CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

209661Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

EXCLUSIVITY SUMMARY

NDA # 209661 SUPPL # HFD # 580

Trade Name Bonjesta

Generic Name doxylamine succinate and pyridoxine hydrochloride

Applicant Name Duchesnay Inc.
c/o Mapi USA, Inc

Approval Date, If Known November 7, 2016

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)

b) 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.

The Application included a food-effect study and single-dose and multiple-dose comparative bioavailability studies. The key endpoints for all three studies were pharmacokinetic endpoints.

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

c) Did the applicant request exclusivity?

YES ☐ NO ☒

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

d) 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:

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:

N/A

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"):

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 # 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: November 7, 2016

Name of 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

Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations

Home (default.cfm?resetfields=1) | Modify Search (default.cfm?panel=0&drugname=doxylamine succinate)

Search Results for Proprietary Name, Active Ingredient or Application Number: *doxylamine succinate*

12 records returned

Download Data (download.cfm?discontinued=1&drugname=doxylamine succinate&type=6)

(•) Show ( ) Hide Discontinued Products in Results

Display 50 records per page

Search for text in the table:

Mkt. Status	Active Ingredient	Proprietary Name	Appl No	Dosage Form	Route	Strength	TE Code (http://www.fda.gov/Drugs/DevelopmentApprovalProcess/ucm079068.htm#tecode)	R
RX	DOXYLAMINE SUCCINATE; PYRIDOXINE HYDROCHLORIDE	DICLEGIS	N021876 (results_product.cfm?Appl_Type=N&Appl_No=021876)	TABLET, DELAYED RELEASE	ORAL	10MG; 10MG	AB	
RX	DOXYLAMINE SUCCINATE; PYRIDOXINE HYDROCHLORIDE	DOXYLAMINE SUCCINATE AND PYRIDOXINE HYDROCHLORIDE	A205811 (results_product.cfm?Appl_Type=A&Appl_No=205811)	TABLET, DELAYED RELEASE	ORAL	10MG; 10MG	AB	
OTC	DOXYLAMINE SUCCINATE	DOXYLAMINE SUCCINATE	A040167 (results_product.cfm?Appl_Type=A&Appl_No=040167)	TABLET	ORAL	25MG		
OTC	DOXYLAMINE SUCCINATE	DOXYLAMINE SUCCINATE	A040564 (results_product.cfm?Appl_Type=A&Appl_No=040564)	TABLET	ORAL	25MG		
OTC	DOXYLAMINE SUCCINATE	UNISOM	N018066 (results_product.cfm?Appl_Type=N&Appl_No=018066)	TABLET	ORAL	25MG		
DISCN	DOXYLAMINE SUCCINATE	UNISOM	N019440 (results_product.cfm?Appl_Type=N&Appl_No=019440)	CAPSULE	ORAL	25MG		
DISCN	DOXYLAMINE SUCCINATE	DECAPRYN	N006412 (results_product.cfm?Appl_Type=N&Appl_No=006412)	TABLET	ORAL	12.5MG		
DISCN	DOXYLAMINE SUCCINATE	DECAPRYN	N006412 (results_product.cfm?Appl_Type=N&Appl_No=006412)	TABLET	ORAL	25MG		
DISCN	DOXYLAMINE SUCCINATE	DOXY-SLEEP-AID	A070156 (results_product.cfm?Appl_Type=A&Appl_No=070156)	TABLET	ORAL	25MG		
DISCN	DOXYLAMINE SUCCINATE	DOXYLAMINE SUCCINATE	A088900 (results_product.cfm?Appl_Type=A&Appl_No=088900)	TABLET	ORAL	25MG		
DISCN	DOXYLAMINE SUCCINATE	DOXYLAMINE SUCCINATE	A088603 (results_product.cfm?Appl_Type=A&Appl_No=088603)	TABLET	ORAL	25MG		
DISCN	DOXYLAMINE SUCCINATE; PYRIDOXINE HYDROCHLORIDE	BENDECTIN	N010598 (results_product.cfm?Appl_Type=N&Appl_No=010598)	TABLET, EXTENDED RELEASE	ORAL	10MG; 10MG **Federal Register determination that product was not discontinued or withdrawn for safety or efficacy reasons**		
Mkt. Status	Active Ingredient	Proprietary Name	Appl No	Dosage Form	Route	Strength	TE Code (http://www.fda.gov/Drugs/DevelopmentApprovalProcess/ucm079068.htm#tecode)	R

Showing 1 to 12 of 12 entries

Previous 1 Next

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
11/08/2016

HYLTON V JOFFE
11/08/2016

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION[1]

NDA # 209661 BLA #	NDA Supplement # BLA Supplement #	If NDA, Efficacy Supplement Type: *(an action package is not required for SE8 or SE9 supplements)*
Proprietary Name: BONJESTA Established/Proper Name: doxylamine succinate and pyridoxine hydrochloride Dosage Form: extended-release tablets		Applicant: Duchesnay Inc. Agent for Applicant (if applicable): c/o Mapi USA, Inc.
RPM: George Lyght, Pharm.D		Division: Division of Bone, Reproductive, and Urologic Products

NDA Application Type: ☐ 505(b)(1) ☒ 505(b)(2)
Efficacy Supplement: ☐ 505(b)(1) ☐ 505(b)(2)

BLA Application Type: ☐ 351(k) ☐ 351(a)
Efficacy Supplement: ☐ 351(k) ☐ 351(a)

For ALL 505(b)(2) applications, two months prior to EVERY action:

- **Review the information in the 505(b)(2) Assessment and submit the draft[2] to CDER OND IO for clearance.**
- **Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity)**

☒ No changes
☐ New patent/exclusivity *(notify CDER OND IO)*
Date of check:

Note: 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.

❖ Actions	
• Proposed action • User Fee Goal Date is November 7, 2016	☒ AP ☐ TA ☐ CR
• Previous actions *(specify type and date for each action taken)*	☐ None
❖ 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 _____	☐ Received
❖ Application Characteristics[3]	

[1] The **Application Information** Section is (only) a checklist. The **Contents of Action Package** Section (beginning on page 2) lists the documents to be included in the Action Package.
[2] For resubmissions, 505(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).
[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.

Review priority: ☒ Standard ☐ Priority
Chemical classification (new NDAs only):
(confirm chemical classification at time of approval)

☐ Fast Track
☐ Rolling Review
☐ Orphan drug designation
☐ Breakthrough Therapy designation
☐ Rx-to-OTC full switch
☐ Rx-to-OTC partial switch
☐ Direct-to-OTC

(NOTE: Set the submission property in DARRTS and notify the CDER Breakthrough Therapy Program Manager;
Refer to the "RPM BT Checklist for Considerations after Designation Granted" for other required actions: CST SharePoint)

NDAs: Subpart H
☐ Accelerated approval (21 CFR 314.510)
☐ Restricted distribution (21 CFR 314.520)
Subpart I
☐ Approval based on animal studies

BLAs: Subpart E
☐ Accelerated approval (21 CFR 601.41)
☐ Restricted distribution (21 CFR 601.42)
Subpart H
☐ Approval based on animal studies

☐ Submitted in response to a PMR
☐ Submitted in response to a PMC
☐ Submitted in response to a Pediatric Written Request

REMS: ☐ MedGuide
☐ Communication Plan
☐ ETASU
☐ MedGuide w/o REMS
☐ REMS not required

Comments:

❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 *(approvals only)*	☐ Yes ☐ No
❖ Public communications *(approvals only)*	
• Office of Executive Programs (OEP) liaison has been notified of action	☒ Yes ☐ No
• Indicate what types (if any) of information were issued	☒ None ☐ FDA Press Release ☐ FDA Talk Paper ☐ CDER Q&As ☐ Other
❖ Exclusivity	
• Is approval of this application blocked by any type of exclusivity (orphan, 5-year NCE, 3-year, pediatric exclusivity)? • If so, specify the type	☒ No ☐ Yes
❖ Patent Information (NDAs only)	
• Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought.	☒ Verified ☐ Not applicable because drug is an old antibiotic.

CONTENTS OF ACTION PACKAGE

Officer/Employee List

❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list *(approvals only)*	☒ Included
Documentation of consent/non-consent by officers/employees	☒ Included

Action Letters	
❖ Copies of all action letters *(including approval letter with final labeling)*	Action(s) and date(s) Nov-07-2016
Labeling	
❖ Package Insert *(write submission/communication date at upper right of first page of PI)*	
• Most recent draft labeling *(if it is division-proposed labeling, it should be in track-changes format)*	☒ Included
• Original applicant-proposed labeling	☒ Included
❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling *(write submission/communication date at upper right of first page of each piece)*	☐ Medication Guide ☒ Patient Package Insert ☐ Instructions for Use ☐ Device Labeling ☐ None
• Most-recent draft labeling *(if it is division-proposed labeling, it should be in track-changes format)*	☒ Included
• Original applicant-proposed labeling	☒ Included
❖ Labels (**full color** carton and immediate-container labels) *(write submission/communication date on upper right of first page of each submission)*	
• Most-recent draft labeling	☒ Included
❖ Proprietary Name • Acceptability/non-acceptability letter(s) *(indicate date(s))* • Review(s) *(indicate date(s)*	Oct-11-2016 Oct-24-2016 (Rev) Oct-31-2016 Occt-31-2016 (Rev)
❖ Labeling reviews *(indicate dates of reviews)*	RPM: ☒ None 12-14-15 DMEPA: ☒ None 10-24-16, 10-31-16, 11-04-16 DMPP/PLT (DRISK): ☐ None 10-27-16 OPDP: ☒ None 10-26-16 SEALD: ☒ None CSS: ☒ None Product Quality ☒ None Other: ☐ None
Administrative / Regulatory Documents	
❖ RPM Filing Review[4]/Memo of Filing Meeting *(indicate date of each review)* ❖ All NDA 505(b)(2) Actions: Date each action cleared by 505(b)(2) Clearance Committee	Dec 14, 2015 ☐ Not a (b)(2) Oct 10, 2016
❖ NDAs/NDA supplements only: Exclusivity Summary *(signed by Division Director)*	☒ Completed
❖ Application Integrity Policy (AIP) Status and Related Documents http://www fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	
• Applicant is on the AIP	☐ Yes ☒ No

[4] Filing reviews for scientific disciplines are NOT required to be included in the action package.

• This application is on the AIP ○ If yes, Center Director's Exception for Review memo *(indicate date)* ○ If yes, OC clearance for approval *(indicate date of clearance communication)*	☐ Yes ☒ No ☐ Not an AP action
❖ Pediatrics *(approvals only)* • Date reviewed by PeRC July 6, 2016 If PeRC review not necessary, explain: _____	
❖ Breakthrough Therapy Designation	☒ N/A
• Breakthrough Therapy Designation Letter(s) (granted, denied, an/or rescinded)	
• CDER Medical Policy Council Breakthrough Therapy Designation Determination Review Template(s) *(include only the completed template(s) and not the meeting minutes)*	
• CDER Medical Policy Council Brief – Evaluating a Breakthrough Therapy Designation for Rescission Template(s) *(include only the completed template(s) and not the meeting minutes)* *(completed CDER MPC templates can be found in DARRTS as clinical reviews or on the MPC SharePoint Site)*	
❖ Outgoing communications: letters, emails, and faxes considered important to include in the action package by the reviewing office/division (e.g., clinical SPA letters, RTF letter, Formal Dispute Resolution Request decisional letters, etc.) *(do not include OPDP letters regarding pre-launch promotional materials as these are non-disclosable; do not include Master File letters; do not include previous action letters, as these are located elsewhere in package)*	
❖ Internal documents: memoranda, telecons, emails, and other documents considered important to include in the action package by the reviewing office/division (e.g., Regulatory Briefing minutes, Medical Policy Council meeting minutes)	Memo to file sNDA 21876/S-10 switch to NDA 209661
❖ Minutes of Meetings	
• If not the first review cycle, any end-of-review meeting *(indicate date of mtg)*	☐ N/A or no mtg
• Pre-NDA/BLA meeting *(indicate date of mtg)*	☐ No mtg
• EOP2 meeting *(indicate date of mtg)*	☐ No mtg
• Mid-cycle Communication *(indicate date of mtg)*	☐ N/A
• Late-cycle Meeting *(indicate date of mtg)*	☐ N/A
• Other milestone meetings (e.g., EOP2a, CMC focused milestone meetings) *(indicate dates of mtgs)*	
❖ Advisory Committee Meeting(s)	☒ No AC meeting
• Date(s) of Meeting(s)	
Decisional and Summary Memos	
❖ Office Director Decisional Memo *(indicate date for each review)*	☒ None
Division Director Summary Review *(indicate date for each review)*	☐ None 11-07-2016
Cross-Discipline Team Leader Review *(indicate date for each review)*	☐ None 11-07-2016
PMR/PMC Development Templates *(indicate total number)*	☐ None
Clinical	

❖ Clinical Reviews	
• Clinical Team Leader Review(s) *(indicate date for each review)*	☒ No separate review 11-07-2016
• Clinical review(s) *(indicate date for each review)*	11-07-2016
• Social scientist review(s) (if OTC drug) *(indicate date for each review)*	☒ None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here ☐ and include a review/memo explaining why not *(indicate date of review/memo)*	See Clinical review page 33
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers *(indicate date of each review)*[5]	☒ None
❖ Controlled Substance Staff review(s) and Scheduling Recommendation *(indicate date of each review)*	☒ N/A
❖ Risk Management • REMS Documents and REMS Supporting Document *(indicate date(s) of submission(s))* • REMS Memo(s) and letter(s) *(indicate date(s))* • Risk management review(s) and recommendations (including those by OSE and CSS) *(indicate date of each review and indicate location/date if incorporated into another review)*	☒ None
❖ OSI Clinical Inspection Review Summary(ies) *(include copies of OSI letters to investigators)*	☒ None requested
Clinical Microbiology ☒ None	
❖ Clinical Microbiology Team Leader Review(s) *(indicate date for each review)*	☐ No separate review
Clinical Microbiology Review(s) *(indicate date for each review)*	☐ None
Biostatistics ☐ None	
❖ Statistical Division Director Review(s) *(indicate date for each review)*	☒ No separate review
Statistical Team Leader Review(s) *(indicate date for each review)*	☒ No separate review
Statistical Review(s) *(indicate date for each review)*	☐ None Feb 29, 2016
Clinical Pharmacology ☐ None	
❖ Clinical Pharmacology Division Director Review(s) *(indicate date for each review)*	☒ No separate review 10-14-2016
Clinical Pharmacology Team Leader Review(s) *(indicate date for each review)*	☐ No separate review
Clinical Pharmacology review(s) *(indicate date for each review)*	☐ None 10-14-2016
❖ OSI Clinical Pharmacology Inspection Review Summary *(include copies of OSI letters)*	☒ None requested

[5] For Part 3 combination products, all reviews from the reviewing Center(s) should be entered into the official archive (for further instructions, see "Section 508 Compliant Documents: Process for Regulatory Project Managers" located in the CST electronic repository).

Nonclinical ☐ None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) *(indicate date for each review)*	☐ No separate review
• Supervisory Review(s) *(indicate date for each review)*	☒ No separate review 6-17-2016 10-28-2016
• Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	☐ None June 17, 2016 Oct 28, 2016
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer *(indicate date for each review)*	☒ None
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	☒ No carc
❖ ECAC/CAC report/memo of meeting	☒ None Included in P/T review, page
❖ OSI Nonclinical Inspection Review Summary *(include copies of OSI letters)*	☐ None requested
Product Quality ☐ None	
❖ Product Quality Discipline Reviews[6]	
• Tertiary review (*indicate date for each review*)	☐ None
• Secondary review (e.g., Branch Chief) *(indicate date for each review)*	☐ None
• Integrated Quality Assessment (contains the Executive Summary and the primary reviews from each product quality review discipline) *(indicate date for each review)*	☐ None 9-21-2016
❖ Reviews by other disciplines/divisions/Centers requested by product quality review team *(indicate date of each review)*	☒ None
❖ Environmental Assessment (check one) (original and supplemental applications)	
☒ Categorical Exclusion *(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)*	Waiver requested by Duchesnay
☐ Review & FONSI *(indicate date of review)*	
☐ Review & Environmental Impact Statement *(indicate date of each review)*	
❖ Facilities Review/Inspection	
☒ Facilities inspections (indicate date of recommendation; within one week of taking an approval action, confirm that there is an acceptable recommendation) *(only original applications and efficacy supplements that require a manufacturing facility inspection(e.g., new strength, manufacturing process, or manufacturing site change)*	☒ Acceptable Re-evaluation date: ☐ Withhold recommendation ☐ Not applicable

[6] Do not include Master File (MF) reviews or communications to MF holders. However, these documents should be made available upon signatory request.

Day of Approval Activities	
❖ For all 505(b)(2) applications: • Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity)	☐ No changes ☐ New patent/exclusivity *(Notify CDER OND IO)*
• Finalize 505(b)(2) assessment	☒ Done
❖ For Breakthrough Therapy (BT) Designated drugs: • Notify the CDER BT Program Manager	☐ Done *(Send email to CDER OND IO)*
❖ For products that need to be added to the flush list (generally opioids): Flush List • Notify the Division of Online Communications, Office of Communications	☐ Done
❖ Send a courtesy copy of approval letter and all attachments to applicant by fax or secure email	☒ Done
❖ If an FDA communication will issue, notify Press Office of approval action after confirming that applicant received courtesy copy of approval letter	☒ Done
❖ Ensure that proprietary name, if any, and established name are listed in the *Application Product Names* section of DARRTS, and that the proprietary name is identified as the "preferred" name	☒ Done
❖ Ensure Pediatric Record is accurate	☒ Done
❖ Send approval email within one business day to CDER-APPROVALS	☒ Done

---

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/s/

GEORGE A LYGHT
11/10/2016

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 209661

INFORMATION REQUEST

John JF Killackey, Ph.D.
Director, US Regulatory Affairs, Mapi Group
T: (905) 690-5782
F: 1-866-863-0243
E-mail: jkillackey@mapigroup.com
www.mapigroup.com
https://www.linkedin.com/company/mapi-group

From: Lyght, George
Sent: Tuesday, November 01, 2016 1:51 PM
To: 'John Killackey'
Subject: RE: Diclegis (b) (4) NDA 209661 Labeling Review/Edits
Importance: High

Hello John,

Recommendation for container labeling changes. These are changes for the Diclegis (b) (4) labeling from the Division of Medication Error Prevention and Analysis (DMEPA). We ask you to make them in accordance with your proposed name and to respond as soon as possible keeping the PDUFA date of November 7, 2016, in mind.

I. Container Label

a) As currently presented, the (b) (4) curve shaped graphic on the container label is (b) (4) the graphic may pose risk of error in product selection. Revise the presentation of the graphic to improve readability of the name of your product.

b) As currently presented, the bolded letter, 'l' appears throughout the label. The bolded letter decreases readability and distracts the reader away from important text. Revise the font style so that all the letters in all statements have consistent font type and style to improve readability.

c) Revise the dosage form statement to read, 'extended-release tablets'.

d) The container label does not include a lot number or expiration date. Lot number and expiration date are required on the immediate container in accordance with

CFR 201.10(i) and 211.137. We recommend that you add an identifying lot number and an expiration date to the container label. Ensure that the lot number is clearly differentiated from the expiration date.

Thanks,
George

George Lyght, PharmD
Sr. Regulatory Health Project Manager
FDA/CDER/ODEIII/DBRUP
George.lyght@fda.hhs.gov

APPEARS THIS WAY ON ORIGINAL

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/s/

GEORGE A LYGHT
11/03/2016

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 209661

INFORMATION REQUEST

John JF Killackey, Ph.D.
Director, US Regulatory Affairs, Mapi Group
T: (905) 690-5782
F: 1-866-863-0243
E-mail: jkillackey@mapigroup.com
www.mapigroup.com
https://www.linkedin.com/company/mapi-group

APPEARS THIS WAY ON ORIGINAL

Lyght, George

From: Lyght, George
Sent: Wednesday, November 02, 2016 5:36 PM
To: 'jkillackey@mapigroup.com'
Cc: 'jsamaniego@mapigroup.com'
Subject: FW: NDA 209661/ Labeling documents

Hello John and Jordan,

Just a follow up email requesting acknowledgement that this communication was received.

Thanks,
George

From: Lyght, George
Sent: Wednesday, November 02, 2016 4:18 PM
To: 'jkillackey@mapigroup.com'
Subject: NDA 209661/ Labeling documents

Duchesnay Inc.
c/o Mapi USA, Inc.
John JF Killackey, Ph.D.
Director, US Regulatory Affairs, Mapi Group

Attached is the marked up Labeling for Bonjesta with revisions and information requests. We request that you return them to the Division by close of business, Thursday, November 3, 2016. We are also requesting the return of the accepted revisions to the Container/Carton labeling also by close of business, November 3, 2016. Please acknowledge receipt of this communication.

APPEARS THIS WAY ON ORIGINAL

Thanks,

George Lyght, Pharm.D
Sr. Regulatory Health Project Manager
FDA/CDER/ONDIII/DBRUP
George.lyght@fda.hhs.gov

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

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/s/

GEORGE A LYGHT
11/03/2016

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 209661

PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE

Duchesnay Inc.
c/o Mapi USA, Inc.
2343 Alexandria Drive
Suite 100
Lexington, KY 40504

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

Dear Dr. Killackey:

Please refer to your New Drug Application dated and received October 7, 2015, submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Doxylamine Succinate and Pyridoxine Hydrochloride Extended-Release Tablets, 20 mg/20 mg.

We also refer to your correspondence, dated and received September 9, 2016, requesting review of your proposed proprietary name, Bonjesta.

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

If any of the proposed product characteristics as stated in your September 9, 2016 submission is altered prior to approval of the marketing application, the proprietary name should be resubmitted for review. Additionally, if your application receives a complete response, a new request for name review for your proposed name should be submitted when you respond to the application deficiencies.

If you require information on submitting requests for proprietary name review or PDUFA performance goals associated with proprietary name reviews, we refer you to the following:

- Guidance for Industry Contents of a Complete Submission for the Evaluation of Proprietary Names (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075068.pdf)
- PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2013 through 2017, (http://www.fda.gov/downloads/ForIndustry/UserFees/PrescriptionDrugUserFee/UCM270412.pdf)

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Mammah Sia Borbor, MS, MBA, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-7731. For any other information regarding this application, contact George A. Lyght, Regulatory Project Manager in the Office of New Drugs, at (301) 796-0948.

Sincerely,

{See appended electronic signature page}

Todd Bridges, 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/

LUBNA A MERCHANT on behalf of TODD D BRIDGES
10/31/2016

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 209661

PROPRIETARY NAME ACKNOWLEDGEMENT

Duchesnay Inc.
c/o Mapi USA, Inc.
2343 Alexandria Drive, Suite 100
Lexington, KY 40504

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

Dear Dr. Killackey:

Please refer to your New Drug Application (NDA) dated October 7, 2015, received October 7, 2015, submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Doxylamine Succinate Tablets, 20 mg and Pyridoxine Hydrochloride Tablets, 20 mg.

We acknowledge receipt of your September 9, 2016, correspondence, received September 9, 2016, requesting a review of your proposed proprietary name, Bonjesta.

The goal date is December 8, 2016.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Mammah Sia Borbor, MS, MBA, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-7731. For any other information regarding this application, contact George A. Lyght, Regulatory Project Manager, in the Office of New Drugs at (301) 796-0948.

Sincerely,

{See appended electronic signature page}

Mammah Sia Borbor, MS, MBA
Safety Regulatory Project Manager
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

MAMMAH S BORBOR
10/11/2016

Administrative change of Application from **sNDA 021876/S-10 to NDA 209661**

Application:
NDA 209661 (doxylamine succinate 20 mg/ pyridoxine hydrochloride 20 mg)

Applicant:	Duchesnay Inc. c/o Mapi USA, Inc.
Stamp date:	October 7, 2015
PDUFA date:	November 7, 2016 (Extended from August 7, 2016)

Diclegis® (10 mg doxylamine succinate and 10 mg pyridoxine hydrochloride) **delayed release tablets**, was approved April 8, 2013, for oral use, in the treatment of nausea and vomiting of pregnancy in patients who do not respond to conservative management. It was a 505(b)(2) application.

Diclegis is a **delayed release tablet** containing 10 mg of doxylamine succinate (an antihistamine) and 10 mg of pyridoxine hydrochloride (vitamin B6). The current dosing regimen is for a maximum of 4 tablets daily given up to three times daily.

Supplement 10 was submitted, proposing to increase the tablet strength from 10-10 mg to 20-20 mg (**new dosing strength**) and a dosing regimen change from three times daily to twice daily dosing (**new dosing regimen**).

- The review determined that the proposed product is a new dosage form, - an **extended release tablet**. That change in dosage form required a new original NDA, which triggered a user fee.
- Duchesnay was asked to pay the user fee and they complied paying the User Fee on August 31, 2016.
- The application was therefore administratively changed from a supplemental NDA to the current status as a NDA

NDA 209661(doxylamine succinate 20 mg/ pyridoxine hydrochloride 20 mg) is being reviewed for

1) New dosing strength
2) New dosing regimen
3) New formulation

George Lyght, PharmD
Sr. Regulatory Health Project Manager
Division of Bone, Reproductive, and Urologic Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

GEORGE A LYGHT
10/04/2016

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 209661

LABELING PMR/PMC DISCUSSION COMMENTS

Duchnesnay Inc.
c/o Mapi USA, Inc.
Attention: John J.K. Killackey, Ph.D.
Director, Regulatory Affairs
2343 Alexandria Drive, Suite 100
Lexington, KY 40504

Dear Dr. Killackey:

Please refer to your New Drug Application (NDA) dated October 7, 2015, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for doxylamine succinate and pyridoxine hydrochloride.

We also refer to our June 27, 2016, letter in which we notified you of our target date of September 14, 2016, for communicating labeling changes and/or postmarketing requirements/commitments in accordance with the "PDUFA Reauthorization Performance Goals and Procedures - Fiscal Years 2013 Through 2017."

On October 7 and November 20, 2015, we received your proposed labeling submissions to this application. We have the following comment:

We request that you change the labeling in the DESCRIPTION section to:

11. DESCRIPTION

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

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

If you have any questions, call me, at (301) 796-0948.

Sincerely,

{See appended electronic signature page}

George Lyght, Pharm.D.
Sr. Regulatory Health Project Manager
Division of Bone, Reproductive, and Urologic Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

GEORGE A LYGHT
09/14/2016

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 021876/S-10

INFORMATION REQUEST

Duchesnay Inc.
c/o Mapi USA, Inc.
Attention: John J.F. Killackey, Ph.D.
Director, Regulatory Affairs
2343 Alexandria Drive, Suite 100
Lexington, KY 40504

Dear Dr. Killackey:

Please refer to your supplemental New Drug Application (sNDA) dated and received October 7, 2015, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA), for doxylamine succinate and pyridoxine hydrochloride.

As communicated to you via telephone conversations with George Lyght, Pharm.D., Sr. Regulatory Health Project Manager on August 3, 2016, and August 12, 2016, we have determined that your proposed product is a new dosage form, and that this change in dosage form requires a new original NDA, which triggers a user fee. As communicated to you on August 12, 2016, we are requesting a decision by August 16, 2016, as to whether you will choose to pay a user fee for this product. If you decide not to pay a user fee, we will send an "unacceptable for filing" letter. Do not withdraw this supplemental NDA because that action could also trigger a user fee. If you choose to pay a user fee, we will inform you of next steps to administratively establish a separate NDA for your product.

We also refer to your submission dated June 27, 2016.

We have reviewed the questions in your submission and have the following responses to your requests for information. These responses are provided under the scenario that both Diclegis and your proposed 20 mg doxylamine and 20 mg pyridoxine extended-release tablets are approved products. Our responses will not be applicable if your proposed 20 mg doxylamine and 20 mg pyridoxine extended-release tablet is not approved.

Question 1
Does the FDA have any concerns with [redacted] (b) (4)

FDA Response:

(b) (4)

However, before definitively answering your question, (b) (4) Diclegis® and your proposed product, 20 mg doxylamine and 20 mg pyridoxine extended-release tablets.

(b) (4)

Question 2

Would the FDA propose (b) (4)?

FDA Response:

See our response to Question 1.

Question 3

Would the FDA refuse (b) (4) pending the reformulation under review and in reference to the (b) (4)?

FDA Response:

We cannot provide a definitive response at this time. In order to help us in our consideration of your question, we have the following question:

Will you, as the sponsor of the NDA, (b) (4)?

If you have 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 Bone, Reproductive, and Urologic Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

HYLTON V JOFFE
08/15/2016

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 021876/S-10

REVIEW EXTENSION –
EFFICACY SUPPLEMENT

Duchesnay Inc.
c/o Mapi USA, Inc.
Attention: John J.F. Killackey, Ph.D.
Director, Regulatory Affairs
2343 Alexandria Drive, Suite 100
Lexington, KY 40504

Dear Dr. Killackey:

Please refer to your supplemental New Drug Application (sNDA) dated and received October 7, 2015, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA), for Diclegis (doxylamine succinate and pyridoxine hydrochloride (b) (4) tablets).

On June 13, 2016, we received your Clinical Study Report for Study 150336, which we consider a major amendment to this application. Therefore, we are extending the goal date by three months to provide time for a full review of the submission. The extended user fee goal date is November 7, 2016.

In addition, we are establishing a new timeline for communicating labeling changes and/or postmarketing requirements/commitments in accordance with "PDUFA REAUTHORIZATION PERFORMANCE GOALS AND PROCEDURES – FISCAL YEARS 2013 THROUGH 2017." If major deficiencies are not identified during our review, we plan to communicate proposed labeling and, if necessary, any postmarketing requirement/commitment requests by September 14, 2016.

If you have 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 Bone, Reproductive, and Urologic Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

HYLTON V JOFFE
06/27/2016

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 021876/S-10

INFORMATION REQUEST

Duchesnay Inc.
c/o Mapi USA, Inc.
Attention: John J.F. Killackey, Ph.D.
Director, Regulatory Affairs
2343 Alexandria Drive, Suite 100
Lexington, KY 40504

From: Lyght, George
Sent: Monday, February 29, 2016 11:18 AM
To: 'John Killackey'
Subject: RE: sNDA 021876/S-10 Update

Received.

We are having a mid-cycle meeting in two weeks so that is one reason we are seeking to receive the information.

Thanks,
George

> **From:** John Killackey [mailto:jkillackey@mapigroup.com]
> **Sent:** Friday, February 26, 2016 4:08 PM
> **To:** Lyght, George
> **Subject:** RE: sNDA 021876/S-10 Update
>
> Hi George:
>
> We have just uploaded a partial response through the ESGateway. It will address the request for datasets:
>
> - Submit datasets for individual concentration-time data for Study 150033.
> - Submit the SAS code for the BE analysis.
>
> On behalf of Duchesnay, I apologize for this response taking so long.

Please let me know if you have any comments or questions. And have a good weekend.

Kind regards,
John

John JF Killackey, Ph.D.
Director, US Regulatory Affairs, Mapi Group
T: (905) 690-5782
F: 1-866-863-0243
E-mail: jkillackey@mapigroup.com
www.mapigroup.com
https://www.linkedin.com/company/mapi-group

From: Lyght, George [mailto:George.Lyght@fda.hhs.gov]
Sent: Wednesday, February 24, 2016 11:48 AM
To: John Killackey
Subject: RE: sNDA 021876/S-10 Update

Hi John,

We will accept any information that's ready as you may send the other information when it's available.

Thanks,
George

> **From:** John Killackey [mailto:jkillackey@mapigroup.com]
> **Sent:** Wednesday, February 17, 2016 12:59 PM
> **To:** Lyght, George
> **Subject:** RE: sNDA 021876/S-10 Update
>
> Hi George:
>
> Duchesnay are still working on the responses. The key project manager for this at Duchesnay had to depart suddenly and, as a result, time was lost in responding.

I will keep you informed of their progress.

Kind regards,
John

John JF Killackey, Ph.D.
Director, US Regulatory Affairs, Mapi Group
T: (905) 690-5782
F: 1-866-863-0243
E-mail: jkillackey@mapigroup.com
www.mapigroup.com
https://www.linkedin.com/company/mapi-group

From: Lyght, George [mailto:George.Lyght@fda.hhs.gov]
Sent: Wednesday, February 10, 2016 5:10 PM
To: John Killackey
Subject: sNDA 021876/S-10

Hi John,

I left a voicemail for you and this is a follow-up. We were wondering if you had any other responses ready for us as we do our review for sNDA 21876/S-10.

Thanks,
George

From: John Killackey [mailto:jkillackey@mapigroup.com]
Sent: Friday, December 18, 2015 7:55 AM
To: Lyght, George
Cc: Jordan Samaniego
Subject: RE: sNDA 021876/S-10 Information request

Hi George:

As requested, attached please find two excel spreadsheets each for the two studies submitted in the Efficacy Supplement.

- Section 5.3.1.1 Study 140115: File: 140115_AE.XLS
- Section 5.3.1.1 Study 140115: File: 140115_Dosing.XLS

- Section 5.3.1.2 Study 150033: File: 150033_AE.XLS
- Section 5.3.1.2 Study 150033: File: 150033_Dosing.XLS

I trust that this is straight forward enough but please let me know if you have any comments or questions.

Kind regards,
John

John JF Killackey, Ph.D.
Director, US Regulatory Affairs, Mapi Group
T: (905) 690-5782
F: 1-866-863-0243
E-mail: jkillackey@mapigroup.com
www.mapigroup.com
https://www.linkedin.com/company/mapi-group

From: Lyght, George [mailto:George.Lyght@fda.hhs.gov]
Sent: Thursday, December 17, 2015 9:25 PM
To: John Killackey
Cc: Jordan Samaniego
Subject: RE: sNDA 021876/S-10 Information request

Hi John,

Please forward the excel spreadsheets for now.
Provide the data sets in SAS format once available.

Regards,
George

From: John Killackey [mailto:jkillackey@mapigroup.com]
Sent: Wednesday, December 16, 2015 1:17 PM
To: Lyght, George
Cc: Jordan Samaniego
Subject: RE: sNDA 021876/S-10 Information request

Hi George:

I apologize in the delay in responding to this request. The company has provided the datasets but in excel format and so we've gone back to request SAS transport file format. We can email the excel files if they are any help at all.

Kind regards,
John

John JF Killackey, Ph.D.
Director, US Regulatory Affairs, Mapi Group
T: (905) 690-5782
F: 1-866-863-0243
E-mail: jkillackey@mapigroup.com
Please note this new e-mail address. Please update your contact list. Thank you.
www.mapigroup.com
https://www.linkedin.com/company/mapi-group

From: Lyght, George [mailto:George.Lyght@fda.hhs.gov]
Sent: Sunday, December 13, 2015 9:59 PM
To: John Killackey
Subject: sNDA 021876/S-10 Information request

John JF Killackey, PhD.
Director, US Regulatory Affairs, Mapi Group

The following is a clinical Information Request:

For NDA21876/Supplement 10 Efficacy received by the Agency on October 7, 2015 for Diclegis, provide the raw data sets that were used to generate the following tables:
Table 14.3.1.2 Adverse events listing for Comparative Bioequivalence study (protocol number 150033)
Table 14.3.1.2 Adverse events listing for Bioavailability study (protocol number 140115)

We would appreciate your response in the earliest possible timeframe.

Thanks,

George Lyght, Pharm.D
FDA/CDER/ODEIII/DBRUP
George.lyght@fda.hhs.gov

From: Lyght, George
Sent: Thursday, December 17, 2015 9:25 PM
To: 'John Killackey'
Cc: Jordan Samaniego
Subject: RE: sNDA 021876/S-10 Information request

Hi John,

Please forward the excel spreadsheets for now.
Provide the data sets in SAS format once available.

Regards,
George

From: John Killackey [mailto:jkillackey@mapigroup.com]
Sent: Wednesday, December 16, 2015 1:17 PM
To: Lyght, George
Cc: Jordan Samaniego
Subject: RE: sNDA 021876/S-10 Information request

Hi George:

I apologize in the delay in responding to this request. The company has provided the datasets but in excel format and so we've gone back to

request SAS transport file format. We can email the excel files if they are any help at all.

Kind regards,
John

John JF Killackey, Ph.D.
Director, US Regulatory Affairs, Mapi Group
T: (905) 690-5782
F: 1-866-863-0243
E-mail: jkillackey@mapigroup.com
Please note this new e-mail address. Please update your contact list. Thank you.
www.mapigroup.com
https://www.linkedin.com/company/mapi-group

From: Lyght, George [mailto:George.Lyght@fda.hhs.gov]
Sent: Sunday, December 13, 2015 9:59 PM
To: John Killackey
Subject: sNDA 021876/S-10 Information request

John JF Killackey, PhD.
Director, US Regulatory Affairs, Mapi Group

The following is a clinical Information Request:

For NDA21876/Supplement 10 Efficacy received by the Agency on October 7, 2015 for Diclegis, provide the raw data sets that were used to generate the following tables:
Table 14.3.1.2 Adverse events listing for Comparative Bioequivalence study (protocol number 150033)
Table 14.3.1.2 Adverse events listing for Bioavailability study (protocol number 140115)

We would appreciate your response in the earliest possible timeframe.

Thanks,

George Lyght, Pharm.D
FDA/CDER/ODEIII/DBRUP
George.lyght@fda.hhs.gov

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/s/

GEORGE A LYGHT
03/18/2016

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 021876/S-10

INFORMATION REQUEST

Duchesnay Inc.
c/o Mapi USA, Inc.
Attention: John J.F. Killackey, Ph.D.
Director, Regulatory Affairs
2343 Alexandria Drive, Suite 100
Lexington, KY 40504

Dear Dr. Killackey:

Please refer to your supplemental New Drug Application (sNDA) dated and received October 7, 2015, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA), for 20 mg doxylamine succinate and 20 mg pyridoxine hydrochloride extended-release tablets.

We also refer to your submissions dated November 20, 2015, December 21, 2015, February 26, 2016, and March 11, 2016.

Our "Filing Review Issues Identified" letter, dated December 18, 2015, gave you preliminary notice of potential review issues for the sNDA. To evaluate these review issues, we requested your response to the following outstanding information requests:

Clinical/Clinical Pharmacology

- Submit supporting information that the safety and efficacy of 20 mg doxylamine succinate and 20 mg pyridoxine hydrochloride extended-release tablets will be similar to those of Diclegis® (10 mg doxylamine succinate and 10 mg pyridoxine hydrochloride) delayed-release tablets, at the dosing regimen of a 20 mg/20 mg daily dose.
- Submit supporting information that different shapes of pharmacokinetic (PK) profiles on Day 11 following multiple doses of 20 mg doxylamine succinate and 20 mg pyridoxine hydrochloride extended-release tablets and Diclegis® (10 mg doxylamine succinate and 10 mg pyridoxine hydrochloride) delayed-release tablets administration will not significantly affect the safety and efficacy of the drug product. If available, submit the dose-response or concentration-response data to support your justification.
- Provide justification as to why the bioequivalence assessment was based on metabolite pyridoxine-5-phophate, rather than parent drug pyridoxine.

Office of Pharmaceutical Quality

- Provide justification and supportive dissolution data that the currently approved quality control (QC) dissolution method for the 10 mg doxylamine succinate and 10 mg pyridoxine hydrochloride delayed-release tablets is adequate as the QC method for the proposed 20 mg doxylamine succinate and 20 mg pyridoxine hydrochloride extended-release tablets. Submit complete dissolution profile data (individual, mean, standard deviation, profiles) for comparative dissolution test results of 20 mg doxylamine succinate and 20 mg pyridoxine hydrochloride extended-release tablets and Diclegis® (10 mg doxylamine succinate and 10 mg pyridoxine hydrochloride) delayed-release tablets.

In addition, your 120-Day Safety Update is overdue.

To date, we have not received your response to any of the requests noted above even though the Division has repeated contacted you about these missing responses. To avoid compromising our ability to review and evaluate the requested information in this review cycle, provide your written response to each of the above items by March 24, 2016.

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

Sincerely,

{See appended electronic signature page}

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

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/s/

HYLTON V JOFFE
03/16/2016

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 021876/S-10

FILING COMMUNICATION -
FILING REVIEW ISSUES IDENTIFIED

Duchesnay Inc.
c/o Mapi USA, Inc.
Attention: John J.F. Killackey, Ph.D.
Director, Regulatory Affairs
2343 Alexandria Drive, Suite 100
Lexington, KY 40504

Dear Dr. Killackey:

Please refer to your supplemental New Drug Application (sNDA) dated and received October 7, 2015, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA), for Diclegis (doxylamine succinate and pyridoxine hydrochloride (b) (4) tablets).

We also refer to your amendment dated November 20, 2015.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is **Standard**. Therefore, the user fee goal date is August 7, 2016. We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, mid-cycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing commitment requests by July 15, 2016.

During our filing review of your application, we identified the following potential review issues:

Clinical/Clinical Pharmacology

- In the proposed labeling for Diclegis (b) (4) the subjects will start with a 20 mg/20 mg daily dose (one tablet at bedtime) and may remain on this regimen if symptoms are adequately controlled. Per survey results for Diclegis (provided by the Sponsor in the

meeting package submitted in 2013), about 20% of study subjects may remain at the 20-20 mg daily dose. However, no bioequivalence (BE) assessment was conducted for this dosing regimen. Therefore, the safety and efficacy of Diclegis (b) (4) at a daily dose of 20 mg/20 mg will be a review issue.

- Study 150033:
  - BE of doxylamine, pyridoxine, and its metabolites (baseline corrected and uncorrected) on Day 1 and Day 11 with the 40 mg/40 mg daily dose between Diclegis (b) (4) and Diclegis formulations will be a review issue.
  - The clinical relevance of failed BE on Day 1 will be a review issue.
  - Although BE appears to have been met for doxylamine and baseline-corrected pyridoxal 5'-phosphate on Day 11 of 40 mg/40 mg daily dosing, the pharmacokinetic (PK) profiles of Diclegis (b) (4) and Diclegis are different. Specifically, time to reach peak concentration (Tmax) of doxylamine from Diclegis is around early morning, which is clinically relevant for the treatment of morning sickness, whereas Tmax of doxylamine from Diclegis (b) (4) is around noon, which may lead to more sedation issues. Whether the difference in the PK profiles between the two formulations could lead to a different clinical response than Diclegis will be a review issue (see FDA BA BE Guidance at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM389370.pdf).

Information Request:

- Submit supporting information that the safety and efficacy of Diclegis (b) (4) will be similar to those of Diclegis at the dosing regimen of a 20 mg/20 mg daily dose.
- Submit supporting information that different shapes of PK profiles on Day 11 following multiple doses of Diclegis (b) (4) and Diclegis administration will not significantly affect the safety and efficacy of the drug product. If available, submit the dose-response or concentration-response data to support your justification.
- Provide justification as to why the BE assessment was based on metabolite pyridoxine-5-phophate, rather than parent drug pyridoxine.
- Submit datasets for individual concentration-time data for Study 150033.
- Submit the SAS code for the BE analysis.

Office of Pharmaceutical Quality

- Provide justification and supportive dissolution data that the approved quality control (QC) dissolution method for Diclegis® Delayed-release Tablets is adequate as the QC method for Diclegis (b) (4) Tablets.
- Submit complete dissolution profile data (individual, mean, standard deviation, profiles) for comparative dissolution test results of Diclegis (b) (4) and Diclegis.
- Evaluate the alcohol-induced dose dumping of your 20 mg strength delayed release product. First, you should conduct the in vitro alcohol-induced dose dumping testing;

however, depending on the result of this testing you may have to follow-up with an in vivo alcohol-dose dumping study. Consider the following points during the evaluation of the in vitro alcohol induced dose dumping of your product:

- Conduct dissolution testing using the optimal dissolution apparatus and agitation speed.
- Generate dissolution data from 12 dosage units (n=12) at multiple time points to obtain a complete dissolution profile.
- The following alcohol concentrations for the in vitro dissolution studies are recommended: 0%, 5%, 10%, 20%, and 40%. In general;
  - **If the optimal dissolution medium is 0.1N HCl**; dissolution profiles in this 0.1 N HCl (pH 1.2) containing the above range of alcohol concentrations would be sufficient.
  - **If the optimal dissolution medium is NOT 0.1N HCl**; dissolution profiles using the above range of alcohol concentrations in 0.1N HCl and in the optimal dissolution medium are recommended.
  - **If the optimal dissolution medium has not been identified**; dissolution profiles using the above range of alcohol concentrations in three physiologically relevant pH media (pH 1.2, 4.5, and 6.8) are recommended.
  - **If the dissolution of the product is pH independent**; then dissolution data in 0.1N HCl with the above range of alcohol concentrations is sufficient.

- Compare the shape of the dissolution profiles to determine if the delayed release characteristics are maintained, especially in the first 2 hours.
- Estimate the f2 values assessing the similarity (or lack thereof) between the dissolution profiles (using 0% alcohol as the reference).
- Provide the report with the complete data (i.e., individual, mean, SD, comparison plots, f2 values, etc.) collected during the evaluation of the in vitro alcohol induced dose dumping study to FDA for review.

We are providing the above comments to give you preliminary notice of potential review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review. Issues may be added, deleted, expanded upon, or modified as we review the application. If you respond to these issues during this review cycle, we may not consider your response before we take an action on your application.

Respond only to the above requests for information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

Note that the tradename, Diclegis (b) (4) is still under review.

PROMOTIONAL MATERIAL

You may request advisory comments on proposed introductory advertising and promotional labeling. Please submit, in triplicate, a detailed cover letter requesting advisory comments (list each proposed promotional piece in the cover letter along with the material type and material identification code, if applicable), the proposed promotional materials in draft or mock-up form with annotated references, and the proposed package insert (PI). Submit consumer-directed, professional-directed, and television advertisement materials separately and send each submission to:

OPDP Regulatory Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

Alternatively, you may submit a request for advisory comments electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft Guidance for Industry (available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM443702.pdf).

Do not submit launch materials until you have received our proposed revisions to the package insert (PI), and you believe the labeling is close to the final version.

For more information regarding OPDP submissions, please see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm. If you have any questions, call OPDP at 301-796-1200.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We reference the partial waiver granted on April 8, 2013, for the pediatric study requirement for this application for pediatric patients for ages birth to eleven years of age.

We also reference the partial deferral granted on April 8, 2013, for the post approval pediatric study requirement for this application for pregnant girls 12 to 17 years of age.

We acknowledge your request (b) (4) for Diclegis (b) (4) which will be reviewed in consultation with the Pediatric Review Committee.

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 Bone, Reproductive, and Urologic Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

HYLTON V JOFFE
12/18/2015

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 021876/S-10

INFORMATION REQUEST

From: Lyght, George
Sent: Sunday, December 13, 2015 9:59 PM
To: 'jkillackey@mapigroup.com'
Subject: sNDA 021876/S-10 Information request

John JF Killackey, PhD.
Director, US Regulatory Affairs, Mapi Group

The following is a clinical Information Request:

For NDA21876/Supplement 10 Efficacy received by the Agency on October 7, 2015 for Diclegis, provide the raw data sets that were used to generate the following tables:
Table 14.3.1.2 Adverse events listing for Comparative Bioequivalence study (protocol number 150033)
Table 14.3.1.2 Adverse events listing for Bioavailability study (protocol number 140115)

We would appreciate your response in the earliest possible timeframe.

Thanks,

George Lyght, Pharm.D
FDA/CDER/ODEIII/DBRUP
George.lyght@fda.hhs.gov

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/s/

GEORGE A LYGHT
12/14/2015

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

NDA 021876/S-10

ACKNOWLEDGMENT --
PRIOR APPROVAL SUPPLEMENT

Duchesnay Inc.
c/o Mapi USA, Inc.
Attention: John J.K. Killackey, Ph.D.
Director, Regulatory Affairs
2343 Alexandria Drive, Suite 100
Lexington, KY 40504

Dear Dr. Killackey:

We have received your supplemental New Drug Application (sNDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA or the Act) for the following:

NDA NUMBER:	021876
SUPPLEMENT NUMBER:	10
PRODUCT NAME:	Diclegis® (doxylamine succinate and pyridoxine hydrochloride (b) (4) tablets)
DATE OF SUBMISSION:	October 7, 2015
DATE OF RECEIPT:	October 7, 2015

This supplemental application proposes the following changes:

1. New tablet strength
2. New dosage regimen

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on December 6, 2015, in accordance with 21 CFR 314.101(a).

If the application is filed, the goal date will be August 7, 2016.

SUBMISSION REQUIREMENTS

Cite the application number listed above at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Bone, Reproductive, and Urologic Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size. Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, see http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFilesDMFs/ucm073080.htm.

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

Sincerely,

{See appended electronic signature page}

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

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/s/

MARGARET M KOBER
11/25/2015
Chief, Project Management Staff