CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

209661Orig1s000

SUMMARY REVIEW

Summary Review for Regulatory Action

Date	(electronic stamp)
From	Hylton V. Joffe, M.D., M.M.Sc.
Subject	Division Director Summary Review
NDA/BLA #	NDA 209661
Applicant Name	Duchesnay, Inc.
Date of Submission	October 7, 2015
PDUFA Goal Date	November 7, 2016
Proprietary Name / Established (USAN) Name	Bonjesta (doxylamine succinate and pyridoxine hydrochloride) extended-release tablets
Dosage Forms / Strength	Extended-release tablet containing 20 mg doxylamine succinate and 20 mg pyridoxine hydrochloride
Proposed Indication(s)	Treatment of nausea and vomiting of pregnancy in women who do not respond to conservative management
Action	Approval

Material Reviewed/Consulted Action Package, including:	**Names of discipline reviewers**
Cross-Discipline Team Leader	Shelley R. Slaughter, M.D., Ph.D.
Medical Officer Review	Theresa van der Vlugt, M.D. and Nneka McNeal-Jackson, M.D.
Pharmacology Toxicology Review	Kimberly Hatfield, Ph.D. and Mukesh Summan, Ph.D.
Office of Pharmaceutical Quality	Jean Salemme, Ph.D., Kalpana Paudel, Ph.D., and David Lewis, Ph.D.
Clinical Pharmacology Review	Chongwoo Yu, Ph.D. and E. Dennis Bashaw, Pharm.D.
Biostatistics	Kate Dwyer, Ph.D. and Mahboob Sobhan, Ph.D.
Division of Medication Error Prevention and Analysis	Walter Fava, R.Ph., M.S.Ed. and Lolita White, Pharm.D.
Division of Medical Policy Programs	Nyedra Booker, Pharm.D., M.P.H., Lynn Panholzer, Pharm.D., Marcia Williams, Ph.D., and LaShawn Griffiths, M.S.H.S-P.H., B.S.N., R.N.
Office of Prescription Drug Promotion	Lynn Panholzer, Pharm.D.
Office of Study Integrity and Surveillance	Shila Nkah

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Signatory Authority Review

1. Introduction

Diclegis is a delayed-release, fixed-dose combination tablet containing 10 mg of doxylamine succinate (a sedating antihistamine) and 10 mg of pyridoxine hydrochloride (a vitamin B_6 analog). Diclegis is approved for the treatment of nausea and vomiting of pregnancy in women who do not respond to conservative management. The starting dose is two tablets at bedtime. If needed, the dose can be increased to three tablets starting on Day 3 (one tablet in the morning and two tablets at bedtime), and to the maximum recommended dose of four tablets per day starting on Day 4 (one tablet in the morning, one tablet mid-afternoon, and two tablets at bedtime).

The Applicant submitted this 505(b)(2) New Drug Application (NDA), seeking approval of a new dosage form (tradename Bonjesta), which is an extended-release tablet containing 20 mg of doxylamine succinate and 20 mg of pyridoxine hydrochloride.

The proposed starting dose of Bonjesta is one tablet orally at bedtime. If symptoms are not adequately controlled on Day 2, the dose can be increased to two tablets per day (one tablet in the morning and one tablet at bedtime). Therefore, this new dosage form reduces the number of tablets taken per day, and reduces the maximum frequency of dosing from three times daily to twice daily. This document serves as FDA's decisional memorandum for the application.

2. Background

This Application was originally submitted and filed as a non-fee paying supplemental NDA. However, during our review, we determined that the Applicant's product is a new dosage form. This required that the submission instead be reviewed under a separate NDA and triggered a user fee, which the Applicant paid.

In the 120-day Safety Update, the Applicant notified us that they had conducted a single-dose bioequivalence study outside of the Investigational New Drug Application (IND). We requested submission of this study report and determined that the data would help provide clarity on how the pharmacokinetics of Bonjesta's starting dose compares to the starting dose of Diclegis. We considered this submission to be a Major Amendment, extending the review clock by three months from August 7, 2016 to November 7, 2016.

3. CMC/Device

Bonjesta's enteric-coated core is (b) (4), consisting of 10 mg doxylamine succinate and 10 mg pyridoxine hydrochloride. Immediate-release (b) (4) 10 mg doxylamine succinate and 10 mg pyridoxine hydrochloride are

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added on top of the enteric-coated core, [redacted] (b) (4). (b) (4) [redacted] the Office of Pharmaceutical Quality (OPQ) determined that it is an extended-release tablet because it also contains immediate-release [redacted] (b) (4)

OPQ found the chemistry, manufacturing, and controls data, as well as the dissolution method and acceptance criteria acceptable. There were no changes in the drug substances, all active ingredients are compatible with the new coating excipients (which are compendial or Generally Recognized as Safe), and all other excipients [redacted] (b) (4). OPQ also concluded that the stability data at six months at accelerated conditions are adequate to support a 12-month shelf-life. Inspection of the manufacturing sites by the Office of Process and Facilities was also found acceptable. OPQ agrees with the Applicant's request for a waiver from requirements to prepare an Environmental Assessment, because the product will not increase use of the active ingredients (the maximum recommended dose of the new dosage form is identical to that of Diclegis).

OPQ recommends approval. See the review by Jean Salemme, Ph.D. for details.

4. Nonclinical Pharmacology/Toxicology

The NDA does not contain new nonclinical pharmacology/toxicology studies. Instead, it relies upon FDA's finding for Bendectin for the nonclinical information. This is the same approach used for Diclegis. Bendectin was previously marketed in the United States, contained 10 mg of doxylamine succinate and 10 mg of pyridoxine hydrochloride, and was relisted in the "Discontinued Drug Products List" section of the Orange book after FDA determined that the product had not been withdrawn from the market for reasons of safety or effectiveness. See my decisional memorandum for Diclegis (NDA 021876) that explains the scientific bridge to Bendectin. The nonclinical pharmacology/toxicology team agrees that no additional nonclinical pharmacology/toxicology studies are needed and recommends approval. See the review by Kimberly Hatfield, Ph.D., for details.

5. Clinical Pharmacology/Biopharmaceutics

The Clinical Pharmacology team finds the NDA acceptable and recommends approval. See the review by Chongwoo Yu, Ph.D. for details.

To support the new dosage form and dosing regimen, the Applicant submitted three clinical pharmacology studies – a single-dose bioequivalence study, a multiple-dose bioequivalence study, and a food-effect study. All three studies used the to-be-marketed formulation of Bonjesta. The Applicant used Diclectin as the comparator in the two bioequivalence studies. Diclectin, which is marketed in Canada, and Diclegis are identical drug products.

Single-Dose Bioequivalence Study: This single-center, open-label, randomized, crossover study in 52 healthy premenopausal women (48 completers) compared one 20 mg / 20 mg

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tablet of Bonjesta to two 10 mg /10 mg tablets of Diclectin, with a 21-day washout period between treatments. As shown in Table 1, these two treatments were bioequivalent for both doxylamine succinate and pyridoxal 5'-phosphate as the 90% confidence intervals were all within the standard 80-125% limits. In this study, and in the multiple-dose bioequivalence study mentioned below, the Applicant based the bioequivalence assessment for pyridoxine (the parent drug) on its main active metabolite, pyridoxal 5'-phosphate. Because pyridoxal 5'-phosphate occurs endogenously, the pharmacokinetic analyses include corrections for baseline (pre-dose) concentrations. The Clinical Pharmacology reviewers agree with the use of pyridoxal 5'-phosphate because of difficulties characterizing the pharmacokinetics of pyridoxine due to its short elimination half-life.

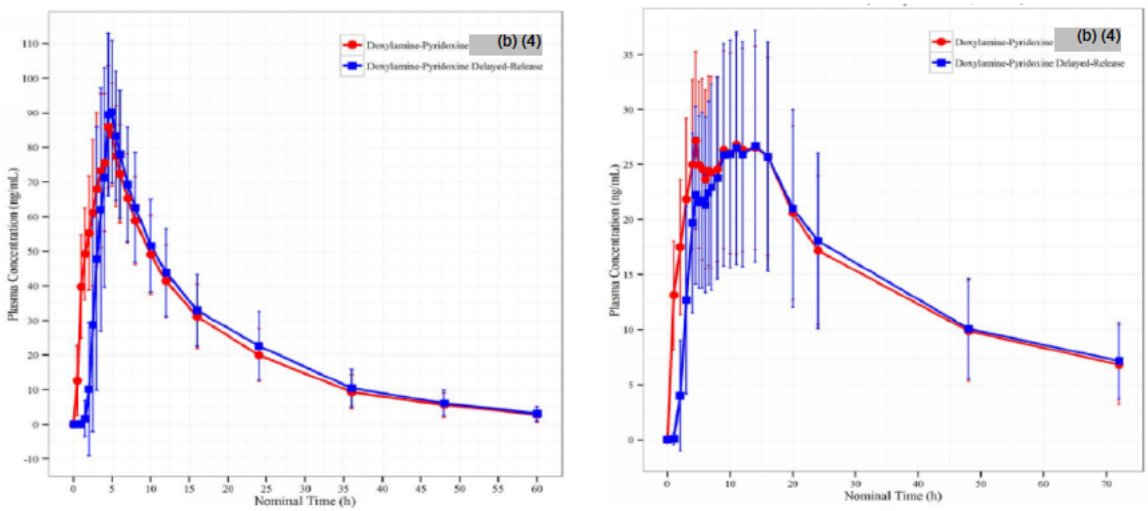
This single-dose study shows that the starting dose of Bonjesta is bioequivalent to the starting dose of Diclectin (and hence, Diclegis).

Table 1. Bioequivalence Results from the Single-Dose Bioequivalence Study (Adapted from Tables 1 and 2 in Dr. Yu's review)

	Point Estimate (%)	90% Confidence Interval
Doxylamine succinate (natural log transformed)		
$AUC_{0\text{-}60hr}$ (ng*hr/mL)	102	98-106
$AUC_{0\text{-}inf}$ (ng*hr/mL)	102	98-106
Cmax (ng/mL)	94	91-98
Pyridoxal 5'-phosphate (baseline-corrected)		
$AUC_{0\text{-}72hr}$ (ng*hr/mL)	104	98-111
Cmax (ng/mL)	104	101-109

In this single-dose study, Bonjesta and Diclectin had similar pharmacokinetic profiles for doxylamine and pyridoxal 5'-phosphate, as shown graphically in Figure 1.

Figure 1. Mean (SD) concentration-time profile for doxylamine (left) and baseline-corrected pyridoxal 5'-phosphate (right) in the single-dose bioequivalence study (red = Bonjesta; blue = Diclectin). Adapted from Figures 5 and 6 in Dr. Yu's review.



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Multiple-Dose Bioequivalence Study: This single-center, open-label, randomized, reference replicated, crossover study in 39 healthy premenopausal women (31 completers) compared 11 days of dosing with Bonjesta to 11 days of dosing with Diclectin, with a washout period of at least 28 days between treatments. There were three treatment periods – one with Bonjesta and two with Diclectin. Bonjesta 20 mg / 20 mg was dosed twice daily. Diclectin was dosed three times daily (one tablet of 10 / 10 mg in the morning and afternoon and two tablets of 10 mg / 10 mg in the evening). Therefore, this study compared the maximum recommended daily doses of Bonjesta and Diclectin. As shown in Table 2, these two treatments were bioequivalent for both doxylamine succinate and pyridoxal 5'-phosphate on Day 11, but not on Day 1.

Table 2. Bioequivalence Results from the Multiple-Dose Bioequivalence Study (Adapted from Tables 3-6 in Dr. Yu's review)

	Day 1		Day 11	
	Point Estimate (%)	**90% Confidence Interval**	**Point Estimate (%)**	**90% Confidence Interval**
Doxylamine succinate (natural log transformed)				
$AUC_{0\text{-}24hr}$ (ng*hr/mL)	140	130-151	99	96-103
Cmax (ng/mL)	80	76-83	105	101-110
Pyridoxal 5'-phosphate (baseline-corrected)				
$AUC_{0\text{-}24hr}$ (ng*hr/mL)	162	148-177	100	96-105
Cmax (ng/mL)	106	100-112	101	97-105

The pharmacokinetic profiles for doxylamine are shown in Figure 2, and for pyridoxal 5'-phosphate in Figure 3. The curves for Bonjesta and Diclectin are more closely aligned on Day 11 than on Day 1.

Figure 2. Mean (SD) concentration-time profile for doxylamine on Day 1(left) and Day 11 (right) in the multiple-dose bioequivalence study (red = Bonjesta; blue and green are the two Diclectin reference arms). Adapted from Figures 7 and 8 in Dr. Yu's review.

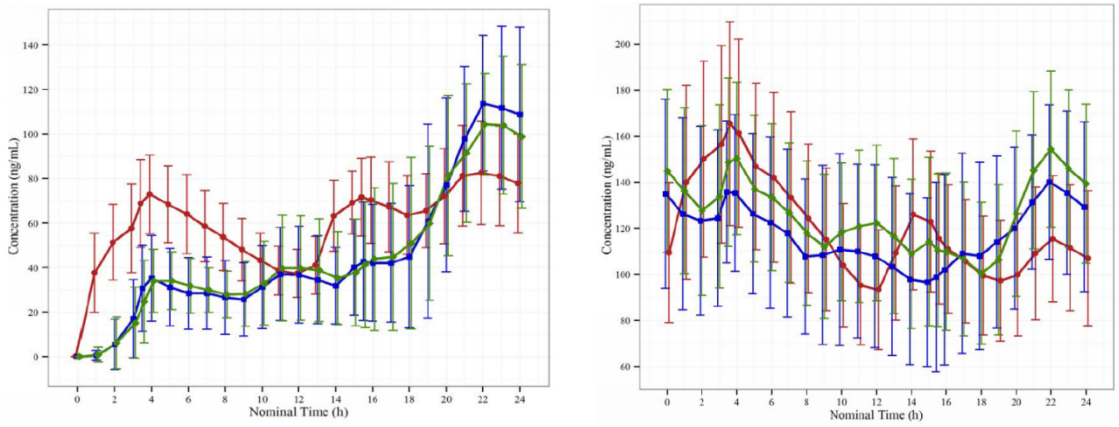

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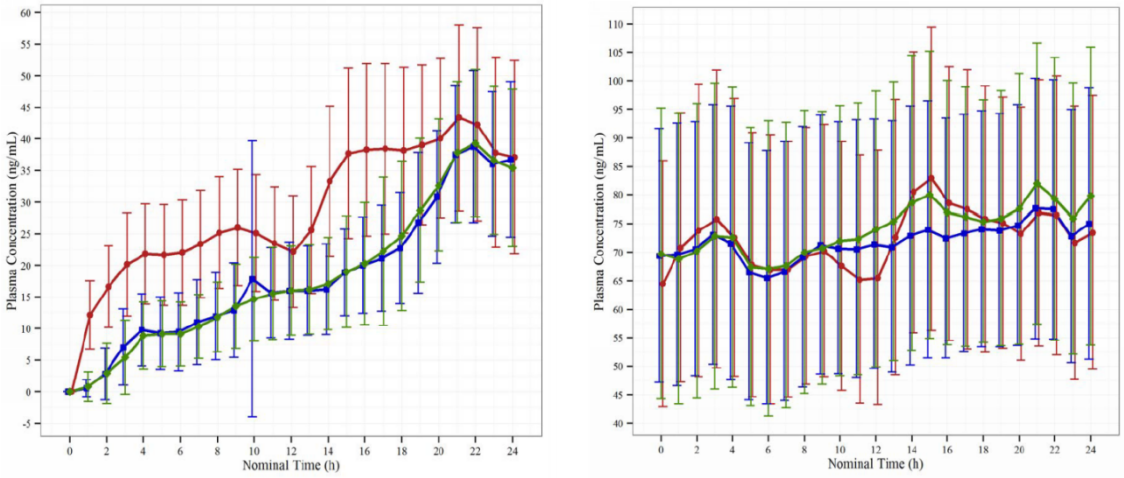
Figure 3. Mean (SD) concentration-time profile for pyridoxal 5'-phosphate on Day 1 (left) and Day 11 (right) in the multiple-dose bioequivalence study (red = Bonjesta; blue and green are the two Diclectin reference arms). Adapted from Figures 9 and 10 in Dr. Yu's review.



As discussed by Dr. Yu, the lack of bioequivalence and different pharmacokinetic profiles on Day 1 is not surprising because the two products were given under different dosing intervals. Bonjesta was given as 20 mg / 20 mg twice daily whereas Diclectin was given as one 10 mg / 10 mg tablet in the morning, another tablet in the afternoon and two tablets in the evening. Accumulation of doxylamine and pyridoxal 5'-phosphate at steady-state results in more similar pharmacokinetic profiles and bioequivalence on Day 11.

Food Effect Study: This single-center, open-label, randomized, crossover study in 24 healthy premenopausal women compared the pharmacokinetics of a single dose of Bonjesta administered with and without food. Food delayed the median Tmax of doxylamine from 3.5 hours to 6.5 hours and pyridoxine 5'-phosphate from 5 hours to 16 hours, and decreased the Cmax for doxylamine (Table 3). Therefore, labeling will state that Bonjesta is to be taken on an empty stomach with a glass of water. This is the same instructions labeled for Diclegis.

Table 3. Food Effect (Adapted from Tables 7 and 8 in Dr. Yu's review)

	Point Estimate (%)	90% Confidence Interval
Doxylamine succinate (natural log transformed)		
AUC_{0-t} (ng*hr/mL)	98	94-102
AUC_{0-inf} (ng*hr/mL)	97	93-101
Cmax (ng/mL)	74	68-80
Pyridoxal 5'-phosphate (baseline-corrected)		
AUC_{0-t} (ng*hr/mL)	103	96-112
Cmax (ng/mL)	109	103-116

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6. Clinical Microbiology

The product does not contain antimicrobial preservatives or inherent antimicrobial activity. OPQ did not identify concerns with the Applicant's microbial tests.

7. Clinical/Statistical-Efficacy

There are no new efficacy data. The Applicant provided data from clinical pharmacology studies to support approval of Bonjesta. See Section 5 of this memorandum.

8. Safety

Theresa van der Vlugt, M.D. and Nneka McNeal-Jackson, M.D., the primary clinical reviewers, discuss the safety data from the three clinical pharmacology studies in detail.

Across the three clinical pharmacology studies there were 115 randomized women and 103 completers. There were no reported deaths or serious adverse events. Discontinuations due to adverse events were few in number, included vomiting (n=2), decreased hemoglobin (n=1), visual impairment (n=1), and pregnancy (n=1), and are not likely related to Bonjesta or Diclectin.

Somnolence is the most important adverse reaction of Diclegis and is caused by the anticholinergic effects of doxylamine. Table 4 summarizes the incidence of somnolence-related adverse events in the two bioequivalence studies. These data do not raise unique concerns with Bonjesta, although the data are limited by the low numbers of events, small samples sizes of the studies, and limited durations of dosing.

Table 4. Somnolence-Related Adverse Events in the Single-Dose and Multiple-Dose Bioequivalence Studies (Adapted from Tables 18 and 21 in the Clinical Review)

Adverse Event	Multiple-Dose Study[1]		Single-Dose Study	
	Bonjesta n=39	Diclectin n=37	Bonjesta n=50	Diclectin n=50
Somnolence	5% (n=2)	11% (n=4)	2% (n=1)	26% (n=7)
Dizziness	13% (n=5)	5% (n=2)	0	0
Fatigue	8% (n=3)	5% (n=2)	0	2% (n=1)

[1]In the multiple-dose study, the duration of exposure to Diclectin was twice as long as the duration of exposure to Bonjesta (there were two 11-day treatment periods for Diclectin and one 11-day treatment period for Bonjesta)

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9. Advisory Committee Meeting

We did not take this application to advisory committee as it did not raise efficacy or safety issues needing input from outside experts.

10. Pediatrics

This Application triggers the Pediatric Research Equity Act (PREA) because of the new dosage form and dosing regimen. The Pediatric Review Committee agrees that the PREA requirements for this NDA can be fulfilled with the ongoing pediatric trial being conducted under the Diclegis NDA. This efficacy and safety trial in pregnant adolescent girls (12-17 years of age) with nausea and vomiting of pregnancy who are appropriate candidates for pharmacologic therapy was nearly one-half enrolled as of May 2016. Therefore, the Pediatric Review Committee agrees with a deferral in (b) (4) patients 12-17 years of age. The Committee also agrees with a waiver for studies in patients 0-11 years of age because those studies are impossible in premenarchal girls and highly impractical in postmenarchal girls younger than 12 years age.

11. Other Relevant Regulatory Issues

Tradename: The Division of Medication Error Prevention and Analysis has concluded that the proposed tradename, Bonjesta, is acceptable. See the review by Walter Fava, R.Ph., M.S.Ed., for details.

Inspections: The Clinical Pharmacology team consulted the Office of Study Integrity and Surveillance (OSIS) to inspect the clinical and bioanalytical study sites for the multiple-dose bioequivalence study. OSIS recommended that FDA accept these data without an on-site inspection based on previous inspection findings.

12. Labeling

The Prescribing Information for Bonjesta is based largely upon the approved label for Diclegis, except in those sections where there are data and information specific to Bonjesta (e.g., the Dosage and Administration, Clinical Pharmacology, Chemistry, and How Supplied sections). In the label, we make clear that there have been no efficacy and safety trials conducted with Bonjesta. We refer to Diclegis as combination 10 mg doxylamine succinate and 10 mg pyridoxine hydrochloride tablets. Lastly, the Pregnancy and Lactation sections have been edited in accordance with the Pregnancy and Lactation Labeling Rule (PLLR).

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Labeling has been reviewed and revised by the Office of Prescription Drug Promotion, the Division of Medication Error Prevention and Analysis, and the Division of Medical Policy Programs. See those reviews for further details.

13. Decision/Action/Risk Benefit Assessment

- Regulatory Action

Approval.

- Risk Benefit Assessment

I concur with the recommendations from all review disciplines and from Shelley Slaughter, M.D., Ph.D., the Cross-Discipline Team Leader, that this application be approved. The Applicant has shown that the starting dose of Bonjesta is bioequivalent to the starting dose of Diclectin (which is identical to FDA-approved Diclegis), and that the maximum recommended daily dose of Bonjesta is bioequivalent to the maximum recommended daily dose of Diclectin. In addition, Bonjesta does not raise any unique safety concerns.

The advantage of Bonjesta is that it reduces the number of tablets taken per day, and reduces the maximum frequency of dosing from three times daily to twice daily. A disadvantage is that there is no 30 mg / 30 mg Bonjesta dose. Therefore, the subset of patients who could be controlled on the 30 mg / 30 mg dose of Diclegis but are prescribed Bonjesta would need the 40 mg / 40 mg dose of Bonjesta. This is not an approvability issue (the 40 mg / 40 mg dose is approved as effective and safe), but limits dosing options and might raise tolerability issues for some patients.

- Recommendation for Postmarketing Risk Evaluation and Mitigation Strategies

None.

- Recommendation for other Postmarketing Requirements and Commitments

None.

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/s/

HYLTON V JOFFE
11/07/2016