

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

021876Orig1s000

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**

EXCLUSIVITY SUMMARY

NDA # 021876

SUPPL #

HFD #

Trade Name Diclegis

Generic Name doxylamine succinate and pyridoxine hydrochloride

Applicant Name Duchesnay Inc. – C/O OptumInsight Life Sciences Inc.

Approval Date, If Known April 8, 2013

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES NO

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3,SE4, SE5, SE6, SE7, SE8

505(b)(2)

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES NO

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

N/A

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

N/A

d) Did the applicant request exclusivity?

YES NO

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

Three years

e) Has pediatric exclusivity been granted for this Active Moiety?

YES NO

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES NO

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# See attachment

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)
IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical

investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES NO

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES NO

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES NO

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES NO

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES NO

If yes, explain:

- (c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Study DIC-301

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

- a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES NO

Investigation #2 YES NO

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

- b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES NO

Investigation #2 YES NO

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Study DIC-310

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1
IND # 72300 YES ! NO
! Explain:

Investigation #2
IND # YES ! NO
! Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1
!
!
YES ! NO
Explain: ! Explain:

Investigation #2
!
!
YES ! NO
Explain: ! Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES NO

If yes, explain:

=====

Name of person completing form: George Lyght, Pharm.D.
Title: Sr. Regulatory Health Project Manager
Date: April 8, 2013

Name of Office/Division Director signing form: Hylton V. Joffe, M.D., M.M.Sc.
Title: Director

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05; removed hidden data 8/22/12

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

HYLTON V JOFFE
04/09/2013

PEDIATRIC PAGE
(Complete for all filed original applications and efficacy supplements)

NDA/BLA#: 021876

Supplement Number: _____

NDA Supplement Type (e.g. SE5): _____

Division Name: Division of Reproductive and Urologic Products (DRUP)

PDUFA Goal Date: 04/8/13

Stamp Date: 6/8/2012

Proprietary Name: Diclegis

Established/Generic Name: 10 mg doxylamine plus pyridoxine 10 mg delayed release tablets

Dosage Form: tablets

Applicant/Sponsor: Duchesnay C/O OptumInsight Life Sciences

Indication(s) previously approved (please complete this question for supplements and Type 6 NDAs only):

(1) Treatment of nausea and vomiting of pregnancy in patients who do not respond to conservative management

(2) _____

(3) _____

(4) _____

Pediatric use for each pediatric subpopulation must be addressed for each indication covered by current application under review. A Pediatric Page must be completed for each indication.

Number of indications for this pending application(s): 1

(Attach a completed Pediatric Page for each indication in current application.)

Indication: _____

Q1: Is this application in response to a PREA PMR?

Yes Continue

No Please proceed to Question 2.

If Yes, NDA/BLA#: _____

Supplement #: _____

PMR #: _____

Does the division agree that this is a complete response to the PMR?

Yes. Please proceed to Section D.

No. Please proceed to Question 2 and complete the Pediatric Page, as applicable.

Q2: Does this application provide for (If yes, please check all categories that apply and proceed to the next question):

(a) NEW active ingredient(s) (includes new combination); indication(s); dosage form; dosing regimen; or route of administration?*

(b) No. PREA does not apply. **Skip to signature block.**

*** Note for CDER: SE5, SE6, and SE7 submissions may also trigger PREA.**

Q3: Does this indication have orphan designation?

Yes. PREA does not apply. **Skip to signature block.**

No. Please proceed to the next question.

Q4: Is there a full waiver for all pediatric age groups for this indication (check one)?

- Yes: (Complete Section A.)
- No: Please check all that apply:
- Partial Waiver for selected pediatric subpopulations (Complete Sections B)
 - Deferred for some or all pediatric subpopulations (Complete Sections C)
 - Completed for some or all pediatric subpopulations (Complete Sections D)
 - Appropriately Labeled for some or all pediatric subpopulations (Complete Sections E)
 - Extrapolation in One or More Pediatric Age Groups (Complete Section F)
- (Please note that Section F may be used alone or in addition to Sections C, D, and/or E.)

Section A: Fully Waived Studies (for all pediatric age groups)

Reason(s) for full waiver: **(check, and attach a brief justification for the reason(s) selected)**

- Necessary studies would be impossible or highly impracticable because:
- Disease/condition does not exist in children
 - Too few children with disease/condition to study
 - Other (e.g., patients geographically dispersed): _____
- Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients AND is not likely to be used in a substantial number of pediatric patients.
- Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- Justification attached.

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please complete another Pediatric Page for each indication. Otherwise, this Pediatric Page is complete and should be signed.

Section B: Partially Waived Studies (for selected pediatric subpopulations)

Check subpopulation(s) and reason for which studies are being partially waived (fill in applicable criteria below):

Note: If Neonate includes premature infants, list minimum and maximum age in "gestational age" (in weeks).

		Reason (see below for further detail):					
		minimum	maximum	Not feasible [#]	Not meaningful therapeutic benefit [*]	Ineffective or unsafe [†]	Formulation failed ^Δ
<input checked="" type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input checked="" type="checkbox"/>	Other	__ yr. <u>1</u> mo.	<u>11</u> yr. <u>11</u> mo.	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

Reason(s) for partial waiver (**check reason** corresponding to the category checked above, and **attach a brief justification**):

Not feasible:

- Necessary studies would be impossible or highly impracticable because:
- Disease/condition does not exist in children; Premenarchal girls in the age range 1 to 11 do not have a mature hypothalamic - pituitary - ovarian axis and do not ovulate. Therefore, these girls are not at risk for pregnancy.
- Too few children with disease/condition to study
- Other (e.g., patients geographically dispersed): _____

***** Not meaningful therapeutic benefit:

- Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in this/these pediatric subpopulation(s) AND is not likely to be used in a substantial number of pediatric patients in this/these pediatric subpopulation(s).

† Ineffective or unsafe:

- Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)
- Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)
- Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)

Δ Formulation failed:

- Applicant can demonstrate that reasonable attempts to produce a pediatric formulation necessary for this/these pediatric subpopulation(s) have failed. (*Note: A partial waiver on this ground may only cover the pediatric subpopulation(s) requiring that formulation. An applicant seeking a partial waiver on this ground must submit documentation detailing why a pediatric formulation cannot be developed. This submission will be posted on FDA's website if waiver is granted.*)

Justification attached.

For those pediatric subpopulations for which studies have not been waived, there must be (1) corresponding study plans that have been deferred (if so, proceed to Sections C and complete the PeRC Pediatric Plan

IF THERE ARE QUESTIONS, PLEASE CONTACT THE CDER PMHS VIA EMAIL (cderpmps@fda.hhs.gov) OR AT 301-796-0700.

Template); (2) submitted studies that have been completed (if so, proceed to Section D and complete the PeRC Pediatric Assessment form); (3) additional studies in other age groups that are not needed because the drug is appropriately labeled in one or more pediatric subpopulations (if so, proceed to Section E); and/or (4) additional studies in other age groups that are not needed because efficacy is being extrapolated (if so, proceed to Section F). Note that more than one of these options may apply for this indication to cover all of the pediatric subpopulations.

Section C: Deferred Studies (for selected pediatric subpopulations).

Check pediatric subpopulation(s) for which pediatric studies are being deferred (and fill in applicable reason below):

Deferrals (for each or all age groups):				Reason for Deferral			Applicant Certification †
Population		minimum	maximum	Ready for Approval in Adults	Need Additional Adult Safety or Efficacy Data	Other Appropriate Reason (specify below)*	Received
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input checked="" type="checkbox"/>	Other	12 yr. 0 mo.	17 yr. 11 mo.	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input checked="" type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	All Pediatric Populations	0 yr. 0 mo.	16 yr. 11 mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Date studies are due (mm/dd/yy): _____							

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

* Other Reason: The sponsor submitted the data to support the efficacy and safety of Diclegis in adults. To date, there appears to be no issues to preclude approval. The sponsor has submitted a pediatric plan for the deferred age group of 12 to 17 yrs.

† Note: Studies may only be deferred if an applicant submits a certification of grounds for deferring the studies, a description of the planned or ongoing studies, evidence that the studies are being conducted or will be conducted with due diligence and at the earliest possible time, and a timeline for the completion of the studies. If studies are deferred, on an annual basis applicant must submit information detailing the progress made in conducting the studies or, if no progress has been made, evidence and documentation that such studies will be conducted with due diligence and at the earliest possible time. This requirement should be communicated to the applicant in an appropriate manner (e.g., in an approval letter that specifies a required study as a post-marketing commitment.)

If all of the pediatric subpopulations have been covered through partial waivers and deferrals, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section D: Completed Studies (for some or all pediatric subpopulations).

Pediatric subpopulation(s) in which studies have been completed (check below):					
Population		minimum	maximum	PeRC Pediatric Assessment form attached?.	
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

Note: If there are no further pediatric subpopulations to cover based on partial waivers, deferrals and/or completed studies, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section E: Drug Appropriately Labeled (for some or all pediatric subpopulations):

Additional pediatric studies are not necessary in the following pediatric subpopulation(s) because product is appropriately labeled for the indication being reviewed:					
Population		minimum	maximum		
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.		
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.		
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.		
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.		
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.		
<input type="checkbox"/>	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.		

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

If all pediatric subpopulations have been covered based on partial waivers, deferrals, completed studies, and/or existing appropriate labeling, this Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section F: Extrapolation from Other Adult and/or Pediatric Studies (for deferred and/or completed studies)

Note: Pediatric efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations if (and only if) (1) the course of the disease/condition AND (2) the effects of the product are sufficiently similar between the reference population and the pediatric subpopulation for which information will be extrapolated. Extrapolation of efficacy from studies in adults and/or other children usually requires supplementation with other information obtained from the target pediatric subpopulation, such as

IF THERE ARE QUESTIONS, PLEASE CONTACT THE CDER PMHS VIA EMAIL (cderpmhs@fda.hhs.gov) OR AT 301-796-0700.

pharmacokinetic and safety studies. Under the statute, safety cannot be extrapolated.

Pediatric studies are not necessary in the following pediatric subpopulation(s) because efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations:					
Population		minimum	maximum	Extrapolated from:	
				Adult Studies?	Other Pediatric Studies?
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	<input type="checkbox"/>	<input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

Note: If extrapolating data from either adult or pediatric studies, a description of the scientific data supporting the extrapolation must be included in any pertinent reviews for the application.

If there are additional indications, please complete the attachment for each one of those indications. Otherwise, this Pediatric Page is complete and should be signed and entered into DFS or DARRTS as appropriate after clearance by PeRC.

This page was completed by:

{See appended electronic signature page}

George Lyght, Pharm.D.
Regulatory Project Manager

(Revised: 6/2008)

NOTE: If you have no other indications for this application, you may delete the attachments from this document.

Attachment A

(This attachment is to be completed for those applications with multiple indications only.)

Indication #2: _____**Q1:** Does this indication have orphan designation?

- Yes. PREA does not apply. **Skip to signature block.**
- No. Please proceed to the next question.

Q2: Is there a full waiver for all pediatric age groups for this indication (check one)?

- Yes: (Complete Section A.)
- No: Please check all that apply:
- Partial Waiver for selected pediatric subpopulations (Complete Sections B)
 - Deferred for some or all pediatric subpopulations (Complete Sections C)
 - Completed for some or all pediatric subpopulations (Complete Sections D)
 - Appropriately Labeled for some or all pediatric subpopulations (Complete Sections E)
 - Extrapolation in One or More Pediatric Age Groups (Complete Section F)
- (Please note that Section F may be used alone or in addition to Sections C, D, and/or E.)

Section A: Fully Waived Studies (for all pediatric age groups)Reason(s) for full waiver: (**check, and attach a brief justification for the reason(s) selected**)

- Necessary studies would be impossible or highly impracticable because:
- Disease/condition does not exist in children
 - Too few children with disease/condition to study
 - Other (e.g., patients geographically dispersed): _____
- Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients AND is not likely to be used in a substantial number of pediatric patients.
- Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- Justification attached.

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please complete another Pediatric Page for each indication. Otherwise, this Pediatric Page is complete and should be signed.

Section B: Partially Waived Studies (for selected pediatric subpopulations)

Check subpopulation(s) and reason for which studies are being partially waived (fill in applicable criteria below):

Note: If Neonate includes premature infants, list minimum and maximum age in "gestational age" (in weeks).

			Reason (see below for further detail):				
	minimum	maximum	Not feasible [#]	Not meaningful therapeutic benefit [*]	Ineffective or unsafe [†]	Formulation failed ^Δ	
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

Reason(s) for partial waiver (**check reason** corresponding to the category checked above, and **attach a brief justification**):

Not feasible:

- Necessary studies would be impossible or highly impracticable because:
 - Disease/condition does not exist in children
 - Too few children with disease/condition to study
 - Other (e.g., patients geographically dispersed): _____

* Not meaningful therapeutic benefit:

- Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in this/these pediatric subpopulation(s) AND is not likely to be used in a substantial number of pediatric patients in this/these pediatric subpopulation(s).

† Ineffective or unsafe:

- Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (Note: if studies are partially waived on this ground, this information must be included in the labeling.)
- Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (Note: if studies are partially waived on this ground, this information must be included in the labeling.)
- Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (Note: if studies are partially waived on this ground, this information must be included in the labeling.)

Δ Formulation failed:

- Applicant can demonstrate that reasonable attempts to produce a pediatric formulation necessary for this/these pediatric subpopulation(s) have failed. (Note: A partial waiver on this ground may only cover the pediatric subpopulation(s) requiring that formulation. An applicant seeking a partial waiver on this ground must submit documentation detailing why a pediatric formulation cannot be developed. This submission will be posted on FDA's website if waiver is granted.)
- Justification attached.

For those pediatric subpopulations for which studies have not been waived, there must be (1) corresponding study plans that have been deferred (if so, proceed to Section C and complete the PeRC Pediatric Plan Template); (2) submitted studies that have been completed (if so, proceed to Section D and complete the PeRC Pediatric Assessment form); (3) additional studies in other age groups that are not needed because the

IF THERE ARE QUESTIONS, PLEASE CONTACT THE CDER PMHS VIA EMAIL (cderpmhs@fda.hhs.gov) OR AT 301-796-0700.

drug is appropriately labeled in one or more pediatric subpopulations (if so, proceed to Section E); and/or (4) additional studies in other age groups that are not needed because efficacy is being extrapolated (if so, proceed to Section F).. Note that more than one of these options may apply for this indication to cover all of the pediatric subpopulations.

Section C: Deferred Studies (for some or all pediatric subpopulations).

Check pediatric subpopulation(s) for which pediatric studies are being deferred (and fill in applicable reason below):

Deferrals (for each or all age groups):				Reason for Deferral			Applicant Certification †
				Ready for Approval in Adults	Need Additional Adult Safety or Efficacy Data	Other Appropriate Reason (specify below)*	Received
Population	minimum	maximum					
<input type="checkbox"/> Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<input type="checkbox"/> All Pediatric Populations	0 yr. 0 mo.	16 yr. 11 mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Date studies are due (mm/dd/yy): _____							

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

* Other Reason: _____

† Note: Studies may only be deferred if an applicant submits a certification of grounds for deferring the studies, a description of the planned or ongoing studies, evidence that the studies are being conducted or will be conducted with due diligence and at the earliest possible time, and a timeline for the completion of the studies. If studies are deferred, on an annual basis applicant must submit information detailing the progress made in conducting the studies or, if no progress has been made, evidence and documentation that such studies will be conducted with due diligence and at the earliest possible time. This requirement should be communicated to the applicant in an appropriate manner (e.g., in an approval letter that specifies a required study as a post-marketing commitment.)

If all of the pediatric subpopulations have been covered through partial waivers and deferrals, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section D: Completed Studies (for some or all pediatric subpopulations).

Pediatric subpopulation(s) in which studies have been completed (check below):					
Population		minimum	maximum	PeRC Pediatric Assessment form attached?	
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

Note: If there are no further pediatric subpopulations to cover based on partial waivers, deferrals and/or completed studies, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section E: Drug Appropriately Labeled (for some or all pediatric subpopulations):

Additional pediatric studies are not necessary in the following pediatric subpopulation(s) because product is appropriately labeled for the indication being reviewed:			
Population		minimum	maximum
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

If all pediatric subpopulations have been covered based on partial waivers, deferrals, completed studies, and/or existing appropriate labeling, this Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section F: Extrapolation from Other Adult and/or Pediatric Studies (for deferred and/or completed studies)

Note: Pediatric efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations if (and only if) (1) the course of the disease/condition AND (2) the effects of the product are sufficiently similar between the reference population and the pediatric subpopulation for which information will be extrapolated. Extrapolation of efficacy from studies in adults and/or other children usually requires supplementation with other information obtained from the target pediatric subpopulation, such as pharmacokinetic and safety studies. Under the statute, safety cannot be extrapolated.

Pediatric studies are not necessary in the following pediatric subpopulation(s) because efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations:

Population	minimum	maximum	Extrapolated from:	
			Adult Studies?	Other Pediatric Studies?
<input type="checkbox"/> Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	<input type="checkbox"/>	<input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

Note: If extrapolating data from either adult or pediatric studies, a description of the scientific data supporting the extrapolation must be included in any pertinent reviews for the application.

If there are additional indications, please copy the fields above and complete pediatric information as directed. If there are no other indications, this Pediatric Page is complete and should be entered into DFS or DARRTS as appropriate after clearance by PeRC.

This page was completed by: George Lyght, Pharm.D. / SUBMITTED TO PERC Feb. 28, 2013 Prior to PERC's March 6, 2013 meeting.

{See appended electronic signature page}

Regulatory Project Manager

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE PEDIATRIC AND MATERNAL HEALTH STAFF at 301-796-0700

(Revised: 6/2008)

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
04/11/2013

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION ¹		
NDA # 021876 BLA #	NDA Supplement # BLA Supplement #	If NDA, Efficacy Supplement Type:
Proprietary Name: Diclegis Established/Proper Name: 10 mg doxylamine succinate plus 10 mg pyridoxine hydrochloride) Dosage Form: delayed release tablets		Applicant: Duchesnay Inc. Agent for Applicant (if applicable):
RPM: George Lyght, Pharm.D.		Division: Division of Reproductive & Urologic Products
<p><u>NDA and NDA Efficacy Supplements:</u></p> <p>NDA Application Type: <input type="checkbox"/> 505(b)(1) <input checked="" type="checkbox"/> 505(b)(2) Efficacy Supplement: <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)</p> <p>(A 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). Consult page 1 of the 505(b)(2) Assessment or the Appendix to this Action Package Checklist.)</p>	<p><u>505(b)(2) Original NDAs and 505(b)(2) NDA supplements:</u></p> <p>Listed drug(s) relied upon for approval (include NDA #(s) and drug name(s):</p> <p>Bendectin NDA 10508</p> <p>Provide a brief explanation of how this product is different from the listed drug.</p> <p>This application adds "in patients who do not respond to conservative management" to the indication, treatment of nausea and vomiting of pregnancy.</p> <p><input type="checkbox"/> This application does not rely upon a listed drug. <input checked="" type="checkbox"/> This application relies on literature. <input type="checkbox"/> This application relies on a final OTC monograph. <input checked="" type="checkbox"/> This application relies on (explain) Bendectin's nonclinical section</p> <p><u>For ALL (b)(2) applications, two months prior to EVERY action, review the information in the 505(b)(2) Assessment and submit the draft² to CDER OND IO for clearance. Finalize the 505(b)(2) Assessment at the time of the approval action.</u></p> <p><u>On the day of approval, check the Orange Book again for any new patents or pediatric exclusivity.</u></p> <p><input checked="" type="checkbox"/> No changes <input type="checkbox"/> Updated Date of check:</p> <p>If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.</p>	
❖ Actions		
<ul style="list-style-type: none"> • Proposed action • User Fee Goal Date is <u>April 8, 2013</u> • Previous actions (<i>specify type and date for each action taken</i>) 		<input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> CR <input type="checkbox"/> None

¹ The **Application Information** Section is (only) a checklist. The **Contents of Action Package** Section (beginning on page 5) lists the documents to be included in the Action Package.

² For resubmissions, (b)(2) applications must be cleared before the action, but it is not necessary to resubmit the draft 505(b)(2) Assessment to CDER OND IO unless the Assessment has been substantively revised (e.g., new listed drug, patent certification revised).

<p>❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain _____</p>	<input type="checkbox"/> Received
<p>❖ Application Characteristics ³</p>	
<p>Review priority: <input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority Chemical classification (new NDAs only):</p> <p><input type="checkbox"/> Fast Track <input type="checkbox"/> Rx-to-OTC full switch <input type="checkbox"/> Rolling Review <input type="checkbox"/> Rx-to-OTC partial switch <input type="checkbox"/> Orphan drug designation <input type="checkbox"/> Direct-to-OTC</p> <p>NDAs: Subpart H <input type="checkbox"/> Accelerated approval (21 CFR 314.510) <input type="checkbox"/> Restricted distribution (21 CFR 314.520) Subpart I <input type="checkbox"/> Approval based on animal studies</p> <p><input type="checkbox"/> Submitted in response to a PMR <input type="checkbox"/> Submitted in response to a PMC <input type="checkbox"/> Submitted in response to a Pediatric Written Request</p> <p>BLAs: Subpart E <input type="checkbox"/> Accelerated approval (21 CFR 601.41) <input type="checkbox"/> Restricted distribution (21 CFR 601.42) Subpart H <input type="checkbox"/> Approval based on animal studies</p> <p>REMS: <input type="checkbox"/> MedGuide <input type="checkbox"/> Communication Plan <input type="checkbox"/> ETASU <input type="checkbox"/> MedGuide w/o REMS <input type="checkbox"/> REMS not required</p> <p>Comments:</p>	
<p>❖ BLAs only: Ensure <i>RMS-BLA Product Information Sheet for TBP</i> and <i>RMS-BLA Facility Information Sheet for TBP</i> have been completed and forwarded to OPI/OBI/DRM (Vicky Carter)</p>	<input type="checkbox"/> Yes, dates
<p>❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 (<i>approvals only</i>)</p>	<input type="checkbox"/> Yes <input type="checkbox"/> No
<p>❖ Public communications (<i>approvals only</i>)</p>	
<ul style="list-style-type: none"> Office of Executive Programs (OEP) liaison has been notified of action 	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
<ul style="list-style-type: none"> Press Office notified of action (by OEP) 	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
<ul style="list-style-type: none"> Indicate what types (if any) of information dissemination are anticipated 	<input type="checkbox"/> None <input checked="" type="checkbox"/> HHS Press Release <input type="checkbox"/> FDA Talk Paper <input type="checkbox"/> CDER Q&As <input type="checkbox"/> Other

³ Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA. For example, if the application is a pending BLA supplement, then a new *RMS-BLA Product Information Sheet for TBP* must be completed.

❖ Exclusivity	
<ul style="list-style-type: none"> Is approval of this application blocked by any type of exclusivity? 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes
<ul style="list-style-type: none"> NDA and BLAs: Is there existing orphan drug exclusivity for the “same” drug or biologic for the proposed indication(s)? <i>Refer to 21 CFR 316.3(b)(13) for the definition of “same drug” for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.</i> 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If, yes, NDA/BLA # _____ and date exclusivity expires: _____
<ul style="list-style-type: none"> (b)(2) NDAs only: Is there remaining 5-year exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i> 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # _____ and date exclusivity expires: _____
<ul style="list-style-type: none"> (b)(2) NDAs only: Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i> 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # _____ and date exclusivity expires: _____
<ul style="list-style-type: none"> (b)(2) NDAs only: Is there remaining 6-month pediatric exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i> 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # _____ and date exclusivity expires: _____
<ul style="list-style-type: none"> NDAs only: Is this a single enantiomer that falls under the 10-year approval limitation of 505(u)? <i>(Note that, even if the 10-year approval limitation period has not expired, the application may be tentatively approved if it is otherwise ready for approval.)</i> 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # _____ and date 10-year limitation expires: _____
❖ Patent Information (NDAs only)	
<ul style="list-style-type: none"> Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought. If the drug is an old antibiotic, skip the Patent Certification questions. 	<input checked="" type="checkbox"/> Verified <input type="checkbox"/> Not applicable because drug is an old antibiotic.
<ul style="list-style-type: none"> Patent Certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent. 	21 CFR 314.50(i)(1)(i)(A) <input checked="" type="checkbox"/> Verified 21 CFR 314.50(i)(1) <input checked="" type="checkbox"/> (ii) <input type="checkbox"/> (iii)
<ul style="list-style-type: none"> [505(b)(2) applications] If the application includes a paragraph III certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval). 	<input checked="" type="checkbox"/> No paragraph III certification Date patent will expire _____
<ul style="list-style-type: none"> [505(b)(2) applications] For each paragraph IV certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). <i>(If the application does not include any paragraph IV certifications, mark “N/A” and skip to the next section below (Summary Reviews)).</i> 	<input checked="" type="checkbox"/> N/A (no paragraph IV certification) <input type="checkbox"/> Verified

- [505(b)(2) applications] For **each paragraph IV** certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation.

Answer the following questions for **each** paragraph IV certification:

- (1) Have 45 days passed since the patent owner's receipt of the applicant's notice of certification?

Yes No

(Note: The date that the patent owner received the applicant's notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e)).

If "Yes," skip to question (4) below. If "No," continue with question (2).

- (2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)?

Yes No

If "Yes," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip the rest of the patent questions.

If "No," continue with question (3).

- (3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant?

Yes No

(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)).

If "No," the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.

- (4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)?

Yes No

If "Yes," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).

If "No," continue with question (5).

<p>(5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the (b)(2) applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification?</p> <p>(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period).</p> <p><i>If "No," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).</i></p> <p><i>If "Yes," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the OND ADRA and attach a summary of the response.</i></p>	<p><input type="checkbox"/> Yes <input type="checkbox"/> No</p>
CONTENTS OF ACTION PACKAGE	
<p>❖ Copy of this Action Package Checklist⁴</p>	<p>Yes</p>
Officer/Employee List	
<p>❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list (<i>approvals only</i>)</p>	<p><input checked="" type="checkbox"/> Included</p>
<p>Documentation of consent/non-consent by officers/employees</p>	<p><input type="checkbox"/> Included</p>
Action Letters	
<p>❖ Copies of all action letters (<i>including approval letter with final labeling</i>)</p>	<p>Action(s) and date(s) April 8, 2013</p>
Labeling	
<p>❖ Package Insert (<i>write submission/communication date at upper right of first page of PI</i>)</p>	
<ul style="list-style-type: none"> • Most recent draft labeling. If it is division-proposed labeling, it should be in track-changes format. 	<p>Yes</p>
<ul style="list-style-type: none"> • Original applicant-proposed labeling 	<p>Yes</p>
<ul style="list-style-type: none"> • Example of class labeling, if applicable 	

⁴ Fill in blanks with dates of reviews, letters, etc.

<ul style="list-style-type: none"> ❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling (<i>write submission/communication date at upper right of first page of each piece</i>) 	<input type="checkbox"/> Medication Guide <input checked="" type="checkbox"/> Patient Package Insert <input type="checkbox"/> Instructions for Use <input type="checkbox"/> Device Labeling <input type="checkbox"/> None
<ul style="list-style-type: none"> • Most-recent draft labeling. If it is division-proposed labeling, it should be in track-changes format. 	Yes
<ul style="list-style-type: none"> • Original applicant-proposed labeling 	Yes
<ul style="list-style-type: none"> • Example of class labeling, if applicable 	
<ul style="list-style-type: none"> ❖ Labels (full color carton and immediate-container labels) (<i>write submission/communication date on upper right of first page of each submission</i>) 	
<ul style="list-style-type: none"> • Most-recent draft labeling 	04/07/13
<ul style="list-style-type: none"> ❖ Proprietary Name <ul style="list-style-type: none"> • Acceptability/non-acceptability letter(s) (<i>indicate date(s)</i>) • Review(s) (<i>indicate date(s)</i>) • Ensure that both the proprietary name(s), if any, and the generic name(s) are listed in the Application Product Names section of DARRTS, and that the proprietary/trade name is checked as the 'preferred' name. 	10/9/12 4/4/13
<ul style="list-style-type: none"> ❖ Labeling reviews (<i>indicate dates of reviews and meetings</i>) 	<input type="checkbox"/> RPM <input checked="" type="checkbox"/> DMEPA 10/18/12 & 3/22/13 <input checked="" type="checkbox"/> DMPP/PLT (DRISK) 3/28/13 <input checked="" type="checkbox"/> ODPD (DDMAC) 3/29/13 <input checked="" type="checkbox"/> SEALD 4/5/13 <input type="checkbox"/> CSS <input type="checkbox"/> Other reviews
Administrative / Regulatory Documents	
<ul style="list-style-type: none"> ❖ Administrative Reviews (<i>e.g., RPM Filing Review⁵/Memo of Filing Meeting</i>) (<i>indicate date of each review</i>) 	8/21/12
<ul style="list-style-type: none"> ❖ All NDA (b)(2) Actions: Date each action cleared by (b)(2) Clearance Cmte 	<input type="checkbox"/> Not a (b)(2) 4/4/13
<ul style="list-style-type: none"> ❖ NDA (b)(2) Approvals Only: 505(b)(2) Assessment (<i>indicate date</i>) 	<input type="checkbox"/> Not a (b)(2) 4/8/13
<ul style="list-style-type: none"> ❖ NDAs only: Exclusivity Summary (<i>signed by Division Director</i>) 	<input checked="" type="checkbox"/> Included
<ul style="list-style-type: none"> ❖ Application Integrity Policy (AIP) Status and Related Documents http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm 	
<ul style="list-style-type: none"> • Applicant is on the AIP 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
<ul style="list-style-type: none"> • This application is on the AIP <ul style="list-style-type: none"> ○ If yes, Center Director's Exception for Review memo (<i>indicate date</i>) ○ If yes, OC clearance for approval (<i>indicate date of clearance communication</i>) 	<input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Not an AP action
<ul style="list-style-type: none"> ❖ Pediatrics (<i>approvals only</i>) <ul style="list-style-type: none"> • Date reviewed by PeRC <u>3/6/13</u> If PeRC review not necessary, explain: _____ • Pediatric Page/Record (<i>approvals only, must be reviewed by PERC before finalized</i>) 	<input checked="" type="checkbox"/> Included
<ul style="list-style-type: none"> ❖ Debarment certification (original applications only): verified that qualifying language was not used in certification and that certifications from foreign applicants are cosigned by U.S. agent (<i>include certification</i>) 	<input checked="" type="checkbox"/> Verified, statement is acceptable

⁵ Filing reviews for scientific disciplines should be filed behind the respective discipline tab.

❖ Outgoing communications (<i>letters, including response to FD RR (do not include previous action letters in this tab), emails, faxes, telecons</i>)	Yes
❖ Internal memoranda, telecons, etc.	
❖ Minutes of Meetings	
• Regulatory Briefing (<i>indicate date of mtg</i>)	<input type="checkbox"/> No mtg
• If not the first review cycle, any end-of-review meeting (<i>indicate date of mtg</i>)	<input type="checkbox"/> N/A or no mtg
• Pre-NDA/BLA meeting (<i>indicate date of mtg</i>)	<input type="checkbox"/> No mtg 12/14/09
• EOP2 meeting (<i>indicate date of mtg</i>)	<input type="checkbox"/> No mtg
• Other milestone meetings (e.g., EOP2a, CMC pilots) (<i>indicate dates of mtgs</i>)	
❖ Advisory Committee Meeting(s)	<input checked="" type="checkbox"/> No AC meeting
• Date(s) of Meeting(s)	
• 48-hour alert or minutes, if available (<i>do not include transcript</i>)	
Decisional and Summary Memos	
❖ Office Director Decisional Memo (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
Division Director Summary Review (<i>indicate date for each review</i>)	<input type="checkbox"/> None 4/8/13
Cross-Discipline Team Leader Review (<i>indicate date for each review</i>)	<input type="checkbox"/> None 4/8/13
PMR/PMC Development Templates (<i>indicate total number</i>)	<input type="checkbox"/> None one
Clinical Information⁶	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) (<i>indicate date for each review</i>)	4/8/13
• Clinical review(s) (<i>indicate date for each review</i>)	3/13/13
• Social scientist review(s) (if OTC drug) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here <input type="checkbox"/> and include a review/memo explaining why not (<i>indicate date of review/memo</i>)	Clin Review page 21
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers (<i>indicate date of each review</i>)	<input checked="" type="checkbox"/> None
❖ Controlled Substance Staff review(s) and Scheduling Recommendation (<i>indicate date of each review</i>)	<input checked="" type="checkbox"/> Not applicable
❖ Risk Management	
• REMS Documents and Supporting Statement (<i>indicate date(s) of submission(s)</i>)	
• REMS Memo(s) and letter(s) (<i>indicate date(s)</i>)	
• Risk management review(s) and recommendations (including those by OSE and CSS) (<i>indicate date of each review and indicate location/date if incorporated into another review</i>)	<input checked="" type="checkbox"/> None
❖ OSI Clinical Inspection Review Summary(ies) (<i>include copies of OSI letters to investigators</i>)	<input type="checkbox"/> None requested 2/15/13

⁶ Filing reviews should be filed with the discipline reviews.

Clinical Microbiology <input type="checkbox"/> None	
❖ Clinical Microbiology Team Leader Review(s) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> None
Clinical Microbiology Review(s) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> None
Biostatistics <input type="checkbox"/> None	
❖ Statistical Division Director Review(s) <i>(indicate date for each review)</i>	<input type="checkbox"/> None
Statistical Team Leader Review(s) <i>(indicate date for each review)</i>	<input type="checkbox"/> None 3/11/13
Statistical Review(s) <i>(indicate date for each review)</i>	<input type="checkbox"/> None 3/9/13
Clinical Pharmacology <input type="checkbox"/> None	
❖ Clinical Pharmacology Division Director Review(s) <i>(indicate date for each review)</i>	<input type="checkbox"/> None 4/4/13
Clinical Pharmacology Team Leader Review(s) <i>(indicate date for each review)</i>	<input type="checkbox"/> None 3/4/13 & 4/5/13
Clinical Pharmacology review(s) <i>(indicate date for each review)</i>	<input type="checkbox"/> None 3/4/13 & 4/5/13
❖ DSI Clinical Pharmacology Inspection Review Summary <i>(include copies of OSI letters)</i>	<input type="checkbox"/> None
Nonclinical <input type="checkbox"/> None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> None
• Supervisory Review(s) <i>(indicate date for each review)</i>	<input type="checkbox"/> None 3/4/13/ & 4/5/13
• Pharm/tox review(s), including referenced IND reviews <i>(indicate date for each review)</i>	<input type="checkbox"/> None 3/4/13 & 4/5/13
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> None
❖ Statistical review(s) of carcinogenicity studies <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> No carc
❖ ECAC/CAC report/memo of meeting	<input checked="" type="checkbox"/> None Included in P/T review, page
❖ OSI Nonclinical Inspection Review Summary <i>(include copies of OSI letters)</i>	<input checked="" type="checkbox"/> None requested
Product Quality <input type="checkbox"/> None	
❖ Product Quality Discipline Reviews	
• ONDQA/OBP Division Director Review(s) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> None
• Branch Chief/Team Leader Review(s) <i>(indicate date for each review)</i>	<input type="checkbox"/> None 3/14/13 & 4/4/13
• Product quality review(s) including ONDQA biopharmaceutics reviews <i>(indicate date for each review)</i>	<input type="checkbox"/> None 3/14/13 & 4/4/13 ONDQA BioPhar- 3/4/13
❖ Microbiology Reviews <input type="checkbox"/> NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) <i>(indicate date of each review)</i> <input type="checkbox"/> BLAs: Sterility assurance, microbiology, facilities reviews (OMPQ/MAPCB/BMT) <i>(indicate date of each review)</i>	<input checked="" type="checkbox"/> Not needed
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer <i>(indicate date of each review)</i>	<input type="checkbox"/> None

❖ Environmental Assessment (check one) (original and supplemental applications)	
<input type="checkbox"/> Categorical Exclusion (<i>indicate review date</i>)(<i>all original applications and all efficacy supplements that could increase the patient population</i>)	Waiver requested
<input type="checkbox"/> Review & FONSI (<i>indicate date of review</i>)	
<input type="checkbox"/> Review & Environmental Impact Statement (<i>indicate date of each review</i>)	
❖ Facilities Review/Inspection	
<input type="checkbox"/> NDAs: Facilities inspections (include EER printout) (<i>date completed must be within 2 years of action date</i>) (<i>only original NDAs and supplements that include a new facility or a change that affects the manufacturing sites⁷</i>)	Date completed: 3/20/13 <input checked="" type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation <input type="checkbox"/> Not applicable
<input type="checkbox"/> BLAs: TB-EER (<i>date of most recent TB-EER must be within 30 days of action date</i>) (<i>original and supplemental BLAs</i>)	Date completed: <input type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation
❖ NDAs: Methods Validation (<i>check box only, do not include documents</i>)	<input type="checkbox"/> Completed <input type="checkbox"/> Requested <input checked="" type="checkbox"/> Not yet requested <input type="checkbox"/> Not needed (per review)

⁷ I.e., a new facility or a change in the facility, or a change in the manufacturing process in a way that impacts the Quality Management Systems of the facility.

Appendix to Action Package Checklist

An NDA or NDA supplemental 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) **Or** 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.
- (3) **Or** 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) **And** 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.
- (3) **And** 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) **Or** 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.
- (3) **Or** 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 ODE's ADRA.

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/s/

GEORGE A LYGHT
04/11/2013



NDA 021876

LABELING PMR/PMC DISCUSSION COMMENTS

Duchnesnay Inc.
Attention: John J.K. Killackey, Ph.D.
Director of Regulatory Affairs
131 Morristown Road
Basking Ridge, NJ 07920

Dear Dr. Killackey:

Please refer to your June 8, 2012, New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Diclegis (10 mg doxylamine succinate and 10 mg pyridoxine HCL) delayed release tablets.

We also refer to our August 21, 2012, letter in which we notified you of our target date of March 11, 2013, for communicating labeling changes and/or postmarketing requirements/commitments in accordance with the "PDUFA REAUTHORIZATION PERFORMANCE GOALS AND PROCEDURES – FISCAL YEARS 2008 THROUGH 2012."

On February 22 and March 7, 2013, we received your proposed labeling submissions to this application. We have the following comment:

We continue to request that you change the presentation of the proprietary name to appear in title case (i.e., Diclegis) on the container labels. We acknowledge that you have provided examples of labels with a presentation not in title case. Our position on this issue has evolved since these products have been approved. Title case lettering is easier to read because people can recognize the shape of the word and letters. When proprietary names are set in all capital letters, the shape of the word is lost because every letter is the same height.

We will be sending other proposed changes as we continue our review of the labeling.

If you have any questions, call George Lyght, Pharm.D., Sr. Regulatory Health Project Manager, at (301) 796-0948.

Sincerely,

{See appended electronic signature page}

Margaret Kober, R.Ph., M.P.A.
Chief, Project Management Staff
Division of Reproductive and Urologic Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

MARGARET M KOBER
03/11/2013
Chief, Project Management Staff



NDA 21876

INFORMATION REQUEST

Duchesnay, Inc.
c/o OptumInsight Life Sciences
Attention: John J.F. Killackey, Ph.D.
Director, Regulatory Affairs
131 Morristown Road
Basking Ridge, NJ 07920

Dear Dr. Killackey:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for (doxylamine succinate and pyridoxine hydrochloride) Tablets.

We are reviewing the Quality section of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

With reference to your response to our IR letter November 27, 2012, we have the following additional questions and comments.

- Regarding Item 8 concerning identity testing of Diclegis tablets, we remind you that you will need to submit an updated specification table and analytical method.
- Regarding item 10 concerning cracked tablets observed during stability studies, we note that your stability data tables contain a line for the number of cracked tablets. Do you intend to propose a limit for the number of defective tablets or is this item included for informational purposes only?
- Concerning the proposed expiry dating period, you have proposed a (b) (4) month expiration date based on stability data from supportive batches. We note that cracked tablets were observed in those batches during stability testing beginning at 18 months. In light of only 3 months of stability data on the proposed commercial product and the observed cracks in the film coat of the supportive batches appearing at 18 months, we recommend an 18 month expiration dating period and note that it may be extended by annual report as described in 21 CFR 314.70 (d) (2) (vi).

If you have any questions, call LT Kerri-Ann Jennings, Regulatory Project Manager, at (301) 796-2919.

Sincerely,

{See appended electronic signature page}

Moo-Jhong Rhee, Ph.D.
Chief, Branch IV
Division of New Drug Quality Assessment II
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

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/s/

MOO JHONG RHEE
01/07/2013
Chief, Branch IV



NDA 021876

INFORMATION REQUEST

Duchesnay Inc.
C/O OptumInsight Life Sciences
Attention: John J.K. Killackey, Ph.D.
Director of Regulatory Affairs
131 Morristown Road
Basking Ridge, NJ 07920

Dear Dr. Killackey:

Please refer to your New Drug Application (NDA) submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act, for 10 mg doxylamine succinate plus 10 mg pyridoxine hydrochloride delayed release tablets.

We also refer to your July 16 and August 3 and 13, 2012, submissions, containing container labels and the proposal for the proprietary name Diclegis.

We are reviewing the labeling sections of your submissions and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

A. General Comments for Container Label and Insert Labeling

Revise the statement (b) (4) (or variations of this statement) where it appears throughout the labeling 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. 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. 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. (b) (4) (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 “**WARNING: Swallow tablets whole. Do not crush, chew, or split the tablets.**” in a prominent fashion (i.e. bold letters) on the principal display panel of the outside front cover after removing the indication statement. As currently presented, this warning statement does not appear on the outside front cover of the container label.
6. Remove the (b) (4) color block that contains the (b) (4) and the (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 (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 (b) (4) from the inside back cover of the label after revisions.
9. Delete the statement (b) (4) 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 Diclegis?” as well as the insert labeling, and is not required to appear on the container label.

C. Insert Labeling

1. Resubmit labeling components using the conditionally acceptable proprietary name Diclegis.
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 [REDACTED] ^{(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. We also 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.
3. Remove the [REDACTED] ^{(b) (4)} that is repeated at the beginning of each page of the Full Prescribing Information. If your intent is to enhance product identification on subsequent pages of the insert labeling, you 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.
4. 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.
5. 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.

If you have any questions, call George Lyght, Pharm.D., Sr. Regulatory Health Project Manager, at (301) 796-0948.

Sincerely,

{See appended electronic signature page}

Hylton V. Joffe, M.D., M.M.Sc.
Director
Division of Reproductive and Urologic Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

HYLTON V JOFFE
12/19/2012



NDA 21876

INFORMATION REQUEST

Duchesnay, Inc.
c/o OptumInsight Life Sciences
Attention: John J.F. Killackey, Ph.D.
Director, Regulatory Affairs
131 Morristown Road
Basking Ridge, NJ 07920

Dear Dr. Killackey:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for (doxylamine succinate and pyridoxine hydrochloride) Tablets.

We are reviewing the Quality section of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

Pyridoxine HCl Drug Substance

There is no identity test for [REDACTED] (b) (4) There should be identity tests for both starting materials.

Submit a list of specified drug substance impurities, if any.

Forced degradation studies should be performed to demonstrate that method [REDACTED] (b) (4) is stability indicating.

There is no commitment to add at least one batch per year to the stability program (see ICH Q7A). Such a commitment should be added.

No information was submitted in section 3.2.S.6 Container Closure System. Correspondence referenced in section 2.3.S.6 of the Quality Overall Summary makes no reference to the drug substance container closure system. Submit information describing the container/closure for the drug substance and indicate its compliance with 21 CFR food contact regulations.

Doxylamine Succinate Drug Substance

The application references 21 CFR 178.1310 to support the use of (b)(4) for packaging the drug substance. That CFR paragraph does not exist. Submit a reference to the applicable food contact regulations.

Drug Product

There is no listing of the components/composition of (b)(4). Provide a listing of the components or a letter of authorization to the appropriate DMF if there is one. Note that your application contains a letter from the supplier (b)(4) dated July 22, 2008 which states “that this product has not been approved for pharmaceutical use.”

The test for identity appears to be HPLC Method (b)(4), which was developed for assay and content uniformity of the drug substances in Dialectin tablets. That method does not address identity of the drug substances. Acceptance Criteria for identity (“Positive”) are not sufficiently specific. Applicant should state specifically what constitutes a positive identity test. Note that HPLC retention times are not considered specific tests for identity [ICH Q6A 3.2.2 (a)].

(b)(4) were referenced in regard to forced degradation studies of the drug substances. Provide copies of those reports.

Comment on the observation that significant numbers of cracked tablets were found during stability studies at 24-36 months (batches 1119, 1120, 1121) but not at 48 months. Note that cracks in the film coating have the potential to affect the dissolution properties of the drug product.

If you have any questions, call LT Kerri-Ann Jennings, Regulatory Project Manager, at (301) 796-2919.

Sincerely,

{See appended electronic signature page}

Moo-Jhong Rhee, Ph.D.
Chief, Branch IV
Division of New Drug Quality Assessment II
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

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/s/

MOO JHONG RHEE
11/27/2012
Chief, Branch IV

From: [Killackey, John](#)
To: [Jennings, Kerri-Ann](#)
Subject: RE: NDA 21876 (doxylamine succinate and pyridoxine hydrochloride)
Date: Tuesday, November 27, 2012 3:50:17 PM

Dear Kerri-Ann:

Message and attachment received. Thank you.

We will get back to you soon.

Kind regards,
John

John JF Killackey, Ph.D.
Director, Regulatory Affairs, USA
Strategic Regulatory and Safety
Life Sciences

OptumInsight

T +1 905-690-5782
F +1 905-689-1465

john.killackey@optum.com
www.optuminsight.com

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From: Jennings, Kerri-Ann [mailto:Kerri-Ann.Jennings@fda.hhs.gov]
Sent: Tuesday, November 27, 2012 3:45 PM
To: Killackey, John
Subject: NDA 21876 (doxylamine succinate and pyridoxine hydrochloride)

Good afternoon Dr. Killackey,

Per our telephone conversation, please find attached a courtesy copy of the Agency's Information Request for the above NDA. The original was mailed to the company today, November 27, 2012. Please respond within 1 week.

Confirm receipt of this email.

Thank you.

Kind regards,

Kerri-Ann E. Jennings, MS, BSN, RN

LT, United States Public Health Service
Regulatory Health Project Manager
FDA/CDER/OPS/ONDQA
Division of New Drug Quality Assessment II
Phone (301) 796-2919

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KERRI-ANN JENNINGS
11/27/2012



NDA 021876

**PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE**

Duchesnay, Inc.
c/o OptumInsight Life Sciences
131 Morristown Road
Basking Ridge, NJ 07920

ATTENTION: John J.F. Killackey, Ph.D.
Director, US Regulatory Affairs

Dear Dr. Killackey:

Please refer to your New Drug Application (NDA) dated December 17, 2004, received December 20, 2004, submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Doxylamine and Pyridoxine Delayed-release Tablets, 10 mg/10 mg.

We also refer to:

- Your class 2 resubmission dated and received June 8, 2012; and
- Your proprietary name submission dated and received your August 3, 2012, requesting review of your proposed proprietary name "Diclegis."

We have completed our review of the proposed proprietary name, Diclegis and have concluded that it is acceptable.

The proposed proprietary name, Diclegis, will be re-reviewed 90 days prior to the approval of the NDA. If we find the name unacceptable following the re-review, we will notify you. Additionally, if **any** of the proposed product characteristics as stated in your August 3, 2012, submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Marcus Cato, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-3903. For any other information regarding this application contact the Office of New Drugs (OND) Regulatory Project Manager, George Lyght at (301) 796-0948.

Sincerely,

{See appended electronic signature page}

Carol Holquist, RPh

Director

Division of Medication Error Prevention and Analysis

Office of Medication Error Prevention and Risk Management

Office of Surveillance and Epidemiology

Center for Drug Evaluation and Research

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/s/

CAROL A HOLQUIST
10/09/2012



NDA 021876

**PROPRIETARY NAME REQUEST
WITHDRAWN**

Duchesnay, Inc.
c/o OptumInsight Life Sciences Inc.
131 Morristown Road
Basking Ridge, NJ 07920

ATTENTION: John J.F. Killackey, Ph.D.
Director, US Regulatory Affairs

Dear Dr. Killackey:

Please refer to your New Drug Application (NDA) dated December 17, 2004, received December 20, 2004, submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Doxylamine and Pyridoxine Delayed-release Tablets, 10 mg/10 mg.

We also refer to:

- Your correspondence, dated and received June 28, 2012, requesting review of the proposed proprietary name (b) (4) for this drug product;
- Our teleconference of July 31, 2012, informing you of (b) (4) issues related to the proposed proprietary name, (b) (4) and
- Your correspondence dated and received on August 1, 2012, notifying us that you are withdrawing your June 28, 2012, request for review of your proposed proprietary.

This proposed proprietary name request is considered withdrawn as of August 1, 2012.

Finally, we acknowledge your request for review of an alternate proposed proprietary name, Diclegis, in your correspondence dated and received August 3, 2012.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, call Marcus Cato, Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-3903. For any other information regarding this application, contact the Office of New Drugs (OND) Regulatory Project Manager, George Lyght at 301-796-0948.

Sincerely,

{See appended electronic signature page}

Carol Holquist, RPh
Director
Division of Medication Error Prevention and Analysis
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

CAROL A HOLQUIST
10/05/2012



NDA 021876

**PROPRIETARY NAME REQUEST
WITHDRAWN**

Duchesnay, Inc.
c/o OptumInsight Life Sciences Inc.
131 Morristown Road
Basking Ridge, NJ 07920

ATTENTION: John J.F. Killackey, Ph.D.
Director, US Regulatory Affairs

Dear Dr. Killackey:

Please refer to your New Drug Application (NDA) dated December 17, 2004, received December 20, 2004, submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Doxylamine and Pyridoxine Delayed-release Tablets, 10 mg/10 mg.

We note that the Division of Reproductive and Urologic Drug Products refused to file this NDA on June 16, 2005.

Please also refer to:

- your resubmission of this NDA on June 8, 2012, and to your correspondence, dated and received June 11, 2012, requesting review of the proposed proprietary name (b) (4) for this drug product.
- Our teleconference of June 25, 2012, informing you of (b) (4) issues related to the proposed proprietary name, (b) (4)
- your correspondence dated and received on June 26, 2012 notifying us that you are withdrawing your June 11, 2012 request for a review of the proposed proprietary name (b) (4)

This proposed proprietary name request is considered withdrawn as of June 26, 2012.

Finally, we acknowledge your new request for review of a proposed proprietary name in your correspondence dated and received June 28, 2012.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, call Maria Wasilik, Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-0567. For any other information regarding this application, contact the Office of New Drugs (OND) Regulatory Project Manager, George Lyght at 301-796-0948.

Sincerely,

{See appended electronic signature page}

Carol Holquist, RPh
Director
Division of Medication Error Prevention and Analysis
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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

/s/

CAROL A HOLQUIST
07/23/2012



IND 072300

MEETING MINUTES

Duchesnay Inc.
c/o Premier Research Group
Attention: Susan Cusack, Director, Regulatory Affairs
755 Business Center Drive
Horsham, PA 19044

Dear Ms. Cusack:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for [REDACTED] ^{(b) (4)} (doxylamine succinate, pyridoxine hydrochloride) 10 mg / 10 mg Delayed Release Tablets.

We also refer to the meeting between representatives of your firm and the FDA on December 14, 2009. The purpose of the Pre-NDA meeting was:

- To obtain clarification and guidance on the CMC, labeling, and Integrated Summaries of Safety and Efficacy
- To receive feedback regarding fast track status
- To obtain concurrence regarding pediatric development plans

A copy of the official minutes of the meeting is attached for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call George Lyght, R.Ph., at (301) 796-0948.

Sincerely,

{See appended electronic signature page}

Sheller R. Slaughter, M.D., Ph.D.
Clinical Team Leader
Division of Reproductive and Urologic Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure

MEMORANDUM OF MEETING MINUTES

Meeting Type: B
Meeting Category: Pre-NDA

Meeting Date and Time: December 14, 2009 at 1:00 PM
Meeting Location: White Oak Building 22, Conference Room 1311

Application Number: IND 072300
Product Name: (b) (4) (doxylamine succinate, pyridoxine hydrochloride) 10 mg / 10 mg Delayed Release Tablets

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

Sponsor/Applicant Name: Duchesnay Inc., c/o Premier Research Group

Meeting Chair: Shelley R. Slaughter, M.D., Ph.D
Meeting Recorder: George Lyght, R.Ph.

FDA ATTENDEES

Scott Monroe, M.D., Director, Division of Reproductive and Urologic Products (DRUP)
Shelley R. Slaughter, M.D., Ph.D., Clinical Team Leader, DRUP
Barbara Wesley, M.D., Clinical Reviewer, DRUP
Doanh Tran, Ph.D., Clinical Pharmacology Reviewer, Office of Clinical Pharmacology (OCP) @ DRUP
Jefrey Bray, Ph.D., Pharmacologist Reviewer, DRUP
Donna Christner, Ph.D., Pharmaceutical Assessment Lead, Office of New Drug Quality Assessment (ONDQA) @ DRUP
Puttagunta, Rao, Ph.D., Chemistry Reviewer, ONDQA @ DRUP
Margaret M. Kober, R.Ph., M.P.A., Chief, Project Management Staff, DRUP
George Lyght, R.Ph., Sr. Regulatory Health Project Manager, DRUP

SPONSOR ATTENDEES

Duchesnay Inc.

Eric Gervais, Executive Vice-President
Liubov Gargaun, M.D., Medical Advisor
Michael Gallo, Director, Regulatory Affairs and Research
Frank Sasinowski, M.S., M.P.H., J.D., Hyman, Phelps & McNamara, P.C.
Gideon Koren, M.D., F.R.C.P.C., Co-Principal Investigator, Director of the Motherisk Program, Professor, Ivey Chair, and NIH Review Panel Chair

(b) (4)

BACKGROUND

The combination of pyridoxine hydrochloride 10 mg and doxylamine succinate 10 mg was marketed as Bendectin® in the United States until 1983 and is currently available in Canada as Diclectin® for the indication of ‘nausea and vomiting of pregnancy.’

The FDA received an NDA application on April 18, 2005, for NDA (021876) (b) (4). On June 16, 2005, the FDA refused to file the application citing the following reasons:

- From a clinical pharmacology perspective, the 505(b)(2) application is not fileable because it does not contain information necessary to establish a link between the proposed formulation of (b) (4) and the Reference Listed Drug (RLD), Bendectin. In the absence of adequate information to address this deficiency, reliance upon our finding of safety and efficacy for the RLD is not sufficient to support approval of (b) (4).
- From a clinical perspective, the 505(b)(2) application is not fileable because the application is seeking an indication for a use not previously approved for the RLD. For example, the proposed indication of (b) (4)

(b) (4) is not supported by substantive data on safety and efficacy.

The Sponsor received comments on their Phase 3 Study DIC-301 (A Double Blind, Multicenter, Randomized, Placebo-Controlled Trial of The Efficacy of Diclectin® For Nausea And Vomiting Of Pregnancy) via a Special Protocol Assessment and subsequent comments on protocol revisions.

DISCUSSION

Preliminary responses to the meeting questions were provided to the Sponsor on December 11, 2009. Additional discussion at the meeting is also presented below.

Chemistry

1. Pyridoxine hydrochloride, an active pharmaceutical ingredient in our drug product, is generally recognized as a dietary supplement component. Duchesnay Inc. proposes to include the following CMC information in the submission for pyridoxine hydrochloride:
 - Name and address of manufacture
 - (b) (4)
 - Confirmation of elucidation of structure
 - Specifications as per USP including impurities with any non-compendial methods and validation
 - Batch analyses for relevant clinical lots
 - Container closure
 - Stability summary

Would this level of CMC information for pyridoxine hydrochloride be considered acceptable to support an NDA?

FDA Response:

Although pyridoxine HCl is marketed as a dietary supplement in the US, it will be reviewed as an Active Pharmaceutical Ingredient (API) in your dosage form and will require more detailed information than that required for a dietary supplement. The proposed CMC information for pyridoxine HCl appears to be adequate, with the following additions:

- *A stability summary is not sufficient.
Submit stability data on at least 3 primary batches as recommended in ICH Q1 (R2).*
- (b) (4)
Complete manufacturing information should be provided, both in a narrative format and in a flow chart. This should also include in-process controls.
- *Refer to the International Conference on Harmonization (ICH): Guidance for Industry: M4Q: The CTD- Quality (<http://www.fda.gov/RegulatoryInformation/Guidances/ucm129901.htm>) for information on how the CMC section of your application should be organized.*
- *Complete drug substance information can be provided either in the application or in a DMF with the appropriate Letter of Authorization provided. If information is provided in a DMF, we request that the following information be provided in the NDA for ease of review: General information, physico-chemical properties, and Specifications. Please submit a Certificate of Analysis of the drug substance.*

- *In addition, for the NDA submission, provide a comprehensive table/list of all facilities involved in production of the drug substance and drug product with full street address of the actual manufacturing and/or testing site (not the corporate office), contact information of an individual at the site, detailed responsibilities of that facility and a date of when the facility was last inspected by FDA. This comprehensive table should be attached to the 356h. Full information should still be provided in the appropriate sections of Modules 2 and 3. Due to a recent software update, inspections cannot be requested unless all the above information is provided. If this information is not provided when the NDA is submitted, it will delay inspection requests and may adversely affect the outcome of a first cycle review decision.*

Meeting Discussion: The Sponsor stated that the drug substance information on pyridoxine hydrochloride is provided in a [REDACTED] ^{(b) (4)}, but that the manufacturer currently does not have a US DMF. The Division advised the Sponsor that a US DMF would be necessary and that it should be submitted as soon as possible so that the information would be available for review when the NDA was submitted. Because the quality of the information is not know, the Sponsor requested that the information be reviewed early in the review cycle to allow adequate time to address any deficiencies with the manufacturer/DMF holder. The Division stated that efforts would be made to expedite the review. Information on the process to submit Drug Master Files can be found at the following website:
<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFilesDMFs/default.htm>

Clinical

Duchesnay Inc. is aware that pregnancy and labeling revisions are being proposed in the United States which includes the elimination of the current pregnancy risk category system. We intend on following the current labeling regulations until a Final Rule is published with new regulations for the format and content of pregnancy and lactation labeling.

1. Does the Division agree with the inclusion of a pregnancy risk category for (b) (4)?

FDA Response:

Yes.

2. Is a prescription drug product specifically labeled and indicated for use in pregnancy considered to be category A? We have provided the online monographs for doxylamine and pyridoxine from the authoritative textbook *Drugs in Pregnancy and Lactation* by Briggs. (Appendix A). It provides a safety summary on the combination of doxylamine and pyridoxine specifically naming (b) (4) and a pregnancy risk factor or category A.

FDA Response:

No, the designation of the pregnancy category will depend on the information available. If the information submitted in the NDA is consistent with the information in the literature, the category is likely to remain the same.

3. The historical data or studies on Bendectin may be impossible to integrate or analysis with the more current (b) (4) data. Duchesnay Inc. proposes to provide a summary on all published and unpublished safety data or information known for Bendectin and (b) (4) in place of an ISS. Considering the nature of this NDA 505(b)(2) submission does the Division agree that an ISS is not required for this NDA? We have included a summary of the safety data from the literature (published and unpublished) in abstract form as Appendix B.

FDA Response:

Yes. We concur that with your proposal to provide summaries on all published and unpublished safety data or information known for Bendectin and (b) (4), an ISS is not necessary. You should, of course, include a separate summary of safety for your primary clinical study for (b) (4)

4. Duchesnay Inc. proposes to provide the pivotal (b) (4) efficacy trial approved through the Investigational New Drug Application (IND 72,300) and a summary of the historical data or studies on the efficacy of Bendectin and (b) (4) in place of an ISE. Again, due to the nature of this NDA 505(b)(2) submission does the Division agree that an ISE is not required for this NDA? We have included a summary of the efficacy data from the literature (published and unpublished) in abstract form as Appendix C. The NDA will include the DIC-301 study report as the primary proof of efficacy.

FDA Response:

Yes. We concur that, as the efficacy is primarily supported by a single clinical trial, an ISE is not necessary.

5. (b) (4) is intended to (b) (4) As pre-adolescent girls do not become pregnant, Duchesnay Inc. is requesting a waiver from pediatric development in children less than 12 years of age. Duchesnay Inc. plans to conduct a study in post-adolescent girls between the ages of 12 and (b) (4) after the NDA is approved and therefore is requesting a deferral for pediatric development in this age group. We will submit the pediatric development plan with our NDA. Does the Division agree that a pediatric waiver in children under 12 years of age and a deferral for children between the ages of 12 and (b) (4) is appropriate?

FDA Response:

Yes.

Regulatory

1. Duchesnay Inc. intends to submit a 505(b)(2) application with Bendectin (doxylamine succinate, pyridoxine hydrochloride) as the reference listed drug. Bendectin was voluntarily removed from the US market in 1983 and in February 2009, approval of NDA 10-598 for Bendectin was withdrawn at the request of Sanofi-Aventis (included as **Appendix D**). Does this have any impact on our plan to submit a 505(b)(2) application?

FDA Response:

No.

2. We initially requested Fast-Track status on May 21, 2007. No action was taken on this request. Recently it came to our attention that according to the “Guidance for Industry Fast Track Drug Development Programs —Designation, Development, and Application Review,” the decision for Fast Track designation should be made within 60 days of the FDA’s receipt of the Fast Track request. Furthermore the request for Fast Track status must occur no later than the pre-NDA meeting. We resubmitted our request on May 13, 2009. We still have not received a decision. We have also included this request in this meeting package as **Appendix E**. Duchesnay believes that (b) (4) qualifies for Fast Track status because it is a serious illness and represents an unmet medical need. (b) (4) if approved will be indicated for the treatment of Nausea and Vomiting of Pregnancy when conservative

measures have failed. The severity and impact of Nausea and Vomiting of Pregnancy has been well documented in the peer-reviewed medical literature and while it is relatively short-lived and self-limiting, if it is not controlled it may become more difficult to treat and result in serious complications. Currently in the United States there are not any approved drugs indicated for the treatment of Nausea and Vomiting of Pregnancy. Therefore, as Fast Track status must be determined no later than the pre-NDA meeting, does the Division agree that (b) (4) qualifies for Fast Track status?

FDA Response:

Yes, (b) (4) qualifies for Fast Track status. However, you should not conclude that the granting of Fast Track status automatically assures that your product will receive a Priority review.

Meeting Discussion: The Sponsor indicated that they were not planning on submitting units for rolling review.

3. Duchesnay originally submitted an NDA for (b) (4) on April 18, 2005 (NDA 21-876) and it was refused for filing. Is this the NDA number that we should use for the resubmission or will a new number be assigned?

FDA Response:

The same number should be used.

Additional Clinical Pharmacology comments:

Confirm that pharmacokinetic studies 70381 and 70294 and Phase 3 study DIC-301 administered the to-be-marketed formulation.

1. The NDA should address ADME (absorption, distribution, metabolism, and excretion) properties of (b) (4). Effect of intrinsic factors (e.g., renal impairment, hepatic impairment) and potential for drug interactions should also be addressed in the NDA. The information may be obtained from literature reports. Copies of literature references should be included in the NDA.
2. Provide in the NDA the following:
 - A table listing all clinical studies and the associated (b) (4) formulation that was administered.
 - Bioanalytical reports and method validation reports for all clinical studies where pharmacokinetic assessments were performed.
 - Raw data and calculated pharmacokinetic parameters for studies 70381, 70294, and DIC-301 in electronic format. The files should be in SAS Transport format (.xpt).

3. Based on discussions at the meeting on 4/17/2007, the Division acknowledges that the Sponsor does not plan to use the pharmacokinetic data from studies 02163 (relative bioavailability versus solution) and 02191 (food effect) to support the NDA. The NDA should include a discussion of the rationale for not relying on the results from these studies. For completeness, study reports for studies 02163 and 02191 should be included in the NDA.

Meeting Discussion:

- *The Sponsor confirmed that pharmacokinetic (PK) studies 70381 and 70294 and Phase 3 study DIC-301 administered the to-be-marketed formulation. The Sponsor also stated that these 3 studies represent the primary information on pharmacokinetics and safety and efficacy to support the NDA.*
- *The Sponsor stated that they have concerns with the reliability of the PK data from studies 02163 and 02191. The Division requested and the Sponsor agreed to submit full study reports for studies 02163 and 02191, including pharmacokinetic results. The Sponsor will also submit in the NDA the independent audit reports of the bioanalysis of these studies.*

Additional Regulatory Comments:

- The Sponsor was advised to contact the User Fee Program staff regarding the small business exemption
- The Sponsor was informed that the proprietary name review process is now being managed by the staff in the Division of Medication Errors and Technical Support. The Division indicated that [REDACTED] (b) (4).
- The Sponsor was advised that the approved indication should appear in promotional materials in its entirety, including any limitations

Post-Meeting Comments:

The DMF and letter of authorization may be submitted to the NDA before the next review cycle begins.

ACTION ITEMS

Action Item/Description	Owner	Due Date
Official meeting minutes to be conveyed in 30 days.	FDA	January 13, 2010

ATTACHMENTS AND HANDOUTS

There were no attachments or handouts for the meeting minutes.

Application
Type/Number

Submission
Type/Number

Submitter Name

Product Name

IND-72300

GI-1

DUCHESNAY INC

 (b) (4)

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

/s/

SHELLEY R SLAUGHTER
01/13/2010