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APPLICATION NUMBER:

209661Orig1s000

MEDICAL REVIEW(S)

CLINICAL REVIEW

Application Type	505(b)(2) NDA
Application Number(s)	209661
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Division / Office	Division of Bone, Reproductive, and Urologic Products (DBRUP), Office of Drug Evaluation III (ODE III)
Reviewer Name(s)	Theresa H. van der Vlugt, MD, MPH Nneka McNeal-Jackson, MD
Review Completion Date	November 7, 2016
Established Name	Doxylamine succinate and pyridoxine hydrochloride
(Proposed) Trade Name	Tradenname
Therapeutic Class	Antihistamine plus vitamin B ₆ analog
Applicant	Mapi USA, Inc., the U.S. representative for Duchesnay Inc.
Formulation(s)	Extended-release tablet

Dosing Regimen	One tablet daily at bedtime. If symptoms are not adequately controlled, the dose can be increased to a maximum recommended dose of two tablets daily (one in the morning and one at bedtime)
Indication(s)	“Treatment of Nausea and Vomiting of Pregnancy in ^{(b) (4)} Who do not Respond to Conservative Management”
Intended Population(s)	Pregnant women

Clinical Review

Theresa H. van der Vlugt, M.D., M.P.H.; Nneka McNeal-Jackson, M.D.

NDA 209661

Tradename (20 mg doxylamine succinate and 20 mg pyridoxine hydrochloride)

extended-release tablets

Table of Contents

1	RECOMMENDATIONS/RISK BENEFIT ASSESSMENT	7
1.1	Recommendation on Regulatory Action	7
1.2	Risk Benefit Assessment	9
1.3	Recommendations for Postmarket Risk Evaluation and Mitigation Strategies	9
1.4	Recommendations for Postmarket Requirements and Commitments	9
2	INTRODUCTION AND REGULATORY BACKGROUND	9
2.1	Product Information	9
2.2	Tables of Currently Available Treatments for Proposed Indications	11
2.3	Availability of Proposed Active Ingredient in the United States	12
2.4	Important Safety Issues With Consideration to Related Drugs	12
2.5	Summary of Presubmission Regulatory Activity Related to Submission	12
2.6	Other Relevant Background Information	18
3	ETHICS AND GOOD CLINICAL PRACTICES	19
3.1	Submission Quality and Integrity	19
3.2	Compliance with Good Clinical Practices	20
3.3	Financial Disclosures	23
3.3.1	Trial 150033 and Trial 140115:	23
3.3.2	Non-IND Trial 150336:	24
4	SIGNIFICANT EFFICACY/SAFETY ISSUES RELATED TO OTHER REVIEW DISCIPLINES	24
4.1	Chemistry Manufacturing and Controls	24
4.2	Clinical Microbiology	28
4.3	Preclinical Pharmacology/Toxicology	28
4.4	Clinical Pharmacology	28
4.4.1	Mechanism of Action	30
4.4.2	Pharmacodynamics	31
4.4.3	Pharmacokinetics	31
5	SOURCES OF CLINICAL DATA	33
5.1	Tables of Studies/Clinical Trials	33
5.2	Review Strategy	34
5.3	Discussion of Individual Studies/Clinical Trials	34
5.3.1	Bioequivalence Trial 150033	34
5.3.2	Bioequivalence Trial 150336	43
5.3.3	Fed/Fasted Bioavailability Trial 140115	49
6	REVIEW OF EFFICACY	54

Clinical Review

Theresa H. van der Vlugt, M.D., M.P.H.; Nneka McNeal-Jackson, M.D.

NDA 209661

Tradename (20 mg doxylamine succinate and 20 mg pyridoxine hydrochloride)
extended-release tablets

Efficacy Summary	54
6.1 Indication	54
6.1.1 Methods	54
6.1.2 Demographics.....	54
6.1.3 Subject Disposition	54
6.1.4 Analysis of Primary Endpoint(s).....	54
6.1.5 Analysis of Secondary Endpoints(s)	55
6.1.6 Other Endpoints	55
6.1.7 Subpopulations	55
6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations	55
6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects	55
6.1.10 Additional Efficacy Issues/Analyses	55
7 REVIEW OF SAFETY	55
<i>Safety Summary</i>	55
7.1 Methods	56
7.1.1 Studies/Clinical Trials Used to Evaluate Safety	56
7.1.2 Categorization of Adverse Events	57
7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence	58
7.2 Adequacy of Safety Assessments	58
7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations.....	58
7.2.2 Explorations for Dose Response	60
7.2.3 Special Animal and/or In Vitro Testing.....	60
7.2.4 Routine Clinical Testing	60
7.2.4.1 Trial 150033:.....	60
7.2.4.2 Trial 150336:.....	61
7.2.4.3 Trial 140115.....	61
7.2.5 Metabolic, Clearance, and Interaction Workup.....	62
7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class	62
7.3 Major Safety Results.....	62
7.3.1 Deaths	62
7.3.2 Nonfatal Serious Adverse Events	63
7.3.3 Dropouts and/or Discontinuations.....	63
7.3.3.1 Trial 150033.....	63
7.3.3.2 Trial 150336.....	64
7.3.3.3 Trial 140115.....	65
7.3.4 Significant Adverse Events	66
7.3.4.1 Trial 150033.....	66
7.3.4.2 Trial 150336.....	66
7.3.4.3 Trial 140115.....	66
7.3.5 Submission Specific Primary Safety Concerns.....	66

Clinical Review

Theresa H. van der Vlugt, M.D., M.P.H.; Nneka McNeal-Jackson, M.D.

NDA 209661

Tradename (20 mg doxylamine succinate and 20 mg pyridoxine hydrochloride)
extended-release tablets

7.4	Supportive Safety Results	66
7.4.1	Common Adverse Events	66
7.4.1.1	Trial 150033	66
7.4.1.2	Trial 150336	69
7.4.1.3	Trial 140115	70
7.4.2	Laboratory Findings	72
7.4.2.1	Trial 150033	72
7.4.2.2	Trial 150336	73
7.4.2.3	Trial 140155	73
7.4.3	Vital Signs	74
7.4.4	Electrocardiograms (ECGs)	75
7.4.5	Special Safety Studies/Clinical Trials	75
7.4.6	Immunogenicity	75
7.5	Other Safety Explorations	75
7.5.1	Dose Dependency for Adverse Events	75
7.5.2	Time Dependency for Adverse Events	76
7.5.3	Drug-Demographic Interactions	76
7.5.4	Drug-Disease Interactions	76
7.5.5	Drug-Drug Interactions	76
7.6	Additional Safety Evaluations	77
7.6.1	Human Carcinogenicity	77
7.6.2	Human Reproduction and Pregnancy Data	77
7.6.3	Pediatrics and Assessment of Effects on Growth	77
7.6.4	Overdose, Drug Abuse Potential, Withdrawal and Rebound	77
7.7	Additional Submissions / Safety Issues	78
8	POSTMARKET EXPERIENCE	78
9	APPENDICES	82
9.1	Literature Review/References	82
9.2	Labeling Recommendations	82
9.3	Advisory Committee Meeting	82

Clinical Review

Theresa H. van der Vlugt, M.D., M.P.H.; Nneka McNeal-Jackson, M.D.

NDA 209661

Tradename (20 mg doxylamine succinate and 20 mg pyridoxine hydrochloride)
extended-release tablets

Table of Tables

Table 1:	Summary of Clinical Trial Analytical Method Validation Reports.....	29
Table 2:	Tradename Clinical Trials and Relevant Formulation	34
Table 3:	Test and Reference Regimen for Bioequivalence Trial 150033.....	37
Table 4:	Blood Sampling Collection Schedule for Bioequivalence Trial 150033.....	37
Table 5:	Test-to-Reference Geometric Mean Ratios and 90% Confidence Interval on AUC ₀₋₂₄ and C _{max} for Baseline Corrected Doxylamine and Pyridoxal 5'- Phosphate	40
Table 6:	Test-to-Reference Geometric Mean Ratios and 90% Confidence Interval on AUC ₀₋₂₄ and C _{max} for Pyridoxine	42
Table 7:	Test-to-Reference Geometric Mean Ratios and 90% Confidence Interval on AUC ₀₋₂₄ and C _{max} for Pyridoxal	42
Table 8:	Blood Sampling Collection Schedule for Bioequivalence Trial 150336.....	45
Table 9:	Test-to-Reference Geometric Mean Ratios and 90% Confidence Interval for Doxylamine, Baseline Corrected Pyridoxal 5'-Phosphate, Pyridoxal 5'- Phosphate, Pyridoxine, Baseline Corrected Pyridoxal, and Pyridoxal	47
Table 10:	Blood Sampling Collection Schedule	50
Table 11:	Trial 140115 Geometric Means, Ratios and 90% Confidence Intervals for PK Parameters Following a Single Dose of Tradename Tablet with (Test) or without Food (Reference). N=23	52
Table 12:	Summary of Clinical Trials Providing Safety Information	56
Table 13:	Overall Extent of Exposure in the Tradename Clinical Development Program.....	59
Table 14:	Summary of the Tradename Trial Demographics and Body Measurements for Safety Population for All Clinical Trials	59
Table 15:	Clinical Laboratory Tests for All Clinical Trials in the Tradename Clinical Development	61
Table 16:	Treatment Emergent Adverse Events for Trial 150033	67
Table 17:	Treatment-Emergent Adverse Events of Interest for Trial 150033.....	68
Table 18:	Treatment-Emergent Adverse Events of Special Clinical Interest by Treatment Arm for Trial 150033	68
Table 19:	Summary of Adverse Events for Trial 150336.....	69
Table 20:	Treatment-Emergent Adverse Events of Interest for Trial 150336.....	70
Table 21:	Treatment-Emergent Adverse Events of Special Clinical Interest by Treatment Arm for Trial 150336	70
Table 22:	Summary of Adverse Events for Trial 140115.....	71
Table 23:	Cases of Somnolence and Abdominal Pain by Treatment Arm for Trial140115	71
Table 24:	Most Common Adverse Events by Treatment Arm and Trial Day for Trial 150033	76

Clinical Review

Theresa H. van der Vlugt, M.D., M.P.H.; Nneka McNeal-Jackson, M.D.

NDA 209661

Tradename (20 mg doxylamine succinate and 20 mg pyridoxine hydrochloride) extended-release tablets

1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

The clinical reviewers recommend Approval for Tradename (20 mg doxylamine succinate and 20 mg pyridoxine hydrochloride) combination extended-release tablets, for oral use, for the treatment of nausea and vomiting of pregnancy in (b) (4) who do not respond to conservative management.

The applicant submitted to NDA 021876, Supplement 10 which proposed for approved Diclegis®, a new oral combination tablet formulation with a total of 20 mg doxylamine succinate and 20 mg pyridoxine hydrochloride and a new dosing regimen: (b) (4)

The new formulation and dosing regimen were considered under a new NDA number 209661 (see Regulatory History).

Three clinical pharmacology trials were conducted: two bioequivalence pharmacokinetic trials and a fed-fasting trial. In the trials combined, 115 non-pregnant women were exposed to the new proposed formulation.

The Clinical Reviewers' recommendation for an Approval is based on the following:

1. Data from single dose bioequivalence Trial 150336, establishes bioequivalence between Diclectin (the proprietary product in Canada identical in formulation to approved formulation for Diclegis®, combination 10 mg doxylamine succinate and 10 mg pyridoxine hydrochloride delayed-release tablets), and the proposed new formulation for Tradename, combination 20 mg doxylamine succinate and 20 mg pyridoxine hydrochloride extended-release tablets.

Trial 150336 was conducted outside of the Investigational New Drug (IND) 72300. Receipt of the Clinical Trial Report for Trial 150336 on June 13, 2016 was considered a major amendment, which extended the review cycle. Results of Trial 150336 presents point estimates and 90% confidence intervals (CIs) of 1) test to reference ratios of the geometric means of the pharmacokinetic parameters of AUC_{0-60} , AUC_{0-inf} , and C_{max} for the analyte doxylamine succinate, and 2) test to reference ratios of the geometric means of the pharmacokinetic parameters of AUC_{0-72} and C_{max} for the analyte baseline corrected pharmacologically active metabolite pyridoxal 5'-phosphate. The point estimates (90% CIs) of test to reference ratios of the geometric means of AUC_{0-60} and AUC_{0-inf} for doxylamine succinate were 102.0% (98.4% - 105.7%) and 101.7% (98.1% - 105.5%), respectively. The point estimates (90% CI) of test to reference ratio of the geometric mean of AUC_{0-72} for the baseline corrected pharmacologically active metabolite pyridoxal 5'-phosphate was 104.2% (97.9% - 111.0%). The point estimate (90% CI) of test to reference ratio of the geometric

Clinical Review

Theresa H. van der Vlugt, M.D., M.P.H.; Nneka McNeal-Jackson, M.D.

NDA 209661

Tradename (20 mg doxylamine succinate and 20 mg pyridoxine hydrochloride) extended-release tablets

mean of C_{max} for doxylamine succinate was 94.2% (90.8% - 97.7%), and the point estimate (90% CI) of test to reference ratio of the geometric mean of C_{max} for baseline corrected pharmaceutically active metabolite pyridoxal 5'-phosphate was 104.8% (101.1% - 108.7%). The 90% confidence intervals (CIs) of test to reference ratios of 1) the geometric means of AUC_{0-60} , AUC_{0-inf} , and C_{max} for doxylamine succinate and 2) the geometric means of AUC_{0-72} and C_{max} for baseline corrected pyridoxal 5'-phosphate, were **all within the acceptable 80-125% range**.

2. Data from multiple dose bioequivalence Trial 150033 establishes bioequivalence at **steady state** on Day 11 between Tradename and Diclegis[®] based on the pharmacokinetic parameters of AUC_{0-24} and C_{max} for the analytes doxylamine succinate and baseline-corrected pharmaceutically active metabolite pyridoxal 5'-phosphate. The point estimates (90% CIs) of test to reference ratios of the geometric means of AUC_{0-24} and C_{max} for doxylamine succinate on Day 11 were 99.1% (95.7% - 102.5%) and 105.3% (100.9% - 109.9%), respectively. The point estimates (90% CIs) of test to reference ratios of the geometric means of AUC_{0-24} and C_{max} for baseline-corrected pharmaceutically active metabolite pyridoxal 5'-phosphate on Day 11 were 100.1% (95.8% - 104.5%) and 100.8% (96.7% - 105.0%), respectively. The 90% confidence intervals (CIs) of test to reference ratios of the geometric means of AUC_{0-24} and C_{max} for doxylamine succinate and baseline corrected pharmaceutically active metabolite pyridoxal 5'-phosphate were **all within the acceptable 80-125% range**.

The single day (Day 1) profile in multiple dose bioequivalence Trial 150033 is a mixed picture. Bioequivalence was not established between Tradename and Diclegis[®] based on Day 1 findings for the pharmacokinetic parameters of AUC_{0-24} and C_{max} for the analyte doxylamine succinate [point estimate (90% CI) of test to reference ratio of the geometric mean of AUC_{0-24} was 140.0% (130.2% - 150.6%) and the point estimate (90% CI) of test to reference ratio of the geometric mean of C_{max} was 79.6 (76.1% - 83.2%)] and the AUC_{0-24} for the analyte baseline corrected pharmaceutically active metabolite pyridoxal 5'-phosphate [the point estimate (90% CI) of test to reference ratio of the geometric mean of AUC_{0-24} was 161.49% (147.58% - 176.71%)]. The 90% confidence intervals (CI) of test to reference ratios of the geometric means for C_{max} for the analyte baseline corrected pharmaceutically active metabolite pyridoxal 5'-phosphate did fall within the acceptable 80-125% range on Day 1.

3. The Office of Clinical Pharmacology has determined that taken in its totality, the data from single dose bioequivalence Trial 150336 and multiple dose bioequivalence Trial 150033 establish bioequivalence between Tradename and Diclegis[®].
4. Compared to the approved formulation for Diclegis[®], no new safety signals are identified for the proposed new formulation in Tradename, combined 20 mg doxylamine succinate

Clinical Review

Theresa H. van der Vlugt, M.D., M.P.H.; Nneka McNeal-Jackson, M.D.

NDA 209661

Tradenname (20 mg doxylamine succinate and 20 mg pyridoxine hydrochloride) extended-release tablets

and 20 mg pyridoxine hydrochloride extended-release tablets, in the totality of the safety data from the three independent clinical pharmacology trials submitted to the NDA.

1.2 Risk Benefit Assessment

In 2013, Diclegis® (10 mg doxylamine succinate and 10 mg pyridoxine hydrochloride) combination delayed-release tablets were approved in the United States by the FDA for the treatment of nausea and vomiting of pregnancy in women who do not respond to conservative management. In the approved labeling for Diclegis®, somnolence is reported as an adverse event in the intended population of pregnant women. Somnolence is a recognized side effect of the doxylamine succinate component of the trial medication. The bioequivalence pharmacokinetic trials in this application also report somnolence in the non-pregnant women. No concerns for safety are generated based on the safety data from Tradename exposure in non-pregnant women.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

No postmarketing risk evaluation and mitigation strategies (REMS) are recommended.

1.4 Recommendations for Postmarket Requirements and Commitments

No postmarketing requirements and commitments are recommended.

2 Introduction and Regulatory Background

2.1 Product Information

The Food and Drug Administration (FDA) approved DICLEGIS® (10 mg doxylamine succinate and 10 mg pyridoxine hydrochloride) combination delayed-release tablets, for oral use on April 8, 2013 for the treatment of nausea and vomiting of pregnancy in women who do not respond to conservative management with the following dosage regimen:

“Initially, take two DICLEGIS delayed-release tablets orally at bedtime (Day 1). If this dose adequately controls symptoms the next day, continue taking two tablets daily at bedtime. However, if symptoms persist into the afternoon of Day 2, take the usual dose of two tablets at bedtime that night then take three tablets starting on Day 3 (one tablet in the morning and two tablets at bedtime). If these three tablets adequately control symptoms on Day 4, continue taking three tablets daily. Otherwise take four tablets starting on Day 4 (one tablet in the morning, one tablet mid-afternoon and two tablets at bedtime).”

Clinical Review

Theresa H. van der Vlugt, M.D., M.P.H.; Nneka McNeal-Jackson, M.D.

NDA 209661

Tradename (20 mg doxylamine succinate and 20 mg pyridoxine hydrochloride) extended-release tablets

“The maximum recommended dose is four tablets (one in the morning, one in the mid-afternoon and two at bedtime) daily.”

The drug product in this NDA is a combination of 20 mg doxylamine succinate and 20 mg pyridoxine hydrochloride (hereafter referred to as doxylamine and pyridoxine, respectively). Duchesnay Inc. (hereafter referred to as Duchesnay) reformulated DICLEGIS® to a 20 mg doxylamine and 20 mg pyridoxine combination extended-release tablet with the proposed proprietary name Tradename. Tradename tablets have (b) (4) 10 mg doxylamine and 10 mg pyridoxine in addition to a delayed-release core containing 10 mg doxylamine and 10 mg pyridoxine. The following is the proposed dosage regimen:

“Initially, take one Tradename extended-release tablet orally at bedtime (Day 1). If this dose adequately controls symptoms the next day, continue taking one tablet at bedtime. However, if symptoms persist on Day 2, (b) (4)

.” “The maximum recommended dose is two tablets (b) (4)

The proposed indication for Tradename is the same as the indication for DICLEGIS®.

On October 8, 2015, Duchesnay requested a review of the proposed proprietary name DICLEGIS® (b) (4). On December 30, 2015, the Division of Medication Error Prevention and Analysis (DMEPA) notified Duchesnay that the proposed proprietary name, DICLEGIS (b) (4), was “unacceptable from a safety perspective as (b) (4)” noting that Duchesnay has (b) (4). “If you intend to have a proprietary name for this product, we recommend that you submit a new request for a proposed proprietary name review.”

On May 25, 2016, amended on May 31, 2016, Duchesnay submitted a Request for Proprietary Name Review for the proposed proprietary name (b) (4) (doxylamine succinate and pyridoxine hydrochloride) (b) (4) extended-release tablets.

On August 23, 2016, DMEPA notified Duchesnay that the proposed proprietary name (b) (4) was “unacceptable” because (b) (4) is orthographically similar to the proprietary name of the currently marketed product, (b) (4).

On August 26, 2016, Duchesnay submitted an Amendment to Request for Proprietary Name Review for a new proprietary name, Bonjesta (b) (4) under NDA 21876. On September 9, 2016, a Resubmission of Amendment to Request for Proprietary Name Review for Bonjesta

Clinical Review

Theresa H. van der Vlugt, M.D., M.P.H.; Nneka McNeal-Jackson, M.D.

NDA 209661

Tradename (20 mg doxylamine succinate and 20 mg pyridoxine hydrochloride) extended-release tablets

(b) (4) was submitted to NDA 209661. On October 31, 2016 the applicant was sent a Proprietary Name Request Conditionally Acceptable letter for Bonjesta.

2.2 Tables of Currently Available Treatments for Proposed Indications

DICLEGIS® (10 mg doxylamine and 10 mg pyridoxine) delayed-release tablets, for oral use, is the only approved and specifically labeled product available in the United States for the treatment of nausea and vomiting of pregnancy (NVP). Many treatment options for NVP have been described in the literature, however. Pyridoxine (vitamin B₆) or vitamin B₆ plus doxylamine is recognized as being “safe and effective” by the American College of Obstetricians and Gynecologists (ACOG) and is recommended as first-line pharmacotherapy.¹

In Canada, 10 mg doxylamine and 10 mg pyridoxine is marketed as Diclectin® (hereafter referred to as Diclectin) and is indicated for the management of nausea and vomiting of pregnancy.

The new formulation, Tradename, extended-release tablets, consists of a single tablet containing 20 mg doxylamine and 20 mg pyridoxine. Tradename is composed of three separate components:

- Tablet core containing 10 mg doxylamine and 10 mg pyridoxine
- (b) (4)
- Printing ink

The delayed-release core in Tradename is (b) (4)

Per the applicant when the tablet is taken, 10 mg doxylamine and 10 mg pyridoxine are delivered immediately ($\leq 60\%$ within 120 minutes), followed by delivery of 10 mg doxylamine and 10 mg pyridoxine approximately 6 to 12 hours later (corresponding roughly to the time that a separate tablet of Diclegis would have been taken). “The concentration of each active ingredient in each tablet was doubled that of the approved formulation and the maximum daily recommended dosing has decreased from four to two tablets (*i.e.* one tablet in the morning and one tablet at bedtime), resulting in the same maximum daily dose as the Diclegis formulation.”

2.3 Availability of Proposed Active Ingredient in the United States

Doxylamine is the sedating ingredient of NyQuil® (contains 6.25 mg doxylamine per 15 mL), an over-the-counter cold medication, and Unisom® (25 mg doxylamine), an over-the-counter

¹ The American College of Obstetricians and Gynecologist. Nausea and Vomiting of Pregnancy. ACOG Practice Bulletin No.153. 2015;Sep; 126(3):e12-24.

Clinical Review

Theresa H. van der Vlugt, M.D., M.P.H.; Nneka McNeal-Jackson, M.D.

NDA 209661

Tradename (20 mg doxylamine succinate and 20 mg pyridoxine hydrochloride) extended-release tablets

sleep-aid tablet, both available in the US. Antihistamines with sedating characteristics, such as doxylamine, are commonly used to treat nausea and vomiting of different causes.

Pyridoxine is available in oral supplements and injectable vitamins, and is used to correct vitamin B₆ deficiency. Pyridoxine is commonly available over the counter (preparations containing 25, 50, 100, 125, and 500 mg tablets and capsules), but is also found in prescription form (100 mg per mL injection).

2.4 Important Safety Issues With Consideration to Related Drugs

Antihistamines inhibit the effects of histamine at H1 receptors. Histamine is a physiologically active, endogenous substance that binds to and activates histamine H1 and H2 receptors in the respiratory tract (including the nose), the gastrointestinal tract, brain, adrenal medulla, skin vasculature, and the heart.² Antihistamines are classified as first generation (sedating) and newer. First generation antihistamines, including doxylamine, are highly lipophilic and therefore readily cross the blood-brain barrier, contributing to adverse central nervous system effects including sedation, drowsiness, and decreased cognitive processing.² First-generation antihistamines have relatively short half-lives, necessitating multiple daily doses. Newer antihistamines were developed to decrease the adverse effects of first generation antihistamines. Adverse events are most commonly associated with first-generation antihistamines include sedation, dizziness, tinnitus, blurred vision, dry mouth, ataxia, urinary retention, drowsiness, memory problems, inability to concentrate, hallucinations, and psychosis. At toxic doses, H1-antihistamines can cause anticholinergic effects, including seizures, rhabdomyolysis and death.

See Section 8 Postmarketing Experience in this review for a detailed discussion of adverse events reported with approved Diclegis in the U.S., and with Diclectin (10 mg doxylamine and 10 mg pyridoxine) approved in Canada.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

Nausea and vomiting of pregnancy is a common condition that affects 70% to 85% of pregnant women. About 50% of women have nausea and vomiting in early pregnancy, and an additional 25% have nausea alone. In about 35% of pregnant women who have this condition, nausea and vomiting are clinically significant, resulting in lost work time and negatively affecting family relationships. ACOG (2015) recommends therapy with pyridoxine or pyridoxine plus doxylamine in these patients when conservative measures, such as dietary and lifestyle modifications, have failed.¹

The etiology of NVP is unknown. Various theories are proposed, however, including psychological predisposition, evolutionary adaptation, and hormonal stimulus.

2 Carson S, Lee N, Thakurta S. Drug Class Review: Newer Antihistamines: Final report Update 2 [Internet]. Portland (OR): Oregon Health & Science University; 2010 May.

Clinical Review

Theresa H. van der Vlugt, M.D., M.P.H.; Nneka McNeal-Jackson, M.D.

NDA 209661

Tradename (20 mg doxylamine succinate and 20 mg pyridoxine hydrochloride) extended-release tablets

The use of doxylamine and pyridoxine in combination as a treatment for nausea and vomiting of pregnancy has a long history. In 1956, FDA approved Bendectin® Delayed Release Tablets (pyridoxine hydrochloride, doxylamine succinate, and dicyclomine hydrochloride) “only for nausea and vomiting of pregnancy which are unresponsive to conservative measures such as eating soda crackers or drinking hot and cold liquids, which interfere with normal eating habits or daily activities, and are sufficiently distressing to require drug intervention.” Bendectin® was reformulated in 1976 to include only 10 mg pyridoxine and 10 mg of doxylamine. Each Bendectin® tablet was formulated with (b) (4)

Bendectin® was marketed in the U.S. from 1956 to 1983.

Bendectin® was withdrawn from the US market in 1983 for non-medical reasons (litigation burdens and adverse publicity in the public media). In 1999, FDA determined that Bendectin® was not withdrawn from sale for “reasons of safety and effectiveness”.³ See the Medical Officer’s Review of NDA 21876 for Diclegis, dated April 8, 2013, for additional information regarding Bendectin®.

On April 8, 2013, Diclegis was approved for the treatment of nausea and vomiting of pregnancy in women who do not respond to conservative management. During the review process, it was determined that a sufficient bridge was presented in the application to rely in part (for preclinical information) on the findings of safety and Efficacy of Bendectin® to support the Diclegis application. The 1976 findings of effectiveness for Bendectin® were determined to be supportive of the effectiveness of Diclegis. The safety profile and the benefit/risk ratio for Diclegis were deemed acceptable without evidence of an increased for teratogenicity with the use of the combination of 10 mg doxylamine and 10 mg pyridoxine. At approval, the Pediatric Research Committee/Pediatric Research Equity Act (PREA) subcommittee and DBRUP determined that a waiver for (b) (4) girls, ages 0-11 years 11 months was appropriate. Duchesnay requested and received deferment for adolescent girls, age range 12-17 years 11 months. Per PREA, “Your deferred pediatric study required by section 505B(a) of the Federal Food, Drug, and Cosmetic Act (FDCA) is a required postmarketing study. The status of this postmarketing study must be reported annually according to 21 CFR 314.81 and section 505B(a)(3)(B) of the FDCA.” The timeline listed below was established for the conduct of “An adequately powered safety and efficacy study in pregnant adolescent girls, 12 to 17 years of age, with nausea and vomiting of pregnancy who are appropriate candidates for pharmacologic therapy.”

Final protocol Submission: January 2014

Study/Trial Completion: January 2018

³ Federal Register/Vol.64, no. 152, August 9, 1999/Notices.

Clinical Review

Theresa H. van der Vlugt, M.D., M.P.H.; Nneka McNeal-Jackson, M.D.

NDA 209661

Tradenname (20 mg doxylamine succinate and 20 mg pyridoxine hydrochloride) extended-release tablets

Final Report Submission: July 2018

Trial PED-301 is ongoing.

On December 10, 2013, DBRUP provided Written Responses Only (WRO) for a Type C meeting request for guidance on reformulating Diclegis from a 10 mg doxylamine and 10 mg pyridoxine delayed-release tablet to a 20 mg doxylamine and 20 mg pyridoxine extended-release tablet with the same approved indication. The maximum approved Diclegis daily dosage regimen of four tablets (one in the morning, one in the mid-afternoon and two at bedtime) would be reduced to a maximum recommended daily dosage regimen of two tablets (one in the morning and one at bedtime) resulting in the same maximum daily dose of 40 mg doxylamine and 40 mg pyridoxine. This reformulated extended-release tablet would include an immediate release portion in addition to a delayed-release portion. The questions posed and the DBRUP's responses are produced verbatim below:

Question 1(a):

“Does the Agency agree that a successful bioequivalence comparison study (as described under Biopharmaceutics) between the Diclegis 10 mg / 10 mg delayed-release tablet and 20 mg / 20 mg (b) (4) tablet formulations in healthy adult female volunteers will be sufficient to support the efficacy and safety of the new formulation?”

FDA Response to Question 1(a):

“We agree that a bioequivalence comparison study between Diclegis 10 mg / 10 mg delayed release tablet and 20 mg / 20 mg (b) (4) 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).

Clinical Review

Theresa H. van der Vlugt, M.D., M.P.H.; Nneka McNeal-Jackson, M.D.

NDA 209661

Tradename (20 mg doxylamine succinate and 20 mg pyridoxine hydrochloride) extended-release tablets

Finally, you should also conduct a fed/fasted bioavailability study with the highest dosage strength.”

Question 2:

“Does the Agency agree that the following two studies will be sufficient to support the efficacy and safety of the new formulation?”

- a) A single-dose, randomized, open-label, 2-way crossover bioequivalence comparison study between the Diclegis 10 mg / 10 mg delayed-release tablet and 20 mg / 20 mg (b) (4) tablet formulations in healthy adult female volunteers under fasting conditions*
- b) A single and multiple dose safety and pharmacokinetic study in healthy adult female volunteers”*

FDA Response to Question 2 a and b:

“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 on 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.

We also recommend that you conduct a fed/fasted bioavailability study for the new formulation.

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

Clinical Review

Theresa H. van der Vlugt, M.D., M.P.H.; Nneka McNeal-Jackson, M.D.

NDA 209661

Tradename (20 mg doxylamine succinate and 20 mg pyridoxine hydrochloride) extended-release tablets

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.”

“We have the following additional comment and question:

1. The term (b) (4) is not listed in the Orange Book Appendix C. If you proceed with development of the proposed (b) (4) 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.
2. Is it your intent to (b) (4) ?

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 advise you that you will need to establish in pregnant adolescents, 12 to 17 years of age, (b) (4), the efficacy and safety of the (b) (4) 20 mg/20 mg formulation administered twice daily and/or the (b) (4) 20 mg/20 mg formulation administered twice daily, (b) (4),”

The reported results of bioequivalence Study 150033 and fed/fasted bioavailability Study 140115 were included in NDA 021876/Supplement 10 received on October 7, 2015.

On 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 (See also page 21 of this review.)

On 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.”

Clinical Review

Theresa H. van der Vlugt, M.D., M.P.H.; Nneka McNeal-Jackson, M.D.

NDA 209661

Tradename (20 mg doxylamine succinate and 20 mg pyridoxine hydrochloride) extended-release tablets

Clinical Reviewers' Comments:

Duchesnay did not provide, for DBRUP review and comments, original protocols for Trials 150033 and 140115. Likewise, Duchesnay did not provide the protocol for non-IND Trial 150336.

In the supplemental application, Duchesnay confirms that NDA 021876/Supplement 10 "is being submitted to support a new formulation for Diclegis, (b) (4) (see 2.5 Clinical Overview, 1 Product Development Rationale, page 2 of 6). On August 3, 2016, August 12, 2016, and August 15, 2016, Duchesnay was advised that the Agency 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. Tradename (20 mg doxylamine and 20 mg pyridoxine) combination extended-release tablets was assigned a new NDA number, 209661.

Duchesnay requests a waiver for pediatric study requirements in (b) (4) for Tradename 20 mg doxylamine and 20 mg pyridoxine combination extended-release tablets. Per the application,

"Tradename is intended to treat nausea and vomiting of pregnancy in women who do not respond to conservative management. (b) (4), Duchesnay Inc. is requesting a waiver from pediatric development in children from birth to (b) (4) years of age. (b) (4)

"Currently, the approved product, Diclegis® (10 mg doxylamine succinate, 10 mg pyridoxine hydrochloride) delayed-release tablets, indicated to treat nausea and vomiting of pregnancy in women who do not respond to conservative management, is under a PREA commitment with the FDA to conduct a pediatric assessment for pregnant adolescents aged 12 to 17 years with the specified milestone:

- 2033-1** *An adequately powered safety and efficacy study in pregnant adolescent girls, 12 to 17 years of age with nausea and vomiting of pregnancy who are appropriate candidates for pharmacologic therapy*
- *Final Protocol Submission: January 2014*
 - *Study/Trial Completion: January 2018*
 - *Final Report Submission: July 2018"*

On January 14, 2015, Duchesnay requested (b) (4)

Clinical Review

Theresa H. van der Vlugt, M.D., M.P.H.; Nneka McNeal-Jackson, M.D.

NDA 209661

Tradename (20 mg doxylamine succinate and 20 mg pyridoxine hydrochloride) extended-release tablets

(b) (4)

DBRUP (b) (4) on March 23, 2015. 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 requested to modify the (b) (4). Following several correspondences the FDA recently provided additional comments and recommendations. 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.

Clinical Reviewers' Comments:

We recommend that Duchesnay's request for a waiver for pediatric study requirements in (b) (4) patients 0 to 11 years of age be granted. We recommend that (b) (4) pediatric study requirements (b) (4) patients 12 to 17 years of age for Tradename 20 mg doxylamine and 20 mg pyridoxine extended-release tablets be deferred.

2.6 Other Relevant Background Information

In Canada, 10 mg doxylamine and 10 mg pyridoxine are the ingredients in Diclectin combination delayed-release tablets. The formulation of Diclectin and Diclegis are identical. No information has been provided in this application regarding use of the proposed reformulated Tradename tablet in Canada.

Per the applicant, the new Tradename formulation offers the following advantages:

Clinical Review

Theresa H. van der Vlugt, M.D., M.P.H.; Nneka McNeal-Jackson, M.D.

NDA 209661

Tradenname (20 mg doxylamine succinate and 20 mg pyridoxine hydrochloride) extended-release tablets

- Reduced variation at steady state for doxylamine and pyridoxal 5'-phosphate plasma levels
- Improved patient compliance by reducing the number of tablets from four to two tablets daily
- A faster rate of absorption delivered by the immediate-release portion in the coating layer while maintaining the extent and exposure of the delayed-release core

On March 24, 2016, in the 120-Day Safety Update covering the reporting period October 7, 2015 to March 21, 2016, Duchesnay provided summary information on non-IND Trial 150336 conducted as part of the clinical development program. This single center (inVentiv Health Clinique, Inc.), randomized, single-dose, open-label, 2-way crossover comparative bioequivalence trial enrolled 52 healthy childbearing potential and non-postmenopausal females with tubal ligation. Per the applicant, the objective of this non-IND trial was to compare the rate and extent of absorption of Tradenname (Treatment A) administered as a single 20 mg/20 mg extended-release tablet versus Diclegis delayed-release tablet (Treatment B) administered a two 10 mg/10 mg tablets, under fasting conditions. The applicant indicated that the complete trial report for non-IND Study 150336 was available upon request.

On June 9, 2016, the Agency requested the clinical trial report for Trial 150336. This report was received on June 13, 2016.

On June 27, 2016, the applicant was advised that the clinical trial report for Trial 150336, received on June 13, 2016, was a major amendment to NDA 209661. "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."

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

Overall, the quality and integrity of this NDA application is good. The NDA application is well organized with appropriately identified heading and sub-heading allowing easy identification and access to information.

The applicant promptly responded with requested information when an Information Request (IR) was sent. For example:

On December 14, 2015, DBRUP sent Duchesnay the following Information Request:

Clinical Review

Theresa H. van der Vlugt, M.D., M.P.H.; Nneka McNeal-Jackson, M.D.

NDA 209661

Tradename (20 mg doxylamine succinate and 20 mg pyridoxine hydrochloride) extended-release tablets

“For NDA 021876/Supplement 10 Efficacy, received by the Agency on October 7, 2015 for Tradename, 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)”

Duchesnay responded via email on December 18, 2015 as follows:

“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”

A formal submission via the Gateway was received on December 21, 2015 stating:

“On behalf of Duchesnay Inc., Mapi, in its capacity of United States Agent, hereby submits the datasets in SAS transport file format as requested. These datasets were submitted in Microsoft Excel format by email on December 18, 2015.”

Clinical Reviewers' Comments:

The datasets received on December 18, 2015 (Microsoft Excel format) and December 21, 2015 (SAS transport file format), were thoroughly reviewed for safety findings reported during the conduct of Trial 150033 and Trial 140115.

3.2 Compliance with Good Clinical Practices

Trial 150033 (bioequivalence trial conducted under fasting conditions) and Trial 140115 (fed/fasted bioavailability trial) appear to have been conducted in accordance with the ethical principles originating from the Declaration of Helsinki and undertaken in accordance with the principles of Good Clinical Practice (GCP) as set forth in the International Conference on Harmonization Guidelines for GCP (ICH-E6). All women in both clinical trials provided written informed consent. The informed consent document was approved by the Institutional Review Board (IRB)/Independent Ethics Committee (IEC).

An ethics committee ((b) (4)) reviewed all relevant associated documents, and informed consent forms (ICFs), prior to beginning

Clinical Review

Theresa H. van der Vlugt, M.D., M.P.H.; Nneka McNeal-Jackson, M.D.

NDA 209661

Tradename (20 mg doxylamine succinate and 20 mg pyridoxine hydrochloride) extended-release tablets

associated trial procedures. The ethics committee that reviewed the trial was an independent service provider located in (b) (4). (b) (4) has no representatives from inVentiv and was, therefore, completely independent.

Canadian authorities sent Duchesnay “No Objection” letters prior to the beginning of both trials. A copy is included in the Final Trial Reports of both trials in Appendix 16.1.1 of the application.

All women were provided with an ICF in their language of preference (either French or English) for review. Trial staff verbally reviewed the ICF with participating women, prior to initiation of trial procedures, allowing sufficient time for review of the information provided and to answer any questions, per the application. Subsequently, women were to be informed of any developments or changes to procedures that could have influenced their continued participation in the trial. Women were informed to not anticipate any direct benefits from participation in these research trials, with the exception that they received a health evaluation. Participating women received compensation for their time and no incentives, per the application.

All clinical work was conducted in compliance with Good Clinical Practices (GCP) as referenced in the International Conference on Harmonization (ICH) guidelines (ICH E6), Good Laboratory Practices (GLP) as referenced in the ICH guidelines, local regulatory requirements, and the recommendations laid down in the most recent version of the Declaration of Helsinki.

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

- inVentiv Health Clinique, Inc., 2500, rue Einstein Québec (Québec), Canada G1P 0A2 Tel.: 418-527-4000 Fax: 418-527-3456
- inVentiv Health Clinique, Inc., 5160, boul. Décarie, suite 800 Montréal (Québec) Canada, H3X 2H9 Tel.: 514-485-7500 Fax: 514-485-7501

The Debarment Statements, dated April 21, 2015 for Trial 150033 and August 25, 2014 for Trial 140115, available in the application states, “inVentiv Health Clinique Inc. hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food Drug and Cosmetic Act or disqualified under the 21 CFR part 312.70/812.119 in connection with the work performed under contract for its clients.”

Per the clinical trial report received on June 13, 2016, Trial 150336 also appears to have been conducted in accordance with the ethical principles originating from the Declaration of Helsinki and undertaken in accordance with the principles of Good Clinical Practice (GCP). All participating women provided written informed consent approved by the Institutional Review Board (IRB)/Independent Ethics Committee (IEC). Health Canada, Office of Clinical

Clinical Review

Theresa H. van der Vlugt, M.D., M.P.H.; Nneka McNeal-Jackson, M.D.

NDA 209661

Tradename (20 mg doxylamine succinate and 20 mg pyridoxine hydrochloride) extended-release tablets

Trials sent Duchesnay a “No Objection” letter, dated September 18, 2015, prior to the beginning of Trial 150336. A copy is included in the Clinical Trial Report in Appendix 16.1.1. Sample subject ICFs and the IRB approvals are located in Appendix 16.1.3.

The facility involved in the conduct of Trial 150336 is:

- inVentiv Health Clinique, Inc., 2500, rue Einstein Québec (Québec), Canada G1P 0A2 Tel.: 418-527-4000 Fax: 418-527-3456

This is the same facility that conducted Trials 150033 and 140115.

(b) (4)
audited the clinical and statistical portion of Trial 150033 on the following dates (reported results reflect the raw data of the trial):

Audit Description	Audit Date(s) (dd-mmm-yyyy)	Date(s) findings were reported to management
Clinical Trial Set-up	12, 18, 19 and 23-FEB-2015	12, 19 and 23-FEB-2015
Clinical In-process	08-MAR-2015	11-MAR-2015
Clinical Raw Data	25 and 26-JUN-2015 06 and 07-JUL-2015	26-Jun-2015 07-Jul-2015
Trial Master File	20-FEB-201520-FEB-2015	20-FEB-2015
Clinical Report	16 and 17-JUL-2015 07, 10 and 11-AUG-2015 01 and 02-SEP-2015	17-JUL-2015 11-AUG-2015 01 and 02-SEP-2015
Statistical Data	25, 26 and 27-AUG-2015	27-AUG-2015
Statistical Report	25, 26, 27, 28 and 31-AUG-2015	28 and 31-AUG-2015

Source: NDA 209661, Clinical Trial 150033, 16.1.18 Audit Certificate(s), page 16.1.8-1.

The clinical and statistical portions of Trial 140115 were audited by the (b) (4) on the following dates (reported results reflect the raw data of the trial):

Audit Description	Audit Date(s) (dd-mmm-yyyy)	Date(s) findings were reported to management
Clinical Trial Set-up	29-SEP-2014 01-OCT-2014	01-OCT-2014
Clinical In-process	14-OCT-2014	14-OCT-22014
Clinical Raw Data	12-NOV-2014	12-NOV-2014
Clinical Report	19-NOV-2014 01 and 02-DEC-2014	19-NOV-2014 02-NOV-2014
Statistical Data	11-DEC-2014	12-DEC-2014
Statistical Report	11 and 12-DEC-2014	12-DEC-2014

Source: NDA 209661, Clinical Trial 140115, 16.1.8 Audit Certificate(s), page 16.1.8-2.

Clinical Review

Theresa H. van der Vlugt, M.D., M.P.H.; Nneka McNeal-Jackson, M.D.

NDA 209661

Tradename (20 mg doxylamine succinate and 20 mg pyridoxine hydrochloride) extended-release tablets

Per the information received on June 13, 2016, the clinical and statistical portions of Trial 150336 were audited by the (b) (4) on the following dates (reported results reflect the raw data of the trial):

Audit Description	Audit Date(s) (dd-mmm-yyyy)	Date(s) findings were reported to management
Clinical Study set-up	18 and 29-SEP-2015	18 and 29-Sep-2015
Clinical In-process	17-OCT-2015	17-OCT-2015
Clinical Raw Data	13-OCT-2015 24 and 30-NOV-215 20-JAN-2016	13-OCT-2015 02 and 08-DEC-2015
Clinical Report	07-JAN-2016	08-JAN-2016
Statistical Data	06 and 27-JAN-2016	20-JAN-2016 05-FEB-2016
Statistical Report	07 and 27-JAN-2016	20-JAN-2016 05-FEB-2016

Source: NDA 209661 Amendment dated June 13, 2016, Clinical Trial 150336, Heading 5 Clinical Study Report, Sub-Heading 5.3.1.2, Audit Certificate Report.

On January 4, 2016, the Office of Clinical Pharmacology (OCP), Division of Clinical Pharmacology 3 (DCP3) requested that the Office of Study Integrity and Surveillance (OSIS) conduct a clinical and bioanalytical site inspection.

Clinical Reviewers' Comments:

On February 22, 2016, the Division of New Drug Bioequivalence Evaluation (DNDBE) in OSIS recommends accepting data without an on-site inspection. DNDBE noted:

- "...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 inspectional outcome from the inspection was classified as No Action Indicated (NAI)." The facility identified by DNDBE is (b) (4).

3.3 Financial Disclosures

3.3.1 Trial 150033 and Trial 140115:

The applicant certifies, "...that 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

Clinical Review

Theresa H. van der Vlugt, M.D., M.P.H.; Nneka McNeal-Jackson, M.D.

NDA 209661

Tradename (20 mg doxylamine succinate and 20 mg pyridoxine hydrochloride) extended-release tablets

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.

3.3.2 Non-IND Trial 150336:

A signed FORM FDA 1572 (2/13) is available in the application for the principal investigator (Dr. Denis Audet) and each of the nine (9) sub-investigators in Trial 150336.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

In the application, Duchesnay requests a waiver from the required environmental assessment for Tradename. Per the applicant, a waiver is justified under provisions of 21 CFR §25.31(a) because “FDA action on this supplement is subject to categorical exclusion from the requirement for an environmental assessment since it will not increase the use of the active ingredients of the drug product, doxylamine succinate and pyridoxine hydrochloride, from the present amount.” “The currently approved Diclegis (10 mg doxylamine and 10 mg pyridoxine) with a recommended dosage of four tablets daily (b) (4) Tradename (20 mg doxylamine and 20 mg pyridoxine) with a maximum dosage regimen of two tablets daily.”

“All manufacturing, packaging and labelling operations for the drug product will be performed in compliance with local, state, and federal environmental laws. In the event that disposition of the drug product becomes necessary, destruction or disposition of the articles, including packaging materials, will be performed in accordance with applicable local, state, and federal requirements.”

Clinical Reviewer’s Comments:

See the Chemistry, Manufacturing and Controls (CMC) review regarding the adequacy of the environmental assessment for Tradename.

Tradename extended-release tablet contains 20 mg of doxylamine and 20 mg of pyridoxine. The two drug substances are both USP. Each Tradename round, pink, film-coated, extended-release tablet is imprinted with the pink image of a pregnant woman on one side and the letter “D” on the other side. Approved Diclegis delayed-release tablets are round, white, film-coated tablets imprinted with the pink image of a pregnant woman on one side.

Tradename extended-release tablets are composed of three separate components:

Clinical Review

Theresa H. van der Vlugt, M.D., M.P.H.; Nneka McNeal-Jackson, M.D.

NDA 209661

Tradename (20 mg doxylamine succinate and 20 mg pyridoxine hydrochloride) extended-release tablets

- Tablet core containing 10 mg doxylamine and 10 mg pyridoxine
- [REDACTED] (b) (4)
- Printing ink.

Tradename contains twice the amount of active drug substances compared to the approved Diclegis formulation. Tradename contains [REDACTED] (b) (4) core component [REDACTED] (b) (4) with 10 mg of doxylamine and 10 mg pyridoxine. The additional 10 mg doxylamine and 10 mg pyridoxine in Tradename is added in the coating of the tablets. The proposed new formulation [REDACTED] (b) (4)

The pharmaceutical development of Tradename, the objective of which was to add an immediate release component to a delayed-release core, utilized [REDACTED] (b) (4) 10 mg doxylamine and 10 mg pyridoxine tablet core [REDACTED] (b) (4). Per the applicant, the immediate release of the drug substances [REDACTED] (b) (4) while maintaining the delayed-release of the drug substances in the core is critical for the performance of the new formulation drug product.

[REDACTED] (b) (4)

Bioequivalence Trial 150033, non-IND bioequivalence Trial 150336, and fed/fasted bioavailability Trial 140115 were performed using the following production-scale batches:

- Reference: Batch #1315 for Diclegis 10 mg doxylamine and 10 mg pyridoxine delayed-release tablets
- Test: Batch #30-001V for Tradename 20 mg doxylamine and 20 mg pyridoxine extended-release tablets (commercial-scale batch)

The Reference product batch #1315 was the “original formulation” with [REDACTED] (b) (4) rather than the “current approved formulation”, which contains [REDACTED] (b) (4). “The bioequivalence of these two formulations has been demonstrated in the Prior Approval Supplement S-002 (approved September 30, 2013)”.

There are no excipients of human or animal origin in Tradename extended-release tablets. A statement indicating that the product is Bovine Spongiform Encephalopathy

Clinical Review

Theresa H. van der Vlugt, M.D., M.P.H.; Nneka McNeal-Jackson, M.D.

NDA 209661

Tradenname (20 mg doxylamine succinate and 20 mg pyridoxine hydrochloride) extended-release tablets

(BSE)/Transmissible Spongiform Encephalopathy (TSE) free is available at 3.2.P.4.5 in the application.

The Office of Pharmaceutical Quality (OPQ) identified the following potential review issues in the 74-day Filing Communications letter dated December 18, 2015:

- “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 Tradenname Extended-release Tablets.
- Submit complete dissolution profile data (individual, mean, standard deviation, profiles) for comparative dissolution test results of Tradenname 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.”

Clinical Review

Theresa H. van der Vlugt, M.D., M.P.H.; Nneka McNeal-Jackson, M.D.

NDA 209661

Tradename (20 mg doxylamine succinate and 20 mg pyridoxine hydrochloride) extended-release tablets

Clinical Reviewers' Comments:

On March 24, 2016, Duchesnay responded as follows:

“The following information is provided in section 3.2.P.2.2:

- Justification and supportive dissolution data that the currently approved QC dissolution method for Diclegis® is adequate as the QC method for Diclegis (b) (4)
- Complete dissolution profile data for comparative dissolution test results.”

Per the information provided, the dissolution profiles of Tradename are comparable in the acid dissolution medium for the three speeds evaluated ((b) (4) rpm). At (b) (4) rpm, the percentage of active dissolved was slightly lower in the tablets coated with (b) (4) compared to the (b) (4) % coating since it took longer to dissolve that coating layer. The difference was noticeable at the 6 minutes time point. For the tablet core, (b) (4)

The OPQ review, dated September 21, 2016, states, “The chemistry, manufacturing, and control data/information provided in this submission are acceptable. The OPQ/ONDP Biopharmaceutics reviewer finds the dissolution method and acceptance criteria to be acceptable. The OPQ/Office of Process and Facilities final recommendation of the manufacturing sites is PENDING.” “Approve” is the OPQ conclusion without any comments/deficiencies to be conveyed to the applicant.

On October 20, 2016, a second Chemistry/Quality Review 2 was issued which states, “The OPQ/Office of Process and Facilities has now, on 20-Oct-2016, issued an approved recommendation for the manufacturing sites for NDA 209661. This NDA is, therefore, acceptable from a chemistry, manufacturing, and controls perspective.”

See the OPQ reviews dated September 21, 2016 and October 20, 2016.

4.2 Clinical Microbiology

Per the application, only skip-lot testing for all microbial tests (microbial testing only during stability) were performed on the commercial product, following the decision tree #8 from the ICH Q6A guidance. Tradename drug product “does not contain antimicrobial preservatives or inherent antimicrobial activity and there is no scientific evidence to demonstrate growth inhibitory properties of the drug product.” Therefore, it was deemed appropriate to perform skip-lot testing for the Tradename (b) (4) based formulation. Microbial testing was performed on lots put in the stability program at the following time points: 0, 12, 24, 36 and 48 months.

Clinical Review

Theresa H. van der Vlugt, M.D., M.P.H.; Nneka McNeal-Jackson, M.D.

NDA 209661

Tradename (20 mg doxylamine succinate and 20 mg pyridoxine hydrochloride) extended-release tablets

Per the Process Validation Report (PV-MAN-015.0R0) in the application, all results are well below the acceptable limit; absence of the 4 specified pathogens is also reported as follows:

Total count:	≤	(b) (4)	colony forming unit (CFU) per gram
Yeasts and Molds:	≤	(b) (4)	CFU per gram
Absence of 4 pathogens:	Absent (Escherichia coli, Pseudomonas aeruginosa, Staphylococcus aureus and Salmonella species)		

Results are summarized in Table 15: Microbiological results of coated tablets on page 26 of 72, and in Table 30: Microbiological results of printed tablets on page 58 of 72 of the Final Trial Report PV-MAN-015.0R0).

Clinical Reviewers' Comments:

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

4.3 Preclinical Pharmacology/Toxicology

This 505(b)(2) NDA 209661 application contains no new preclinical pharmacology/toxicology information. See the Pharmacology/Toxicology Review of original NDA 021876, dated March 4, 2013, for a full discussion of preclinical pharmacology/toxicology information for the approved formulation of Diclegis.

Per the Pharmacology/Toxicology Review of NDA 209661, dated June 17, 2016, "Changes to the formulation to create the delayed action core and immediate release outer layer of Tradename are acceptable. From a nonclinical perspective, this supplement is approvable."

4.4 Clinical Pharmacology

A comparative bioavailability (bioequivalence) trial, 150033, was conducted to evaluate the pharmacokinetic profiles of Tradename (test product) versus Diclegis (reference product) based on the rate and extent of absorption using methods available to analyze doxylamine, pyridoxine, as well as active B₆ metabolites.

A comparative food-effect bioavailability trial, 140115, was conducted under fed and fasting conditions using methods available to analyze doxylamine, pyridoxine, as well as active B₆ metabolites.

In addition, a non-IND bioequivalence trial, 150336, was conducted to compare the rate and extent of absorption of Tradename (Test), administered as one (1) combination tablet of 20 mg of doxylamine and 20 mg pyridoxine versus approved Diclegis (Reference),

Clinical Review

Theresa H. van der Vlugt, M.D., M.P.H.; Nneka McNeal-Jackson, M.D.

NDA 209661

Tradename (20 mg doxylamine succinate and 20 mg pyridoxine hydrochloride) extended-release tablets

administered as two (2) combination tablets of 10 mg of doxylamine and 10 mg pyridoxine, under fasting conditions.

Per the application, the analytical methods used to determine the levels of doxylamine, pyridoxine, and metabolites in all three trials were validated in compliance with (b) (4). implemented standard operating procedures (SOPs). For Trials 150033 and 140115, doxylamine, pyridoxine, pyridoxal and pyridoxal 5'-phosphate were measured. The analytical method validation reports are summarized in the following table.

Table 1: Summary of Clinical Trial Analytical Method Validation Reports for Trials 150033 and 140115

Report Number*	Substance	Matrix	Applicable to Clinical Trial Reports	
			150033	140115
65187OBT	Doxylamine	Human EDTA Plasma	x	x
125031AFLO	Pyridoxine	Human NaF/K ₂ C ₂ O ₄ Plasma	x	x
135110ALEG	Pyridoxal-5-Phosphate	Human NaF/K ₂ C ₂ O ₄ Plasma	x	x
125040AFZQ	Pyridoxal	Human EDTA K ₂ Whole Blood	-	x
1115018AMBI	Pyridoxal	Human EDTA K ₂ Whole Blood	x	-

* Reports are available in Section 5.3.1.1 and 5.3.1.2

Source: Adapted from NDA 209661, subsection 2.7.1 Summary of Biopharmaceutics and Associated Analytical Methods (Human), Table 2, page 6 of 42.

Doxylamine was assayed using a high performance liquid chromatographic method developed and validated by (b) (4). Pyridoxine was assayed using an LC/MS method developed and validated by (b) (4).

The same biological matrix (Human EDTA Plasma for doxylamine, Human NaF/K₂C₂O₄ Plasma for pyridoxine and pyridoxal-5-phosphate, and Human EDTA K₂ Whole Blood for pyridoxal) was used in Trial 150336.

Trial 150033, non-IND Trial 150336, and Trial 140115 are discussed under Section 5 Sources of Clinical Data, Subsection 5.3 Discussion of Individual Studies/Clinical Trials in this review.

4.4.1 Mechanism of Action

Clinical Review

Theresa H. van der Vlugt, M.D., M.P.H.; Nneka McNeal-Jackson, M.D.

NDA 209661

Tradename (20 mg doxylamine succinate and 20 mg pyridoxine hydrochloride) extended-release tablets

Per the last approved Diclegis labeling, dated December 16, 2014, the mechanism of action of Diclegis is unknown.

The applicant proposes the following text under Section 12 CLINICAL PHARMACOLOGY, Subsection 12.1 Mechanism of Action of labeling for Tradename:

“The mechanism of action of Tradename is unknown.



The following historical information was provided in the original NDA 021876 application:

“Doxylamine is primarily metabolized by the liver, and both parent drug and metabolites are excreted in the urine, patients with renal and/or liver disease may be at greater risk for adverse effects due to drug and metabolite accumulation. Therapy with doxylamine should be administered cautiously in such patients.” “Doxylamine is biotransformed in the liver by n-dealkylation to its principle metabolites, N-desmethyldoxylamine and N, N-didesmethyldoxylamine, which are excreted by the kidneys.”

“About half of the intake of vitamin B₆ is excreted as the inactive 4-pyridoxic acid in urine. Vitamin B₆ is also excreted in feces to a limited extent.....Pyridoxine is a prodrug that undergoes complex metabolic transformation in the blood resulting in the metabolites: pyridoxal, pyridoxal 5'-phosphate, pyridoxamine, and pyridoxamine 5'-phosphate. Pyridoxine is readily absorbed in the gastrointestinal tract, mainly in the jejunum and is primarily metabolized in the liver. The pharmacokinetics and disposition of vitamin B₆ are very complex and some metabolites have biological activity. Vitamin B₆ in coenzyme form performs a wide variety of functions in the body with involvement in more than 100 enzyme reactions. These are mostly concerned with protein metabolism, amino acid metabolism and metabolism of one carbon units, carbohydrates, and lipids. Vitamin B₆ plays a role in cognitive development through the biosynthesis of neurotransmitters and in maintaining normal levels of homocysteine, an amino acid in the blood. Vitamin B₆ is also involved in gluconeogenesis and glycogenolysis, immune function (it promotes lymphocyte and interleukin-2 production), and hemoglobin formation.”

This NDA application includes the following information:

Clinical Review

Theresa H. van der Vlugt, M.D., M.P.H.; Nneka McNeal-Jackson, M.D.

NDA 209661

Tradename (20 mg doxylamine succinate and 20 mg pyridoxine hydrochloride) extended-release tablets

- Similar to other H1 blockers, doxylamine is well absorbed from the gastrointestinal tract.
- Pyridoxine is readily absorbed in the gastrointestinal tract, mainly in the jejunum. Pyridoxine is primarily metabolized in the liver; following phosphorylation, its main active metabolite, pyridoxal 5'-phosphate, is released into the circulation (accounting for at least 60% of circulating vitamin B6) and is highly protein bound, primarily to albumin. The metabolic scheme for pyridoxine is complex, with formation of primary and secondary metabolites along with interconversion back to pyridoxine. All metabolites including pyridoxal have biologic activity, except the major metabolite 4-pyridoxic acid, which is inactive and is excreted in urine.

4.4.2 Pharmacodynamics

Per the original NDA 021876 for Diclegis, "Limited pharmacokinetic data are available for doxylamine and other older, first generation, antihistamines.

Per this NDA application, no pharmacodynamics analysis was planned or performed during the conduct of Trial 150033, non-IND Trial 150336, and Trial 140115.

4.4.3 Pharmacokinetics

Per the original NDA 021876 for Diclegis, "Limited pharmacokinetic data are available for doxylamine and other older, first generation, antihistamines."

Per the application, the pharmacokinetics of Diclegis and Tradename has been characterized in healthy non-pregnant adult women.

Clinical Reviewers' Comments:

The reported findings for trials submitted to support the pharmacokinetics of Tradename 20 mg doxylamine and 20 mg pyridoxine extended-release tablets, bioequivalence Trials 150033 and 150336 and comparative food-effect bioavailability Trial 140115, are discussed in Section 5.3 of this review.

At filing, the Office of Clinical Pharmacology (OCP) reviewer determined that on the face of it, the submitted data shows that single dose bioequivalence was not met for Tradename 20 mg doxylamine and 20 mg pyridoxine combination extended-release tablets formulation. This decision was based on the apparent failure to show bioequivalence of Tradename 20 mg doxylamine and 20 mg pyridoxine combination extended-release tablets formulation to Diclegis 10 mg doxylamine and 10 mg pyridoxine combination delayed-release tablets on trial Day 1. DBRUP management determined that the application should be filed and failure to demonstrate bioequivalence on Day 1 would be a review issue.

Clinical Review

Theresa H. van der Vlugt, M.D., M.P.H.; Nneka McNeal-Jackson, M.D.

NDA 209661

Tradename (20 mg doxylamine succinate and 20 mg pyridoxine hydrochloride) extended-release tablets

In the 74-Day “Filing Communication – Filing Review Issues Identified” letter dated December 18, 2015, the following concerns from the OCP, Division of Clinical Pharmacology 3 (DCP3) were identified:

- “In the proposed labeling for Tradename, 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 Tradename at a daily dose of 20mg/20 mg will be a review issue.”
- “Study 150033:
 - BE of doxylamine, pyridoxine, and its metabolites on Day 1 and Day 11 with the 40 mg/40 mg daily dose between Tradename 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 Tradename 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 Tradename 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>).”

In the letter, OCP requested that the sponsor:

- “Submit supporting information that the safety and efficacy of Tradename 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 Tradename 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-phosphate, rather than parent drug pyridoxine.”
- “Submit datasets for individual concentration-time data for Study 150033.”
- “Submit the SAS code for the BE analysis.”

Clinical Reviewers' Comments:

Clinical Review

Theresa H. van der Vlugt, M.D., M.P.H.; Nneka McNeal-Jackson, M.D.

NDA 209661

Tradename (20 mg doxylamine succinate and 20 mg pyridoxine hydrochloride) extended-release tablets

On February 26, 2016, Duchesnay provided datasets for individual concentration-time data for Trial 150033 and the SAS code for the BE analysis.

As previously noted, Duchesnay submitted the clinical trial report for completed, non-IND Study 150336 on June 13, 2016.

See the Clinical Pharmacology Review for a full discussion of the information provided by the applicant for Trials 150033, 150336, and 140115.

“The Office of Clinical Pharmacology (OCP)/Division of Clinical Pharmacology 3 (DCP-3) has reviewed NDA 209661 submitted on October 7, 2015, November 20, 2015, March 24, 2016, May 25, 2016, May 26, 2016, May 31, 2016, and June 13, 2016. The overall Clinical Pharmacology information submitted to support this NDA is **acceptable** and the proposed product, TRADENAME is **recommended for approval** from the Clinical Pharmacology standpoint.”

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

Overall, three *in vivo* trials were performed and submitted to the NDA in support of the safe and effective use of Tradename extended-release tablets. See Table 2.

Trial 150033 evaluated the bioequivalence of Tradename (20 mg doxylamine and 20 mg pyridoxine) combination extended-release tablets compared to approved Diclegis (10 mg doxylamine and 10 mg pyridoxine) combination delayed-release tablets.

Trial 150336 evaluated the bioequivalence of a single dose of Tradename (20 mg doxylamine and 20 mg pyridoxine) combination extended-release tablets compared to approved Diclegis (10 mg doxylamine and 10 mg pyridoxine) combination delayed-release tablets under fasting conditions.

Trial 140115 evaluated the effects of food on the pharmacokinetics of Tradename (20 mg doxylamine and 20 mg pyridoxine) extended-release tablets.

Table 2: Tradename Clinical Trials and Relevant Formulation

Clinical Trial	Trial Type	Drug Product	Formulation
150033	Bioequivalence	30-001V	Proposed commercial formulation
150336	Bioequivalence	30-001V	
140115	Food effect	30-001V	

Source: Adapted from NDA 209661 received October 7, 2015, Clinical Overview, Table 1, page 3 of 6; and Table 9.4.2-1, Integrated Clinical and Statistical Report, received June 13, 2016, page 58 of 1121.

Clinical Review

Theresa H. van der Vlugt, M.D., M.P.H.; Nneka McNeal-Jackson, M.D.

NDA 209661

Tradenname (20 mg doxylamine succinate and 20 mg pyridoxine hydrochloride) extended-release tablets

5.2 Review Strategy

The available safety and pharmacokinetic data from Trials 150033, 150336, and 140115 provide the basis for consideration regarding the bioequivalence (Trials 15033 and 150336) and safety (Trials 15033, 150336, and 140115) of Tradenname for the treatment of nausea and vomiting of pregnancy in patients who do not respond to conservative management.

5.3 Discussion of Individual Studies/Clinical Trials

5.3.1 Bioequivalence Trial 150033

Objective:

The objective of Trial 150033 was to compare the rate and extent of absorption of the Tradenname tablet formulation (Test), administered at a total dose of 40 mg doxylamine and 40 mg pyridoxine daily (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), administered at a total dose of 40 mg doxylamine and 40 mg pyridoxine daily (three times daily oral administration of 10 mg doxylamine and 10 mg pyridoxine combination extended release tablets; one tablet at 9 am, one tablet at 3 pm, and two tablets at 9 pm), following a single day (Day 1) of administration and 11 consecutive days of administration, under fasting conditions.

Design:

This was a single center (inVentiv Health Clinique, Inc.), randomized, open-label, 3-period, 3-sequence, reference replicated, crossover bioequivalence trial to compare the rate and extent of absorption of Tradenname (test 20 mg doxylamine and 20 mg pyridoxine) versus approved Diclegis (reference 10 mg doxylamine and 10 mg pyridoxine), under fasting conditions following single day and multiple day administrations.

Clinical Reviewers' Comments:

As stated previous, preliminary discussion of a single and multiple dose bioequivalence trial of the revised formulation compared to Diclegis was provided in a December 10, 2013 Written Response to the Applicant's Type C Meeting request. The Agency recommended single dose and multiple doses bioequivalence assessment in a single trial with the same women as follows: Day 1 - assessment of bioequivalence of Tradenname with one tablet (20 mg x 20 mg) given twice daily in the morning and at night versus a Diclegis reference arm of the approved regimen (10 mg x 10 mg) given three times daily as follows, one tablet in the morning, one tablet at approximately 4 PM, and two tablets at night; and Day 10 bioequivalence assessment utilizing the same segment of a single day trial repeated for the multiple doses segment. The applicant requested no further meetings with the Division nor did they present a protocol for Trial 150033, which was conducted in Quebec

Clinical Review

Theresa H. van der Vlugt, M.D., M.P.H.; Nneka McNeal-Jackson, M.D.

NDA 209661

Tradenname (20 mg doxylamine succinate and 20 mg pyridoxine hydrochloride) extended-release tablets

Canada, to the IND for the Agency's review and comments before conducting the trial.

Inclusion Criteria:

In order to be eligible for participation in the trial, women had to meet the following criteria:

1. Women of childbearing potential and non-postmenopausal women with tubal ligation, moderate smoker ($\leq$ nine cigarettes daily) or non-smoker, ≥ 18 and ≤ 45 years of age, with body weight ≥ 45.0 kg and BMI > 18.5 and < 30.0 kg/m².
2. Healthy as defined by the:
 - absence of clinically significant illness and surgery within four weeks prior to dosing
 - absence of clinically significant history of neurological, cardiovascular, pulmonary, hematological, immunologic, psychiatric, gastrointestinal, renal, hepatic, and metabolic disease
 - absence of clinically significant history of asthma
 - absence of known or suspected narrow angle glaucoma, increased intraocular pressure, stenosing peptic ulcer, pyloroduodenal obstruction, and bladder neck obstruction
3. Women of childbearing potential, sexually active with a male partner, must be willing to use one of the following acceptable contraceptive method throughout the trial and for 30 days after last dose:
 - intra-uterine contraceptive device
 - condom with intravaginally applied spermicide starting at least 14 days prior to trial drug administration
 - hormonal contraceptive starting at least four weeks prior to trial drug administration
 - sterile male partner (vasectomized at least six months prior)
4. Capable of consent.

Exclusion Criteria:

Women for whom the following exclusion criteria applied were excluded from trial participation:

1. Any clinically significant abnormality or abnormal laboratory test results during screening or a positive test for hepatitis B, hepatitis C, or HIV.
2. Positive urine drug screen, positive pregnancy test at screening.
3. History of allergic reaction to doxylamine, other ethanolamine derivative antihistamines, pyridoxine, or any inactive ingredient in the formulation.
4. Clinically significant ECG abnormalities; systolic blood pressure over 140 mmHg, diastolic blood pressure over 90 mmHg, or heart rate over 100 BPM at screening.
5. History of significant hard drug abuse within 1 year prior to screening (cocaine, PCP, and crack) or soft drug abuse within three months (marijuana); history of significant

Clinical Review

Theresa H. van der Vlugt, M.D., M.P.H.; Nneka McNeal-Jackson, M.D.

NDA 209661

Tradename (20 mg doxylamine succinate and 20 mg pyridoxine hydrochloride) extended-release tablets

alcohol abuse within one year prior to screening or regular use of alcohol within 6 months prior to screening.

6. Participation in a clinical trial within 30 days (90 days for biologics) prior to first dosing.
7. Use of medication other than topical products without significant systemic absorption and hormonal contraceptives:
 - prescription medication within 14 days prior to first dosing
 - over-the-counter products (exception of up to 2 g daily of acetaminophen) including food and herbal supplements within seven days prior to first dosing
 - multivitamins or supplements containing vitamin B6 within 28 days prior to first dosing
 - depot injection or implant of any drug (other than hormonal contraceptives) within three months prior to first dosing
 - monoamine oxidase (MAO) inhibitors within 30 days prior to first dosing
8. Donation of plasma within seven days prior to dosing.
9. Hemoglobin <125 g/L and hematocrit <0.32 L/L at screening.
10. Breast-feeding woman.

Excluded and Concomitant Medications:

Prescription and over-the-counter medications was prohibited throughout the trial. No concomitant drug therapy was allowed during the trial except one(s) required for the medical management of an AE. The use of hormonal contraceptives was allowed and documented. 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 are not allowed to take MAO inhibitors for 30 days before dosing and until 14 days after the last drug administration.

Methods:

Prior to trial commencement, women were randomly assigned to a treatment group in accordance with the randomization scheme generated by inVentiv. Women were confined to the inVentiv Clinical Facility from the evening of Day -1 until after the last blood draw on the morning of Day 12, in each crossover period. 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 test drug Tradename was administered during one of the three crossover periods. Diclegis (reference drug) was administered during two of the three crossover periods. In each crossover period, according to the randomization scheme, women were administered multiple oral dose of either the Test or Reference medication for 11 consecutive days as shown in Table 3:

Table 3: Test and Reference Regimen for Bioequivalence Trial 150033

Clinical Review

Theresa H. van der Vlugt, M.D., M.P.H.; Nneka McNeal-Jackson, M.D.

NDA 209661

Tradename (20 mg doxylamine succinate and 20 mg pyridoxine hydrochloride) extended-release tablets

TEST; Treatment A (Tradename):	Women were administered the trial medication BID as one - 20 mg-20 mg extended-release tablet at approximately 09:00 am and 9:00 pm for 11 consecutive days.
REFERENCE; Treatment B (Diclegis):	Women were administered the trial medication TID as one - 10 mg-10 mg tablet at approximately 09:00 am and 3:00 pm and two - 10 mg-10 mg delayed-release tablets at approximately 9:00 pm for 11 consecutive days.

Source: Adapted from NDA 209661, Integrated Clinical and Statistical Report, sub-section 9.4.1 Treatments Administered, page 21 of 2480.

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. For every dosing period, both the planned and exact dosing time was documented.

Pharmacokinetic (PK) Characterization:

In each period, a total of 116 blood samples (via dead volume intravenous catheter or direct venipuncture) were drawn over 12 days (total volume of blood drawn did not exceed 1515 mL), from each woman for PK analyses. Blood samples for plasma (or whole blood in the case of pyridoxal) concentration measures were collected as presented in the following Table 4.

Table 4: Blood Sampling Collection Schedule for Bioequivalence Trial 150033

Pyridoxine	
Days 1 and 11	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
Days 3 through 10	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
Pyridoxal 5'-phosphate:	
Days 1 and 11	pre-dose (-1, -0.5 hours, and -10 minutes) and 1, 2, 3, 4, 5, 6 (prior to dosing if applicable), 7, 8, 9, 10, 11, 12 (prior to dosing), 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, and 24 hours (prior to Day 2 dosing) post-morning dose
Days 3 through 10	Blood samples were collected prior to each morning's dose
Pyridoxal	

Clinical Review

Theresa H. van der Vlugt, M.D., M.P.H.; Nneka McNeal-Jackson, M.D.

NDA 209661

Tradename (20 mg doxylamine succinate and 20 mg pyridoxine hydrochloride) extended-release tablets

Days 1 and 11	pre-dose (-1, -0.5 hours, and -10 minutes) and 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6 (prior to dosing if applicable), 7, 8, 9, 10, 11, 12 (prior to dosing), 12.5, 13, 13.5, 14, 14.5, 15, 15.5, 16, 16.5, 17, 17.5, 18, 19, 20, 22, 23, and 24 hours (prior to Day 2 dosing) post-morning dose
Days 3 through 10	Blood samples were collected prior to each morning's dose
Doxylamine	
Days 1 and 11	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
Days 3 through 10	Blood samples were collected prior to each morning's dose

Source: Adapted from NDA 209661, Integrated Clinical and Statistical Report, sub-section 9.5.4 Drug Concentration Measurements, pages 26 and 27 of 2480.

Clinical Reviewers' Comments:

Per the applicant, if evidence of high variability in the bioequivalence PK parameters was demonstrated, the reference-scaled average bioequivalence approach was applied to doxylamine and pyridoxal 5'-phosphate, as well as to pyridoxine as supportive data, for the statistical analyses in accordance with the Agency's guidance "Statistical Approaches to Establishing Bioequivalence" for highly variable drugs in a replicated trial design. Plasma concentrations of pyridoxine are known to be low with a very rapid elimination phase. In order to have an adequate characterization of its PK profile, following two or three trial drug administrations over a period of 24 hours, and two different mechanisms of release, an extensive sampling was required.

The analytical methods used to determine the levels of doxylamine, pyridoxine, and pyridoxine metabolites were validated in compliance with (b) (4). Pyridoxine was assayed using an LC/MS method developed and validated by (b) (4). Doxylamine was assayed using a high performance liquid chromatographic method developed and validated by (b) (4).

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.

PK parameters were assessed on Day 1 following administration of one 20 mg tablet of test (Tradename) and one 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. AUC₀₋₆, AUC₀₋₁₂, AUC₀₋₂₄: partial area under the concentration-time curve.

Clinical Review

Theresa H. van der Vlugt, M.D., M.P.H.; Nneka McNeal-Jackson, M.D.

NDA 209661

Tradename (20 mg doxylamine succinate and 20 mg pyridoxine hydrochloride) extended-release tablets

2. $AUC_{0-6\text{ ss}}$, $AUC_{0-12\text{ ss}}$, $AUC_{0-24\text{ ss}}$: partial area under the concentration-time curve at steady-state.
3. $T_{\text{max}0-24}$: time of observed $C_{\text{max}0-24}$ during the 24-hours period.
4. $T_{\text{max}0-24\text{ ss}}$: time of observed $C_{\text{max}0-24\text{ ss}}$ during the 24-hours period at steady-state.
5. $C_{\text{max}0-24}$: 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. FI(%): percentage of fluctuation.

Pharmacokinetic and statistical analyses were performed at (b) (4). The PK population consisted of all women who completed at least two periods and for whom the PK profile could be adequately characterized. The safety population included all women who received at least one dose of the trial medication. Demographic parameters were summarized descriptively. No statistical tests were performed.

Clinical Reviewers' Comments:

See the Clinical Pharmacology Review for a detailed description of Trial 150033.

Demographics:

A total of 37 healthy women of childbearing potential or non-postmenopausal with tubal ligation were included in the PK population on Day 1, 34 women were included in the PK population on Day 11, with a mean age (years) $\pm$ standard deviation (SD) of 34 ± 8 ; mean BMI (kg/m^2) $\pm$ SD of 23.95 ± 2.93 with a mean weight (kg) $\pm$ SD of 64.34 ± 9.46 .

Clinical Reviewers' Comments:

For Trial 150033, all participating women were Caucasian. While it may have been more informative to enroll a more racially diverse population of women, the total number of women in the trial is a limiting factor.

Major Protocol Deviations:

Protocol deviations included dosing more than 10 minutes from scheduled time in participating women Numbers 07, 16, and 22 (test) and 13, 22, and 31 (Reference). These deviations occurred on days when no PK evaluation was performed and therefore, were not expected to have an impact on the steady state attainment. Participating women Numbers 02, 03, 08, 10, 15, and 18 (Test) and 01, 04, 05, 09, 11, 12, 13, 17, and 20 were provided vegetarian pizza in addition to their regular evening snack. No impact on trial results are expected, however, as the additional food did not have a high content of vitamin B₆. Deviations in the blood sampling schedule also occurred during the study, including pre-dose samples collected more than 10 minutes prior to dosing (participating woman Numbers 07, 14, 16, 22 (test)). See Section 14.2 in the trial report for a listing of all samples not

Clinical Review

Theresa H. van der Vlugt, M.D., M.P.H.; Nneka McNeal-Jackson, M.D.

NDA 209661

Tradename (20 mg doxylamine succinate and 20 mg pyridoxine hydrochloride) extended-release tablets

collected at the schedule time. There was no impact on the statistical analyses due to these time deviations since only the actual collection times were used in the PK calculations.

Results:

The applicant considered the design of the trial to be **adequate** to determine the pharmacokinetic parameters of the Test and the Reference formulations. Further the applicant concluded that the washout period of 28 days between the last dose of a period and the first dose of the subsequent period was sufficient to avoid any carry-over effects.

The applicant's results for doxylamine and pyridoxal 5'-phosphate (Table 5) are provided below.

Table 5: Test-to-Reference Geometric Mean Ratios and 90% Confidence Interval on AUC₀₋₂₄ and C_{max} for Baseline Corrected Doxylamine and Pyridoxal 5'-Phosphate

		Parameters	Ratio ¹	90% Confidence Intervals ²
Doxylamine	Day 1	AUC ₀₋₂₄	140.04%	130.24% -150.58%
		C _{max}	79.57%	76.11% - 83.19%
	Day 11	AUC ₀₋₂₄	99.05%	95.73% - 102.49%
		C _{max}	105.26%	100.84% - 109.88%
Pyridoxal 5'-phosphate	Day 1	AUC ₀₋₂₄	161.49%	147.58% – 176.71%
		C _{max}	105.64%	99.64% – 112.00%
	Day 11	AUC ₀₋₂₄	100.08%	95.82% - 104.53%
		C _{max}	100.76%	96.68% - 105.00%

Source: Adapted from NDA 209661, Integrated Clinical and Statistical Report for Trail 150033, Table 11.4.2.3-3 and Table 11.4.2.3-6 for doxylamine, pages 53 and 59 of 2480, respectively; Table 11.4.2.3-9 and Table 11.4.2.3-12 for pyridoxal 5'-phosphate, pages 63 and 68 of 2480, respectively.

¹Point estimate of the geometric mean ratio (A/B).

²90% Geometric Confidence Interval using ln-transformed data.

The Day 1 evaluations of the 90% confidence intervals of the point estimate of the ratios of test to reference for C_{max} and AUC₀₋₂₄ for doxylamine, 76.11% – 83.19% and 130.24% – 150.58%, respectively were both outside of the range to declare bioequivalence. On trial Day 1, the 90% confidence interval of the point estimate of the ratio of test to reference for the rate of absorption (C_{max}) for the pharmaceutically active metabolite pyridoxal 5'-phosphate, 99.64% - 112.00%, was within the accepted range, 80% - 125%, to establish bioequivalence while the 90% confidence interval of the point estimate of the ratio of test to reference of the extent of absorption from 0-24 hours (AUC₀₋₂₄) for pyridoxal 5'-phosphate, 147.58% -176.71%, was outside of the range for bioequivalence.

Clinical Review

Theresa H. van der Vlugt, M.D., M.P.H.; Nneka McNeal-Jackson, M.D.

NDA 209661

Tradename (20 mg doxylamine succinate and 20 mg pyridoxine hydrochloride) extended-release tablets

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.”

Clinical Reviewer’s Comments:

The trial Day 1 single dose component of the bioequivalence trial, as designed by the sponsor, did not reflect the proposed regimen of the new formulation and the existing formulation for Diclegis. On Day 1, PK parameters were assessed following administration of one **20 mg** tablet of test (Tradename) and one **10 mg** tablet of reference (Diclegis) at 9 am. Evaluations of single dose PK should have occurred after one tablet of the new formulation (combination 20 mg doxylamine and 20 mg pyridoxine) and the same strength i.e. two tablets of Diclegis (combination 10 mg doxylamine and 10 mg pyridoxine).

On trial Day 11, evaluations of the 90% confidence intervals of the point estimate of the ratios of test to reference for C_{max} and AUC_{0-24} for doxylamine and pyridoxal 5'-phosphate (see Table 5) were all within the accepted 80% - 125% range to establish bioequivalence.

Clinical Reviewers’ Comments:

Per the applicant, data from a previous multi-dose trial conducted in the original NDA 021876 (Trial 70381) with Diclegis demonstrated that steady-state is attained after 9-10 days of consecutive dosing. Analysis was carried out on pre-morning dose concentrations (on Days 9 to 11) in original Trial 70381 to determine attainment of the steady-state. To ensure that steady-state is attained for all women, Trial 150033 is designed with 11 days of dosing. Analysis in Trial 150033 is also carried out on pre-morning dose concentrations (on Days 9 to 11) to determine attainment of steady-state.

The applicant’s results for pyridoxine (Table 6) are provided below.

Table 6: Test-to-Reference Geometric Mean Ratios and 90% Confidence Interval on AUC_{0-24} and C_{max} for Pyridoxine

	Parameters	Ratio ¹	90% Upper Confidence Bound ²	90% Confidence Intervals ³	CV _{WR}
Day 1	AUC_{0-24}	80.79%	-	75.69% - 86.24%	26.14%
	C_{max}	98.21%	-0.1373	-	53.37%
Day 11	AUC_{0-24}	80.53%	-	74.72% - 86.80%	19.95%
	C_{max}	108.66%	-0.0288	-	33.33%

Source: Adapted from NDA 209661, Integrated Clinical and Statistical Report for Trail 150033,

Clinical Review

Theresa H. van der Vlugt, M.D., M.P.H.; Nneka McNeal-Jackson, M.D.

NDA 209661

Tradename (20 mg doxylamine succinate and 20 mg pyridoxine hydrochloride) extended-release tablets

Table 11.4.2.3-21 and Table 11.4.2.3-24, pages 84 and 90 of 2480, respectively.

¹Point estimate of the geometric mean ratio (A/B).

²Reference-scaled average bioequivalence approach.

³90% Geometric Confidence Interval using ln-transformed data.

The trial Day 1 and Day 11 evaluations of the 90% confidence intervals of the point estimate of the ratios of test to reference for AUC₀₋₂₄ for pyridoxine were both outside of the range for bioequivalence. The 90% confidence intervals of the point estimate of the ratios of test to reference for C_{max} could not be determined.

Clinical Reviewers' Comments:

Per the applicant, "given the mechanism of release of the new formulation of Tradename and the pharmacokinetic of pyridoxine, with its very short T_{1/2} el, it was not expected that BE criteria were to be met for this parent drug". The applicant states that the trial "has been designed and powered to bring robust statistical comparisons for pyridoxine parameters, even though only the parent drug doxylamine and the pyridoxine's main active metabolite, pyridoxal 5'-phosphate, were used for determination of bioequivalence."

A second pyridoxine major metabolite, pyridoxal, was also measured and presented (Table 7) as supportive information.

Table 7: Test-to-Reference Geometric Mean Ratios and 90% Confidence Interval on AUC₀₋₂₄ and C_{max} for Pyridoxal

	Parameters	Ratio ¹	90% Upper Confidence Bound ²	90% Confidence Intervals ³	CV _{WR}
Day 1	AUC ₀₋₂₄	117.39%	-	110.79% - 124.37%	26.14%
	C _{max}	79.77%	-0.0251	-	33.63%
Day 11	AUC ₀₋₂₄	Group 1 = 103.31% Group 2 = 94.33%	-	98.54% - 108.31% 89.85% - 99.03%	13.57% 11.22%
	C _{max}	67.01%	-0.1750	-	31.55%

Source: Adapted from NDA 209661, Integrated Clinical and Statistical Report for Trail 150033, Table 11.4.2.3-27 and Table 11.4.2.3-30, pages 95 and 101 of 2480, respectively.

¹Point estimate of the geometric mean ratio (A/B).

²Reference-scaled average bioequivalence approach.

³90% Geometric Confidence Interval using ln-transformed data.

Conclusion:

Based on these results, the applicant concludes that Tradename "can be considered bioequivalent to Diclegis." "The difference between the two formulations may be explained by the difference in dosing regimen of Diclegis vs Tradename."

Clinical Reviewers' Comments:

Clinical Review

Theresa H. van der Vlugt, M.D., M.P.H.; Nneka McNeal-Jackson, M.D.

NDA 209661

Tradename (20 mg doxylamine succinate and 20 mg pyridoxine hydrochloride) extended-release tablets

Trial 150033 assessed the bioequivalence between the maximum daily doses of:

- Tradename (40 mg doxylamine and 40 mg pyridoxine) given in twice daily doses of 20 mg doxylamine and 20 mg pyridoxine at 9:00 am and 9:00 pm
versus
- Diclegis (40 mg doxylamine and 40 mg pyridoxine) given three times daily at 9:00 am (10 mg doxylamine and 10 mg pyridoxine), 3:00 pm (10 mg doxylamine and 10 mg pyridoxine), and 9:00 pm (2 tablets for a total of 20 mg doxylamine and 20 mg pyridoxine)

Per the Clinical Pharmacology Review, **Trial 150033** “lacks the bridging for the proposed starting dose of TRADENAME (i.e., one 20 mg doxylamine succinate / 20 mg pyridoxine hydrochloride tablet given at bedtime) to the currently approved starting dose for Diclegis® (i.e., two 10 mg doxylamine succinate / 10 mg pyridoxine hydrochloride tablets given at bedtime).” See discussion of bioequivalence Trial 150366 below. The Sponsor concludes that “BE is established for both doxylamine and pyridoxal 5'-phosphate based on AUC(0-24) and C_{max} on Day 11 but not for Day 1.”

5.3.2 Bioequivalence Trial 150336

Objective:

The objective of non-IND Trial 150336 was to compare the rate and extent absorption of one 20 mg doxylamine and 20 mg pyridoxine extended-release tablet (Test) versus two Diclegis (10 mg doxylamine and 10 mg pyridoxine) delayed-release tablets (Reference), under fasting conditions.

Design:

This was a single center (inVentiv Health Clinique, Inc.), randomized, single-dose, open-label, 2-way crossover bioequivalence trial to compare the rate and extent of absorption of Tradename (test, single tablet of 20 mg doxylamine and 20 mg pyridoxine) versus approved Diclegis (reference, two tablets of 10 mg doxylamine and 10 mg of pyridoxine) after a single day administration, under fasting conditions.

Per the applicant, “A randomized crossover design is typically employed in BE studies, and was considered to be the most appropriate for this study.”

Clinical Reviewers' Comments:

As previously stated, Trial 150336 was conducted outside of IND 72300 and was not known to the Agency until included in the 120-Day Safety Update Report received on March 24, 2016. Therefore, a protocol for Trial 150336 was never presented for review by the Agency. DBRUP requested and received Trial 150336 Integrated Clinical and Statistical Report on June 13, 2016 after the NDA submission date.

Clinical Review

Theresa H. van der Vlugt, M.D., M.P.H.; Nneka McNeal-Jackson, M.D.

NDA 209661

Tradename (20 mg doxylamine succinate and 20 mg pyridoxine hydrochloride) extended-release tablets

The clinical reviewers agree that a single-dose, crossover bioequivalence trial, as presented, is appropriate. The single-dose of two tablets of Diclegis (for a total of 20 mg doxylamine and 20 mg of pyridoxine) is the same dose as one tablet of Tradename (20 mg doxylamine and 20 mg pyridoxine).

Inclusion Criteria:

The inclusion criteria for Trial 150336 are the same as employed for Trial 150033. See page 35 of this review.

Exclusion Criteria:

The exclusion criteria for Trial 150336 are the same as employed for Trial 150033. See page 36 of this review.

Excluded and Concomitant Medications:

As in Trial 150033, prescription and over-the-counter medications were prohibited throughout the trial. No concomitant drug therapy was allowed during the trial except as required for the medical management of an AE. The use of hormonal contraceptives was allowed and documented. 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.

Subjects were advised that they were not allowed to take MAO inhibitors for the period of time encompassing 30 days prior to the initiation of trial medication dosing through 14 days after the final trial medication administration.

Methods:

Prior to trial commencement, women were randomly assigned to a treatment group in accordance with the randomization scheme generated by inVentiv. 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 hours 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.

Pharmacokinetic (PK) Characterization:

Clinical Review

Theresa H. van der Vlugt, M.D., M.P.H.; Nneka McNeal-Jackson, M.D.

NDA 209661

Tradename (20 mg doxylamine succinate and 20 mg pyridoxine hydrochloride) extended-release tablets

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 8.

Table 8: Blood Sampling Collection Schedule for Bioequivalence Trial 150336

Doxylamine
Pre-dose (-1, -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
Pyridoxal 5'-phosphate:
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-morning dose
Pyridoxine
Pre-dose (-1, -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
Pyridoxal
Pre-dose (-1, -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

Source: Adapted from NDA 209661, Integrated Clinical and Statistical Report, sub-section 9.5.4 Drug Concentration Measurements, page 63 of 1121.

Clinical Reviewers' Comments:

This trial was conducted using a sampling truncated at 72 hours for pyridoxal 5'-phosphate. Per the applicant, the metabolite pyridoxal 5'-phosphate has a long $T_{1/2}$ el therefore, samples were collected up to 72 hours for this analyte. "...drugs with long $T_{1/2}$ el that also demonstrates low intra-subject variability in distribution and clearance, an AUC truncated at 72 hours (AUC_{0-72}) can be used in place of AUC_{0-t} or AUC_{0-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 $T_{1/2}$ 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_{max} : maximum observed concentration.
4. Residual area: calculated as $100 \cdot (1 - AUC_{0-t} / AUC_{0-inf})$.

Clinical Review

Theresa H. van der Vlugt, M.D., M.P.H.; Nneka McNeal-Jackson, M.D.

NDA 209661

Tradename (20 mg doxylamine succinate and 20 mg pyridoxine hydrochloride) extended-release tablets

5. T_{max} : time of observed C_{max} .
6. $T_{1/2\text{el}}$: 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_{max} : maximum observed concentration.
2. T_{max} : time of observed C_{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 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 (b) (4).

Clinical Reviewers' Comments:

See the Clinical Pharmacology Review for a detailed description of Trial 150336.

Demographics:

A total of 52 healthy women of childbearing potential or non-postmenopausal with tubal ligation were included in the PK analyses with a mean age (years) $\pm$ SD of 32 ± 7 ; mean BMI (kg/m^2) $\pm$ SD of 24.62 ± 3.04 with a mean weight of 64.92 ± 10.68 . Forty-seven (47) of the 52 participating women were Caucasian, 3 were African American, and 2 were Asian.

Clinical Reviewers' Comments:

The demographics of participating women in bioequivalence Trials 150033 and 150336 are similar.

Major Protocol Deviations:

In Period 1 in Trial 150336, thirteen (13) women in Test and 13 women in Reference had samples of the 6.50-hour timepoint for pyridoxal 5'-phosphate stored for 2 hour at -20°C instead of -80°C . No impact was anticipated since there is product stability of 26 hours and 27 minutes at 4°C . In Period 2, twelve (12) women in Test and 14 women in Reference had blood samples of pyridoxine centrifuged for 10 non-consecutive minutes due to a power outage. No impact resulted since separation was adequately done. Six (6) women in Test and 6 women in Reference had blood samples for pyridoxal, doxylamine and pyridoxine stored at -80°C for one day. No impact resulted due to the following stabilities at -80°C : 95 days for pyridoxal, 371 days for doxylamine, and 100 days for pyridoxine. Trial participant Number 18 obtained a positive home pregnancy test approximately 13 days after dosing in Period 1. This woman discontinued Trial 150336 in Period 1.

Clinical Review

Theresa H. van der Vlugt, M.D., M.P.H.; Nneka McNeal-Jackson, M.D.

NDA 209661

Tradename (20 mg doxylamine succinate and 20 mg pyridoxine hydrochloride) extended-release tablets

Results:

Per the applicant, the design of Trial 150336 was adequate to determine the pharmacokinetic parameters of the Test and the Reference formulations. The results reported in Trial 150336 are shown in Table 9.

Table 9: Test-to-Reference Geometric Mean Ratios and 90% Confidence Interval for Doxylamine, Baseline Corrected Pyridoxal 5'-Phosphate, Pyridoxal 5'-Phosphate, Pyridoxine, Baseline Corrected Pyridoxal, and Pyridoxal

	Parameter	Ratio ¹	90% Geometric Confidence Interval ²
Doxylamine	AUC _{0-t}	101.95%	98.38% - 105.65%
	AUC _{0-inf}	101.72%	98.07% - 105.51%
	C _{max}	94.16%	90.75% - 97.69%
Pyridoxal 5'-Phosphate (baseline -corrected)	AUC ₀₋₇₂	104.22%	97.85% - 111.01%
	C _{max}	104.83%	101.14% - 108.65%
Pyridoxal 5'-Phosphate	AUC ₀₋₇₂	102.58%	99.12% - 106.16%
	C _{max}	104.03%	101.06% - 107.08%
Pyridoxine	AUC _{0-t}	86.38%	81.25% - 91.84%
	AUC _{0-inf}	86.37%	81.28% - 91.77%
	C _{max}	94.28%	83.15% - 106.89%
Pyridoxal (baseline-corrected)	AUC _{0-t}	118.86%	103.42% - 136.60%
	AUC _{0-inf}	106.74%	103.16% - 110.45%
	C _{max}	95.85%	81.87% - 112.22%
Pyridoxal	AUC _{0-t}	114.88%	104.91% - 125.81%
	C _{max}	94.73%	82.78% - 108.41%

Source: Adapted from NDA 209661, Integrated Clinical and Statistical Report for Trial 150336 received June 13, 2016, sub-section 11.4.2.3 Pharmacokinetic Analysis, Table 11.4.2.3-3 for doxylamine on page 80 of 1121, Table 11.4.2.3-6 for baseline corrected pyridoxal 5'-phosphate on page 83 of 1121, Table 11.4.2.3-9 for pyridoxal 5'-phosphate on page 84 of 1121, Table 11.4.2.3-12 for pyridoxine on page 89 of 1121, Table 11.4.2.3-15 for baseline corrected pyridoxal on page 92 of 1121, and Table 11.4.2.3-18 for pyridoxal on page 95 of 1121.

¹Calculated using least-squares means according to the formula: $e^{(\text{DIFFERENCE})} \times 100$.

²90% Geometric Confidence Interval using ln-transformed data.

Conclusion:

Per the applicant, determination of bioequivalence was based on doxylamine and baseline-corrected pyridoxal 5'-phosphate data. Based on the above results for doxylamine and baseline-corrected pyridoxal 5'-phosphate, the applicant concludes that the test doxylamine and pyridoxine extended-release tablet is bioequivalent to the reference Diclegis delayed-release tablet under fasting conditions.

Clinical Reviewers' Comments:

Trial 150336 compared the rate and extent of absorption of Test (20 mg doxylamine and 20 mg pyridoxine) administered as 1 tablet versus Reference (Diclegis: 10 mg

Clinical Review

Theresa H. van der Vlugt, M.D., M.P.H.; Nneka McNeal-Jackson, M.D.

NDA 209661

Tradename (20 mg doxylamine succinate and 20 mg pyridoxine hydrochloride) extended-release tablets

doxylamine and 10 mg pyridoxine) administered as 2 tablets, under fasting conditions.

Fifty-two non-pregnant women were dosed in Trial 150336. Forty-eight (48) women completed the clinical trial [Trial participant Number 18 discontinued for safety reasons (pregnancy) and Trial participant Number 23 for pharmacokinetic reasons (vomiting)].

Determination of bioequivalence was based on doxylamine and baseline-corrected pyridoxal 5'-phosphate data in Trial 150336. In accordance with the study protocol, the hypothesis of bioequivalence is accepted if:

- the 90% CI of the ratio of least-squares means of the Test to Reference product of In-transformed AUC_{0-t} , AUC_{0-inf} , and C_{max} are within the acceptance range of 80.00 to 125.00% for doxylamine
- the 90% CI of the ratio of least-squares means of the Test to Reference product of In-transformed AUC_{0-72} , and C_{max} are within the acceptance range of 80.00 to 125.00% for pyridoxal 5'-phosphate

Table 9 shows that Trial 150336 met the bioequivalence criteria for doxylamine and pyridoxal 5'-phosphate. All 90% confidence intervals of the geometric of the evaluated parameter are within the acceptance range.

Per the Clinical Pharmacology Review, "it was concluded that BE regarding the rate and extent of both doxylamine and baseline corrected pyridoxal 5'-phosphate exposures between TRADENAME and Diclectin was established following a single dose of 20 mg doxylamine succinate / 20 mg pyridoxine hydrochloride."

Considering that bioequivalence between the beginning dose (that users will stay on in the case symptoms are controlled) of Tradename and Diclegis was established in bioequivalence Trial 150336 and bioequivalence on Day 11 was established in Trial 150033, the clinical reviewers concur with the Office of Clinical pharmacology that the safety and efficacy of Tradename has been adequately bridged to those of Diclegis based on these two trials.

5.3.3 Fed/Fasted Bioavailability Trial 140115

Objective:

The objective of this trial was to evaluate the effect of food on the pharmacokinetics (PK) of Tradename administered as a single combination 20 mg doxylamine and 20 mg pyridoxine extended-release tablet, which 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.

Clinical Review

Theresa H. van der Vlugt, M.D., M.P.H.; Nneka McNeal-Jackson, M.D.

NDA 209661

Tradename (20 mg doxylamine succinate and 20 mg pyridoxine hydrochloride) extended-release tablets

Design:

This 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 $T_{1/2\text{el}}$ 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."

Inclusion Criteria:

The inclusion criteria for Trial 140115 are the same as those listed for Trial 150033 on page 35 of this review.

Exclusion Criteria:

The exclusion criteria for Trial 140115 are the same as those listed for Trial 150033 on page 36 of this review.

Excluded and Concomitant Medications:

As in Trial 150033, prescription and over-the-counter medication use was prohibited throughout the trial. No concomitant drug therapy was allowed during the trial except one(s) required for the medical management of an AE. The use of hormonal contraceptives was allowed and documented. 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.

Methods:

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

Clinical Review

Theresa H. van der Vlugt, M.D., M.P.H.; Nneka McNeal-Jackson, M.D.

NDA 209661

Tradename (20 mg doxylamine succinate and 20 mg pyridoxine hydrochloride) extended-release tablets

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.

Pharmacokinetic (PK) Characterization:

Doxylamine, pyridoxine and pyridoxal 5'-phosphate were analyzed in plasma samples and pyridoxal was analyzed in whole blood at the (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 10: Blood Sampling Collection Schedule

Pyridoxine	
Fed	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
Fasted	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
Pyridoxal 5'-phosphate:	
Fed	pre-dose (-1, -0.5 hours, and -5 minutes) and 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 14, 15, 16, 18, 20, 22, 24, 30, 36, 48, and 72 hours post-dose.
Fasted	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
Pyridoxal	
Fed	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
Fasted	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.
Doxylamine	
Fed	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
Fasted	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

Clinical Review

Theresa H. van der Vlugt, M.D., M.P.H.; Nneka McNeal-Jackson, M.D.

NDA 209661

Tradename (20 mg doxylamine succinate and 20 mg pyridoxine hydrochloride) extended-release tablets

Source: Adapted from NDA 209661, Integrated Clinical and Statistical Report, sub-section 9.5.4 Drug Concentration Measurements, pages 23 and 24 of 483.

Clinical Reviewers' Comments:

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

The pharmacokinetic parameters assessed were AUC_{0-t} , AUC_{0-inf} , C_{max} , Residual area, T_{max} , $T_{1/2el}$, 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-t} , C_{max} , and T_{max} . PK and statistical analyses were performed at (b) (4).

Per the applicant, a total of 24 women were assessed as sufficient to meet the trial objectives. No additional information on sample size determination was provided in the application.

Clinical Reviewers' Comments:

Refer to the Clinical Pharmacology Review for additional description of the design for Trial 140155.

Demographics:

A total of 24 healthy women of childbearing potential or non-postmenopausal with tubal ligation were included in the PK analyses with a mean age (years) $\pm$ SD of 32 ± 8 ; mean BMI (kg/m^2) $\pm$ SD of 24.15 ± 3.16 with a mean weight of 65.42 ± 8.83 . Twenty-three (23) of the 24 participating women were Caucasian, 1 was African American.

Clinical Reviewers' Comments:

The demographics of participating women in fed/fasted bioavailability Trial 140115 are similar to bioequivalence Trials 150033 and 150336.

Major Protocol Deviations:

One woman (No. 20) was excluded from the PK population for all analytes since it was not possible to adequately characterize her PK profiles (many consecutive missing samples). Therefore, data from 23 women were used for PK and statistical analyses.

Results:

Bioavailability under fed/fasted conditions is presented in Table 11.

Table 11: Trial 140115 Geometric Means, Ratios and 90% Confidence Intervals for PK Parameters Following a Single Dose of Tradename Tablet with (Test) or without Food (Reference). N=23

Clinical Review

Theresa H. van der Vlugt, M.D., M.P.H.; Nneka McNeal-Jackson, M.D.

NDA 209661

Tradename (20 mg doxylamine succinate and 20 mg pyridoxine hydrochloride) extended-release tablets

Pyridoxine				
Parameter	Geometric Mean		Ratio % ¹ (Test/Reference)	90% Confidence Interval ²
	Test	Reference		
AUC _(0-t) ng.hr/mL	20.6	33.1	62.8	54.5-72.3
AUC _(0-inf) ng.hr/mL	25.3	34.2	70.7	53.8-92.9
C _{max} ng/mL	11.4	35.1	32.7	26.9-39.6
Pyridoxal 5'-phosphate – Baseline Corrected				
Parameter	Geometric Mean		Ratio % (Test/Reference)	90% Confidence Interval
	Test	Reference		
AUC _(0-t) ng.hr/mL	1005.4	975.1	103.4	95.6-111.8
C _{max} ng/mL	28.7	26.4	109.3	103.4-115.5
Pyridoxal– Baseline Corrected				
Parameter	Geometric Mean		Ratio % (Test/Reference)	90% Confidence Interval
	Test	Reference		
AUC _(0-t) ng.hr/mL	202.5	207.4	97.9	93.4-102.6
AUC _(0-inf) ng.hr/mL	245.4	242.0	101.8	96.2-107.8
C _{max} ng/mL	32.6	59.7	54.2	48.6-60.5
Doxylamine				
Parameter	Geometric Mean		Ratio % (Test/Reference)	90% Confidence Interval
	Test	Reference		
AUC _(0-t) ng.hr/mL	1219.1	1247.0	97.6	93.6-101.7
AUC _(0-inf) ng.hr/mL	1253.5	1289.1	97.0	92.9-101.3
C _{max} ng/mL	62.7	85.3	73.6	68.0-79.8

Source: Adapted from NDA 209661, sub-section 11.4.2 Analysis of Pharmacokinetics and Statistical Issues, sub-section 11.4.2.1 Adjustment of Factors in the ANOVA, Table 11.4.2.3-3 for doxylamine on page 41 of 483, Table 11.4.2.3-7 for pyridoxine on page 44 of 483, Table 11.4.2.3-13 for pyridoxal (baseline corrected) on page 50 of 483, Table 11,4,2,3020 for pyridoxal 5'-phosphate of page 56 of 483.

¹Calculated using least-squares means according to the formula: $e^{(\text{DIFFERENCE})} \times 100$.

²90% Geometric Confidence Interval using ln-transformed data.

No food effect was to be concluded if the 90% geometric CIs of the ratio (T/R: fed conditions/fasting conditions) of least-squares means from the ANOVA of the ln-transformed AUC(0-t), AUC(0-inf), and C_{max} were within 80 to 125%.

The AUC_(0-t) were all within the acceptable 80 to 125% range for pyridoxal 5'-phosphate, pyridoxal, and doxylamine. AUC_(0-inf) was not calculated for pyridoxal 5'-phosphate, but was in the 80-125% range to declare no food effect for pyridoxal and doxylamine. AUC_(0-t) and AUC_(0-inf) were not in the 80-125% range to declare no food effect for pyridoxine. C_{max} was outside of the range for pyridoxine, pyridoxal and doxylamine but was within the 80-125% range to declare no food effect for pyridoxal 5'-phosphate.

Per the final trial report for Trial 140115, the administration of Tradename extended-release tablets with a standard high-fat, high caloric meal delayed the absorption and reduced the bioavailability comparatively to its administration under fasting conditions. Food delayed the absorption of doxylamine by 3 hours (median T_{max}). The C_{max} of doxylamine is decreased by 26% while the AUC remains unchanged.

Clinical Review

Theresa H. van der Vlugt, M.D., M.P.H.; Nneka McNeal-Jackson, M.D.

NDA 209661

Tradename (20 mg doxylamine succinate and 20 mg pyridoxine hydrochloride) extended-release tablets

The effect of food on the pyridoxine component is more complex in that pyridoxine and active metabolites, pyridoxal and pyridoxal 5'-phosphate also contribute to the biological activity. A lower rate and extent of absorption was observed for pyridoxine when compared to its administration under fasting conditions. Food significantly reduced bioavailability of pyridoxine, compared to fasting conditions. The C_{max} and AUC of pyridoxine are decreased by 67% and up to 37%, respectively. Conversely, food slightly increased pyridoxal 5'-phosphate C_{max} by approximately 25%. The absorption of pyridoxine and the production of pyridoxal and pyridoxal 5'-phosphate are delayed by 7.25 hours, 3.75 hours and 11 hours, respectively (median T_{max}).

Conclusion:

Per the final trial report, in accordance with the trial protocol, for doxylamine and pyridoxine, no food effect was to be concluded if the 90% geometric confidence intervals of the ratio (A/B: fed conditions/fasting conditions) of least-squared means from the ANOVA of the In-transformed AUC_{0-t} , AUC_{0-inf} , and C_{max} are within 80 to 125%.

The “no food-effect” criteria were not completely met for doxylamine, pyridoxine and pyridoxal. The metabolite pyridoxal 5'-phosphate did meet no food effect criteria for the two parameters evaluated, AUC_{0-t} and C_{max} .

The reviewers concur that “no food effect” cannot be concluded. Based on these findings, labeling for Tradename, will state: “Take on an empty stomach with a glass of water [see *Clinical Pharmacology* (12.3)]. Swallow tablets whole. Do not crush, chew, or split Tradename tablets.” See Section 2 DOSAGE AND ADMINISTRATION, Subsection 2.1 Dosage Information of proposed labeling.

Clinical Reviewers' Comments:

Per the Clinical Pharmacology Review, “Food delayed the median T_{max} of doxylamine and pyridoxine 5'-phosphate for 3 and 11 hours, respectively. In addition, food decreased the C_{max} for doxylamine by 26.4%. TRADENAME tablets should be administered under fasting conditions to avoid food affecting the rate of absorption (i.e., T_{max}) and the extent of exposure (i.e., C_{max} and AUC).”

The Clinical Team concurs with the applicant's labeling recommendation to take Tradename on an empty stomach with a glass of water.

6 Review of Efficacy

Efficacy Summary

Clinical Review

Theresa H. van der Vlugt, M.D., M.P.H.; Nneka McNeal-Jackson, M.D.

NDA 209661

Tradename (20 mg doxylamine succinate and 20 mg pyridoxine hydrochloride) extended-release tablets

The safety and efficacy of Diclegis (10 mg doxylamine and 10 mg of pyridoxine) was determined in the original NDA application approved April 8, 2013.

NDA 021876/Supplement 10, received October 7, 2015 and converted to NDA 209661 on September 1, 2016, and Amendment-S0065 received June 13, 2016 do not contain new efficacy data. Efficacy was not an objective of the trial design for bioequivalence Trials 150033 and 150336, and fed/fasted bioavailability Trial 140115. Efficacy was to be considered based on bioequivalence. Bioequivalence was established at Day 11 in Trial 150033 and following single dose administration in 150336 (refer to Subsection 5.3.2 of this review).

6.1 Indication

6.1.1 Methods

See discussion of individual trial methods for bioequivalence Trials 150033 and 150336, and fed/fasted bioavailability Trial 140115 in Sections 5.3.1 and 5.3.2., respectively.

6.1.2 Demographics

See discussion of individual trial demographics bioequivalence Trials 150033 and 150336, and fed/fasted bioavailability Trial 140115 in Sections 5.3.1 and 5.3.2., respectively, and Section 7.2.1. The intended population for Tradename is pregnant women [REDACTED]^{(b) (4)} with nausea and vomiting of pregnancy.

6.1.3 Subject Disposition

See discussion of the disposition of women in bioequivalence Trials 150033 and 150336, and fed/fasted bioavailability Trial 140115 in Sections 5.3.1 and 5.3.2., respectively.

6.1.4 Analysis of Primary Endpoint(s)

NDA 209661 does not contain efficacy data. Efficacy was not an objective of the trial design for bioequivalence Trials 150033 and 150336, or fed/fasted bioavailability Trial 140115.

6.1.5 Analysis of Secondary Endpoints(s)

NDA 209661 does not contain efficacy data. Efficacy was not an objective of the trial design for bioequivalence Trials 150033 and 150336, or fed/fasted bioavailability Trial 140115.

6.1.6 Other Endpoints

Clinical Review

Theresa H. van der Vlugt, M.D., M.P.H.; Nneka McNeal-Jackson, M.D.

NDA 209661

Tradename (20 mg doxylamine succinate and 20 mg pyridoxine hydrochloride) extended-release tablets

NDA 209661 does not contain efficacy data. Efficacy was not an objective of the trial design for bioequivalence Trials 150033 and 150336 or fed/fasted bioavailability Trial 140115.

6.1.7 Subpopulations

NDA 209661 does not contain efficacy data. Efficacy was not an objective of the trial design for bioequivalence Trials 150033 and 150336, or fed/fasted bioavailability Trial 140115.

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

NDA 209661 does not contain efficacy data. Efficacy was not an objective of the trial design for bioequivalence Trials 150033 and 150336, or fed/fasted bioavailability Trial 140115.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

NDA 209661 does not contain efficacy data. Efficacy was not an objective of the trial design for bioequivalence Trials 150033 and 150336, or fed/fasted bioavailability Trial 140115.

6.1.10 Additional Efficacy Issues/Analyses

NDA 209661 does not contain efficacy data. Efficacy was not an objective of the trial design for bioequivalence Trials 150033 and 150336, or fed/fasted bioavailability Trial 140115.

7 Review of Safety

Safety Summary

The safety and efficacy of Diclegis (10 mg doxylamine and 10 mg of pyridoxine) was determined in the original NDA application approved April 8, 2013.

7.1 Methods

In this supplemental NDA (sNDA), data supporting the safety of Tradename is derived from the following sources:

- Data from Clinical Trial Report for phase 1 bioequivalence trial, 150033
- Data from Clinical Trial Report for phase 1 bioequivalence trial, 150336
- Data from Clinical Trial Report for phase 1 bioavailability trial, 140115
- Data from the 120-Day Safety Update received on March 24, 2016

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

See Table 12 for a summary of the clinical trials providing safety information for this NDA.

Clinical Review

Theresa H. van der Vlugt, M.D., M.P.H.; Nneka McNeal-Jackson, M.D.

NDA 209661

Tradename (20 mg doxylamine succinate and 20 mg pyridoxine hydrochloride) extended-release tablets

Table 12: Summary of Clinical Trials Providing Safety Information

Trial Identifier Trial Type	Design Objective	Number of Women Enrolled Route of Administration and Regimen	Duration of Treatment
Trial 150033 Bioequivalence	Open-label randomized, multiple dose, 3-period, 3-sequence, reference replicated, crossover comparative trial to evaluate bioequivalence under fasting conditions with each treatment period separated by a minimum 28-day washout period.	39 Oral <u>Treatment A:</u> One Tradename (20 mg doxylamine and 20 mg pyridoxine) tablet taken at 09:00 and 21:00 hours under fasting conditions <u>Treatment B:</u> One Diclegis (10 mg doxylamine and 10 mg pyridoxine) tablet taken at 09:00 and 15:00 hours, and two tablets taken at 21:00 hours; each under fasting conditions	<u>Treatment A:</u> Tradename (20 mg doxylamine and 20 mg pyridoxine) taken 11 consecutive days <u>Treatment B:</u> Diclegis (10 mg doxylamine and 10 mg pyridoxine) taken 11 consecutive days
Trial 150336 Bioequivalence	Open-label, randomized, single dose, 2-way crossover comparative trial to evaluate bioequivalence under fasting conditions with a treatment period separated by a 21-day washout period.	52 Oral <u>Treatment A:</u> One Tradename (20 mg doxylamine and 20 mg pyridoxine) tablet <u>Treatment B:</u> Two Diclegis (10 mg doxylamine and 10 mg pyridoxine) tablets under fasting conditions	A single oral dose of Tradename (20 mg doxylamine and 20 mg pyridoxine) tablet or two Diclegis (10 mg doxylamine and 10 mg pyridoxine) administered in each trial period.
Trial 140115 Bioavailability	Open-label, randomized, single dose, 2-way crossover comparative trial to evaluate the effect of food on the pharmacokinetics of Tradename under fed and fasting conditions	24 Oral <u>Treatment A:</u> Tradename (20 mg doxylamine and 20 mg pyridoxine) one tablet under fed conditions	A single oral dose of Tradename (20 mg doxylamine and 20 mg pyridoxine) administered in each trial period.

Clinical Review

Theresa H. van der Vlugt, M.D., M.P.H.; Nneka McNeal-Jackson, M.D.

NDA 209661

Tradenname (20 mg doxylamine succinate and 20 mg pyridoxine hydrochloride) extended-release tablets

	with treatment periods separated by a 21-day washout period.	<u>Treatment B:</u> Tradenname (20 mg doxylamine and 20 mg pyridoxine) one tablet under fasting conditions	

Source: Adapted from NDA 209661, Module 5.2, Tabular Listing of All Clinical Trials.

In the 120-Day Safety Update received March 24, 2016, the applicant included a summary of non-IND Trial 150336, which was conducted independent of the Tradenname clinical development program. Non-IND Trial 150336 was an open-label, randomized, single dose, 2-way crossover comparative trial to evaluate the rate and extent of absorption of Tradenname 20 mg doxylamine and 20 mg pyridoxine extended-release tablet compared with approved Diclegis 10 mg doxylamine and 10 mg pyridoxine, under fasting condition. Fifty-two (52) women of childbearing potential and non-postmenopausal women with tubal ligations received either 1 tablet of Tradenname (Treatment A) or 2 tablets of approved Diclegis (Treatment B) separated by a 21-day washout period. The Clinical Trial Report for Trial 150336 was received on June 13, 2016.

7.1.2 Categorization of Adverse Events

A serious adverse event (SAE) was defined as:

1. Any event that was fatal or life threatening.
2. Any event that resulted in persistent or significant disability/incapacity.
3. Any event that required in-patient or prolonged hospitalization.
4. Any event that resulted in congenital anomalies/birth defects.
5. Any event that was considered an important medical event that jeopardized the subject and required medical or surgical intervention to prevent one of the previously listed outcomes.

A significant adverse event (significant AE) was defined as any event (other than those reported as serious) that led to an intervention, including withdrawal of treatment, dose reduction, or significant additional concomitant therapy.

A treatment-emergent adverse event (TEAE) was defined as:

1. An AE beginning on or after the first trial drug administration.
2. An AE beginning before the first trial drug administration and worsened in severity after the trial drug administration of the trial drug.
3. An AE that may have been prolonged due to administration of the trial drug.

Clinical Review

Theresa H. van der Vlugt, M.D., M.P.H.; Nneka McNeal-Jackson, M.D.

NDA 209661

Tradename (20 mg doxylamine succinate and 20 mg pyridoxine hydrochloride) extended-release tablets

TEAEs with an onset during the washout period or just prior to the next trial drug administration were attributed to the trial drug dose taken during the previous treatment period.

Clinical Reviewers' Comments:

The clinical reviewers find the applicant's classification acceptable for serious adverse events, significant adverse events, and treatment-emergent adverse events.

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

For Trials 150033, 150336, and 140115, safety data was not pooled due to the different trial designs previously discussed in Subsection 5.3 Discussion of Individual Studies/Clinical Trials.

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

A summary of the overall extent of exposure in the Tradename clinical development program is shown in Table 13:

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Clinical Review

Theresa H. van der Vlugt, M.D., M.P.H.; Nneka McNeal-Jackson, M.D.

NDA 209661

Tradename (20 mg doxylamine succinate and 20 mg pyridoxine hydrochloride) extended-release tablets

Table 13: Overall Extent of Exposure in the Tradename Clinical Development Program

Trial	Population	N = Number of Women Randomized N = Number of Women Completed	Total Daily Dose of Trial Medication	Duration of Use
Trial 150033	Healthy, non-pregnant, adult women 18-45 years of age	39 randomized 31 completed	40 mg doxylamine and 40 mg pyridoxine	11 consecutive days per period with a 28 day washout between each period
Trial 150336	Healthy, non-pregnant, adult women 18-45 years of age	52 randomized 48 completed	20 mg doxylamine and 20 mg pyridoxine	1 day per period with a 21 day washout period between each period
Trial 140115	Healthy, non-pregnant, adult women 18-45 years of age	24 randomized 24 completed	20 mg doxylamine and 20 mg pyridoxine	1 day per period with a 21-day washout between each period

Source: Adapted from NDA 209661, Module 5.2 Tabular Listing of All Clinical Trials; Numbers of completers in Trials 150033, 150336, and 140115; Clinical Trial Reports, Section 13, Discussions and Overall Conclusions.

The demographics of the three biopharmaceutical trials for the safety population are summarized in Table 14. The applicant defined the safety population as any woman that received at least one dose of the trial drug.

Table 14: Summary of the Tradename Trial Demographics and Body Measurements for Safety Population for All Clinical Trials

Category Statistics	Trial 150033 Safety Population N (Total Number of Women) = 39	Trial 150336 Safety Population N (Total Number of Women) = 52	Trial 140115 Safety Population N (Total Number of Women) = 24
Age Mean ± SD Range	33 ± 8 20 – 45	31 ± 6 20-45	32 ± 8 18 – 44
Race Asian Black White	74.4% (N=29) 25.6% (N=10)	3.8% (N=2) 3.8% (N=2) 92.3% (N=48)	95.8% (N=23) 4.2% (N=1)
Ethnicity Non-Hispanic Hispanic	74.4% (N=29) 25.6% (N=10)	90.4% (N=47) 9.6% (N=5)	83.3% (N=20) 16.7% (N=4)

Clinical Review

Theresa H. van der Vlugt, M.D., M.P.H.; Nneka McNeal-Jackson, M.D.

NDA 209661

Tradenname (20 mg doxylamine succinate and 20 mg pyridoxine hydrochloride) extended-release tablets

Weight (kg) Mean $\pm$ SD Range	64.36 $\pm$ 9.26 48 – 83.2	64.94 $\pm$ 10.64 48.2 – 89	65.3 $\pm$ 8.65 50.2 – 80.3
Height (cm) Mean $\pm$ SD Range	164.0 $\pm$ 5.6 154.0 – 181.5	162.1 $\pm$ 6.3 145 – 178	164.4 $\pm$ 5.3 154.0 – 176.5
BMI (kg/m²) Mean $\pm$ SD Range	23.89 $\pm$ 2.91 18.99 – 29.40	24.61 $\pm$ 3.01 19.31 – 29.81	24.12 $\pm$ 3.10 19.01 – 28.79

Source: Adapted from NDA 209661, Trials 150033 and 150336 Section 5.3.1.2, Trial Body Report, Table 14.1.1-1; Trial 140115, Section 5.3.1.1, Trial Body Report, Table 14.1.1-1.

Clinical Reviewers' Comments:

For Trials 150033, 150336, and 140115, the majority of the participating women were Caucasian. It may have been more informative to enroll a more racially diverse population of women.

7.2.2 Explorations for Dose Response

Dose response data is not included in this NDA.

7.2.3 Special Animal and/or In Vitro Testing

This NDA does not present new data from special animal studies or in-vitro studies. Refer to the Pharmacology/Toxicology review, finalized March 4, 2013, for a full discussion of special animal and/or in-vitro testing conducted for the Diclegis development program under NDA 021876.

7.2.4 Routine Clinical Testing

7.2.4.1 Trial 150033:

At Screening, the safety assessments included medical history, physical exam, concomitant medications, clinical laboratory tests (biochemistry, hematology, and urinalysis), serology, urinary pregnancy test, electrocardiogram, vital signs (blood pressure, heart rate, respiratory rate, and oral temperature), and urine drug test.

Prior to each trial period, the safety assessments included hematology (before Periods 2 and 3), alcohol breath test, urine drug screen, and a serum pregnancy test.

During each trial period, women underwent monitoring for adverse events.

Clinical Review

Theresa H. van der Vlugt, M.D., M.P.H.; Nneka McNeal-Jackson, M.D.

NDA 209661

Tradename (20 mg doxylamine succinate and 20 mg pyridoxine hydrochloride) extended-release tablets

At trial exit, the safety assessments included clinical laboratory tests (biochemistry, hematology, and urinalysis), and a urine pregnancy test.

7.2.4.2 Trial 150336:

At Screening, the safety assessments included medical history, physical exam, concomitant medications, clinical laboratory tests (biochemistry, hematology, and urinalysis), serology, urinary pregnancy test, electrocardiogram, vital signs (blood pressure, heart rate, respiratory rate, and oral temperature), and urine drug test.

Prior to each trial period, the safety assessments included an alcohol breath test, urine drug screen, and a serum pregnancy test.

During each trial period, women underwent monitoring for adverse events.

At trial exit, the safety assessments included clinical laboratory tests (biochemistry, hematology, and urinalysis), and a urine pregnancy test.

7.2.4.3 Trial 140115

At Screening, the safety assessments included medical history, physical exam, concomitant medications, clinical laboratory tests (biochemistry, hematology, and urinalysis), serology, urinary pregnancy test, electrocardiogram, vital signs (blood pressure, heart rate, respiratory rate, and oral temperature), and urine drug test.

Prior to each trial period, the safety assessments included an alcohol breath test, urine drug screen, and a serum pregnancy test.

During each trial period, women underwent monitoring for adverse events.

At trial exit, the safety assessments included clinical laboratory tests (biochemistry, hematology, and urinalysis), and a urine pregnancy test.

For a detailed list of the specific clinical laboratory tests for all trials in the Tradename clinical development program, see Table 15.

Clinical Review

Theresa H. van der Vlugt, M.D., M.P.H.; Nneka McNeal-Jackson, M.D.

NDA 209661

Tradename (20 mg doxylamine succinate and 20 mg pyridoxine hydrochloride) extended-release tablets

Table 15: Clinical Laboratory Tests for All Clinical Trials in the Tradename Clinical Development

Biochemistry	Serology	Hematology	Urinalysis
Albumin	Hepatitis B Antibody	Complete Blood Count	Macroscopic Exam
Alkaline Phosphatase	Hepatitis C Antibody	with Differential	pH
AST	HIV Antibody	Hemoglobin	Specific Gravity
ALT		Hematocrit	Protein
Urea			Glucose
Calcium			Ketones
Chloride			Bilirubin
Glucose			Occult Blood
Phosphorus			Nitrite
Potassium			Urobilinogen
Serum Creatinine			Leukocytes
Sodium			Microscopic Exam (if indicated)
Total Bilirubin			
Total Protein			

Source: Adapted from NDA 209661 Trials 150033 and 150336, Section 5.3.1.2 Protocol or Amendment, Section 9.7.6 Laboratory Assessments; Trial 140115, Section 5.3.1.1 Protocol or Amendment, Section 9.7.6 Laboratory Assessments.

Clinical Reviewers' Comments:

The clinical reviewers find the applicant's classification for the safety assessments completed in Trials 150033, 150336, and 140115, acceptable.

7.2.5 Metabolic, Clearance, and Interaction Workup

No outstanding biopharmaceutical issues were identified by the biopharmaceutics reviewer. Refer to the archived review entered, October 14, 2016 for details.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

In double blind, randomized, placebo-controlled, multi-centered Trial DIC-301 completed in 261 pregnant women (mean gestational age at trial enrollment 9.3 weeks) during the Diclegis development program, somnolence was the most common adverse event reported with a higher incidence in women who received Diclegis versus women who received placebo [14.3% (19 of 133) versus 11.7% (15 of 128), respectively].⁴

⁴ Diclegis labeling approved April 2013.

Clinical Review

Theresa H. van der Vlugt, M.D., M.P.H.; Nneka McNeal-Jackson, M.D.

NDA 209661

Tradename (20 mg doxylamine succinate and 20 mg pyridoxine hydrochloride) extended-release tablets

7.3 Major Safety Results

7.3.1 Deaths

Deaths are not reported for Trials 150033, 150336, and 140115

Deaths are also not reported in the 120-Day Safety Update received March 24, 2016.

7.3.2 Nonfatal Serious Adverse Events

Non-fatal SAEs are not reported in Trials 150033, 150336, and 140115.

Non-fatal SAEs are not reported in the 120-Day Safety Update received March 24, 2016.

7.3.3 Dropouts and/or Discontinuations

7.3.3.1 Trial 150033

For Trial 150033, the applicant reports three cases of significant TEAEs that prompted trial discontinuation as a precautionary measure. A summary of these three cases follows:

- Trial participant No. 16 is a 22 years-old woman who experienced “vomiting” following administration of Treatment A (Tradename 20 mg doxylamine and 20 mg pyridoxine) in Period 1. Her past medical history includes viral pericarditis, tonsillectomy, and myopia. She experienced her first episode of vomiting on trial Day 9 prior to her morning dose of the drug and three episodes of loose stools that same day. The investigator placed the woman in isolation as a precautionary measure and deemed her ineligible to receive her Day 9 evening dose of the drug. Her symptoms resolved spontaneously eight hours after the symptom onset. The investigator assessed the TEAE as mild in severity and possibly related to Tradename.
- Trial participant No. 19 is a 33 year-old woman who had a “decreased hemoglobin” noted prior to administration of Treatment B (Diclegis 10 mg doxylamine and 10 mg pyridoxine) in Period 3. Her past medical history includes breast implants, abdominoplasty, previous cesarean section, and myopia. During her screening exam, her hemoglobin was normal at 134 g/L (normal range 120-160 g/L). Her hemoglobin dropped to 105 g/L prior to starting Period 3 at which point she was withdrawn from the trial. Repeat hemoglobin taken eleven days after her last dose of medication was stable at 104 g/L. She was referred to her family physician for further workup. The investigator assessed this TEAE as mild in severity and possibly related to trial medication.
- Trial participant No. 20 is a 34 years-old woman who experienced “visual impairment” following administration of Treatment B Diclegis (10 mg doxylamine and 10 mg

Clinical Review

Theresa H. van der Vlugt, M.D., M.P.H.; Nneka McNeal-Jackson, M.D.

NDA 209661

Tradename (20 mg doxylamine succinate and 20 mg pyridoxine hydrochloride) extended-release tablets

pyridoxine) in Period 1. Starting trial Day 2, she experienced multiple eye symptoms (veiled vision, halo around lights, reduction in her visual acuity, and a sensation of heaviness in her eyeballs) which persisted but worsened in severity. Consequently, the women reported the symptoms to the investigator on trial Day 9. She was referred to the hospital for ophthalmic exam (by an ophthalmologist) and thyroid function tests. Her ocular exam, free T4 and TSH measurements were all normal. Since there were no expected safety concerns, the woman returned to the trial for Period 2 and Period 3. Over the course of the trial, her symptoms gradually improved. The TEAE resolved spontaneously. The investigator assessed the TEAE as mild in severity and possibly related to the trial medication.

Clinical Reviewers' Comments:

For participating women Nos. 16, 19, and 20, the clinical reviewers agree with the applicant's assessments that the AEs were mild in severity and possibly related to the trial medication. While the clinical reviewers agree that Nos. 16 and 19 were discontinued from the study secondary to AEs, it is unclear why the applicant classified No. 20 as discontinued given that she resumed and completed the trial.

Five women discontinued the trial for reasons other than AEs. A summary of these cases follows:

- Trial participant No. 6 is a 41-year-old woman who withdrew from the trial while taking Treatment A (Tradename) during Period 2. She returned to the trial for Period 3 but discontinued after receiving her trial Day 1 drug dose. She left the trial for personal reasons.
- Trial participant No. 7 is a 27-year-old woman who withdrew from the trial while taking Treatment B (Diclegis) during Period 2 for personal reasons.
- Trial participant No. 14 is a 21-year-old woman who withdrew from the trial when she failed to check in for Period 2. The investigator's multiple attempts to contact the woman were unsuccessful.
- Trial participant No. 29 is a 43-year-old woman who withdrew for personal reasons from the trial in Period 2 following completion of trial Day 1. She resumed the trial in Period 3, but withdrew a second time for personal reasons on trial Day 4.
- Trial participant No. 30 is a 43-year-old woman who withdrew for personal reasons from the trial in Period 3.

Clinical Reviewers' Comments:

After reviewing the individual case report form for each participating woman, the clinical reviewers agree that all five women withdrew from the trial for reasons other than the experience of AEs.

Clinical Review

Theresa H. van der Vlugt, M.D., M.P.H.; Nneka McNeal-Jackson, M.D.

NDA 209661

Tradename (20 mg doxylamine succinate and 20 mg pyridoxine hydrochloride) extended-release tablets

7.3.3.2 Trial 150336

For Trial 150336, the applicant reports one significant TEAE that prompted trial discontinuation as a precautionary measure. A summary of this single case is as follows:

Subject No. 18 is a 26-year-old female that experienced “pregnancy” following administration of Treatment A (Tradename 20 mg doxylamine and 20 mg pyridoxine) in Period 1. The first day of her last menstrual period was September 19, 2015. Prior to receiving the trial drug, she had a negative urine pregnancy test on September 20, 2015 and a negative serum pregnancy test on October 16, 2015. On October 17, 2015, she received one tablet of Treatment A. On October 30, 2015, she tested positive for pregnancy on a home pregnancy test. On November 4, 2015 when she informed the clinical staff of her positive pregnancy test, she was discontinued from the trial. On November 10, 2015 during her trial exit procedure, her pregnancy was confirmed with a urine pregnancy test.

Clinical Reviewers’ Comments:

The clinical reviewers agree with the applicant’s classification of this adverse event as treatment emergent given the applicant’s inability to confirm the date of conception relative to the dosing of the trial drug.

Three women discontinued the trial for reasons other than AEs. A summary of these cases follows:

- Trial participant No. 16 is a 34-year-old woman who withdrew for personal reasons from the trial in Period 1.
- Trial participant No. 23 is a 34-year-old woman who was discontinued from the trial during Period 1 when she experienced a vomiting episode 3 hours after taking the trial drug.
- Trial participant No. 33 is a 22 year old who withdrew for personal reasons from the trial after Period 1.

Clinical Reviewers’ Comments:

After reviewing the individual case forms of the participating women, the clinical reviewers agree with applicant’s assessment that No. 16 and 33 withdrew from the trial for reasons other than AEs.

The clinical reviewers do not agree with the applicant’s assessment that No. 23 withdrew from the trial for reasons other than AEs. No. 23 should have been listed as a withdrawal from the trial for AEs given the participating woman met the

Clinical Review

Theresa H. van der Vlugt, M.D., M.P.H.; Nneka McNeal-Jackson, M.D.

NDA 209661

Tradename (20 mg doxylamine succinate and 20 mg pyridoxine hydrochloride) extended-release tablets

discontinuation criterion when she vomited less than 9 hours after taking the trial drug.

7.3.3.3 Trial 140115

No women discontinued from Trial 140115.

7.3.4 Significant Adverse Events

7.3.4.1 Trial 150033

The applicant reports three significant TEAEs that required trial discontinuation of women from Trial 150033, as a precautionary measure. The AEs reported are “vomiting”, “decreased hemoglobin”, and “visual impairment”. All women were followed to resolution of AE or until they were clinically stable. See Section 7.3.3.1 for a detailed discussion of these significant adverse events and the clinical reviewers’ comments.

7.3.4.2 Trial 150336

The applicant reports one significant TEAE that required trial discontinuation of a participating woman from Trial 150336. The AE reported is “pregnancy”. See Section 7.3.3.2 for a detailed discussion of this significant adverse event and the clinical reviewers’ comments.

7.3.4.3 Trial 140115

No significant AEs were reported for participating women in Trial 140115.

7.3.5 Submission Specific Primary Safety Concerns

There were no other primary safety concerns that arose from the review of this NDA.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

7.4.1.1 Trial 150033

Per protocol, each woman received one 11-day period of Tradename and two 11-day periods of Diclegis.

Clinical Review

Theresa H. van der Vlugt, M.D., M.P.H.; Nneka McNeal-Jackson, M.D.

NDA 209661

Tradename (20 mg doxylamine succinate and 20 mg pyridoxine hydrochloride) extended-release tablets

A total of 126 TEAEs were reported by 34 of the 39 women who received at least one dose of the trial medication (safety population). The breakdown by treatment group is as follows:

- 59 TEAEs reported by 48.7% (n=19) of the 39 subjects who received Test, Treatment A
- 67 TEAEs reported by 86.5% (n=32) of the 37 subjects who received Reference, Treatment B

Per the application, the most commonly reported TEAEs were headache reported by 30.8% (n=12) of women who constituted the safety population, dizziness reported by 15.4% (n=6) of women who constituted the safety population, and constipation, nausea, fatigue, and somnolence reported by 12.8% (n=5 each) of women who constituted the safety population. See Table 16 for all treatment-emergent adverse events.

Table 16: Treatment Emergent Adverse Events for Trial 150033

Adverse Event	Frequency
	Safety population N (Total number of women) = 39 subjects
Headache	30.8% (n=12)
Dizziness	15.4% (n=6)
Constipation	12.8% (n=5)
Nausea	12.8% (n=6)
Fatigue	12.8% (n=5)
Somnolence	12.8% (n=5)
Abdominal pain	10.3% (n=4)
Diarrhea	10.3% (n=4)
Gastroesophageal reflux disease	10.3% (n=4)
Nasopharyngitis	10.3% (n=4)
Post procedural discomfort	10.3% (n=4)
Hot Flush	10.3% (n=4)
Visual impairment	7.7% (n=3)
Procedural dizziness	7.7% (n=3)
Menstruation irregular	7.7% (n=3)
Lip dry	5.1% (n=1)
Hemoglobin decreased	5.1% (n=2)
Neck pain	5.1% (n=2)
Pain in extremity	5.1% (n=1)
Anemia	2.7% (n=1)
Lymphadenopathy	2.7% (n=1)
Eyelid edema	2.7% (n=1)
Ocular Hyperemia	2.7% (n=1)
Dry mouth	2.7% (n=1)
Vomiting	2.7% (n=1)
Asthenia	2.7% (n=1)
Catheter site swelling	2.7% (n=1)
Chest discomfort	2.7% (n=1)

Clinical Review

Theresa H. van der Vlugt, M.D., M.P.H.; Nneka McNeal-Jackson, M.D.

NDA 209661

Tradename (20 mg doxylamine succinate and 20 mg pyridoxine hydrochloride) extended-release tablets

Hunger	2.7% (n=1)
Peripheral Swelling	2.7% (n=1)
Cystitis	2.7% (n=1)
Lip injury	2.7% (n=1)
Skin Abrasion	2.7% (n=1)
Decreased appetite	2.7% (n=1)
Back pain	2.7% (n=1)
Myalgia	2.7% (n=1)
Postural Dizziness	2.7% (n=1)
Hypoesthesia	2.7% (n=1)
Paresthesia	2.7% (n=1)
Presyncope	2.7% (n=1)
Abnormal dreams	2.7% (n=1)
Anxiety	2.7% (n=1)
Nightmares	2.7% (n=1)
Pollakiuria	2.7% (n=1)
Dysmenorrhea	2.7% (n=1)
Epistaxis	2.7% (n=1)
Dry skin	2.7% (n=1)
Erythema	2.7% (n=1)

Source: Adapted from NDA 209661, Trial 150033, Clinical Trial Report, Table 14.3.1.2-2 Treatment Emergent Adverse Events Listing

Dizziness, fatigue, and somnolence are of special clinical interest to the clinical reviewers since these TEAEs pose the greatest potential safety risk to the pregnant woman. See Table 17.

Table 17: Treatment-Emergent Adverse Events of Interest for Trial 150033

Adverse Event	Safety Population
	N (Total number of women) = 39
Dizziness	15.4% (N=6)
Fatigue	12.8% (N=5)
Somnolence	12.8% (N=5)

Source: Adapted from NDA 209661, Trial 150033 Report, Section 13 Discussions and Overall Conclusion.

According to the NDA, a woman was counted as experiencing a TEAE, one time per adverse event per treatment arm. Participating woman No. 20 experienced dizziness in both treatment arms (A and B). As a result, the total number of cases of dizziness in Table 16 (5 for treatment arm A; 2 for treatment arm B; total 7 cases) differs from the total number of women who experienced dizziness (6) in Table 17. See Table 18 for a summary of the TEAEs by treatment arm in Trial 150033.

Table 18: Treatment-Emergent Adverse Events of Special Clinical Interest by Treatment Arm for Trial 150033

Adverse Event	Safety Population	
	A (n=39)	B (n=37)

Clinical Review

Theresa H. van der Vlugt, M.D., M.P.H.; Nneka McNeal-Jackson, M.D.

NDA 209661

Tradename (20 mg doxylamine succinate and 20 mg pyridoxine hydrochloride) extended-release tablets

Somnolence	5.1% (n=2)	10.8% (n=4)
Dizziness	12.8% (n=5)	5.4% (n=2)
Fatigue	7.7% (n=3)	5.4% (n=2)

Source: Adapted from NDA 209661, Clinical Trial Report, Table 14.3.1-1 Frequency of Subjects Experiencing TEAE By Treatment Arm for Trial 150033.

A = Tradename (20 mg doxylamine and 20 mg of pyridoxine)

B = Diclegis (10 mg doxylamine and 10 mg of pyridoxine)

Clinical Reviewers' Comments:

For somnolence, the frequency is greater in Diclegis than in Tradename in Table 18. For dizziness and fatigue, the frequency is greater in Tradename than Diclegis. However, this crossover trial exposed women to Diclegis twice, two 11-day periods with Diclegis vs. one 11-day period with Tradename. The double exposure to Diclegis is a possible confounding factor for data comparison between the two trial drugs.

Table 16 suggests that there is no trend toward a difference in any of the TEAEs of special clinical interests between the two formulations. The number of TEAEs is too small to conclude that an absence of difference between the two treatment formulations is clinically meaningful.

7.4.1.2 Trial 150336

For Trial 150336, 23 of the 52 women experienced 36 TEAEs. The most common TEAEs that women experienced were somnolence and headache at 13.5% (n=7). For a summary of TEAEs experienced in Trial 150336, see Table 19.

Table 19: Summary of Adverse Events for Trial 150336

Adverse Events	Frequency Safety population N (total number of women) = 52
Somnolence	13.5% (n=7)
Headache	13.5% (n=7)
Nausea	3.8% (n=2)
Asthenia	3.8% (n=2)
Nasopharyngitis	3.8% (n=2)
Hot Flush	3.8% (n=2)
Abdominal pain	3.8% (n=2)
Vomiting	1.9% (n=1)
Fatigue	1.9% (n=1)
Gastroenteritis	1.9% (n=1)
Eye Contusion	1.9% (n=1)
Procedural dizziness	1.9% (n=1)
Procedural nausea	1.9% (n=1)
Platelet count decreased	1.9% (n=1)
Back pain	1.9% (n=1)

Clinical Review

Theresa H. van der Vlugt, M.D., M.P.H.; Nneka McNeal-Jackson, M.D.

NDA 209661

Tradename (20 mg doxylamine succinate and 20 mg pyridoxine hydrochloride) extended-release tablets

Pregnancy	1.9% (n=1)
Rhinorrhea	1.9% (n=1)

Source: Adapted from NDA 209661, Trial 150336, Clinical Trial Report, Table 14.3.1.2-2 Treatment Emergent Adverse Events Listing.

Dizziness, fatigue, and somnolence in Trial 150336 are also of special clinical interest to the clinical reviewers. See Table 20.

Table 20: Treatment-Emergent Adverse Events of Interest for Trial 150336

Adverse event	Safety Population
	N (Total Number of Women) = 52 subjects
Dizziness	0% (N=0)
Fatigue	1.9% (N=1)
Somnolence	13.5% (N=7)

Source: Adapted from NDA 209661, Trial 150336 Clinical Trial Report, Table 14.3.1.2-2 Treatment-Emergent Adverse Events Listing.

According to the NDA, a woman was counted as experiencing a TEAE, one time per adverse event per treatment arm. Participating woman No. 10 experienced somnolence in both treatment arms (A and B). As a result, the total number of cases of somnolence differs in Table 19 (1 for treatment A, 7 for treatment arm B, 8 total cases) differs from the total number of women that experienced somnolence in Table 20. See Table 21 for a summary of TEAEs by treatment arm in Trial 150336.

Table 21: Treatment-Emergent Adverse Events of Special Clinical Interest by Treatment Arm for Trial 150336

Adverse Event	Safety Population	
	Treatment A (n= 50)	Treatment B (n=50)
Somnolence	2% (n=1)	26% (n=7)
Dizziness	0% (n=0)	0% (n=0)
Fatigue	0% (n=0)	2% (n=1)

Source: Adapted from NDA 209661, Trial 150336 Clinical Trial Report, Table 14.3.1.1-1 Frequency of Subjects Experiencing TEAE Summarized By Treatment Arm.

A = Tradename (20 mg doxylamine and 20 mg of pyridoxine).

B = Diclegis (10 mg doxylamine and 10 mg of pyridoxine).

Clinical Reviewers' Comments:

For somnolence, the frequency is greater in Diclegis than in Tradename in Table 21. For dizziness and fatigue, there is little difference between the two formulations given there were so few incidents of either of these adverse events in this clinical trial. Somnolence in the pregnant patient population of is concern. While the percentage of women experiencing somnolence during the Diclegis treatment period is greater

Clinical Review

Theresa H. van der Vlugt, M.D., M.P.H.; Nneka McNeal-Jackson, M.D.

NDA 209661

Tradename (20 mg doxylamine succinate and 20 mg pyridoxine hydrochloride) extended-release tablets

than that for the Tradename treatment period, the numbers are too small to speculate that Tradename offers an advantage over Diclegis with respect to somnolence.

7.4.1.3 Trial 140115

For Trial 140115, 11 of 24 women experienced 24 TEAEs. The most common TEAEs that women experienced were somnolence at 25% (n=6) and abdominal pain at 8.3% (n=2). All of the other TEAEs were singularly reported. For a summary of these results, see Table 22.

Table 22: Summary of Adverse Events for Trial 140115

Adverse Event	Frequency
	Safety population N (Total number of women) = 24 subjects
Somnolence	25% (n=6)
Abdominal pain	8.3% (n=2)
Influenza	4.2% (n=1)
Nasopharyngitis	4.2% (n=1)
Oral Herpes	4.2% (n=1)
Rhinitis	4.2% (n=1)
Post procedural discomfort	4.2% (n=1)
Procedural dizziness	4.2% (n=1)
Procedural nausea	4.2% (n=1)
Nitrite urine present	4.2% (n=1)
White blood cells urine positive	4.2% (n=1)
Back pain	4.2% (n=1)
Neck pain	4.2% (n=1)
Dizziness	4.2% (n=1)
Hot flush	4.2% (n=1)

Source: Adapted from NDA 209661, Trial 140115 Clinical Trial Report, Table 14.3.1.2-2 Treatment Emergent Adverse Events Listing.

The TEAEs for Trial 140115 were assessed by treatment arms (Treatment A under fed conditions; Treatment B under fasted conditions). According to the NDA, women were counted one time per adverse event per treatment arm. Trial participant No.1 experienced somnolence in both treatment arms (A and B). As a result, the total number of cases of somnolence in Table 23 (3 for treatment arm A; 4 for treatment arm B; total 7 cases) differs from the total number of women (6) who experienced somnolence in Table 22.

Table 23: Cases of Somnolence and Abdominal Pain by Treatment Arm for Trial140115

Adverse Event	Treatment Arms	
	A (N=24)	B (N=24)
Somnolence	12.5% (n=3)	16.7% (n=4)
Abdominal pain	4.2% (n=1)	4.2% (n=1)

Source: NDA 209661, Clinical Study Report, Table 14.3.1.1-1 Frequency of Subjects Experiencing Treatment-Emergent Adverse Events Summarized by Treatment

A= fed conditions; B = fasting conditions

Clinical Review

Theresa H. van der Vlugt, M.D., M.P.H.; Nneka McNeal-Jackson, M.D.

NDA 209661

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Clinical Reviewers' Comments:

Table 23 shows that somnolence occurs in a greater percentage of fasting women than fed women. Given the limited number of women in the trial, a meaningful assessment of clinical significance of this data is difficult.

7.4.1.4 120-Day Safety Update

In the 120-Day Safety Update, no additional AEs were reported for Trials 150033 or 140115.

7.4.2 Laboratory Findings

Per the trial protocol, laboratory assessments included biochemistry, serology, hematology, and urinalysis. The individual laboratory assessments are outlined in the Section 7.2.4 Routine Clinical Testing this review. The scheduling of the safety assessments are as follows:

7.4.2.1 Trial 150033

In Trial 150033, biochemistry laboratory evaluations were performed at screening and trial exit. Serology was performed at screening only. Hematology was performed at screening, prior to dosing of Periods 2 and 3, and at trial exit. Urinalysis was performed at screening and exit only. When needed, laboratory tests were repeated to confirm initial out of range results.

All of the laboratory results for Trial 150033 were reported within normal limits, or the investigator assessed the results as clinically insignificant except for the following:

- Trial participant No. 19 had abnormal hemoglobin of 105 g/L (normal 120-160 g/L) prior to Period 3. Her initial hemoglobin during screening was 134 g/L. She was discontinued from the trial at this point. Eleven days after the last dose of medication, her repeat hemoglobin was 104 g/L. A referral letter was mailed to the woman for follow up with her family physician.
- Trial participant No. 23 had abnormal hemoglobin of 101 g/L (normal 120 – 160 g/L) at trial exit. Her initial hemoglobin during screening was 127 g/L. One week later, her repeat hemoglobin was 101 g/L. She was referred to her primary physician for further workup.
- Trial participant No. 24 had abnormal hemoglobin of 94 (normal 120-160 g/L) and hematocrit of 0.3 L/L (normal 0.36 – 0.45 L/L) at trial exit. Her hemoglobin and hematocrit during screening was normal at 129 g/L and 0.402 L/L, respectively. She was enrolled in the trial. Her hemoglobin and hematocrit prior to Period 2 dosing was 114 g/L and 0.344 L/L, respectively. Her hemoglobin and hematocrit prior to Period 3

Clinical Review

Theresa H. van der Vlugt, M.D., M.P.H.; Nneka McNeal-Jackson, M.D.

NDA 209661

Tradename (20 mg doxylamine succinate and 20 mg pyridoxine hydrochloride) extended-release tablets

dosing was 106 g/L and 0.345 L/L, respectively. Her hemoglobin and hematocrit at trial exit was 94 g/L and 0.3 L/L, respectively. The investigator contacted her by phone and confirmed that she was asymptomatic. The investigator requested a repeat CBC in one week. The follow up results were not reported. A letter was mailed to the woman to follow up with her family physician.

- Trial participant No. 33 had an abnormal urinalysis with bacteria, >50 WBC, and 3+ blood and 10-20/LPF epithelial cells during Period 3, Trial Day 3 with Treatment B (Diclegis) for which she was treated with ciprofloxacin. Her follow up urinalysis was negative for bacteria and blood.

Clinical Reviewers' Comments:

In each of the instances noted above, the protocol should have directed that the investigators arrange for follow-up of woman with these laboratory abnormalities either in the clinical trial facilities or with private practitioners. Further, the investigator should have verified that the woman received follow-up care through resolution of any abnormal laboratory values and/or clinical signs or symptoms. Unfortunately, the protocol did not provide these instructions. The protocol was not presented to the Agency for review prior to initiation of this trial.

7.4.2.2 Trial 150336

In Trial 150336, biochemistry was performed at screening and trial exit. Serology was performed during the screening only. Hematology was performed at screening and trial exit. Urinalysis was performed at screening and the trial exit.

All of the laboratory results for Trial 150336 were reported within normal limits, or the investigator assessed the results as clinically insignificant except for the following:

- Trial participant No. 44 had a decreased platelet level noted during her trial exit. She had a normal platelet level of $140 \times 10^9/L$ at screening. At trial exit, her platelet level decreased to $115 \times 10^9/L$. While the lab result was deemed of no clinical significance, the investigator repeated the lab eleven days later. The platelet level was $48 \times 10^9/L$. The result of a confirmatory test conducted with a different anticoagulant was $53 \times 10^9/L$. Platelet levels were reassessed one week later. The platelet levels on follow up tests were $116 \times 10^9/L$ and $59 \times 10^9/L$. A letter was mailed to the woman to follow up with her family physician.

Clinical Reviewers' Comments:

As noted in our comments to Trial 150033, the applicant should have indicated in the trial protocol that any woman with a laboratory abnormality receive follow up at the trial facilities or with her private practitioner. Further, the investigator should have verified that the woman received follow-up care through resolution of any abnormal laboratory values and/or clinical signs or symptoms. The protocol did not provide these instructions. This protocol was not presented to the Agency for review prior to initiation of this trial.

Clinical Review

Theresa H. van der Vlugt, M.D., M.P.H.; Nneka McNeal-Jackson, M.D.

NDA 209661

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7.4.2.3 Trial 140155

In Trial 140155, biochemistry was performed at screening and trial exit. Serology was performed during the screening only. Hematology was performed at screening and trial exit. Urinalysis was performed at screening and trial exit.

All of the laboratory results for Trial 140115 were reported within normal limits, or the investigator assessed the results as clinically insignificant except for the following:

- Trial participant No. 24, had a normal urinalysis at screening, but presented at trial exit with an abnormal urinalysis with nitrites and white blood cells. The urinalysis was repeated three days later and the repeat lab evaluation confirmed the abnormal result. The investigator referred the patient to her family physician for follow up

Clinical Reviewers' Comments:

As noted in our comments to Trial 150033 and 150336, the applicant should have indicated in the trial protocol that any woman with a laboratory abnormality receive follow-up at the trial facilities or with her private practitioner. Further, the investigator should have verified that the woman received follow-up care through resolution of any abnormal laboratory values and/or clinical signs or symptoms.

Per the applicant in Trials 150033, 150336, and 140115, "Some subjects had clinically significant safety measurement results at the time of trial exit procedures or during the trial (hematology and urinalysis); however, data from the subjects completing trial exit procedures (including clinical laboratory tests) confirmed the absence of significant changes in the subject's state of health."

Clinical Reviewers' Comments:

The clinical reviewers agree with the investigator's assessment that the abnormal laboratory results do not appear to represent significant changes in participating women's health in these clinical trials. During the course of each trial, the investigators regularly monitored women and treated them appropriately for adverse events, when indicated. As stated, we disagree with referral as the sole action taken for abnormal laboratory parameters at end-of-trial. We believe that investigators should have ensured that all women received follow up through resolution of abnormal laboratory values and/or clinical signs and symptoms.

This holds particularly true for Trial 150336, where inappropriate follow up of the woman's unexplained thrombocytopenia may have placed her at increased risk for bleeding.

Clinical Review

Theresa H. van der Vlugt, M.D., M.P.H.; Nneka McNeal-Jackson, M.D.

NDA 209661

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7.4.3 Vital Signs

For Trials 150033, 150336, and 140115, participating women had vital signs performed only during the trial screening prior to the administration of trial drugs.

Clinical Reviewers' Comments:

None of the women screened were disqualified on the basis of an abnormal vital signs, from participating in either trial.

7.4.4 Electrocardiograms (ECGs)

For Trials 150033, 150336 and 140115, participating women received electrocardiograms only during the trial screening prior to the administration of the trial administration.

Clinical Reviewers' Comments:

None of the women screened were disqualified on the basis of an abnormal ECG, from participating in these trial.

7.4.5 Special Safety Studies/Clinical Trials

The applicant did not report any special safety studies data in this NDA. All trials enrolled healthy pre-menopausal women between the ages of 18 and 45. "Healthy" was defined as "the absence of clinically significant history of neurological, endocrinological, cardiovascular, pulmonary, hematological, immunologic, psychiatric, gastrointestinal, renal, hepatic, and metabolic disease."

Women with renal and hepatic impairment were excluded from all trials.

7.4.6 Immunogenicity

Applicant-conducted trials, other data, and/or published literature regarding human immunogenicity trials/studies were not reported in this NDA.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

For Trial 150033, the applicant presented AEs by treatment arm: Treatment arm A [test, Tradenname (20 mg doxylamine and 20 mg pyridoxine)] and Treatment arm B [reference, Diclegis (10 mg doxylamine and 10 mg pyridoxine)]. See Table 16 in Section 7.4.1 of this review. Trial participants received a total daily dose of 40 mg doxylamine and 40 mg of pyridoxine in both treatment arms.

Clinical Review

Theresa H. van der Vlugt, M.D., M.P.H.; Nneka McNeal-Jackson, M.D.

NDA 209661

Tradename (20 mg doxylamine succinate and 20 mg pyridoxine hydrochloride) extended-release tablets

An exploratory sub-analysis was conducted by the clinical reviewers to evaluate the frequency per treatment arm of women who experienced an adverse event on Trial Day 1 versus Trial Day 11. For a summary of these results, see Table 24.

Table 24: Most Common Adverse Events by Treatment Arm and Trial Day for Trial 150033

Adverse event	Trial Day 1		Trial Day 11	
	A (N=39)	B (N=37)	A (N=39)	B (N=37)
Dizziness	5.1% (n=2)	0% (n=0)	2.6% (n=1)	0% (n=0)
Fatigue	7.7% (n=3)	0% (n=0)	0% (n=0)	2.7% (n=1)
Somnolence	5.1% (n=2)	10.8% (n=4)	0% (n=0)	0% (n=0)

Source: NDA 209661 Table generated by the clinical reviewer from Datasets provided on December 18, 2015.

A = Tradename (20 mg doxylamine and 20 mg of pyridoxine)

B = Diclegis (10 mg doxylamine and 10 mg of pyridoxine)

Clinical Reviewers' Comments:

Table 24 shows that the frequency of somnolence is greater in Diclegis versus Tradename on Trial Day 1. The frequency of fatigue and dizziness is greater in Tradename versus Diclegis on Trial Day 1. On Trial Day 11 none of the AEs of special clinical interest was seen in both treatment arms.

The numbers for each of the AEs of special clinical interest are too small to draw any clinically meaningful conclusions on the frequency of AEs between the two formulations on Trial Day 1.

7.5.2 Time Dependency for Adverse Events

An exploratory sub-analysis of the time to onset of somnolence, the AE of interest in Trial 150033, 150336, and 140115, was conducted to evaluate whether or not notable differences existed between Tradename and Diclegis. The number of cases of somnolence in Tradename and Diclegis is too small to do a meaningful analysis of time dependency for AEs.

7.5.3 Drug-Demographic Interactions

Drug-demographic interactions were not reported in the NDA.

7.5.4 Drug-Disease Interactions

Drug-disease interactions were not investigated in the NDA.

Clinical Review

Theresa H. van der Vlugt, M.D., M.P.H.; Nneka McNeal-Jackson, M.D.

NDA 209661

Tradename (20 mg doxylamine succinate and 20 mg pyridoxine hydrochloride) extended-release tablets

7.5.5 Drug-Drug Interactions

Drug-drug interactions were not investigated in the NDA.

In the approved labeling for Diclegis, the following are described:

- “Monoamine oxidase (MAO) inhibitors intensify and prolong the adverse central nervous system effects of Diclegis” – Section 4 CONTRAINDICATIONS
- “Use of Diclegis is contraindicated in women who are taking monoamine oxidase inhibitors (MAOIs), which prolong and intensify the anticholinergic (drying) effects of antihistamines.” – Subsection 7.1 Drug Interactions
- Concurrent use of alcohol and other CNS depressants (such as hypnotic sedatives and tranquilizers) with Diclegis is not recommended.” – Subsection 7.1 Drug Interactions

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

See the Pharmacology/Toxicology review, dated March 4, 2013, from the original Diclegis NDA for a full discussion on the carcinogenicity studies results in the Diclegis clinical development program.

7.6.2 Human Reproduction and Pregnancy Data

Human reproduction or pregnancy data were not reported for Trials 150033, 150336 and 140115.

7.6.3 Pediatrics and Assessment of Effects on Growth

Neither pediatric trial data nor growth data were reported in the NDA.

For Diclegis, the applicant has an outstanding Pediatric Research Equity Act (PREA) requirement to conduct a pediatric assessment for pregnant adolescents aged 12 to 17 with nausea and vomiting of pregnancy who are appropriate candidates for pharmacologic therapy.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

No overdose, drug abuse potential, withdrawal, or rebound information was reported in the NDA. See also the February 26, 2013 Medical Officer’s review, Section 7.6.4 Overdose, Drug Abuse Potential, Withdrawal, and Rebound.

Clinical Review

Theresa H. van der Vlugt, M.D., M.P.H.; Nneka McNeal-Jackson, M.D.

NDA 209661

Tradename (20 mg doxylamine succinate and 20 mg pyridoxine hydrochloride) extended-release tablets

No cases of overdose, drug abuse potential, withdrawal, or rebound were reported in the 120-Day Safety Update Report dated March 24, 2016.

Two cases of overdose were reported in the Periodic Adverse Drug Experience Report (PADER) -11 (reporting period: July 8, 2015 to October 7, 2015) and PADER -12 (reporting period: October 8, 2015 to January 7, 2016)

- Case US15-307 describes a pregnant woman at 12 weeks gestational age who took five tablets of Diclegis daily for one month and was found upon testing to be positive for methadone. She stopped taking Diclegis and one month later when retested her drug screen was negative. The woman's medical history and concomitant medications were not reported.

Clinical Reviewers' Comments:

Published literature supports the applicant's assertion that doxylamine use can produce false positive methadone result in urine drug screen.⁵ The safety report does not clarify whether or not the woman took methadone which would have produced a positive methadone result.

- Case CA15-710 describes a 20-year old, 180-pound pregnant woman who orally administered 8 tablets of Diclectin daily from 5^{4/7} weeks gestation to 9^{2/7} weeks gestation. At 9^{2/7} weeks, the woman experienced a spontaneous abortion.

Clinical Reviewers' Comments:

The applicant assessed the spontaneous abortion as unrelated to the Diclectin (Diclegis) overdose. Given the limited information provided by the applicant, causality cannot be established or ruled out.

7.7 Additional Submissions / Safety Issues

No additional safety issues were identified in this NDA.

8 Postmarket Experience

The approved labeling for Diclegis, last revised December 16, 2014, lists the following AEs by system organ class in the Postmarketing Experience section:

⁵ Commonly prescribed medications and potential false-positive urine drug screens. Brahm NC, Yeager LL, Fox MD, Farmer KC, Palmer TA. Am J Health Syst Pharm. 2010 Aug 15;67(16):1344-50.

Clinical Review

Theresa H. van der Vlugt, M.D., M.P.H.; Nneka McNeal-Jackson, M.D.

NDA 209661

Tradenname (20 mg doxylamine succinate and 20 mg pyridoxine hydrochloride) extended-release tablets

Cardiac disorders: dyspnea, palpitation, tachycardia

Ear and labyrinth disorders: vertigo

Eye disorders: vision blurred, visual disturbances

Gastrointestinal disorders: abdominal distension, abdominal pain, constipation, diarrhea

General disorders and administration site conditions: chest discomfort, fatigue, irritability, malaise

Immune system disorders: hypersensitivity

Nervous system disorders: dizziness, headache, migraines, paresthesia, psychomotor hyperactivity

Psychiatric disorders: anxiety, disorientation, insomnia, nightmares

Renal and urinary disorders: dysuria, urinary retention

Skin and subcutaneous tissue disorders: hyperhidrosis, pruritus, rash, rash maculopapular

The PADERs submitted by Duchesnay for Diclegis and Diclectin (approved in Canada), covering the reporting period from April 8, 2013 to April 7, 2016, were reviewed.

No maternal deaths were reported during the reporting period.

Five (5) spontaneous abortions were reported in PADER -6 (reporting period: April 8, 2014 to July 7, 2014), PADER -9 (reporting period: January 8, 2015 to April 7, 2015), and PADER -12 (reporting period: October 8, 2015 to January 7, 2016):

- Case US14-72 describes a pregnant woman who started taking Diclegis at 9 weeks gestational age and had a spontaneous abortion at 12 weeks gestational age. No additional information was provided. (See PADER -6)
- Case US14-117 describes a 39 year old pregnant woman with a twin gestation who started taking Diclegis at 7 weeks (dose not reported) gestational age. She had a spontaneous abortion of one of the fetuses at 9 weeks gestational age. She continued taking Diclegis. No concomitant medication use was reported. No additional information was provided and follow-up was declined. (See PADER -6)
- Case CA15-94 involved a 38 year old who experienced a spontaneous abortion (gestational age not reported). In addition to Diclectin, she took Zofran®, both orally

Clinical Review

Theresa H. van der Vlugt, M.D., M.P.H.; Nneka McNeal-Jackson, M.D.

NDA 209661

Tradenname (20 mg doxylamine succinate and 20 mg pyridoxine hydrochloride) extended-release tablets

and intravenously, for three months duration. Dosing details and treatment dates were not reported. Suspected products were Diclectin and Zofran®. No concomitant medications or medical history was provided. (See PADER -9)

- Case CA15-710 describes a 20-year old, 180-pound woman who took Diclectin® 8 tablets by mouth daily from 5^{4/7} weeks gestation to 9^{2/7} weeks gestation. At 9^{2/7} weeks, the woman experienced a spontaneous abortion. (See PADER -12)
- Case CA15-711 describes a 28-year old, 154-pound woman that took Diclectin three tablets by mouth daily from 4^{1/7} to 9^{6/7} weeks gestation who discovered during a dating ultrasound at 9^{6/7} weeks that the fetal heart rate was absent. (See PADER -12)

Clinical Reviewers' Comments:

Approximately 10-15% of all confirmed pregnancies end in spontaneous abortions.⁶ The clinical reviewers are unable, however, to calculate the incidence of spontaneous abortions associated with Diclectin/Diclegis use for these five cases. These five cases of spontaneous abortions (three for Diclectin and two for Diclegis) do not change the safety profile for Diclegis.

One case of premature birth was reported in PADER -4 (reporting period from January 8, 2014 to April 7, 2014) with follow up in PADER -7 (reporting period: July 8, 2014 to October 7, 2014).

- Case CA14-111 describes a male baby born prematurely with low birth weight and hand tremor. This case is linked to Case CA14-112 that describes a 36-year-old woman who received Diclectin in the index pregnancy. She had a history of opioid addiction, anxiety, HELLP syndrome in two previous pregnancies, premature delivery in first pregnancy, preeclampsia, spinocerebellar ataxia, and tobacco use. The report listed her concomitant medications as Leucovorin (folinic acid), Paxil, Suboxone, and Subutex (both opiate partial antagonists). (See PADER -4)

Follow-up information to Case CA14-112 reported the mother developed preeclampsia, which led to an induced delivery. The applicant assessed both Cases CA14-111 and CA14-112 as possibly related the drug. (See PADER -7)

Clinical Reviewers' Comments:

The applicant assessed the causality of Case CA14-111 as unlikely related to the use of Diclectin. This reviewer concurs with this assessment given that the obstetrician made a decision to induce labor in a preterm pregnancy because of the severity of

⁶ The American College of Obstetricians and Gynecologists Practice Bulletin No. 150. Early Pregnancy Loss. Obstetrics and Gynecology. 2015, May:1258-67.

Clinical Review

Theresa H. van der Vlugt, M.D., M.P.H.; Nneka McNeal-Jackson, M.D.

NDA 209661

Tradenname (20 mg doxylamine succinate and 20 mg pyridoxine hydrochloride) extended-release tablets

the maternal preeclampsia. The applicant assessed the causality of Case CA14-112 as possibly related to the use of Diclectin. The obstetrician initially suspected HELLP syndrome but later diagnosed non-alcoholic steatohepatitis. This case is complicated by the maternal history and concomitant drug use. However, it is not possible to rule out Diclectin drug involvement.

Six (6) cases of congenital anomaly were reported in PADER -4 (reporting period: January 8, 2014 to April 7, 2014), PADER -6 (reporting period: April 8, 2014 to July 7, 2014), PADER -7 (reporting period: July 8, 2014 to October 7, 2014), and PADER -10 (reporting period: April 8, 2015 to July 7, 2015), PADER -13 (reporting period: January 8, 2016 to April 7, 2016), and Federal Adverse Events Reporting System (FAERS) case report (submitted June 13, 2016):

- Case CA14-113 describes a female infant, age unspecified, born with congenital limb hypoplasia and congenital anomaly of the digits with missing toenails and small foot toenails and fingernails. The mother of the baby had taken Diclectin six tablets daily for 117 days. No additional information was available. (See PADER -4)
- Case CA14-337 describes to a 27-year-old gravida 1, whose fetus had multiple congenital anomalies (exomphalos, cardiac malposition, and congenital spinal cord anomaly). The woman took 4 to 5 Diclectin tablets per day when her pregnancy was 5 to 6 weeks gestational age. Ultrasound at 12 weeks gestational age showed all of the fetal abdominal organs existing outside of its body and the heart located in the abdomen. Amniocentesis showed no genetic or chromosomal alterations. Termination by curettage was performed. (See PADER -6)
- Case CA14-738 describes a 32-year-old, gravida 2 who was noted to have a fetal congenital anomaly (gestational age unspecified). Additionally, she had heparin-induced thrombocytopenia. The PADER reported Diclectin as the suspect product. The woman reportedly took 4 Diclectin tablets daily (approximately 150 tablets) during her pregnancy. (See PADER -7)
- Case US15-98 was reported by an attorney. It represents a woman, age unspecified, who took Diclegis during her pregnancy (dose and medication duration were not reported). She gave birth to a baby boy with a "subclavicular malformation." No further details of the deformity were reported. No information on the mother was reported. Multiple attempts made by the Duchesnay to obtain additional information were unsuccessful. (See PADER -10)
- Case CA16-85 describes a female child (age not specified) born with Trisomy 21, cardiac septal defect, and congenital aortic anomalies to a mother whose pregnancy was complicated by Crohn's disease. The mother of the female child took Diclectin during her pregnancy. The report did not include when during her pregnancy she took Diclectin. Other listed concomitant medications taken by the mother during her

Clinical Review

Theresa H. van der Vlugt, M.D., M.P.H.; Nneka McNeal-Jackson, M.D.

NDA 209661

Tradenname (20 mg doxylamine succinate and 20 mg pyridoxine hydrochloride) extended-release tablets

pregnancy were Elavil, Synthroid, Magnesium, Remicade, Iron, and Multivitamins. (PADER-13)

- Case 12329346 describes a baby with hypoplastic left heart born to a 33-year old woman who started taking Diclegis at 12 weeks gestational age for nausea and vomiting of pregnancy. The mother of the baby was prescribed two tablets by mouth at bedtime. The report did not include when during her pregnancy she took Diclegis.

Clinical Reviewers' Comments:

All pregnancies carry a 1-3% baseline risk of major malformations.⁷ In case CA14-337, the attending physician suspected Amniotic Band Syndrome (ABS). For case US15-98, the causality of the trial drug could not be assessed given the limited details provided in the report. For case CA16-85, these are common cardiac findings found in babies born with Trisomy 21. The clinical reviewers are unable, however, to calculate the incidence of congenital anomalies associated with Diclectin/Diclegis use for these six cases. These six cases of reported congenital anomalies do not change the safety profile of Diclegis.

9 Appendices

9.1 Literature Review/References

The application includes scientific literature related to doxylamine and pyridoxine. The reviewers did not conduct an extensive search of additional literature, except where specific articles referenced an associated publication that was of particular interest.

Clinical Reviewers' Comments:

The literature provided in the application, and footnoted in this review, clarified our understanding of the safety profile of approved Diclegis (10 mg doxylamine and 10 mg pyridoxine).

9.2 Labeling Recommendations

The clinical reviewers recommend the approval of Tradename for the treatment of nausea and vomiting of pregnancy in (b) (4) who do not respond to conservative management once the DBRUP final agreed upon labeling with the applicant has been approved.

9.3 Advisory Committee Meeting

No advisory committee was needed or conducted for NDA 209661.

⁷ Centers for Disease Control and Prevention (CDC). 2008. Update on overall prevalence of major birth defects – Atlanta, Georgia, 1978-2005. MMWR Morbidity and Mortality Weekly Rep 57:1-5.

Clinical Review

Theresa H. van der Vlugt, M.D., M.P.H.; Nneka McNeal-Jackson, M.D.

NDA 209661

Tradenname (20 mg doxylamine succinate and 20 mg pyridoxine hydrochloride) extended-release tablets

APPEARS THIS WAY ON ORIGINAL

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

/s/

NNEKA N MCNEAL-JACKSON
11/07/2016

THERESA H VAN DER VLUGT
11/07/2016

SHELLEY R SLAUGHTER
11/07/2016

I concur with the conclusions and recommendations of Drs. van der Vlugt and McNeal-Jackson.
See also Cross-Discipline Team Leader Review of Dr. Slaughter.