage and Handling, and How do I take (b) (4) in the Patient Labeling) and container label (i.e. inside front cover and back ribbon) to read as follows: “Swallow tablets whole. Do not crush, chew, or split the tablets.” As currently presented, the warning statement contains negative language which may be overlooked by patients and have the opposite effect of the intended meaning.

B. Container Label

1. We note that the proprietary name is presented in all capital letters (i.e. DICLEGIS) which decrease readability. Words set in upper and lower case form recognizable shapes, making them easier to read than the rectangular shape that is formed by words set in all capital letters. Thus we request you revise the proprietary name to appear in title case (i.e. Diclegis).
2. Ensure that the established name is printed in letters that are at least half as large as the letters comprising the proprietary name. Taking into account all pertinent factors, including typography, layout, contrast, and other printing features in accordance with 21 CFR 201.10(g)(2). Additionally, replace the comma within the established name with the word “and”.

3. Relocate the product strength to immediately follow the dosage form. Additionally, replace the comma with “/” to be consistent with other approved multi ingredient products. Furthermore, increase the prominence of the dosage form and the product strength to be commensurate with the established name presentation and place a hyphen in between Delayed Release (i.e. Delayed-release). The final presentation of the proprietary name, the established name, dosage form, and product strength should appear as follows:

Diclegis

(Doxylamine Succinate and Pyridoxine Hydrochloride)

Delayed-release Tablets

10 mg/10 mg

4. [REDACTED] (b) (4) [REDACTED] (b) (4) that currently appears on the principal display panel of the container label. This information is redundant because it also appears on the inside back cover as well as the insert labeling. Additionally, the space provided after removing this statement can be utilized for the proper presentation of the proprietary name, the established name, the dosage form, and the product strength, as well as the important warning statement (discussed in #5 below) after revisions.
5. Include the statement “**WARNINGS: Swallow tablets whole. Do not crush, chew, or split the tablets.**” on the principal display panel of the outside front cover after removing the indication statement, in a prominent fashion (i.e. bold letters). As currently presented, this warning statement does not appear on the outside front cover of the container label.
6. Remove the [REDACTED] (b) (4) color block that contains the [REDACTED] (b) (4) and the [REDACTED] (b) (4) statements. The use of color, boxing, or other means of enhancing prominence is generally utilized to allow adequate differentiation between different product strengths. Additionally, relocate the “Rx only” statement to further down on the label (i.e. below or next to the graphic of the tablet) and debold and decrease the size of the net quantity statement.
7. Reduce the prominence of the company name and logo. As currently presented, the company logo appears too prominent and can distract from other important information such as the proprietary name, the established name, and the product strength.
8. To improve clarity on the outside front and inside back covers of the container label, revise the statement [REDACTED] (b) (4) to state: “PHARMACIST: Dispense in original container or equivalent air tight, light resistant container. Dispense the accompanying patient package insert to the patient.” Additionally, delete [REDACTED] (b) (4) [REDACTED] from the inside back cover of the label after revisions.
9. Delete the statement [REDACTED] (b) (4) [REDACTED] from the outside front cover side panel to minimize crowding. This

information also appears in the Consumer Information section of the back ribbon under “What are the ingredients in (b) (4) as well as the insert labeling, and is not required to appear on the container label.

C. Insert Labeling

1. Remove all instances of the name, (b) (4) because it was found unacceptable by DMEPA for marketing this product in the United States.
2. Highlights of Prescribing Information: as currently presented, the established name contains the product strength and uses a comma to separate the two ingredients. Additionally, the route of administration statement does not immediately follow the dosage form. To ensure consistency with the Agency’s labeling guidelines and the most recent approved products, we recommend removing the (b) (4) from the established name, replacing the comma with the word “and”, and including the dosage form. The revised format may appear as follows:

DICLEGIS (doxylamine succinate and pyridoxine hydrochloride)
delayed-release tablets, for oral use

However, we defer to ONDQA for their input regarding the appropriate presentation.

3. Highlights of Prescribing Information: we recommend adding the following warning statements: “Take tablets on an empty stomach. Swallow tablets whole. Do not crush, chew, or split the tablets.” to the *Dosage and Administration* Section.
4. We recommend removing the (b) (4) that is repeated at the beginning of each page of the Full Prescribing Information. Alternatively, if the Applicant’s intent is to enhance product identification on subsequent pages of the insert labeling, the Applicant may use the proprietary and the established names as a header on top of each page, to ensure consistency with the Agency’s labeling guidelines. We defer to ONDQA for their input regarding the exclusion or the appropriate presentation of a header on each page of the Full Prescribing Information.
5. Patient Labeling: revise the dosage form statement in the title to include “Delayed-release”. The revised format would appear as follows:

DICLEGIS (pronunciation)
(Doxylamine Succinate and Pyridoxine Hydrochloride) Delayed-release Tablets
6. Section 17 Patient Counseling Information: as currently presented, this section refers prescribers to Patient Labeling [17.2]. We recommend highlighting some important information such as drowsiness, swallowing tablets whole, not crushing, chewing, or splitting the tablets, etc. in this section before referring prescribers to patient labeling.

APPENDICES

APPENDIX A. DATABASE DESCRIPTIONS

Adverse Event Reporting System (AERS)

The Adverse Event Reporting System (AERS) is a computerized information database designed to support the FDA's post-marketing safety surveillance program for drug and therapeutic biologic products. The FDA uses AERS to monitor adverse events and medication errors that might occur with these marketed products. The structure of AERS complies with the international safety reporting guidance ([ICH E2B](#)) issued by the International Conference on Harmonisation. Adverse events in AERS are coded to terms in the Medical Dictionary for Regulatory Activities terminology (MedDRA).

AERS data do have limitations. First, there is no certainty that the reported event was actually due to the product. FDA does not require that a causal relationship between a product and event be proven, and reports do not always contain enough detail to properly evaluate an event. Further, FDA does not receive all adverse event reports that occur with a product. Many factors can influence whether or not an event will be reported, such as the time a product has been marketed and publicity about an event. Therefore, AERS cannot be used to calculate the incidence of an adverse event in the U.S. population.

5 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS)
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This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MANIZHEH SIAHPOUSHAN
10/18/2012

ZACHARY A OLESZCZUK
10/18/2012

CAROL A HOLQUIST
10/18/2012

RPM FILING REVIEW

(Including Memo of Filing Meeting)

To be completed for all new NDAs, BLAs, and Efficacy Supplements [except SE8 (labeling change with clinical data) and SE9 (manufacturing change with clinical data)]

Application Information		
NDA # 021876 BLA#	NDA Supplement #:S- BLA Supplement #	Efficacy Supplement Type SE-
Proprietary Name: TBD Established/Proper Name: doxylamine succinate, pyridoxine hydrochloride Dosage Form: delayed release tablets Strengths: 10 mg /10 mg		
Applicant: Duchesnay Inc. Agent for Applicant (if applicable): OptumInsight		
Date of Application: June 8, 2012 Date of Receipt: June 8, 2012 Date clock started after UN:		
PDUFA Goal Date: April 8, 2013		Action Goal Date (if different):
Filing Date: August 7, 2012		Date of Filing Meeting: August 1, 2012
Chemical Classification: (1,2,3 etc.) (original NDAs only)		
Proposed indication(s)/Proposed change(s): Treatment of Nausea and vomiting of pregnancy in patients who do not respond to conservative management		
Type of Original NDA: AND (if applicable)	<input type="checkbox"/> 505(b)(1) <input checked="" type="checkbox"/> 505(b)(2)	
Type of NDA Supplement:	<input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)	
<i>If 505(b)(2): Draft the "505(b)(2) Assessment" review found at: http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499 and refer to Appendix A for further information.</i>		
Review Classification:	<input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority	
<i>If the application includes a complete response to pediatric WR, review classification is Priority.</i>		
<i>If a tropical disease priority review voucher was submitted, review classification is Priority.</i>		
Resubmission after withdrawal? <input type="checkbox"/>		Resubmission after refuse to file? <input checked="" type="checkbox"/>
Part 3 Combination Product? <input type="checkbox"/>	<input type="checkbox"/> Convenience kit/Co-package <input type="checkbox"/> Pre-filled drug delivery device/system (syringe, patch, etc.) <input type="checkbox"/> Pre-filled biologic delivery device/system (syringe, patch, etc.) <input type="checkbox"/> Device coated/impregnated/combined with drug <input type="checkbox"/> Device coated/impregnated/combined with biologic <input type="checkbox"/> Separate products requiring cross-labeling <input type="checkbox"/> Drug/Biologic <input type="checkbox"/> Possible combination based on cross-labeling of separate products <input type="checkbox"/> Other (drug/device/biological product)	
<i>If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults</i>		

<input type="checkbox"/> Fast Track <input type="checkbox"/> Rolling Review <input type="checkbox"/> Orphan Designation <input type="checkbox"/> Rx-to-OTC switch, Full <input type="checkbox"/> Rx-to-OTC switch, Partial <input type="checkbox"/> Direct-to-OTC Other:	<input type="checkbox"/> PMC response <input type="checkbox"/> PMR response: <input type="checkbox"/> FDAAA [505(o)] <input type="checkbox"/> PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] <input type="checkbox"/> Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) <input type="checkbox"/> Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)			
Collaborative Review Division (if OTC product):				
List referenced IND Number(s): 072300				
Goal Dates/Product Names/Classification Properties	YES	NO	NA	Comment
PDUFA and Action Goal dates correct in tracking system? <i>If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.</i>	X			
Are the proprietary, established/proper, and applicant names correct in tracking system? <i>If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into tracking system.</i>		X		(b) (4) will not be the proper name. Sponsor's address is incorrect
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug)? <i>For NDAs/NDA supplements, check the New Application and New Supplement Notification Checklists for a list of all classifications/properties at: http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm</i> <i>If no, ask the document room staff to make the appropriate entries.</i>	X			
Application Integrity Policy	YES	NO	NA	Comment
Is the application affected by the Application Integrity Policy (AIP)? <i>Check the AIP list at: http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</i>		X		
If yes, explain in comment column.				
If affected by AIP, has OC/OMPQ been notified of the submission? If yes, date notified:			X	
User Fees	YES	NO	NA	Comment
Is Form 3397 (User Fee Cover Sheet) included with authorized signature?	X			

<p><u>User Fee Status</u></p> <p><i>If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send Unacceptable for Filing (UN) letter and contact user fee staff.</i></p>	<p>Payment for this application:</p> <p><input type="checkbox"/> Paid <input type="checkbox"/> Exempt (orphan, government) <input checked="" type="checkbox"/> Waived (e.g., small business, public health) <input type="checkbox"/> Not required</p>																			
<p><i>If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.</i></p>	<p>Payment of other user fees:</p> <p><input checked="" type="checkbox"/> Not in arrears <input type="checkbox"/> In arrears</p>																			
<p>505(b)(2) (NDAs/NDA Efficacy Supplements only)</p>	<p>YES</p>	<p>NO</p>	<p>NA</p>	<p>Comment</p>																
<p>Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?</p>		<p>X</p>																		
<p>Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? [see 21 CFR 314.54(b)(1)].</p>		<p>X</p>																		
<p>Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug [see 21 CFR 314.54(b)(2)]?</p> <p><i>If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the 505(b)(2) review staff in the Immediate Office of New Drugs</i></p>		<p>X</p>																		
<p>Is there unexpired exclusivity on the active moiety (e.g., 5-year, 3-year, orphan, or pediatric exclusivity)? Check the <i>Electronic Orange Book</i> at: http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm</p> <p>If yes, please list below:</p> <table border="1" data-bbox="203 1451 1349 1587"> <thead> <tr> <th>Application No.</th> <th>Drug Name</th> <th>Exclusivity Code</th> <th>Exclusivity Expiration</th> </tr> </thead> <tbody> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> </tbody> </table>	Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration														<p>X</p>		
Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration																	
<p><i>If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 314.108(b)(2). Unexpired, 3-year exclusivity will only block the approval, not the submission of a 505(b)(2) application.</i></p>																				
<p>Exclusivity</p>	<p>YES</p>	<p>NO</p>	<p>NA</p>	<p>Comment</p>																
<p>Does another product (same active moiety) have orphan exclusivity for the same indication? <i>Check the Orphan Drug Designations and Approvals list at:</i> http://www.accessdata.fda.gov/scripts/opdlisting/opd/index.cfm</p>		<p>X</p>																		

If another product has orphan exclusivity , is the product considered to be the same product according to the orphan drug definition of sameness [see 21 CFR 316.3(b)(13)]? <i>If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy</i>			X	
Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? (<i>NDAs/NDA efficacy supplements only</i>) If yes, # years requested: 3 <i>Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i>	X			
Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use (<i>NDAs only</i>)?		X		
If yes , did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)? <i>If yes, contact Mary Ann Holovac, Director of Drug Information, OGD/DLPS/LRB.</i>			X	

Format and Content				
<i>Do not check mixed submission if the only electronic component is the content of labeling (COL).</i>	<input type="checkbox"/> All paper (except for COL) <input checked="" type="checkbox"/> All electronic <input type="checkbox"/> Mixed (paper/electronic) <input checked="" type="checkbox"/> CTD <input type="checkbox"/> Non-CTD <input type="checkbox"/> Mixed (CTD/non-CTD)			
If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?				
Overall Format/Content	YES	NO	NA	Comment
If electronic submission, does it follow the eCTD guidance? ¹ If not, explain (e.g., waiver granted).	X			
Index: Does the submission contain an accurate comprehensive index?	X			
Is the submission complete as required under 21 CFR 314.50 (<i>NDAs/NDA efficacy supplements</i>) or under 21 CFR 601.2 (<i>BLAs/BLA efficacy supplements</i>) including:	X			

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<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf>

<input type="checkbox"/> legible <input checked="" type="checkbox"/> English (or translated into English) <input type="checkbox"/> pagination <input type="checkbox"/> navigable hyperlinks (electronic submissions only)				
If no, explain.				
BLAs only: Companion application received if a shared or divided manufacturing arrangement?				
If yes, BLA #				
Applications in “the Program” (PDUFA V) (NME NDAs/Original BLAs)	YES	NO	NA	Comment
Was there an agreement for any minor application components to be submitted within 30 days after the original submission?		X		
<ul style="list-style-type: none"> If yes, were all of them submitted on time? 				
Is a comprehensive and readily located list of all clinical sites included or referenced in the application?	X			
Is a comprehensive and readily located list of all manufacturing facilities included or referenced in the application?	X			
Forms and Certifications				
<i>Electronic forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise, paper forms and certifications with hand-written signatures must be included. Forms include: user fee cover sheet (3397), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674); Certifications include: debarment certification, patent certification(s), field copy certification, and pediatric certification.</i>				
Application Form	YES	NO	NA	Comment
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)?	X			
<i>If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].</i>				
Are all establishments and their registration numbers listed on the form/attached to the form?	X			
Patent Information (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?	X			
Financial Disclosure	YES	NO	NA	Comment
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)?	X			

<i>Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].</i>				
<i>Note: Financial disclosure is required for bioequivalence studies that are the basis for approval.</i>				
Clinical Trials Database	YES	NO	NA	Comment
Is form FDA 3674 included with authorized signature?	X			
<i>If yes, ensure that the application is also coded with the supporting document category, "Form 3674."</i>				
<i>If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant</i>				
Debarment Certification	YES	NO	NA	Comment
Is a correctly worded Debarment Certification included with authorized signature?	X			
<i>Certification is not required for supplements if submitted in the original application; If foreign applicant, both the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].</i>				
<i>Note: Debarment Certification should use wording in FD&C Act Section 306(k)(1) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as, "To the best of my knowledge..."</i>				
Field Copy Certification (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included?			X	
<i>Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)</i>				
<i>If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.</i>				
Controlled Substance/Product with Abuse Potential	YES	NO	NA	Comment
<u>For NMEs:</u> Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)?			X	
<i>If yes, date consult sent to the Controlled Substance Staff:</i>				
<u>For non-NMEs:</u> <i>Date of consult sent to Controlled Substance Staff:</i>				
Pediatrics	YES	NO	NA	Comment

<u>PREA</u>	X			
Does the application trigger PREA? <i>If yes, notify PeRC RPM (PeRC meeting is required)²</i> <i>Note: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.</i>		X		
If the application triggers PREA , are the required pediatric assessment studies or a full waiver of pediatric studies included?	X			
If studies or full waiver not included , is a request for full waiver of pediatric studies OR a request for partial waiver and/or deferral with a pediatric plan included? <i>If no, request in 74-day letter</i>	X			
If a request for full waiver/partial waiver/deferral is included , does the application contain the certification(s) required by FDCA Section 505B(a)(3) and (4)? <i>If no, request in 74-day letter</i>	X			
<u>BPCA</u> (NDAs/NDA efficacy supplements only): Is this submission a complete response to a pediatric Written Request? <i>If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)³</i>		X		
Proprietary Name	YES	NO	NA	Comment
Is a proposed proprietary name submitted? <i>If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."</i>	X			
REMS	YES	NO	NA	Comment
Is a REMS submitted? <i>If yes, send consult to OSE/DRISK and notify OC/OSI/DSC/PMSB via the CDER OSI RMP mailbox</i>		X		
Prescription Labeling	<input type="checkbox"/> Not applicable			
Check all types of labeling submitted.	<input checked="" type="checkbox"/> Package Insert (PI) <input checked="" type="checkbox"/> Patient Package Insert (PPI) <input type="checkbox"/> Instructions for Use (IFU) <input type="checkbox"/> Medication Guide (MedGuide) <input checked="" type="checkbox"/> Carton labels			

² <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027829.htm>

³ <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027837.htm>

	<input checked="" type="checkbox"/> Immediate container labels <input type="checkbox"/> Diluent <input type="checkbox"/> Other (specify)			
	YES	NO	NA	Comment
Is Electronic Content of Labeling (COL) submitted in SPL format? <i>If no, request applicant to submit SPL before the filing date.</i>	X			
Is the PI submitted in PLR format? ⁴	X			
If PI not submitted in PLR format , was a waiver or deferral requested before the application was received or in the submission? If requested before application was submitted , what is the status of the request? <i>If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.</i>				
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to OPDP?	X			
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (send WORD version if available)	X			
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office (OBP or ONDQA)?	X			
OTC Labeling	<input checked="" type="checkbox"/> Not Applicable			
Check all types of labeling submitted.	<input type="checkbox"/> Outer carton label <input type="checkbox"/> Immediate container label <input type="checkbox"/> Blister card <input type="checkbox"/> Blister backing label <input type="checkbox"/> Consumer Information Leaflet (CIL) <input type="checkbox"/> Physician sample <input type="checkbox"/> Consumer sample <input type="checkbox"/> Other (specify)			
	YES	NO	NA	Comment
Is electronic content of labeling (COL) submitted? <i>If no, request in 74-day letter.</i>				
Are annotated specifications submitted for all stock keeping units (SKUs)? <i>If no, request in 74-day letter.</i>				
If representative labeling is submitted, are all represented SKUs defined? <i>If no, request in 74-day letter.</i>				

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<http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/StudyEndpointsandLabelingDevelopmentTeam/ucm025576.htm>

All labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEPA?				
Other Consults	YES	NO	NA	Comment
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team)		X		
<i>If yes, specify consult(s) and date(s) sent:</i>				
Meeting Minutes/SPAs	YES	NO	NA	Comment
End-of Phase 2 meeting(s)? Date(s):				
<i>If yes, distribute minutes before filing meeting</i>				
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? Date(s): December 14, 2009				
<i>If yes, distribute minutes before filing meeting</i>				
Any Special Protocol Assessments (SPAs)? Date(s): No agreement- November 7, 2005				
<i>If yes, distribute letter and/or relevant minutes before filing meeting</i>				

ATTACHMENT

MEMO OF FILING MEETING

DATE: August 1, 2012

NDA #: 021876

PROPRIETARY NAME: TBD

ESTABLISHED/PROPER NAME: doxylamine succinate, pyridoxine hydrochloride

DOSAGE FORM/STRENGTH: delayed release tablets 10 mg /10 mg

APPLICANT: Duchesnay Inc.

PROPOSED INDICATION(S)/PROPOSED CHANGE(S): Treatment of nausea and vomiting of pregnancy in patients who do not respond to conservative management.

BACKGROUND: On April 18, 2005, Duschesnay Inc. submitted a 505(b)(2) New Drug Application (NDA) for (b) (4) (doxylamine succinate/pyridoxine hydrochloride) 10mg/10 mg Delayed Release Tablets. The Reference Listed Drug (RLD), Bendectin®, was first approved to be marketed in 1956, but withdrawn from the US market in 1983. In a June 10, 2005, teleconference, the Division requested clarification for the three drug formulations of (b) (4) and for bridging data between Bendectin®, and (b) (4). On June 16, 2005, a refuse to file letter was sent to the sponsor because: 1) the NDA does not contain information necessary to establish a link between the proposed formulation of Dicletin® and Bendectin®, and 2) the NDA is seeking an indication (b) (4). The Division recommended that the indication should capture treatment that did not respond to conservative measures.

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	George Lyght	Y
	CPMS/TL:	Margaret M. Kober	Y
Cross-Discipline Team Leader (CDTL)	Shelley R. Slaughter		Y
Clinical	Reviewer:	Theresa van der Vlugt	Y
	TL:	Shelley R. Slaughter	Y
Social Scientist Review (for OTC)	Reviewer:		

<i>products)</i>			
	TL:		
OTC Labeling Review (<i>for OTC products)</i>	Reviewer:		
	TL:		
Clinical Microbiology (<i>for antimicrobial products)</i>	Reviewer:		
	TL:		

Clinical Pharmacology	Reviewer:	Sayed Al-Habet	Y
	TL:	Myong-Jin Kim	Y
Biostatistics	Reviewer:	Kate Dwyer	Y
	TL:	Mahboob Sobhan	Y
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Laurie McLeod-Flynn	
	TL:	Alexander Jordan	
Statistics (carcinogenicity)	Reviewer:		
	TL:		
Immunogenicity (assay/assay validation) (<i>for BLAs/BLA efficacy supplements</i>)	Reviewer:		
	TL:		
Product Quality (CMC)	Reviewer:	Gene Holbert	Y
	TL:	Donna Christner	Y
Quality Microbiology (<i>for sterile products</i>)	Reviewer:		
	TL:		
CMC Labeling Review	Reviewer:		
	TL:		
Facility Review/Inspection	Reviewer:		
	TL:		
OSE/DMEPA (proprietary name)	Reviewer:	Manizheh Siahpoushan	Y
	TL:	Zachary Oleszczuk	
OSE/DRISK (REMS)	Reviewer:		
	TL:		
OC/OSI/DSC/PMSB (REMS)	Reviewer:		
	TL:		

Bioresearch Monitoring (OSI)	Reviewer:		
	TL:		
Controlled Substance Staff (CSS)	Reviewer:		
	TL:		
Other reviewers	Karen Riviere		Y
Other attendees	Joffe Hylton Maria Walsh Randazzo, Giuseppe Roy Blay		

FILING MEETING DISCUSSION:

<p>GENERAL</p> <ul style="list-style-type: none"> 505(b)(2) filing issues? <p>If yes, list issues:</p>	<input type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
<ul style="list-style-type: none"> Per reviewers, are all parts in English or English translation? <p>If no, explain:</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> Electronic Submission comments <p>List comments:</p>	<input checked="" type="checkbox"/> Not Applicable
<p>CLINICAL</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> Clinical study site(s) inspections(s) needed? <p>If no, explain:</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> Advisory Committee Meeting needed? <p>Comments:</p> <p><i>If no, for an NME NDA or original BLA, include the reason. For example:</i></p>	<input type="checkbox"/> YES Date if known: <input checked="" type="checkbox"/> NO <input type="checkbox"/> To be determined Reason:

<ul style="list-style-type: none"> ○ <i>this drug/biologic is not the first in its class</i> ○ <i>the clinical study design was acceptable</i> ○ <i>the application did not raise significant safety or efficacy issues</i> ○ <i>the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease</i> 	
<ul style="list-style-type: none"> • Abuse Liability/Potential <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> • If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<p>CLINICAL MICROBIOLOGY</p> <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>CLINICAL PHARMACOLOGY</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input checked="" type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> • Clinical pharmacology study site(s) inspections(s) needed? 	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
<p>BIOSTATISTICS</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>NONCLINICAL (PHARMACOLOGY/TOXICOLOGY)</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter

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<p>IMMUNOGENICITY (BLAs/BLA efficacy supplements only)</p> <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>PRODUCT QUALITY (CMC)</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p><u>Environmental Assessment</u></p> <ul style="list-style-type: none"> • Categorical exclusion for environmental assessment (EA) requested? <p style="padding-left: 40px;">If no, was a complete EA submitted?</p> <p style="padding-left: 40px;">If EA submitted, consulted to EA officer (OPS)?</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO
<p><u>Quality Microbiology (for sterile products)</u></p> <ul style="list-style-type: none"> • Was the Microbiology Team consulted for validation of sterilization? (NDAs/NDA supplements only) <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<p><u>Facility Inspection</u></p> <ul style="list-style-type: none"> • Establishment(s) ready for inspection? ▪ Establishment Evaluation Request (EER/TBP-EER) submitted to OMPQ? <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO
<p><u>Facility/Microbiology Review (BLAs only)</u></p> <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter

<u>CMC Labeling Review</u>	
Comments:	<input type="checkbox"/> Review issues for 74-day letter
REGULATORY PROJECT MANAGEMENT	
Signatory Authority: DRUP	
Date of Mid-Cycle Meeting (for NME NDAs/BLAs in “the Program” PDUFA V): November 8, 2012	
21st Century Review Milestones (see attached) (listing review milestones in this document is optional):	
Comments:	
REGULATORY CONCLUSIONS/DEFICIENCIES	
<input type="checkbox"/>	The application is unsuitable for filing. Explain why:
<input checked="" type="checkbox"/>	The application, on its face, appears to be suitable for filing. <u>Review Issues:</u> <input type="checkbox"/> No review issues have been identified for the 74-day letter. <input checked="" type="checkbox"/> Review issues have been identified for the 74-day letter. List (optional): <u>Review Classification:</u> <input checked="" type="checkbox"/> Standard Review <input type="checkbox"/> Priority Review
ACTIONS ITEMS	
<input type="checkbox"/>	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug).
<input type="checkbox"/>	If RTF, notify everybody who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER).
<input type="checkbox"/>	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
<input type="checkbox"/>	BLA/BLA supplements: If filed, send 60-day filing letter
<input type="checkbox"/>	If priority review:

	<ul style="list-style-type: none"> notify sponsor in writing by day 60 (For BLAs/BLA supplements: include in 60-day filing letter; For NDAs/NDA supplements: see CST for choices) notify OMPQ (so facility inspections can be scheduled earlier)
<input checked="" type="checkbox"/>	Send review issues/no review issues by day 74
<input checked="" type="checkbox"/>	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
<input type="checkbox"/>	Update the PDUFA V DARRTS page (for NME NDAs in “the Program”)
<input type="checkbox"/>	BLA/BLA supplements: Send the Product Information Sheet to the product reviewer and the Facility Information Sheet to the facility reviewer for completion. Ensure that the completed forms are forwarded to the CDER RMS-BLA Superuser for data entry into RMS-BLA one month prior to taking an action [These sheets may be found in the CST eRoom at: http://eroom.fda.gov/eRoom/CDER2/CDERStandardLettersCommittee/0_1685f]
<input type="checkbox"/>	Other

Appendix A (NDA and NDA Supplements only)

NOTE: The term "original application" or "original NDA" as used in this appendix denotes the NDA submitted. It does not refer to the reference drug product or "reference listed drug."

An original application is likely to be a 505(b)(2) application if:

- (1) it relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application,
- (2) it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval, or
- (3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

- (1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies),
- (2) No additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application, and.
- (3) All other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely

for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

- (1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2),
- (2) The applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement, or
- (3) The applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your OND ADRA or OND IO.

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

/s/

GEORGE A LYGHT
08/21/2012