APPLICATION NUMBER:

209661Orig1s000

CROSS DISCIPLINE TEAM LEADER REVIEW
Cross-Discipline Team Leader (CDTL) Review

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<tr>
<th>Date</th>
<th>November 7, 2016</th>
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<tbody>
<tr>
<td>From</td>
<td>Shelley R. Slaughter, M.D., Ph.D.</td>
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<tr>
<td>Subject</td>
<td>Cross-Discipline Team Leader Review</td>
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<tr>
<td>NDA/BLA # Supplement#</td>
<td>209661</td>
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<tr>
<td>Type of Submission</td>
<td>505(b)(2) Original NDA</td>
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<tr>
<td>Applicant</td>
<td>Duchesnay</td>
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<tr>
<td>Date of Submission</td>
<td>October 7, 2015</td>
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<td>PDUFA Goal Date</td>
<td>Extended Goal Date: November 7, 2016; Original Goal Date: August 7, 2016</td>
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<tr>
<td>Proprietary Name / Established (USAN) names</td>
<td>Bonjesta/</td>
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<tr>
<td>Dosage forms / Strength</td>
<td>Tablets</td>
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<td>Proposed Indication(s)</td>
<td>Per Form 356h “Treatment of nausea and vomiting of pregnancy in women who do not respond to conservative management”</td>
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<td>Recommendation:</td>
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1. Introduction and Executive Summary

With this 505(b)(2) New Drug Application (NDA) submission, the applicant is seeking approval of Bonjesta for the treatment of nausea and vomiting of pregnancy in women who do not respond to conservative management. To support the sNDA, the applicant initially submitted a single- and multiple-dose comparative bioavailability (bioequivalence) trial of Bonjesta to Diclegis® (Trial 150033) under fasted conditions and a comparative food effect bioavailability trial (Trial 140115) of Bonjesta under fed and fasting conditions.

On June 13, 2016, following the Agency’s request the applicant submitted the report of Trial 150336, a single dose comparative bioavailability (bioequivalence) trial which had not been conducted under the IND.

Issues emerging during the review and consideration of this application were:

1. New NDA Assignment for a New Formulation and Dosage Regimen

Diclegis®, combination 10 mg doxylamine succinate and 10 mg pyridoxine hydrochloride delayed-release tablets, was approved on April 8, 2013 for the treatment of nausea and vomiting of pregnancy in women who do not respond to conservative management. The maximum recommended daily dosage of Diclegis® is four tablets (one in the morning, one in the mid-afternoon and two at bedtime), 40 mg doxylamine succinate and 40 mg of pyridoxine hydrochloride.

NDA 021876/Supplement 10 was submitted on October 7, 2015 for a new formulation and dosage regimen, combination 20 mg doxylamine succinate and 20 mg pyridoxine hydrochloride tablets, with both immediate and delayed release of active components. The applicant proposed a twice daily administration with a maximum daily dose of 40 mg doxylamine succinate and 40 mg of pyridoxine hydrochloride.

This proposed maximum dosage for Bonjesta was intended to: 1) reduce variation at steady state for doxylamine succinate and pyridoxal 5'-phosphate, (PLP), the expected active metabolite of pyridoxine hydrochloride, plasma concentrations and 2) improve compliance in pregnant women by reducing the maximum number of tablets from four to two tablets daily.

The Bonjesta tablet containing a delayed-release core coated with immediate-release coatings was determined to be an extended-release tablet, during the course of the
application review, necessitated assignment of a new NDA number, 209661, and the requirement that the applicant pay a User Fee.

2. Information submitted to support Bioequivalence of Bonjesta to Diclegis®

To support the NDA, the applicant submitted single- and multiple-dose comparative bioavailability (bioequivalence) Trial 150033, conducted under fasted conditions and a comparative food effect bioavailability (bioequivalence) Trial 140115 under fed and fasting conditions.

The results of Trial 150033 did not support bioequivalence of Bonjesta to Diclegis® following single dose administration on Day 1. However, the results of Trial 150033 did establish bioequivalence of the maximum dose of 40 mg doxylamine hydrochloride and 40 mg pyridoxal 5'-phosphate (major metabolite of pyridoxine hydrochloride) in Bonjesta compared to Diclegis® following multiple dose administration to Day 11 at steady state.

In support of the starting dose of Bonjesta, the Agency asked the applicant to submit the report for Trial 150336, a single dose comparative bioavailability (bioequivalence) trial, conducted under fasted conditions; Trial 150036 was not conducted under an IND. The results of non-IND Trial 150336 did support bioequivalence of one tablet of Bonjesta (combination 20 mg of doxylamine hydrochloride and 20 mg pyridoxine hydrochloride) to two tablets of Diclegis® (combination 10 mg of doxylamine hydrochloride and 10 mg pyridoxine hydrochloride) following single dose administration and thus supported the starting dose of Bonjesta.

The results of comparative bioavailability food effect Trial 140105 demonstrated that food caused a delay in the median Tmax of doxylamine and pyridoxine 5'-phosphate. In addition, food decreased the Cmax for doxylamine by 26.4%. The OCP and Clinical reviewers are in agreement that labeling for Bonjesta tablets indicate that tablets be administered on an empty stomach (i.e. fasting conditions) with a glass of water to avoid the effect of food.

3. Efficacy
   As stated, support for this NDA was based on comparative bioavailability trials. New efficacy and safety data from phase 3 trials were not submitted to this NDA.

4. Safety
   No safety signals were seen in the individual or combined safety data from the three small trials considered in this NDA.

5. Labeling
   The agreed to labeling is attached to this review. There were no major areas of disagreement in the labeling.
6. Deferred PREA Trial

In addition to waiver of Pediatric Research Equity Act (PREA) requirements for children 0 to 11 years of age, [b/(4)]

At the July 6, 2016 Pediatric Research Committee (PeRC)/Pediatric Research Equity Act (PREA) subcommittee meeting, PeRC agreed with the plan for a partial waiver for studies/trials in [b/(4)] patients 0 to 11 years of age because studies are impossible or highly impractical and to a deferral in [b/(4)] patients 12 to 17 years of age. A trial to evaluate Bonesta would be satisfied if Duchesnay conducts and completes Phase 4 Trial Requirement for ongoing PED-301 in pregnant adolescent girls, 12 to 17 years of age, to evaluate Diclegis® in this population.

2. Background and Regulatory History

The following is an abbreviated summary featuring important recommendations and decisions in the regulatory history of Bonesta. The reader is referred to the Medical Officer Review by Drs. Theresa van der Vlugt and Nneka McNeal Jackson for additional regulatory background.

**Diclegis®**

Diclegis® is a fixed dose combination drug product containing 10 mg doxylamine succinate, an antihistamine, and 10 mg pyridoxine hydrochloride, a vitamin B6 analog for the treatment of NVP in women who do not respond to conservative management. Diclegis® formulation is classified as a delayed-release tablet. The applicant holds that the delayed release action of Diclegis® allows effectiveness in the morning hours for the nighttime-administered dose.

The combination of 10 mg doxylamine succinate and 10 mg pyridoxine hydrochloride (first as part of a three drug combination product with dicyclomine and then later reformulated as the two drug combination) was originally approved in 1956 under the proprietary name Bendectin® (NDA 010598) and was subsequently removed from the U.S. market in 1983 due to its potential teratogenic effect. Since its removal from the market, additional research including a number of epidemiological and reproductive animal studies demonstrated no increased teratogenic risk posed by use of this combination. It should be noted that both doxylamine succinate and pyridoxine hydrochloride are available over-the-counter (OTC) as separate products. Doxylamine is available as sleeping aide (e.g., Unisom 25 mg tablets) and pyridoxine is available by several suppliers (e.g., tablets and capsules ranging 25-500 mg).

This fixed dose combination product of 10 mg doxylamine succinate and 10 mg pyridoxine hydrochloride delayed-release tablets was reintroduced as Diclegis® and approved under NDA 021876 on April 8, 2013. NDA 021876 included the following:
• Single and multiple dose PK trial (Trial 70281)
• Food effect trial (Trial 70294)
• Phase 3, efficacy and safety trial (Trial DIC-301)
• Relative bioavailability (BA) trial between Diclegis® tablets and a combined oral solution (Trial 02163)

The approved starting dose of Diclegis® is 2 tablets orally at bedtime (Day 1). If this dose adequately controls symptoms the next day, pregnant women should continue taking 2 tablets daily at bedtime. However, if symptoms persist into the afternoon of Day 2, symptomatic pregnant women should take the usual dose of 2 tablets at bedtime that night then take 3 tablets starting on Day 3 (i.e., 1 tablet in the morning and 2 tablets at bedtime). If these 3 tablets adequately control symptoms on Day 4, pregnant women should continue taking 3 tablets daily. Otherwise, symptomatic pregnant women should take 4 tablets starting on Day 4 (i.e., 1 tablet in the morning, 1 tablet mid-afternoon, and 2 tablets at bedtime). The maximum recommended dose is 4 tablets daily. Diclegis® should be given on an empty stomach with a glass of water.

At approval of Diclegis®, the Pediatric Research Committee (PeRC) concluded that a waiver for girls, ages 0-11 years 11 months was appropriate. Duchesnay requested and received deferment for adolescent girls, age range 12-17 years 11 months. The timeline listed below was established for the conduct of “An adequately powered safety and efficacy trial (PED-301) in pregnant adolescent girls, 12 to 17 years of age, with nausea and vomiting of pregnancy who are appropriate candidates for pharmacologic therapy.”

• Final protocol Submission: January 2014
• Study/Trial Completion: January 2018
• Final Report Submission: July 2018.

Diclectin® and Diclegis® are two different trade names of the same drug product. Ten (10) mg doxylamine succinate and 10 mg pyridoxine hydrochloride delayed-release tablets are sold under the name Diclectin® in Canada and under the name Diclegis® in the United States. Even though both names are mentioned throughout this review, it refers to the same reference product.

On January 14, 2015, Duchesnay requested
Duchesnay was advised that a PREA Deferral Extension could be submitted up to 90 days prior to the final report milestone.

In an Advice/Information Request letter, dated July 28, 2015, DBRUP provides several comments and recommendations regarding ongoing Clinical Trial PED-301. In the application, Duchesnay states:

“In an effort to increase enrollment rates in the PED-301 study, Duchesnay has added additional participating trial centers to the study and is in the process of screening additional sites affiliated with or located in large university health care systems and those located in urban areas as recommended by the FDA.”

As of May 25, 2016, Trial PED-301 has screened 1124 pregnant adolescent girls, 12 to 17 years of age. Trial PED-301 currently has seven (7) active sites in the U.S. Seventy-one (71) pregnant adolescent girls have completed Trial PED-301; seven (7) pregnant adolescent girls have discontinued/early terminated Trial PED-301. The total number of trial participants planned is 160 pregnant adolescent to achieve 128 evaluable participants based on a drop-out rate of 20%. Per ClinicalTrials.gov, the estimated completion date for Trial PED-301 is December 2017.

Propose Revised Formulation and Dosing for Fixed-Dose Combination of Doxylamine Succinate and Pyridoxine Hydrochloride

- **December 10, 2013.** - The Division of Bone, Reproductive and Urologic Products [DBRUP] provided Written Responses Only (WRO) in lieu of a face-to-face (or teleconference) Type C Meeting requesting Agency guidance on revising Diclegis® from a fixed combination 10 mg doxylamine and 10 mg pyridoxine delayed-release tablet to a 20 mg doxylamine and 20 mg pyridoxine tablet with the same approved indication. The maximum approved daily administration regimen of four tablets (one in the morning, one in the mid-afternoon and two at bedtime) for Diclegis® would be reduced to a maximum recommended daily administration regimen of two tablets of the new drug product (one in the morning and one at bedtime), but still resulting in the same maximum daily dose of 40 mg doxylamine and 40 mg pyridoxine. This revised tablet would include an immediate release portion in addition to a delayed-release portion. Major items communicated in the written response were:

  - “We (DBRUP) agree that a bioequivalence comparison study between Diclegis® 10 mg / 10 mg delayed release tablet and 20 mg / 20 mg tablet formulations in healthy adult female volunteers may be sufficient to support the efficacy and safety of the new formulation. However, the final determination of acceptability of the bioequivalence study will depend on the results of the study and will be a review issue."
As you are also considering a different regimen with the new formulation (twice daily dosing instead of three times per day dosing), we recommend that you provide us with graphical comparisons of pyridoxal 5'-phosphate and doxylamine pharmacokinetics at steady state for the approved and proposed dosing regimen. You will need clinical trial data to support the efficacy and safety of the proposed twice daily dosing regimen if you are unable to establish a pharmacokinetic bridge between the proposed twice daily dosing regimen and the approved three times per day dosing regimen. In addition, we recommend that the proposed bioequivalence comparison utilize 2 tablets of the reference (i.e., 10 mg / 10 mg) and one tablet of test (i.e., 20 mg / 20 mg).”

“We concur that a bioequivalence study, and single and multiple dose pharmacokinetic studies may be sufficient to bridge efficacy and safety information between this new formulation/regimen and the previously approved regimen. However, acceptability of these data will depend on the results and will be a review issue.”

“For the bioequivalence study, we recommend using a single day crossover design as follows:

- **Day 1:**
  - **Treatment A (Twice Daily Arm):** One tablet of test formulation (20 mg x 20 mg) given twice daily as follows: one in the morning and one at night
  - **Treatment B (Three Times Daily Arm):** Reference formulation (10 mg x10 mg) given three times daily as follows: one in the morning, one at 4 PM, and 2 tablets at night (as approved).

- **Day 10:**
  The same segment of a single day study described above can be repeated for the multiple doses segment on Day 10. In this case, bioequivalence can be assessed after single dose and multiple doses in one study in the same subjects.”

- “You should also conduct a fed/fasted bioavailability study with the highest dosage strength.”

- “In the absence of acceptable bioequivalence results, you will need clinical trial data to establish the efficacy and safety of your new formulation/regimen. In this situation, we would likely recommend that you conduct with the proposed new formulation (with immediate and delayed release components), a randomized, placebo-controlled clinical trial, in pregnant adult women, 7 to 14 weeks gestation, with nausea and vomiting of pregnancy unresponsive to conservative management. This clinical trial
should have the same study design that was conducted in support of the approval of Diclegis (10 mg doxylamine plus 10 mg pyridoxine) delayed-release product. Submit the protocol for such a trial with sufficient lead time to allow for our review and comment.”

- “The term [REDACTED] is not listed in the Orange Book Appendix C. If you proceed with development of the proposed [REDACTED] formulation, we will consult the Labeling and Nomenclature Committee and the Division of Medical Error Prevention and Analysis (DMEPA) to determine the correct designation of the proposed dosage form.”

- “Is it your intent to [REDACTED]”

October 7, 2015 – The Agency received NDA 021876/Supplement 10 containing the reported results of comparative bioavailability (bioequivalence) Trial 150033 and fed/fasted comparative bioavailability Trial 140115. In the supplemental application, Duchesnay confirms that NDA 021876/Supplement 10 “is being submitted to support a new formulation for Diclegis, [REDACTED]” (see 2.5 Clinical Overview, 1 Product Development Rationale, page 2 of 6). Additionally, Duchesnay requested a waiver for pediatric study requirements in [REDACTED] for the revised formulation of combination 20 mg doxylamine and 20 mg pyridoxine tablets. Per the application,

“Tradename is intended to treat nausea and vomiting of pregnancy in women who do not respond to conservative management. [REDACTED], Duchesnay Inc. is requesting a waiver from pediatric development in children from birth to [REDACTED] years of age.”

June 13, 2016 - The Agency received from Duchesnay, at the request of DBRUP, the Clinical Trial Report for Trial 150336, a single-dose bioequivalence trial. Trial 150336 was conducted outside of the IND. DBRUP became aware of this study following review of a 120-Day Safety Update submitted by the Applicant March 24, 2016.

June 27, 2016 - The Agency sent Duchesnay a Review Cycle Extension letter for NDA 021876, Supplement 10 which stated, “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.”
August 3, 2016, August 12, 2016, and August 15, 2016 - Duchesnay was advised that the Agency [CDER/Nomenclature Committee] had determined that the proposed reformulated product “is a new dosage form, and that this change in dosage form requires a new original NDA, which triggers a user fee.” Duchesnay complied with submission of the user fee. Bonjesta (combination 20 mg doxylamine and 20 mg pyridoxine) extended-release tablets was assigned a new NDA number, 209661.

3. CMC/Biopharmaceutics/Device

The Chemistry and Biopharmaceutics information in the application were reviewed by Jean Salemme, Ph.D., Office of Pharmaceutical Quality (OPQ), Office of Lifecycle Drug Products, Division of Post-Marketing Activities 1.

Much of the support of the chemistry, manufacturing and controls, including drug substance, excipients, container/closure, and specifications, methods, method validations, and container/closure, to support NDA 209661, are referenced to NDA 021876.

The proposed tablets contain 10 mg doxylamine succinate and 10 mg pyridoxine hydrochloride as approved Diclegis®. The proposed tablet has additional 10 mg of doxylamine succinate and 10 mg pyridoxine hydrochloride, added to the coating of the tablets. The active components are compatible with GRAS or compendial.

The components of the coatings for the proposed extended release tablets are compatible with The proposed 3-stage dissolution method, acceptance criteria, and data have been evaluated by the OPQ/ONDP/Biopharmaceutics reviewer, Dr. Kalpana Paudel, and are acceptable.

Stability data to 6 months at accelerated conditions are provided and support the stability of the proposed formulation.

No changes have been made in the drug substances manufacturing and controls from that approved for NDA 21876. The drug substances are doxylamine succinate USP and pyridoxine hydrochloride USP No changes have been made in the drug substances manufacturing and controls from that approved for NDA 021876. The suppliers of both drug substances are unchanged from those for the original NDA 021876 application.

The manufacturing sites for NDA 209661 are:

- Duchesnay, Inc., Québec Canada for fabrication, tablet printing, packaging, labeling of finished product storage and distribution
- [Redacted] for release testing of drug substances and excipients prior to manufacture of drug product and fabrication of drug product up to core tablets
• for release testing of drug substances and excipients prior to manufacture of drug product and drug product release testing and stability testing

• for release testing of drug substances prior to manufacture of drug product and drug product release testing and stability testing

On October 20, 2016, the OPQ/Office of Process and Facilities issued an Approve recommendation for the manufacturing sites for NDA 209661.

The Office of Pharmaceutical Quality (OPQ), Office of Lifecycle Drug Products, Division of Post-Marketing Activities 1 concludes that NDA 209661 is acceptable from a chemistry, manufacturing and controls perspective and recommends approval.

4. Nonclinical Pharmacology/Toxicology
The non-clinical pharmacology and toxicology information presented in the application was reviewed by Kimberly Hatfield, Ph.D., Office of New Drugs (OND), Office of Drug Evaluations 3 (ODE 3), DBRUP. No nonclinical studies were submitted in support of the application. The Non-Clinical-Pharmacology/Toxicology concludes that from their perspective, the application is approvable. The following recommended labeling revisions to Section 8 Use in Specific Populations were incorporated in the final applicant and Agency agree-to labeling:

• Section 8.1 Pregnancy

5. Clinical Pharmacology/Biopharmaceutics
The Clinical Pharmacology Review was performed by Chongwoo Yu, Ph.D., Office of Clinical Pharmacology (OCP), Division of Clinical Pharmacology (DCP) 3.

The following is based on information included in the OCP Review, archived October 14, 2016 and Medical Officers’ Review (MOR) archived November 7, 2016.

This NDA is supported solely by three in vivo pharmacokinetics trials: 1) Trial 150033 a single- and multiple-dose comparative bioavailability (bioequivalence) trial of Bonjesta fixed-dose combination 20 mg doxylamine succinate and 20 mg pyridoxine hydrochloride extended-release tablets versus Diclegis® fixed-dose combination 10 mg doxylamine succinate and 10 mg pyridoxine hydrochloride delayed-release tablets, 2) Trial 150336 a single dose comparative bioavailability (bioequivalence) trial of Bonjesta extended-release tablets versus Diclegis® delayed-release tablets and 3) Trial 140115, a comparative bioavailability study of Bonjesta under fed and fasted conditions

Trial 150033 – Multiple Dose (Maximum Dose) Bioequivalence Trial

The objective of Trial 150033 was to compare the rate and extent of absorption, following a single day (Day 1) of administration and 11 consecutive days of administration, under
fasting conditions, of Bonjesta (Test), twice daily oral administration of 20 mg doxylamine and 20 mg pyridoxine combination extended release tablets at 9 am and 9 pm versus Diclegis® (Reference), three times daily oral administration of combination 10 mg doxylamine and 10 mg pyridoxine extended release tablets, one tablet at 9 am, one tablet at 3 pm, and two tablets at 9 pm.

The trial was a single-center, open-label, randomized, 3-period, 3-sequence, reference replicated, crossover study conducted in 39 healthy premenopausal females (31 completed; 18-45 years of age) with a BMI within the range of 18.6-29.9 kg/m2. With exception of the use of hormonal contraceptives, which was allowed and documented, prescription and over-the-counter medication use was prohibited throughout the trial. No concomitant drug therapy, except as noted, was allowed during the trial other than those required for the medical management of an adverse event. Any concomitant medication use other than the occasional use of acetaminophen was evaluated on a case-by-case basis by the investigator or a physician. All concomitant medication use was documented. Women were advised that they were not allowed to take MAO inhibitors for a time interval encompassing 30 days before the initiation of trial medication dosing up to 14 days after the last trial medication administration. Refer to the MOR for a complete discussion of enrollment criteria, excluded and concomitant medications, and baseline demographics.

Women were confined to the inVentiv Clinical Facility from the evening of Day (-) 1 until after the last blood sampling on the morning of Day 12, in each period. The first dose of trial medication was administered at 9:00 AM for the test and at 9:00 AM for the reference medication. Test and reference medications were administered to each woman with 240 mL of water and a hand and mouth check was performed to ensure consumption of the medication. A time window of ±10 minutes from the scheduled time was allowed. Any deviation in the trial drug administration that was greater than the allowed time window was considered as a protocol deviation.

In order to minimize endogenous concentrations of pyridoxine and metabolites, women participating in the trial were asked to avoid consuming vitamin B6 supplements and foods with high content of vitamin B6 for appropriate periods of time before drug administration and during the trial. No food was allowed from at least 2.5 hours before until at least 2 hours after each dosing. Fluids were not permitted from 1 hour pre-dose and to 1 hour post-dose. Water was allowed *ad libitum* at all other times. For every dosing phase, both the planned and exact dosing time was documented.

The treatment phases were separated by washout periods of at least 28 days between the last dose of each period and the first dose of the subsequent period.
The blood samples for plasma (or whole blood in the case of pyridoxal) concentration measures were collected as presented in Table 1

**Table 1: Blood Sampling Collection Schedule for Comparative Bioavailability (Bioequivalence) Trial 150033**

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<thead>
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<th>Days 1 and 11</th>
<th>Pyridoxine</th>
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<td>pre-dose (-1, -0.5 hours, and -10 minutes) and 0.25, 0.5, 1, 1.5, 1.75, 2, 2.25, 2.5, 2.75, 3, 3.5, 4, 4.5, 5, 5.5, 6 (prior to dosing if applicable), 6.5, 7, 7.5, 7.75, 8, 8.25, 8.5, 8.75, 9, 9.5, 10, 10.5, 11, 11.5, 12 (prior to dosing), 12.5, 13, 13.5, 13.75, 14, 14.25, 14.5, 14.75, 15, 15.5, 16, 16.5, 17, 17.5, 18, 19, 20, 21, 22, 23, and 24 hours (prior to Day 2 dosing) post-morning dose</td>
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<tr>
<td>Days 3 through 10</td>
<td>Pyridoxal</td>
</tr>
<tr>
<td>pre-dose (-1, -0.5 hours, and -5 minutes) and at 0.25, 0.5, 0.75, 1, 1.25, 1.5, 1.75, 2, 2.25, 2.5, 2.75, 3, 3.33, 3.67, 4, 4.33, 4.67, 5, 5.5, 6, and 8 hours post-dose</td>
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**Pyridoxal 5’-phosphate**

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<th>Pyridoxal</th>
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<tr>
<td>Days 3 through 10</td>
<td>Blood samples were collected prior to each morning’s dose</td>
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**Pyridoxal**

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<th>Pyridoxal</th>
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<tr>
<td>Days 3 through 10</td>
<td>Blood samples were collected prior to each morning’s dose</td>
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**Doxylamine**

<table>
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<th>Doxylamine</th>
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<td>pre-dose and 1, 2, 3, 3.5, 4, 5, 6 (prior to dosing if applicable), 7, 8, 9, 10, 11, 12 (prior to dosing), 13, 14, 15, 15.5, 16, 17, 18, 19, 20, 21, 22, 23, and 24 hours (prior to Day 2 dosing) post-morning dose</td>
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<tr>
<td>Days 3 through 10</td>
<td>Blood samples were collected prior to each morning’s dose</td>
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Source: Adapted from Medical Officer Review (MOR) Table 4 and NDA 209661, Integrated Clinical and Statistical Report, sub-section 9.5.4 Drug Concentration Measurements, pages 26 and 27 of 2480.

PK parameters were assessed on Day 1 following administration of one 20/20 mg tablet of test (Bonjesta) and one 10/10 mg tablet of reference (Diclegis®) at 9 AM and on Day 11, following multiple day administration. The following PK parameters were calculated by standard non-compartmental (mathematical determination of the degree of exposure following administration of a drug and the drug’s associated PK parameters, such as clearance, elimination half-life, etc.) methods for doxylamine, pyridoxine, pyridoxal, and pyridoxal 5’-phosphate:

1. \( AUC_{0.6} \), \( AUC_{0.12} \), \( AUC_{0.24} \): partial area under the concentration-time curve.
2. \( AUC_{0.6 ss} \), \( AUC_{0.12 ss} \), \( AUC_{0.24 ss} \): partial area under the concentration-time curve at steady-state.
3. \( T_{max} \): time of observed \( C_{max} \) during the 24-hours period.
4. \( T_{max} \): time of observed \( C_{max} \) during the 24-hours period at steady-state.
5. \( C_{max} \): maximum observed concentration during the 24-hours period.
6. $C_{\text{max}0-24 \text{ss}}$: maximum observed concentration during the 24-hours period at steady-state.
7. $C_{\text{min}ss}$: last observed concentration at steady-state.
8. Fl (%): percentage of fluctuation.

The point estimates and 90% Test and Reference ratios of $\text{AUC}_{(0-24)}$ and $C_{\text{max}}$ for doxylamine and baseline corrected pyridoxal 5'-phosphate on Days 1 and 11 using natural log transformed data are summarized in Tables 2.

Table 2: Summary of Bioequivalence Analyses of Doxylamine Succinate and Baseline Corrected Pyridoxal 5'-Phosphate in Trial 150033

<table>
<thead>
<tr>
<th>Analyte Parameter</th>
<th>Geometric Mean</th>
<th>Point estimate (%) (Test/Reference)</th>
<th>90% CI</th>
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<tr>
<td></td>
<td></td>
<td>Test</td>
<td>Reference</td>
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<tr>
<td>$\text{AUC}_{(0-24)}$ (ng hr/mL)</td>
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<td>1397.1</td>
<td>1010.6</td>
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<tr>
<td>$C_{\text{max}}$ (ng/mL)</td>
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<td>92.3</td>
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<td>Day 1</td>
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<td>$\text{AUC}_{(0-24)}$ (ng hr/mL)</td>
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</tr>
<tr>
<td>$C_{\text{max}}$ (ng/mL)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline Corrected</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pyridoxal 5'-Phosphate</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$\text{AUC}_{(0-24)}$ (ng hr/mL)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$C_{\text{max}}$ (ng/mL)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day 11</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Doxylamine Succinate</td>
<td></td>
<td>2802.2</td>
<td>2720.4</td>
</tr>
<tr>
<td>$\text{AUC}_{(0-24)}$ (ng hr/mL)</td>
<td></td>
<td>168.3</td>
<td>155.6</td>
</tr>
<tr>
<td>$C_{\text{max}}$ (ng/mL)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline Corrected</td>
<td></td>
<td>1661.5</td>
<td>1657.4</td>
</tr>
<tr>
<td>Pyridoxal 5'-Phosphate</td>
<td></td>
<td>82.2</td>
<td>81.4</td>
</tr>
<tr>
<td>$\text{AUC}_{(0-24)}$ (ng hr/mL)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$C_{\text{max}}$ (ng/mL)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Source: Adapted from OCP Review Tables 17, 18, 21 and 22, and MOR Table 5

In single- and multiple dose comparative bioavailability (bioequivalence) Trial 150033, results demonstrate bioequivalence of Bonjesta to Diclegis on Day 11 (per the applicant steady state is assured following Day 10) for both doxylamine succinate and baseline pyridoxal 5'-phosphate for the pharmacokinetic parameters of $\text{AUC}_{(0-24)}$ and $C_{\text{max}}$. The 90% confidence intervals of the Test:Reference ratio of geometric means of these parameters fall within the 80-125% acceptable range for establishment of bioequivalence.

However, the Day 1, single dose results from the multiple dose comparative bioavailability (bioequivalence) trial do not demonstrate bioequivalence of Bonjesta to Diclegis®. The 90% confidence intervals of the Test:Reference ratio of geometric means of $\text{AUC}_{(0-24)}$ and $C_{\text{max}}$ for doxylamine succinate and the $\text{AUC}_{(0-24)}$ for pyridoxal 5'-phosphate fall outside of the 80-125% acceptable range for establishment of bioequivalence. Per the applicant, the
failure to demonstrate bioequivalence is explained by “… the challenge of evaluating single day and multiple days in one trial design considering the dosing schedule. The first daily dose was given in the morning after an overnight fasting conditions, the last daily dose was administered 12 hours later after a normal controlled dinner. The C_{max} of the last daily dose occurred at around 22 hours from initial dose. Measuring the first day AUC_{0-24} does not allow sufficient time to properly characterize the elimination PK profile.” The Clinical and OCP reviewers agree that the multiple dose trial, as designed and conducted by the applicant, did not adequately assess bioequivalence after a single dose administration of Bonjesta vs. Diclegis®.

Additionally Trial 150033 lacks the bridging for the proposed starting dose of Bonjesta (i.e., one fixed dose combination 20 mg doxylamine succinate and 20 mg pyridoxine hydrochloride extended-release tablet given at bedtime) to the currently approved starting dose for Diclegis® (i.e., two fixed-dose combination 10 mg doxylamine succinate and 10 mg pyridoxine hydrochloride delayed-release tablets given at bedtime). There is no information from Trial 150033 supporting that the efficacy and safety of one Bonjesta tablet will be comparable to those of two Diclegis® tablets. Establishment of bridging for the beginning dose is important as some women may be maintained on the initial dose, if symptoms are controlled with this dose.

During the course of the review on June 9, 2016, the Agency asked the applicant to submit the report for Trial 150336, a single dose comparative bioavailability trial conducted by the applicant in Canada but never submitted to the IND. On June 13, 2016, the Agency received from Duchesnay, the requested Clinical Trial Report for Trial 150336

**Trial 150336 – Single Dose (Starting Dose) Bioequivalence Trial**

The objective of non-IND Trial 150336 was to compare the rate and extent absorption of a single (one) combined Bonjesta extended-release tablet (Test) versus two Diclegis® delayed-release tablets (Reference), under fasting conditions. Trial 150336 was a single center (inVentiv Health Clinique, Inc.), randomized, single-dose, open-label, 2-way crossover bioequivalence trial. Enrollment criteria and allowed- and prohibited medications for Trial 150336 were the same as employed for Trial 150033.

Women meeting enrollment criteria were randomly assigned to a treatment group in accordance with the randomization scheme generated by inVentiv. Women were advised that they were not allowed to take MAO inhibitors for a time interval encompassing 30 days before the initiation of trial medication dosing up to 14 days after the last trial medication administration. Refer to the MOR for a complete discussion of enrollment criteria, excluded and concomitant medications, and baseline demographics.

In each period, according to randomization schedule, all women received single oral doses of either Test or Reference study medication as follows:

- **Test**: One Bonjesta combination tablet (20 mg doxylamine succinate and 20 mg pyridoxine hydrochloride), between 7-8 am
Reference: Two Diclectin® tablets (10 mg doxylamine succinate / 10 mg pyridoxine hydrochloride), at between 7-8 am

Women were confined to the inVentiv Clinical Facility from the evening of Day (-) 1 (at least 10 hours prior to drug administration) until after the 24 hour post-dose blood draw in each period. The treatment phases were separated by washout periods of at least 21 days between the last dose of each period and the first dose of the subsequent period. Blood samples were collected pre-dose and up to 72 hours post-dose for PK characterization depending on analyte. After a supervised overnight fast of at least 10 hours, participating women assigned Numbers 01 to 26 were dosed on the mornings of October 17, 2015 and November 7, 2015 between 07:00 and 07:50. Likewise following a supervised overnight fast of at least 10 hours, participating women assigned Numbers 27 to 52 were dosed on the mornings of October 24, 2016 and November 14, 2015 between 07:00 and 07:53. Following drug administration, all trial participants subsequently fasted for a period of at least 4 hours. Women were served a controlled meal not less than four hour post-dose and at appropriate times thereafter, in each period. All meals served on trial had a low content in vitamin B₆ (no tuna, chicken, turkey, cod, salmon, beef tenderloin, or banana were served).

Trial medication was administered to each woman with 240 mL of water and a hand and mouth check was performed to ensure consumption of the medication.

In each period, a total of 40 blood samples (via dead volume intravenous catheter or direct venipuncture) were drawn over 72 hours for PK analysis as presented in the following Table 3.

**Table 3: Blood Sampling Schedule for Comparative Bioavailability (Bioequivalence Trial) 150336**

<table>
<thead>
<tr>
<th>Doxylamine</th>
<th>Pre-dose (-1.0-0.5 hours, and -5 minutes) and at 0.5, 1, 1.5, 2, 2.5, 2.75, 3, 3.5, 4, 4.5, 5, 5.5, 6, 7, 8, 10, 12, 16, 24, 26, 48, and 60 hours post dose hours (prior to Day 2 dosing) post-morning dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pyridoxal 5'-phosphate</td>
<td>Pre-dose (-1.0-0.5 hours, and -5 minutes) and 1, 2, 3, 4, 4.5, 5, 5.5, 6, 6.5, 7, 8, 9, 10, 11, 12, 14, 16, 20, 24, 48, and 72 hours post-morning dose</td>
</tr>
<tr>
<td>Pyridoxine</td>
<td>Pre-dose (-1.0-0.5 hours, and -5 minutes) and 0.25, 0.5, 0.75, 1, 1.25, 1.5, 1.75, 2, 2.25, 2.5, 2.75, 3, 3.33, 3.67, 4, 4.33, 4.67, 5, 5.5, 6, and 8 hours post-morning dose</td>
</tr>
<tr>
<td>Pyridoxal</td>
<td>Pre-dose (-1.0-0.5 hours, and -5 minutes) and 0.25, 0.5, 0.75, 1, 1.25, 1.5, 1.75, 2, 2.25, 2.5, 2.75, 3, 3.33, 3.67, 4, 4.33, 4.67, 5, 5.5, 6, 8, 10, 12 and 16 hours post-morning dose</td>
</tr>
</tbody>
</table>

Source: Adapted from MOR Table 8 and NDA 209661, Integrated Clinical and Statistical Report, subsection 9.5.4 Drug Concentration Measurements, page 63 of 1121.

Trial 150036 was conducted using a sampling truncated at 72 hours for pyridoxal 5'-phosphate. Per the applicant, the metabolite pyridoxal 5'-phosphate has a long T½ el, therefore, samples were collected up to 72 hours for this analyte. "...drugs with long T½ el that also demonstrates low intra-subject variability in distribution and clearance, an AUC truncated at 72 hours (AUC0-72) can be used in place of AUC0-t or AUC0-inf. The applicant..."
also judged that the period of 72 hours was sufficiently long enough to adequately characterize the concentration time-profile of doxylamine, pyridoxine, and pyridoxal.

Based on data from previous studies, which indicate that the elimination T\(\frac{1}{2}\) el of doxylamine, pyridoxine, pyridoxal, and pyridoxal-5'-phosphate averages 12 hours, 0.5 hour, two hours, and from 36 to 95 hours, respectively, in healthy individuals, a washout period of at least 21 days was chosen to allow the complete elimination of the drug before subsequent dosing and to avoid carry-over effects.

The following PK parameters were calculated by standard non-compartmental methods for doxylamine, pyridoxine, and pyridoxal:

1. AUC\(_{0-t}\): area under the concentration-time curve from time zero to the last non-zero concentration.
2. AUC\(_{0-inf}\): area under the concentration-time curve from time zero to infinity (extrapolated).
3. C\(_{\text{max}}\): maximum observed concentration.
4. Residual area: calculated as 100\(^{-}\) (AUC\(_{0-t}\) / AUC\(_{0-inf}\)).
5. T\(_{\text{max}}\): time of observed C\(_{\text{max}}\).
6. T\(\frac{1}{2}\) el: elimination half-life.
7. K\(_{el}\): elimination rate constant.

The following PK parameters were calculated by standard non-compartmental methods for pyridoxal-5'-phosphate:

1. C\(_{\text{max}}\): maximum observed concentration.
2. T\(_{\text{max}}\): time of observed C\(_{\text{max}}\).
3. AUC\(_{0-72}\): area under the concentration-time curve from time zero to the time of the last measureable concentration.

Pyridoxine and its metabolites, pyridoxal and pyridoxal 5'-phosphate (thought to be the active metabolite), are endogenous compounds and were analyzed both with and without correction for baseline levels. PK parameters were calculated based on plasma/whole blood total concentrations and baseline subtracted plasma/whole blood concentrations, as appropriate. Pharmacokinetic and statistical analyses were performed at ______.

Trial 150336 was conducted in 52 healthy premenopausal females (48 completed; 20-45 years of age) with a BMI within the range of 19.3-29.8 kg/m\(^2\). Refer to the MOR, archived on November 7, 2016 for a complete discussion of trial demographics.
The point estimates and 90% Test and Reference ratios of AUC\(_{(0-60)}\), AUC\(_{(0-\text{inf})}\) and C\(_{\text{max}}\) for doxylamine and AUC\(_{(0-72)}\) and C\(_{\text{max}}\) for baseline corrected pyridoxal 5'-phosphate using natural log transformed data are summarized in Table 4.

**Table 4** Summary of Comparative Bioavailability (Bioequivalence) Analyses of Doxylamine Succinate and Baseline Corrected Pyridoxal 5'-Phosphate in Trial 150336

<table>
<thead>
<tr>
<th>Analyte Parameter</th>
<th>Geometric Mean</th>
<th>Point estimate (%)</th>
<th>90% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Test</td>
<td>Reference</td>
<td>(Test/Reference)</td>
</tr>
<tr>
<td>Doxylamine Succinate</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AUC(_{(0-60)}) (ng·hr/mL)</td>
<td>1325.3</td>
<td>1301.4</td>
<td>102.0</td>
</tr>
<tr>
<td>AUC(_{(0-\text{inf})}) (ng·hr/mL)</td>
<td>1375.6</td>
<td>1353.9</td>
<td>101.7</td>
</tr>
<tr>
<td>C(_{\text{max}}) (ng/mL)</td>
<td>91.0</td>
<td>96.7</td>
<td>94.2</td>
</tr>
<tr>
<td>Baseline Corrected Pyridoxal 5'-Phosphate</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AUC(_{(0-72)}) (ng·hr/mL)</td>
<td>1006.9</td>
<td>964.9</td>
<td>104.2</td>
</tr>
<tr>
<td>C(_{\text{max}}) (ng/mL)</td>
<td>28.8</td>
<td>27.5</td>
<td>104.8</td>
</tr>
</tbody>
</table>

Source: Adapted from OCP Review Tables 1 and 2 and MOR Table 9

In single-dose comparative bioavailability (bioequivalence) Trial 150336, results demonstrate bioequivalence of Bonjesta to Diclegis\textsuperscript{\textregistered} for doxylamine succinate for the pharmacokinetic parameters of AUC\(_{(0-60)}\), AUC\(_{(0-\text{inf})}\) and C\(_{\text{max}}\) and baseline pyridoxal 5'-phosphate for the pharmacokinetic parameters of AUC\(_{(0-72)}\) and C\(_{\text{max}}\). The 90% confidence intervals of the Test:Reference ratio of geometric means of all of these parameters fall within the 80-125% acceptable range for establishment of bioequivalence.

**Trial 140115 – Comparative Bioavailability “Food Effect” Trial**

The objective of Trial 140115 was to evaluate the effect of food on the pharmacokinetics (PK) of Bonjesta administered as a single fixed-dose combination 20 mg doxylamine and 20 mg pyridoxine extended-release tablet; the tablet consists of a 10 mg doxylamine and 10 mg pyridoxine delayed-release core and a 10 mg doxylamine and 10 mg pyridoxine immediate-release coating component.

Trial 140115 was a single center (inVentiv Health Clinique, Inc.), randomized, single-dose, open-label, 2-way crossover comparative food-effect bioavailability trial conducted in 24 healthy premenopausal women to compare the rate and extent of absorption of Tradename tablets under fasting and fed conditions. Women were randomly assigned to a treatment in accordance with the randomization scheme generated by inVentiv Health. Participating women were confined to the inVentiv Clinical Facility from at least 11 hours prior to drug administration until after the 36.0-hour post-dose blood draw, in each crossover period. The treatment phases were separated by a washout period of at least 21 days. Per the applicant, “Based on data from literature and previous studies, which indicate that the T\(_{1/2}\)\(_{el}\) of doxylamine, pyridoxine, pyridoxal, and pyridoxal 5'-phosphate averages 10 to 12 hours,
half an hour, two hours and 36 to 80 hours, respectively, in healthy individuals, a washout period of at least 21 days was chosen to allow the complete elimination of the drug before subsequent dosing and to avoid carry-over effects.”

Enrollment criteria, allowed-, and prohibited medications for Trial 140115 were the same as employed for Trial 150033. Women were advised that they were not allowed to take MAO inhibitors for a time interval encompassing 30 days before the initiation of trial medication dosing up to 14 days after the last trial medication administration.

Women meeting enrollment criteria were randomly assigned to a treatment group in accordance with the randomization scheme generated by inVentiv. Refer to the MOR for a complete discussion of enrollment criteria, excluded and concomitant medications, and baseline demographics.

All women fasted overnight for at least 10 hours prior to drug administration. Women in the fed group received a standardized high-fat (approximately 50% of the total caloric content of the meal), high-caloric (800-1000 calories) breakfast 30 minutes before drug administration (and consumed within 30 minutes). Following drug administration, all women subsequently fasted for a period of at least 4 hours. Women were served a controlled meal 4 hours post-dose and at appropriate times thereafter, in each period. Except for fluids provided with breakfast (Test) and 240 mL water given with trial medication, no fluids were allowed from 1 hour before dosing until 1 hour post-dose. Water was provided ad libitum at all other times.

Doxylamine, pyridoxine and pyridoxal 5'-phosphate were analyzed in plasma samples and pyridoxal was analyzed in whole blood at \((b)(4)\). Because pyridoxine and its metabolites pyridoxal 5'-phosphate and pyridoxal are endogenous compounds, they were analyzed both with and without correction for baseline levels. Per the applicant, all pre-dose concentrations of pyridoxine were below the lower limit of quantitation for all women and, therefore, no baseline adjustment was performed. For pyridoxal 5'-phosphate and pyridoxal, baseline-uncorrected and baseline-corrected data are presented per protocol.

A total of 24 women were enrolled and dosed in this trial; all of these 24 women completed the trial. Women were dosed under direct supervision, and a mouth (using a tongue depressor and a flashlight) and hand check was performed to ensure subjects swallowed the trial medication.
Blood samples for plasma (or whole blood in the case of pyridoxal) concentration measures were collected as presented in the following Table 10.

Table 5  Blood Sampling Collection Schedule

<table>
<thead>
<tr>
<th></th>
<th>Pyridoxine</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Fed</strong></td>
<td>pre-dose (-1, -0.5 hours, and -5 minutes) and 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, and 24 hours post-dose</td>
</tr>
<tr>
<td><strong>Fasted</strong></td>
<td>pre-dose (-1, -0.5 hours, and -5 minutes) and at 0.25, 0.5, 0.75, 1, 1.25, 1.5, 1.75, 2, 2.25, 2.5, 2.75, 3, 3.33, 3.67, 4, 4.33, 4.67, 5, 5.5, 6, and 8 hours post-dose</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Pyridoxal 5'-phosphate:</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Fed</strong></td>
<td>pre-dose (-1, -0.5 hours, and -5 minutes) and 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 18, 20, 22, 24, 30, 36, 48, and 72 hours post-dose.</td>
</tr>
<tr>
<td><strong>Fasted</strong></td>
<td>pre-dose (-1, -0.5 hours, and -5 minutes) and 1, 2, 3, 4, 4.5, 5, 5.5, 6, 6.5, 7, 8, 9, 10, 11, 12, 14, 16, 20, 24, 48, and 72 hours post-dose</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Pyridoxal</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Fed</strong></td>
<td>pre-dose (-1, -0.5 hours, and -5 minutes) and 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, and 30 hours post-dose.</td>
</tr>
<tr>
<td><strong>Fasted</strong></td>
<td>pre-dose (-1, -0.5 hours, and -5 minutes) and at 0.25, 0.5, 0.75, 1, 1.25, 1.5, 1.75, 2, 2.25, 2.5, 2.75, 3, 3.33, 3.67, 4, 4.33, 4.67, 5, 5.5, 6, 8, 10, 12, and 16 hours post-dose.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Doxylamine</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Fed</strong></td>
<td>Pre-dose and 1, 2, 3, 3.5, 4, 5, 5.5, 6, 6.5, 7, 7.5, 8, 8.5, 9, 9.5, 10, 10.5, 11, 11.5, 12, 13, 14, 16, 20, 24, 36, 48, and 72 hours post-dose.</td>
</tr>
<tr>
<td><strong>Fasted</strong></td>
<td>pre-dose and 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 5.5, 6, 7, 7.5, 8, 10, 12, 16, 24, 36, 48, and 60 hours post-dose</td>
</tr>
</tbody>
</table>

Source: Adapted from MOR Table 10 and NDA 209661, Integrated Clinical and Statistical Report, subsection 9.5.4 Drug Concentration Measurements, pages 23 and 24 of 483.

Per the applicant, intensive sample collection was done within the first hours for pyridoxine in order to get a good characterization of the PK profile because pyridoxine reaches maximum concentrations relatively rapidly under fasting conditions, and is eliminated rapidly.

The pharmacokinetic parameters assessed were AUC$_{0-t}$, AUC$_{0-inf}$, C$_{max}$, Residual area, T$_{max}$, T$_{1/2}$, and K$_{el}$, for doxylamine, pyridoxine, and baseline corrected pyridoxal. For pyridoxal 5'-phosphate and baseline corrected pyridoxal 5'-phosphate, the pharmacokinetic parameters were AUC$_{0-72}$, C$_{max}$, and T$_{max}$. For pyridoxal, the pharmacokinetic parameters were AUC$_{0-4}$, C$_{max}$, and T$_{max}$. PK and statistical analyses were performed at...
Trial 140115 was conducted in 24 healthy premenopausal females, (mean 32 ± 8 years of age with a BMI 24. ± 15 3.16 kg/m²). The summary of food effects [point estimates and 90% Test and Reference ratios of AUC\(_{(0-t)}\), AUC\(_{(0-inf)}\) and C\(_{\text{max}}\) for doxylamine and AUC\(_{(0-t)}\) and C\(_{\text{max}}\) for baseline corrected pyridoxal 5'-phosphate] using natural ln- transformed data are summarized in Tables 6.

### Table 6  Summary of Food Effect [Comparative Bioavailability (Bioequivalence) Analyses of Doxylamine Succinate and Baseline Corrected Pyridoxal 5'-Phosphate in Trial 140115]

<table>
<thead>
<tr>
<th>Analyte Parameter</th>
<th>Geometric Mean</th>
<th>Point estimate (%)</th>
<th>90% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Test</td>
<td>Reference</td>
<td></td>
</tr>
<tr>
<td>Doxylamine Succinate</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AUC(_{(0-t)}) (ng·hr/mL)</td>
<td>1219.1</td>
<td>1247.0</td>
<td>97.6</td>
</tr>
<tr>
<td>AUC(_{(0-inf)}) (ng·hr/mL)</td>
<td>1253.5</td>
<td>1289.1</td>
<td>97.0</td>
</tr>
<tr>
<td>C(_{\text{max}}) (ng/mL)</td>
<td>62.7</td>
<td>85.3</td>
<td>73.6</td>
</tr>
<tr>
<td>Baseline Corrected Pyridoxal 5'-Phosphate</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AUC(_{(0-t)}) (ng·hr/mL)</td>
<td>1005.4</td>
<td>975.1</td>
<td>103.4</td>
</tr>
<tr>
<td>C(_{\text{max}}) (ng/mL)</td>
<td>28.7</td>
<td>26.4</td>
<td>109.3</td>
</tr>
</tbody>
</table>

Source: Adapted from OCP Review Tables 7 and 8, and MOR Table 11

For doxylamine and pyridoxine, no food effect was to be concluded if the 90% confidence intervals of the point estimate of the ratio (A/B: fed conditions/fasting conditions) of least-squared means from the ANOVA of the ln-transformed AUC\(_{0-t}\), AUC\(_{0-inf}\), and C\(_{\text{max}}\) are within 80 to 125%. The 90% confidence intervals of the point estimate of the ratio for the parameter C\(_{\text{max}}\) of the analyte doxylamine falls outside of the acceptable range.

Food caused a delay in the median T\(_{\text{max}}\) of doxylamine and pyridoxine 5'-phosphate to 6.5 and 16.0 hours, respectively (data not shown). In addition, food decreased the C\(_{\text{max}}\) for doxylamine by 26.4%. The OCP and Clinical reviewers are in agreement that, Bonjesta tablets should be administered under fasting conditions to avoid food affecting the T\(_{\text{max}}\) and C\(_{\text{max}}\), as noted above.

Based on the comparative bioavailability information in single dose Trial 150336, multiple dose Trial 150033 and food effect Trial 140115, OCP finds that the overall Clinical Pharmacology Information submitted to support NDA 209661 is acceptable to recommend approval of Bonjesta.
6. Clinical Microbiology

Review of NDA 209661 by Clinical Microbiology was not necessary and, therefore, no review was performed.

7. Clinical/Statistical – Efficacy

No new phase 3 safety and efficacy data were submitted to support Bonjesta. The Medical Officers’ Review of Drs. Theresa van der Vlugt and Nneka McNeal-Jackson evaluated the pharmacokinetic data from the three comparative bioavailability trials, as noted under Section 5.5. “Clinical Pharmacology/Biopharmaceutics” of the MOR review, for the acceptability of this data to support the proposed labeling. Clinical agrees with OCP that the submitted trials provide acceptable bioequivalence information to support approval of Bonjesta.

8. Safety

No new phase 3 safety and efficacy data were submitted to support Bonjesta. The Clinical Review Team reviewed the safety data from the three comparative bioavailability trials, as noted under Section 5.5. “Clinical Pharmacology/Biopharmaceutics” of the CDTL review, for the acceptability of this data to support the proposed labeling. No new safety signals were identified upon review of each of the comparative bioavailability trials separately or pooled. The adverse events (AE), serious adverse event (SAE), treatment-emergent adverse events (TEAE), and TEAEs of special clinical interest profiles were all consistent with those of Diclegis®.

9. Advisory Committee Meeting

Advisory Committee input was not sought for the decision on this application seeking approval of a revised formulation and dose of an approved product.

10. Pediatrics

A pediatric waiver for ages 0-11 (under age 12) was requested by Duchesnay with the rationale that Duchesnay Inc. is requesting a waiver from pediatric development in children from birth to [redacted] years of age.”

Duchesnay’s requests were discussed at the July 6, 2016 Pediatric Research Committee (PeRC)/Pediatric Research Equity Act (PREA) subcommittee meeting. PeRC agreed with the plan for a partial waiver for studies/trials in [redacted] patients 0 to 11 years of age because studies are impossible or highly impractical and to a deferral in [redacted] patients 12 to 17 years of age.
11. Other Relevant Regulatory Issues

**Inspections by the Office of Scientific Investigations (OSI)**

As there were no phase 3 trials conducted specifically to support this NDA, only the sites critical comparative bioavailability trials were inspected.

The facilities involved in the conduct of the Trials 150033, 150336 and 140115 include:

(b) (4) involved in the conduct and statistical evaluation of Trial 150336. Requests to the Office of Study Integrity and Surveillance (OSIS) for clinical and bioanalytical site inspections of Trials 150033 and 140115 were made by OCP/DCP3 on January 4, 2015.

On February 22, 2016, the Division of New Drug Bioequivalence Evaluation (DNDBE) in OSIS recommends accepting data without an on-site inspection, noting “…based on the findings from the last inspection, and our recommendation to the review division, an inspection of the site will not be needed at this time.” “…OSIS recently inspected the site listed below. The inspctional outcome from the inspection was classified as No Action Indicated (NAI).” The facility identified by DNDBE is (b) (4).

Based on this recommendation, no request was made to OSIS for clinical and bioanalytical site inspection of Trials 150036

**Financial Disclosure**

The Applicant was compliant with the Financial Disclosure Requirements (21 CFR § 54). Per the applicant, “…each listed clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b), did not disclose any such interest.” The applicant further certifies, “that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).”

A signed FORM FDA 1572 (2/13) is available in the application for the principal investigator and each sub-investigator. See 5.3.1.2, List Description Investigator Site, Financial Disclosure Statements, pages 16.1.4-108 through 118 for the Principal Investigator and 11 Sub-Investigators in Trial 150033. See 5.3.1.1, List Description Investigator Site, Financial Disclosure Statements, pages 16.1.4-145 through 158 for the principal investigator and nine (9) sub-investigators in Trial 140115.
Clearance by 505(b)(2) Committee

505(b)(2) designation for NDA 209661 for Bonjesta was discussed by 505(b)(2) Committee on October 10, 2016. Discussion focused on:

1. The non-clinical Section relied upon NDA 10598 for Bendectin Tablets.
2. A bridge between the delayed release tablets formulation and Bendectin Tablets was established in Duchesnay’s NDA 021876 (Diclegis Delayed Release Tablets). In Duchesnay’s NDA 209661 (Diclegis Extended Release Tablets), an in vivo Bioequivalence (BE) study was conducted between the delayed release tablets formulation and the extended release tablets formulation. Bioequivalence was established.

The 505(b)(2) Committee confirmed 505(b)(2) status for NDA 209661.

Tradename Review

On November, the Division of Medication Error Prevention and Analysis (DMEPA) concluded that the tradename “Bonjesta” was acceptable.

The Office of Prescription Drug Promotion (OPDP)

OPDP’s recommendations (Review dated October 26, 2016) for Highlights and Full Prescribing Information, Patient Information and Carton/Container labeling were taken into consideration for negotiations with the applicant to reach agreed-to labeling.

OPDP’s recommendation to remove the image of a pregnant woman from one side of the tablet because it suggests Bonjesta “is approved for use in all pregnant women” was rejected. Bonjesta is indicated for all pregnant women with nausea and vomiting of pregnancy who do not respond to conservative management as long as these women do not have contraindications and they are properly made aware of all Warnings and Precautions.

Office of Medical Policy/Division of Medical Policy Programs (DMPP)

DMPP’s recommendations for the Patient Information were taken into consideration for negotiations with the applicant to reach agreed-to labeling. The majority of the recommendations were incorporated into the final Patient Information.

The recommendations from DMPP on dosing did not appropriately track those recommendations as provided in Highlights and Full Prescribing Information and were, therefore, revised.

12. Labeling

Labeling agreed-to by the applicant and the Agency is attached to this review.

13. Conclusions/Recommendations/Risk Benefit Assessment

I concur with the primary review disciplines (Preclinical/Pharmacology-Toxicology, OPQ, OCP and Clinical) conclusions that NDA 209661 for Bonjesta should receive an Approval action.
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
11/07/2016