CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

021876Orig1s000

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader (CDTL) Review

Date	March 19, 2013
From	Shelley R. Slaughter, M.D., Ph.D., Division of Reproductive and Urologic Products (DRUP)
Subject	Cross-Discipline Team Leader Review for DICLEGIS
NDA/BLA # Supplement#	21876
Type of Submission	505(b)(2)/Standard Review
Applicant	OptumInsight (Basking Ridge, NJ) for Duchesnay Inc.(Blainville, PQ Canada)
Date of Submission	June 08, 2012
PDUFA Goal Date	April 08, 2013
Proprietary Name / Established (USAN) names	DICLEGIS/ Doxylamine Succinate/Pyridoxine Hydrochloride
Dosage forms / Strength	Delayed Release Oral Tablet (10 mg doxylamine succinate/10 mg pyridoxine hydrochloride) Two Tablets at Bedtime, One Morning Tablet if Needed, One Mid-afternoon Tablet if Needed, Total of Four Oral Tablets Daily
Proposed Indication(s)	Treatment of Nausea and Vomiting of Pregnancy in Patients Who do not Respond to Conservative Management
Recommended:	Approval is recommended. A Pediatric Research Equity Act (PREA) postmarketing requirement to conduct a study to support the efficacy and safety of DICLEGIS in postmenarchal girls, ages 12-17 years 11 months is recommended.

1. Introduction and Executive Summary

With this 505(b)(2) NDA submission, the Sponsor is seeking approval for DICLEGIS for the treatment of nausea and vomiting of pregnancy. The Agency has previously approved one other drug product, Bendectin® (refer to Background and Regulatory History), the reference listed drug for this application.

Major issues emerging during the review and consideration of this application were:

1. Efficacy
   It was agreed during the IND development phase that efficacy information for DICLEGIS would be obtained from a single clinical trial. It was also determined that the prior information on Bendectin® would be reviewed as supporting information only. Study DIC-301, the sole clinical trial conducted to support efficacy, demonstrated that the DICLEGIS clinical treatment arm was statistically significantly superior to placebo in reduction of the PUQE score, a measure of nausea and vomiting experienced by study participants. Though statistically significant, the treatment effect was small. Secondary analyses from Study DIC-301 and the previous findings on efficacy of Bendectin® were considered supportive.
2. Safety
   Safety information on DICLEGIS derives mainly from Study DIC-301 and from known safety issues with the combination of doxylamine succinate and pyridoxine hydrochloride and from the individual components alone.
3. Labeling
   The Sponsor submitted labeling highly modeled after the Diclectin Canadian Monograph. The Agency's recommendation on labeling provided to the Sponsor is based primarily on efficacy and safety data for DICLEGIS obtained in Study DIC-301 with inclusion, where appropriate, of safety information relative to the combination of doxylamine succinate and pyridoxine hydrochloride and the individual components alone. The final agreed-upon Physician Insert and Patient Package Insert are attached to this review.
4. Regulatory
   It was determined that a sufficient bridge was presented in the application to rely in part (Preclinical information) on the findings of safety and efficacy of Bendectin to support the DICLEGIS application (see Memorandum from Captain E. Dennis Bashaw, Pharm.D., Director, Division of Clinical Pharmacology-3, Office of Clinical Pharmacology, Office of Translational Sciences.

2. Background and Regulatory History

Nausea and vomiting of pregnancy is by definition a condition associated with pregnancy. Other causes of nausea and vomiting should be eliminated. The percentage of pregnant

women experiencing some level of nausea and/or vomiting can be as high as 80 percent. More than 50% of pregnant women report having daily episodes of vomiting. Symptoms generally begin during the 5th or 6th week of pregnancy (relative to the last menstrual period). Symptoms resolve in the majority of subjects by the end of the first trimester or early in the 2nd trimester. Approximately 20% will have symptoms into the 3rd trimester. The vast majority of pregnant women with nausea and vomiting have mild to moderate symptoms and are managed as outpatients. Women with uncomplicated mild to moderate nausea and vomiting of pregnancy can respond to conservative measures and should be first offered dietary modification (frequent small meals, high-carbohydrate low fat meals, high protein snacks, crackers, carbonated beverages) and/or ginger supplements. Pharmacologic therapy is recommended as second line therapy after a trial of dietary modification and/or ginger supplements.

At the most severe end of the spectrum is hyperemesis gravidarum, which affects approximately 1% of pregnancies. This condition can result in dehydration, loss of greater than 5% body weight, electrolyte imbalances, elevated hepatic enzymes, ketonuria, significant maternal morbidity (such as Wernicke's encephalopathy, splenic avulsion, esophageal rupture, pneumothorax, and acute tubular necrosis), maternal death (rare), compromise of fetal growth, and fetal death. Women with hyperemesis gravidarum require hospitalization for intravenous fluid replacement and management of electrolytes. DICLEGIS is not intended for the treatment of hyperemesis gravidarum.

There has been one product previously approved in the U.S. for the treatment of nausea and vomiting of pregnancy, Bendectin®.

The following is a summary of the regulatory history of DICLEGIS and the reference listed drug, Bendectin®:

- **1956,** The Agency approved NDA 10598 Bendectin® Delayed Release Tablets (doxylamine succinate, pyridoxine hydrochloride, and dicyclomine hydrochloride) manufactured by Hoechst Marion Roussel, Inc. (HMR) with the indication of "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." Each Bendectin® tablet was formulated with (b) (4)

- **1976**, Bendectin® was reformulated to include only 10 mg of doxylamine and 10 mg pyridoxine because the FDA Drug Efficacy Study Implementation (DESI) program determined that dicyclomine hydrochloride was ineffective for treating nausea and vomiting of pregnancy. The reformulated product, containing 10 mg of doxylamine succinate plus 10 mg pyridoxine hydrochloride, was determined to be effective following the DESI review.

- **November 04, 1976**, reformulated Bendectin® received FDA Approval.

- **Late 1970's – early 1980's**, Bendectin® was subject to more than 300 lawsuits alleging Bendectin caused birth defects, particularly limb defects.

- **September 16, 1980,** the Fertility and Maternal Drug Advisory Committee recommended 1) continuation of epidemiological studies of Bendectin® and 2) instructions to physicians that Bendectin® should be used only for significant nausea and vomiting unresponsive to non-drug therapy.

- **June 09, 1983,** Merril Dow ceased marketing Bendectin® citing the financial burden of litigation and adverse publicity.

- **October 20, 1997**, Cato Research filed a citizen petition, under 21 CFR § 10.30, on behalf of Duchesnay (Docket No. 97P-0437/CPI), requesting that the FDA determine that Bendectin® was not withdrawn from sale for reasons of safety or effectiveness and to relist Bendectin® in the "Approved Drug Products with Therapeutic Equivalence Evaluations" (the "Orange Book").

- **August 09, 1999**, FDA made a determination that Bendectin® was indeed not withdrawn from sale for "reasons of safety and effectiveness." Per the Federal Register Notice (Docket Nos. 92P-0274 and 97P-0437)

  "The agency's review of the withdrawal of Bendectin from the market has considered the sponsor's explanation of the basis for the withdrawal of the product in 1983 and information available to the agency regarding safety and effectiveness concerns for Bendectin. As noted previously, the sponsor has consistently maintained that it withdrew Bendectin from the market for reasons other the safety and effectiveness. The agency has reviewed information submitted with the petitions, published studies, U.S. and foreign adverse event reports, and FDA records. The current evidence supports the conclusion that Bendectin was not withdrawn from the market for reasons of safety or effectiveness."

- (b) (4)

(b) (4)

- [redacted]
- [redacted]
  - [redacted]
- [redacted]
- **April 18, 2005**, Duchesnay submitted a 505(b)(2) NDA (NDA 10598) application for DICLEGIS (original proposed proprietary name – [redacted]) for the indication [redacted] citing Bendectin as the reference listed drug.
- **June 16, 2005**, the Division of Reproductive and Urologic Products (DRUP) sent a "refuse to file" letter to Duchesnay stating, "After a preliminary review, we find your application is not sufficiently complete to permit a substantive review. Therefore, we are refusing to file this application under 21 CFR 314.101(d) for the following reasons:
  - From a clinical pharmacology perspective, the 505(b)(2) application was not fileable because it did not contain information necessary to establish a link between the proposed formulation of [redacted] and the Reference Listed Drug (RLD), Bendectin®. In the absence of adequate information to address this deficiency, reliance upon our finding of safety and efficacy for the RLD is not sufficient to support approval of [redacted].
  - From a clinical perspective, the 505(b)(2) application is not fileable because the application is seeking an indication [redacted]
  - The proposed indication [redacted] is not supported by substantive data on safety and efficacy."
- **September 23, 2005**, Duchesnay submitted to the Agency, a Special Protocol Assessment (SPA) for the Phase 3 trial. Revised SPA submitted November 22, 2005

- **November 07, 2005,** A SPA non-agreement letter was sent from DRUP with the following concerns and recommendations.
  - "We recommend a multicenter (either in Canada or the United States)-based study that enrolls an ethnically, educationally and socio-economically diverse population that is reflective of the population of intended use in the United States."
  - (b) (4)
  - "A detailed statistical plan must be provided."
  - "We recommend that you obtain entry ultrasound to document viable pregnancy and gestational age as well as to exclude gestational trophoblastic disease and multifetal gestation."
  - "If a revised protocol for special protocol assessment is submitted, it will constitute a new request under this program.
- **November 22, 2005**, Duchesnay submitted a revised SPA
- **February 22, 2006,** SPA non-agreement letter from DRUP with the following comments:
  - "We concur with a single proof of efficacy study. Approvability of the drug product, however, is a review issue and will be determined after submission of the NDA."
  - "The current standard of care is to give a trial of conservative management before initiation of pharmacological therapy in patients experiencing Nausea and Vomiting of Pregnancy (NVP). We believe that the indication for (b) (4) should be consistent with this approach. Therefore, we recommend that (b) (4) be indicated for the treatment of nausea and vomiting of pregnancy in those patients who do not respond to conservative

management. We may also seek labeling that includes the wording to this effect."

- "We recommend that all study subjects start with the same dose of (b) (4). If a dosage increase is contemplated, precise criteria for failure of lower-dose therapy should be provided."
- "Clarify and add to the protocol that the primary outcome measure is the change from baseline in the Pregnancy Unique Quantification of Emesis (PUQE) score between (b) (4) and placebo."
- "Add the following statistical points to the protocol:
    - null and alternative hypotheses
    - level of statistical significance for testing
    - method to account for missing data, e.g., if last evaluation is missing but other postbaseline evaluations are available
    - 95% confidence interval for the treatment difference
    - define the ITT population as any randomized patient who has taken at least one treatment dose
    - primary efficacy analysis is based on the ITT population
    - describe how the overall PUQE score and how the PUQE baseline value are derived"
- "Add text to the protocol to account for the following points:
    - the timepoint when the patient has their enrollment PUQE score assessed, as mentioned in inclusion criteria 4
    - that the patient who is assigned placebo will have a similar dosing regimen as the patient assigned to (b) (4)
    - that the placebo tablet matches in appearance to the (b) (4) tablet"

- **March 21, 2006**, Duchesnay accepted all of the FDA comments and recommendations on the SPA and proposed the following dosing adjustments:
    - *"All patients will start with the same dose of (b) (4) The physician will prescribe two (2) (b) (4) delayed release tablets at bedtime to control nausea and vomiting occurring in the morning. At the second day, after the afternoon telephone call, if the symptoms extend to the noon-afternoon hours an additional one (1) delayed release tablet in the next morning will be*

given. At the clinic visit (day 3), after assessment one (1) delayed release tablet mid afternoon will be added to control symptoms in women suffering symptoms in the evening. While all women will receive the 2 tablets before sleep, the dosage schedule will be individualized according to timing, duration, severity and frequency of the symptoms experienced by the patient. The minimum dosage prescribed will be two tablets daily at bedtime, increasing, when indicated to the maximal dosage of four tablets. The first dose will be taken at bedtime on the day of admission to the study (Day 1).”

- **April 27, 2006**, DRUP concurred with the dosing schedule.

- **April 17, 2007**, Type C meeting was held to review the 10 mg doxylamine succinate and 10 pyridoxine hydrochloride development program.

  - Duchesnay informed DRUP that the two bioavailability studies (Study 02163 and Study 02191) submitted in the 2005 original NDA application had been independently audited based on the Division’s concerns about the quality of data in studies performed at certain (b) (4) facilities in (b) (4). Bioanalytical work for both of these studies was conducted at one of the audited facilities: (b) (4)

    - Data in at least one of the studies was considered unreliable. Duchesnay decided not to use either study in support of the NDA.

    - Duchesnay proposed to conduct a new food effect study (Study 70294) and a new pharmacokinetic study (Study 70381) using the to-be-marketed DICLEGIS formulation to provide additional support to the single efficacy Study DIC-301.

    - DRUP agreed to the proposal that bioavailability data from the studies at (b) (4) be removed from the NDA application.

  - DRUP sought clarification from Duchesnay as to the administration of the PUQE questionnaire.

  - Duchesnay clarified that the staff would initially train the subject as to how to fill out the questionnaire and would send the training script to the Agency. Subsequently, the questionnaire would be self-administered by the patient.

- **December 14, 2009**, Type B pre NDA meeting. The following key items were discussed:

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

- Submit stability data on at least 3 primary batches as recommended in ICH Q 1 (R2).

- Provide complete manufacturing information, both in narrative format and in a flow chart. This should also include in-process controls.

- Refer to the International Conference on Harmonization (ICH): Guidance for Industry: M4Q: The CTD- Quality (http://www.fda.gov/RegulatoryInformation/Guidances/ucm129901.htm) for information on how the CMC section of your application should be organized.

- Complete drug substance information can be provided either in the application or in a DMF with the appropriate Letter of Authorization provided. If information is provided in a DMF, we request that the following information be provided in the NDA for ease of review: General information, physico-chemical properties, and Specifications. Submit a Certificate of Analysis of the drug substance.

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

- The Division advised the Sponsor that a US DMF would be necessary and that it should be submitted as soon as possible so that the information would be available for review when the NDA was submitted. Because the quality of the information is not known, the Sponsor requested that the information be reviewed early in the review cycle to allow adequate time to address any deficiencies with the manufacturer/DMF holder.

- DRUP agreed with inclusion of a pregnancy risk category for the drug product and that designation will depend on the information provided in the NDA.

- DRUP concurred that efficacy for the proposed product is to be supported by a single clinical trial and no ISE was necessary.

- DRUP agreed that the Sponsor could provide summaries on all published and unpublished safety data for Bendectin® and [redacted] and that an ISS is not required for these summaries. A separate summary of safety should be provided for the primary clinical trial.

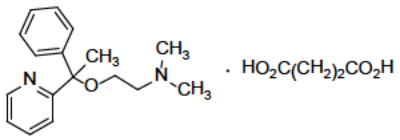
- DRUP concurred that it was appropriate to ask for a pediatric waiver in children under 12 years of age and a deferral in the NDA for children between the ages of 12 and [redacted] is appropriate pending conducting a study in post-adolescent girls between the ages of 12 and [redacted].

3. CMC/Biopharmaceutics/Device

The Chemistry and Biopharmaceutics information in the application were reviewed by Gene W. Holbert, Ph.D., Office of New Drug Quality Assessment (ONDQA), Division of New Drug Quality Assessment II, Branch IV and Kareen Riviere, Ph.D., ONDQA, Division of Biopharmaceutics.

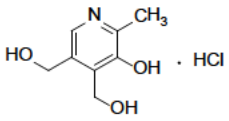
DICLEGIS Delayed Release Tablets are round, white film-coated tablets containing 10 mg doxylamine succinate, USP and 10 mg pyridoxine hydrochloride and imprinted with a pink image of a pregnant woman. The chemical structure, molecular formula and molecular weight are shown in Figure 1.

Figure 1 Chemical Structure, Molecular Formula and Molecular Weight of DICLEGIS (doxylamine succinate and pyridoxine hydrochloride)



Doxylamine Succinate

Molecular Formula: $C_{17}H_{22}N_2O \cdot C_4H_6O_4$
Molecular Weight: 388.46



Pyridoxine Hydrochloride

Molecular Formula: $C_8H_{11}NO_3 \cdot HCl$
Molecular Weight: 205.64

Active ingredients are doxylamine succinate and pyridoxine hydrochloride. Inactive ingredients include ammonium hydroxide, n-butanol, carnauba wax powder, colloidal silicon dioxide, croscarmellose sodium, D&C Red #27, FD&C Blue #2, hypromellose, isopropyl alcohol, magnesium stearate, magnesium trisilicate, methacrylic acid copolymer, microcrystalline cellulose 102, PEG 400, PEG 8000, polysorbate 80, propylene glycol, shellac glaze, simethicone, talc and titanium dioxide. With the exception of the film coating and printing ink, all excipients are compendial. The flavoring, film coating and ink are composed of ingredients that are compendial and/or GRAS.

The drug product is packaged in a 75-mL opaque bottle [manufactured by (b) (4) with a 38-mm child-resistant cap [manufactured by (b) (4) and a silica gel desiccant canister [manufactured by (b) (4) The cap contains an induction inner seal consisting of a (b) (4) manufactured by (b) (4) and a (b) (4) manufactured by (b) (4) respectively]. All DMF's were previously reviewed and found to be adequate for packaging of solid oral dosage forms.

DICLEGIS Delayed Release Tablets are manufactured for Duchesnay by (b) (4) The manufacturing process consists of (b) (4)

Doxylamine succinate, a white or creamy white powder, is an antihistamine with sedative and hypnotic properties. It is a component of many of the over-the-counter (OTC) cold medications purchased in the US and is also the active ingredient in certain OTC sleep aids. Doxylamine succinate is supplied by (b) (4) The DMF was previously reviewed and found to be adequate. Release testing of the drug substance (doxylamine succinate) is performed by (b) (4) Impurities and residual solvent release testing of the drug substance (doxylamine succinate) is performed by (b) (4)

Pyridoxine hydrochloride is a white or practically white crystalline powder or crystals. Pyridoxine is one of the compounds along with pyridoxal and pyridoxamine that are referred to as vitamin B6. Pyridoxine hydrochloride is used in oral vitamin supplements and injectable vitamin formulations for correction of vitamin B6 deficiency. It is widely available over the counter as well as in prescription products. Pyridoxine hydrochloride is water-soluble and is the salt most commonly found in vitamin B6 nutritional supplements. Pyridoxine HCl as supplied to Duchesnay is manufactured by (b) (4) Release testing is performed by (b) (4) Impurities testing is performed by (b) (4)

The application contains 3 months of long term and accelerated stability data on three full scale registration batches manufactured by (b) (4) using pyridoxine HCl manufactured by the proposed commercial supplier (b) (4) There were no significant changes in any of the lots stored at the long term or accelerated condition. Forty-eight months of supporting stability data were also submitted for drug product manufactured by (b) (4) using pyridoxine HCl manufactured by the historical drug substance supplier (b) (4) The applicant has proposed a 24 month expiry dating period when stored at 20-25ºC (68-77ºF) in tightly closed containers and protected from light and moisture. Data for an additional three batches (24 months) was submitted to demonstrate the efficacy of the desiccant canister in maintaining product quality during storage. The Agency proposed a 24-month expiry date based on all stability data submitted to date, and that the applicant extend the expiry data according to the annual reporting procedures. The Sponsor agreed to this approach and submitted a revised proposal for

expiration dating of 24 months on February 26, 2013. The proposed expiration dating period of 24 months is Satisfactory.

Duchesnay submitted a claim of categorical exclusion from environmental assessment under the provisions of 21 CFR 25.31 (a), "action on this application does not increase the use of the active moiety". ONDQA determined that the claim of categorical exclusion from environmental assessment may be granted under the provisions of 21 CFR 25.31 (a).

For a complete description of the manufacture and control of the drug substances and drug product, refer to the Chemistry NDA Review of Dr. Holbert.

The Office of Compliance issued an overall Acceptable recommendation for the manufacturing facilities on March 20, 2013.

Per the ONDQA Chemistry reviewer, the NDA is recommended for Approval from a CMC perspective. The applicant has provided sufficient information to assure the identity, strength, purity and quality of the drug product.

Per the ONDQA Biopharmaceutics reviewer, Kareen Riviere, Ph.D., DICLEGIS delayed release Tablets 10mg/10mg are recommended for approval from a Biopharmaceutics standpoint with the following dissolution method and acceptance criteria for both strengths:

Acid Stage:
Dissolution Method: Apparatus II, 100 rpm paddle speed/medium: 1000 mL of 0.1 N HCl buffer at 37 °C ***Dissolution acceptance criterion:*** Q = NMT (b) (4) at 2 hours.
Buffer Stage
Dissolution Method: Apparatus II, 100 rpm paddle speed/medium: 1000 ml of pH 6.8 buffer at 37 °C ***Dissolution acceptance criterion:*** Q = (b) (4) at 15 minutes.

4. Nonclinical Pharmacology/Toxicology

The non-clinical pharmacology and toxicology information presented in the application was reviewed by Kimberly Hatfield, Ph.D., Office of New Drugs (OND), Office of Drug Evaluations 3 (ODE 3), Division of Reproductive and Urologic Products (DRUP).

The submitted nonclinical evidence supporting safety of the combination of 10 mg doxylamine succinate and 10 mg pyridoxine hydrochloride in DICLEGIS is based on the Agency's determination of the safety of the reference listed drug Bendectin® (NDA 10598), according to section 505(b)(2) of the Federal Food, Drug and Cosmetic Act. Relevant submitted literature regarding the nonclinical assessment of doxylamine and pyridoxine, alone and in combination was also reviewed. Repeat dose toxicity studies were carried out for doxylamine and pyridoxine individually in mice, rat and dog.

In the rodent model, toxicity of doxylamine was observed as decreased body weights, organ weight changes, and liver histopathology. However, these toxicities occurred at doses that were 91-1536-fold the proposed clinical dose of 10 mg doxylamine in DICLEGIS. The NOAELs in mice and rat were 325 mg/kg (39-fold) and 1012 mg/kg (246-fold), respectively. In the dog model, the toxicity of pyridoxine was neuromuscular (ataxia) and occurred at a dose 121-fold the proposed clinical dose of 10 mg pyridoxine in

DICLEGIS. Genotoxicity studies with doxylamine were negative, and doxylamine is not considered to have carcinogenic potential. Based on the high safety margins, and lack of mutagenicity/carcinogenicity, there is no concern for the safety of the individual components of DICLEGIS.

Reproductive toxicity studies were carried out with the original Bendectin® product (10 mg doxylamine succinate and 10 mg pyridoxine hydrochloride) approved in the 1970s. In rats, a maternal and fetal NOAEL was established at a 24-fold dose multiple, with fetal toxicity [reduced fetal weight, reduced fetal ossification of limbs, increased resorptions, and increased malformations (short 13th rib) occurring mainly due to maternal toxicity (reduced maternal body weight and food consumption, 17% mortality at high dose)] occurring at doses of 500 and 800 mg/kg (61-97-fold). In monkeys, ventral septum defects in the heart were noted at doses of 20-82 mg/kg (5-20-fold). Ventral septal defects were noted in early sacrifice animals but not in full-term infants, indicating a potential delay in closure rather than lack of closure. A second study in monkeys with 1.3-13.3 mg/kg doses (0.3-3.2-fold) showed no teratogenic effects, and no embryo-, fetal- or maternal toxicity.

Pharmacokinetic data in animals were not available for the combination of doxylamine and pyridoxine. Preclinical concludes that with the similarity of DICLEGIS to Diclectin and other 10 mg doxylamine succinate and 10mg pyridoxine hydrochloride drug products approved in other countries and the vast amount of human exposure data (millions of pregnant women), the potential risks due to treatment with DICLEGIS are very low. Both components of DICLEGIS are also individually available in over-the-counter products, and the proposed clinical dose of each component of DICLEGIS is within the range of over-the-counter use of each compound individually. Preclinical concludes that based on the safety margins of the NOAELs for the DICLEGIS combination (as Bendectin®) or the individual components, and the observation of some toxicity at very high dose multiples, there is little concern for toxicity with DICLEGIS.

For a complete presentation and discussion of the Pharmacology-Toxicology program presented in the application refer to the Pharmacology/Toxicology NDA Review and Evaluation by Kimberly Hatfield, Ph.D. Per the recommendation of Dr. Hatfield, "the nonclinical data support approval of DICLEGIS (combination of doxylamine succinate and pyridoxine hydrochloride) for the treatment of nausea and vomiting of pregnancy in patients who do not respond to conservative management."

5. Clinical Pharmacology/Biopharmaceutics

Per the Office of Clinical Pharmacology (OCP) reviewer Sayed Al Habet, Ph.D., the Sponsor included two pivotal pharmacokinetics studies, one to characterize the pharmacokinetics after single and multiple dose administration (Study 70381) and the other is to investigate the effect of food (Study 70294). In addition, sparse pharmacokinetic sampling was performed in Study DIC-301. Two other pharmacokinetic studies, Study 02163 and Study 02191, were conducted by the Sponsor but were subject to audit due to the (b) (4) bioanalytical quality issues at the facility located in (b) (4) It was agreed during preNDA development that these two studies would be submitted to the NDA only to present all studies conducted, but they would not be reviewed.

Studies 70381, 70294 and DIC-301 were all conducted using the to-be-marketed formulation.

Study 70381 was conducted to assess the pharmacokinetic profile of the active ingredients of DICLEGIS delayed release tablets after single and multiple doses in 18 healthy non-pregnant women. Subjects were administered a single oral dose of 2 tablets of DICLEGIS at 22:00 hours on Days 1 and 2, and multiple repeat oral doses of DICLEGIS on Days 3 through 18, according to the following schedule: 1 tablet at 09:00 and 16:00 hours, and 2 tablets at 22:00 hours on an empty-stomach (defined as at least 2 hours after eating).

The results of Study 70381 demonstrated that the parent drug products (doxylamine and prydoxine) and the pyridoxine metabolites accumulate in the body following multiple dose administration as seen for the Cmax (see Table 1) and AUC (see Table 2) of doxylamine and pyridoxine.

Table 1 Mean ± SD of Cmax and Half-life from Study 70381

Analytes/Components	Cmax (ng/mL)		Half Life (h)	
	Single	Multiple	Single	Multiple
Doxylamine	83 ± 21	168 ± 38	10.05 ± 2.09	11.91 ± 3.33
Pyridoxine	32.57 ± 15.03	46.05 ± 28.30	0.49 ± 0.23	0.45 ± 0.14
Pyridoxal	74.29 ± 21.80	210.02 ± 54.36	1.29 ± 0.50	19.44 ± 14.46
Pyridoxal 5'-Phosphate	30.01± 10.03	84.91 ± 16.83	36.99 ± 12	53.46 ± 15.30
Pyridoxamine	532.21 ± 737	535 ± 158	10.98 ± 8.82	2.90 ± 1.52
Pyridoxamine 5'-Phosphate	739 ± 451	2291 ± 1703	5.42 ± 3.37	44.33 ± 21.70

Source: Adapted from Clinical Pharmacology Review (CPR) Table 1.3.2 and NDA 21876, Clinical Study Report, 70381

Table 2 Mean ± SD of AUC (0-last) and AUC (0-inf) from Study 70381

Analytes/Components	AUC (0-last) ng h/mL		AUC (0-inf) ng h/mL	
	Single	Multiple	Single	Multiple
Doxylamine	911 ± 206	3661 ± 1279	1281 ± 369	3721 ± 1318
Pyridoxine	39 ± 16	59 ± 33	43 ± 16	64 ± 36
Pyridoxal	187 ± 45	1297 ± 363	212 ± 46	1587 ± 550
Pyridoxal 5'-Phosphate	442 ± 156	4766 ± 1137	1536 ± 721	6099 ± 1383
Pyridoxamine	467 ± 514	1607 ± 696	4121 ± 2713	2608 ± 825
Pyridoxamine 5'-Phosphate	3458 ± 2393	58859 ± 58293	5232 ± 3839	94459 ± 58010

AUC (0-last): AUC from time zero to the last measurable/observed concentration
AUC (0-inf): AUC from zero to infinity (calculated/predicted)
Source: Adapted from Clinical Pharmacology Review (CPR) Table 1.3.1 and NDA 21876, Clinical Study Report, 70381

There was a high degree of variability in the data, primarily associated with low and undetectable concentration in the terminal elimination phases. Because of this, the elimination rate constants were not adequately determined or not determined in many subjects. Dr. Al Habet determined that the half-life and the AUC to infinity were not adequate under these circumstances and should be interpreted carefully.

Study 70294 was a single-dose, randomized, two-way crossover study conducted to assess the effect of food on the bioavailability of DICLEGIS, administered as two delayed release tablets under both fasting and fed conditions (following ingestion of a high-fat, high-caloric meal within 30 minutes before drug administration. There was a 10 hours period of fasting

before the period of drug administration and a fast of 4 hours after drug administration. A washout period of 27 days separated the two phases of the study.

The results of Study 70294 (food effects study) demonstrate that when DICLEGIS is taken with food, a delay in Tmax is observed in addition to a reduction of both Cmax (Table 3) and AUC (Table 4) of the parent pyridoxine and most of its metabolites.

Table 3 Mean ± SD of Cmax and Median Tmax from Study 70294

Analytes/Components	Cmax (ng/ml)		Tmax (h)	
	Fasting	Fed	Fasting	Fed
Doxylamine	94.90 ± 18.40	75.74 ± 16.59	4.5 ± 0.5	11.8 ± 14.9
Pyridoxine	35.54 ± 21.40	13.71 ± 10.77	2.5 ± 1	9.00 ± 4.48
Pyridoxal	85.39 ± 21.53	45.63 ± 25.00	3.03 ± 1.50	10.0 ± 8.00
Pyridoxal 5'-Phosphate	29.75 ± 10.93	34.16 ± 11.88	13.0 ± 9.4	16.0 ± 10.00
Pyridoxamine	487 ± 651	367 ± 381	3.00 ± 2.01	8.75 ± 3.63
Pyridoxamine 5'-Phosphate	1325 ± 745	994 ± 653	4.00 ± 12.50	20.00 ± 39.00

Source: Adapted from Clinical Pharmacology Review (CPR) Table 1.3.4 and NDA 21876, Clinical Study Report 70294

Table 4 Mean ± SD of AUC (0-last) and AUC (0-inf) from Study 70294

Analytes/Components	AUC (0-last) ng h/ml		AUC (0-inf) ng.h/ml	
	Fasting	Fed	Fasting	Fed
Doxylamine	1407 ± 336	1488 ± 463	1448 ± 333	1579 ± 423
Pyridoxine	34 ± 14	18 ± 14	39 ± 13	24 ± 14
Pyridoxal	194 ± 54	138 ± 71	231 ± 72	197 ± 76
Pyridoxal 5'-Phosphate	1975 ± 882	2097 ± 916	2415 ± 1088	2838 ± 1470
Pyridoxamine	5647 ± **19038***	342 ± 399	1531 ± 823	3239 ± ?
Pyridoxamine 5'-Phosphate	51967 ± 41092	52045 ± 47014	47527±28290	184751±259064

AUC (0-last): AUC from time zero to the last measurable/observed concentration
AUC (0-inf): AUC from zero to infinity (calculated/predicted)
*High variability: the %CV for this parameter was 337.16%
Source: Adapted from Clinical Pharmacology Review (CPR) Table 1.3.3 and NDA 21876, Clinical Study Report 70294

Based on Study 70294, the DICLEGIS labeling will recommend that drug be taken on an empty stomach.

In Study DIC-301, blood sampling was done on Day 4 (± 1 day), Day 8 (± 1 day), and Day 15 (± 1 day) to explore for a relationship between plasma concentrations of the parent compounds/ metabolites and the measure of efficacy. However, there were several limitations with this approach:

1. Only a single concentration measurement was obtained on the listed days which hinder evaluation of other potential PK parameters (i.e., AUC).

2. The exploratory analyses were limited by the number of subjects with drug concentrations (e.g., pyridoxine and pyridoxal) below the limit of detection. For example, the median pyridoxine exposure on Day 4, 8, and 15 was 0, which means

that over 50% of the population had a reported pyridoxine concentration of zero. This was not unexpected given pyridoxine's short half-life (i.e., ~30 min).

3. There was high variability in the data, which is in agreement with the observations from the PK studies

Overall, review of the sparse pharmacokinetic sampling revealed that the exposure-response analysis did not demonstrate any correlation between pyridoxine levels and doxylamine and change in the primary efficacy variable on Days 4, 8, and 15.

From the OCP perspective, Dr. Al Habet determined that the NDA is acceptable.

6. Clinical Microbiology

Not applicable to this NDA.

7. Clinical/Statistical - Efficacy

The primary review of the efficacy information in NDA 203505 was performed by Theresa van der Vlugt, M.D., OND/ODE 3/DRUP and Kate Dwyer, Ph.D., Office of Translational Science/Division of Biometrics III. For a detailed discussion of design and conduct of the clinical trials including evaluated primary and secondary endpoints and their analyses the reader is referred to Dr. van der Vlugt's and Dr. Dwyer's reviews.

Study DIC-301 was a randomized, double-blind, multi-center, placebo-controlled, parallel-group study conducted in the US in women aged 18 years or older with nausea and vomiting of pregnancy and a Pregnancy Unique Quantification of Emesis (PUQE) score ≥ 6. The study was conducted between February 2008 and June 2009 at 6 trial centers. The primary endpoint of study was the change from baseline in the PUQE score evaluated at Day 15 (± 1 day). Secondary endpoints were:

- The three individual components constituting the PUQE (hours of nausea, number of times vomiting, and number of times retching)
- Global Assessment of Well-Being
- Number of tablets taken
- Time loss from household tasks and/or employment
- Total number of visits and phone calls to healthcare providers
- Rates of hyperemesis gravidarum
- Compliance with study medication (0 = less than 28 tablets, 1 = 28 tablets, 2 = more than 28 tablets).

Major enrollment criteria included:

- Gravid woman at least 18 years of age
- Single viable fetus at 7-14 weeks gestational age by ultrasound at entry (or within 4 weeks of entry
- Suffering from nausea and vomiting of pregnancy that had not responded to lifestyle/dietary conservative non-pharmacologic measures
- Other etiologies of nausea and vomiting ruled out

- A minimum PUQE score ≥ 6

See Dr. van der Vlugt's review for a full discussion of entrance criteria. Two tablets of DICLEGIS were administered at bedtime on Day 1. If symptoms of nausea and vomiting persisted into the afternoon hours of Day 2, the subject was directed to take her usual dose of two tablets at bedtime and an additional tablet the next morning on Day 3. Based upon assessment in the clinic on Day 4 (± 1 day), the subject may have been directed to take an additional tablet mid-afternoon to address evening symptoms. Because the primary objective of this protocol was to control symptoms of NVP and, as stated previously, the number of tablets could be adjusted up depending on whether or not symptoms were resolved, the total number of tablets given to the subject depended on her PUQE score. If two evening tablets did not ease her symptoms (PUQE score above 3), she received a third tablet the next morning. If with three tablets her PUQE score was still above 3, a fourth tablet was added in the mid-afternoon. While all subjects received two tablets before sleep, the dosage schedule was individualized according to the timing, duration, severity, and frequency of the symptoms experienced by the subject. The maximum number of tablets taken daily was four.

Study DIC-301 had a 15 day period consisting of 14 dosing days. Subjects returned to the clinic prior to their morning dose on Day 4 (± 1 day), Day 8 (± 1 day), and on Day 15 (± 1 day; end of study visit) in order to time the drawing of blood samples to correspond with steady state trough levels (12 mL sample was collected for PK measurements of pyridoxine, pyridoxal, pyridoxal 5-phosphate, and doxylamine concentrations. Additionally, telephone contact was made at Day 2, 6, 12, and 14 in order to assess subject diary information, adverse events (AEs), concomitant medication use, and compliance with the study medication. Laboratory tests were conducted on Day 1 and Day 15.

Subjects were instructed on how to use the PUQE tool and completed the PUQE score (once daily every morning prior to the administration of the study dose at approximately the same time each day) and the study diary. The Day 15 PUQE score reflected the subject's response to treatment on Day 14. Subjects completed the Global Assessment of Well-Being on Days 1, 8, and 14 at the same time that the PUQE score was completed. Subjects were instructed to indicate their general state of well-being over the last week compared to their pre-pregnancy state of health.

Adverse events (AEs) and use of concomitant medications were recorded at all visits and phone calls. The frequency and severity of all AEs were collected from subject diaries and visit and phone call interviews and tabulated by treatment group, system organ class (SOC), preferred term, severity, and relationship to study medication. The AE relationship to plasma/whole blood drug concentrations (collected on Days 1, 4, 8, and 15) was also evaluated. In addition, laboratory tests were conducted on Day 1 and Day 15 (± 1 day). An obstetric ultrasound and physical examination including vital signs were conducted on Day 1.

The agreed upon primary efficacy endpoint was the change from baseline in the PUQE score at Day 15 (± 1 day). The PUQE score is a composite assessment of hours of nausea, number of times of vomiting per day and the number of episodes of retching. The PUQE

scoring is a validated scoring system which has been used in multiple clinical studies. Initial validation was confirmed in pregnant women with correlation of the PUQE scoring to the validated Rhodes score. The Rhodes score is considered the "gold standard" for assess nausea and vomiting in patients receiving chemotherapy for cancer. Information on PUQE scoring in Study DIC-301 was collected daily (with intended collection at the same time of day) from baseline through Day 15 (± 1 day) as in Table 5. Change from baseline (enrollment) was calculated as post-baseline score minus baseline value. For subjects who discontinued the study prematurely, a last-observation-carried-forward (LOCF) approach for the subsequent visit(s) was used to replace missing PUQE scores.

Table 5 Pregnancy Unique-Quantification of Emesis (PUQE) Scale and Global Assessment of Well-Being

Pregnancy Unique-Quantification of Emesis

Motherisk PUQE Scoring System ***(please tick box and write total score)***

1. In the last 24 hours, for how long have you felt **nauseated or sick at your stomach**,	Not at all (1)	1 hour or less (2)	2-3 hours (3)	4-6 hours (4)	More than 6 hours (5)
2. In the last 24 hours, have you **vomited or thrown up**,	7 or more times (5)	5-6 (4)	3-4 (3)	1-2 (2)	I did not throw up (1)
3. In the last 24 hours, **how many** times have you had **retching or dry heaves** without bringing anything up,	No time (1)	1-2 (2)	3-4 (3)	5-6 (4)	7 or more (5)

Global Assessment

How many hours have you slept out of 24 hours?_____

If this is not your normal sleep hours, Why?_____

On a scale of 0-10, how would you rate your *Well Being* in the last week?___

Reference Scale 0 (Worst possible) to 10 (The best you felt before pregnancy)

Can you tell me what causes you to feel that way?

_____

_____

The secondary efficacy endpoints included evaluation of the three components constituting the PUQE score (vomiting, nausea, and retching), the Global Assessment of Well Being, the number of tablets taken, the time loss from household tasks and/or employment, the total number of visits and phone calls to health care providers, the rates of hyperemesis gravidarum, and, finally, the compliance with study medication regimen

Baseline Demographics are shown in Table 6

Table 6: Demographics for Study DIC-301; Intent-to-Treat Population

Parameter and Statistic	DICLEGIS N = 133	Placebo N = 128	Total N = 261
Age (Years)			
N	132	128	260
Mean (SD)	25.9 ± 6.0	25.0 ± 5.6	25.5 ± 5.8
Median	25.0	23.5	24.0
(Min, Max)	(18, 45)	(18, 42)	(18, 45)
Body Mass Index (kg/m^2)			
N	133	128	261
Mean (SD)	28.88 ± 7.61	29.79 ± 11.13	29.32 ± 9.49
Median	28.00	26.86	27.46
(Min, Max)	(16.7, 53.2)	(11.6, 116.8)	(11.6, 116.8)
Weight (kg)			
N	133	128	261
Mean (SD)	74.35 ± 22.39	76.41 ± 22.33	75.38 ± 22.34
Median	69.85	68.72	68.95
(Min, Max)	(40.6, 163.4)	(44.9, 157.3)	40.6, 163.4)
Race			
N	133	128	261
African-American	50 (37.6%)	49 (38.3%)	99 (37.9%)
Caucasian	80 (60.2%)	75 (58.6%)	3 (1.1%)
Asian	2 (1.5%)	1 (0.8%)	155 (59.4%)
Other	1 (0.8%)	3 (2.3%)[a]	4 (1.5%)[a]
Gestational Age at Start of NVP symptoms (Weeks)			
N	132	128	260
Mean (SD)	5.5 ± 1.8	5.3 ± 1.8	5.4 ± 1.8
Median	5.0	5.0	5.0
(Min, Max)	(2, 10)	(0, 11)	(0, 11)
Gestational Age at Enrollment (Weeks)			
N	133	128	261
Mean (SD)	9.3 ± 1.9	9.3 ± 1.8	8.3 ± 1.9
Median	9.0	9.0	9.0
(Min, Max)	(7, 13)	(7, 14)	(7, 14)
PUQE score at Enrollment			
N	133	128	261
Mean (SD)	9.0 ± 2.1	8.8 ± 2.1	8.8 ± 2.1
Median	9.0	8.0	8.0
(Min, Max)	(6, 15)	(5, 15)	(5, 15)

[a]Includes: Other and Not Reported.
Definitions: SD = standard deviation, Min = minimum, Max = maximum.
Source: Adapted from Medical Officer Review (MOR) Table 4 and NDA 21876, Clinical Study Report, Table 10.2, page 43 of 84 and Table 10.3, page 44 of 84.

The demographic data between treatment groups in Study DIC-301 were similar. Overall, in the two treatment groups, subjects were approximately the same age (mean 25.5 years of age and median 24 years of age), developed NVP at approximately the same time (mean

5.4 weeks and median 5.0 weeks of gestation), and were the same number of weeks of gestation at enrollment (mean 8.3 and median 9.0 weeks of gestation). Approximately 60% of study participants were Caucasian (155 of 261 subjects, 59.4%) and 38% of subjects were African-American (99 of 261 subjects).

Of the 280 subject enrolled into Study DIC-301, only 261 subjects received study medication [19 subjects did not receive study medication: 7 in the DICLEGIS treatment group (5.0%) and 12 in the placebo treatment group (8.6%)]. Overall, 203 subjects completed Study DIC-301 (72.5%, 203 of 280 enrolled subjects). More DICLEGIS-treated subjects completed Study DIC-301 (80.0%, 112 of 140 randomized subjects) than placebo-treated subjects 65.0%, 91 of 140 randomized subjects). Table 7 presents subject disposition.

Table 7 Disposition of Subjects in Study DIC-301, Intent-to-Treat Population (Randomized)

Disposition	Study 15-50310		
	DICLEGIS N (%)	Placebo N (%)	Total N (%)
Randomization	140 (100)	140 (100)	280 (100)
Completed Study[a]	112 (80)	91 (65.0)	203 (72.5)
Discontinued Study[a]	28 (20.0)	49 (35.0)	77 (27.5)
Subject withdrew consent	9 (6.4)	18 (12.9)	27 (9.6)
Lost to follow-up	7 (5.0)	19 (13.6)	26 (9.3)
Adverse event	5 (3.6)	5 (3.6)	10 (3.6)
Investigator discretion	0 (1.4)	1 (0.7)	1 (0.4)
Lack of efficacy	2 (1.4)	5(3.6)	7 (2.5)
Other	5 (3.6)	1 (0.7)	6 (2.1)

[a]The denominator is the number of subjects randomized
Source: Adapted from MOR Table 5 and NDA 21876, Clinical Study Report, Table 10.1, page 41 of 84.

Discontinuation rates were higher in the placebo group than in the DICLEGIS arm. Discontinuations due to lack of efficacy are also higher in the placebo arm. These are not unexpected findings. Discontinuations due to adverse events were similar between the two groups.

In Study DIC-301, there were 256 subjects in the modified intent-to-treat efficacy population [(mITT), defined by the sponsor as intent-to-treat-efficacy (ITT-E) and 261 subjects in the intent-to-treat safety population (ITT-S)]. The Sponsor's ITT-E population (defined by this reviewer as a mITT population) included any subject who took at least one dose of study medication and had at least one post-baseline PUQE measurement. Of those subjects who received DICLEGIS, 19% remained on 2 tablets per day, while 21% remained on 3 tablets per day and 60% took 4 tablets per day to address their symptoms. The Sponsor's ITT-S population included all enrolled subjects.

The PUQE score was evaluated using an analysis of covariate (ANCOVA) model where change from baseline to Day 15 (± 1 day) was the response variable, the baseline PUQE score was the covariate, and the treatment group and study center were the fixed effects.

The following ANCOVA assumptions were tested at 5% significance level unless otherwise noted: (1) normality of errors, (2) homogeneity of variances, and (3) equality of slopes among treatment groups at 10% significance level. If the assumptions were severely violated, a nonparametric approach (rank-based analysis of covariance method) was to be used, stratifying by study center. The Sponsor's analyses for efficacy are presented in Table 8.

Table 8 Sponsor's Primary Efficacy Analysis: Change from Baseline to Day 15 (± 1 day) in the PUQE Score. ITT-E (mITT) Population; LOCF.

Data/Category - Statistics	DICLEGIS Treatment Group (N = 131)	Placebo Treatment Group (N = 125)
Baseline		
- Mean ± SD	9.0 ± 6.1	8.8 ± 2.1
- Median	9.0	8.0
- (Min, Max)	(6, 15)	(6, 15)
Day 15 (± 1 day)		
- Mean ± SD	4.2 ± 1.9	4.9 ± 2.3
- Median	3.0	4.0
- (Min, Max)	(3, 11)	(3, 12)
Change from Baseline		
- Mean ± SD	-4.8 ± 2.7	-3.9 ± 2.6
- Median	-5.0	-4.0
- (Min, Max)	(-11, 3)	(-11, 2)
p-value for Comparison	0.006[1]	-

[1]p-value for treatment comparison (DICLEGIS versus placebo) from rank-based analysis of variance stratified by center.

Definitions: LOCF = last observation carried forward, SD = standard deviation, Min = minimum, max = maximum.

Source: Adapted from MOR Table 6 and NDA 21876; Clinical Overview, Table 1.5-6, page 24 of 61; and Clinical Study Report, Table 11.1, page 47 of 84.

The Sponsor did not initially provide a point estimate or a 95% confidence interval of the treatment difference between DICLEGIS and placebo for the PUQE score or its three components. An information request (IR) was sent to the Sponsor on November 8, 2012. Subsequently, the Sponsor submitted additional efficacy analyses in response to the IR on December 5, 2012. The Statistical Reviewer, Dr. Dwyer, performed independent analyses of the change from baseline to Day 15 for the PUQE score and each of the individual components of the PUQE score. Combined Sponsor and Statistical Reviewer analyses are presented in the following Table 9.

Table 9 Study DIC- 301 Primary Analyses of the Mean (SE) Change from Baseline to Day 15 (± 1 day) in the PUQE Score for DICLEGIS vs. Placebo, mITT Population, Last Observation Carried Forward (LOCF). Secondary Analyses of the Individual PUQE Score Components (Length of Daily Nausea in Hours, The Number of Daily Vomiting Episodes and Number of Daily Retching Episodes (Heaves). mITT Population, Last Observation Carried Forward (LOCF)

	DICLEGIS	Placebo
PUQE Score		
N	131	125
Baseline Mean (±SD)[a]	9.0 (6.1)	8.8 (2.1)
Day 15 (± 1 day) Mean[a]	4.2 (1.9)	4.9 (2.3)
Mean Change from Baseline (SD) to Day 15 [b]	-4.67	-3.94
Difference (95% CI) vs. placebo [b]	-0.73 (-1.25, -0.22)	---
p-value[b]	0.006	---
Hours of Nausea		
N	131	125
Baseline Mean (±SD)[a]	4.0 (1.0)	4.1 (0.9)
Day 15 (± 1 day) Mean[a]	1.5 (1.0)	1.6 (0.9)
Mean Change from Baseline (SD) to Day 15 [b]	-2.35	-2.13
Difference (95% CI) vs. placebo[b]	-0.21 (-0.49, 0.06)	---
p-value[b]	0.126	---
Number of Times Vomited Per Day		
N	131	125
Baseline Mean (±SD)[a]	2.2 (1.2)	2.1 (1.2)
Day 15 (± 1 day) Mean[a]	1.1 (0.3)	1.2 (0.5)
Mean Change from Baseline (SD) to Day 15[b]	-0.95	-0.72
Difference (95% CI) vs. placebo[b]	-0.22 (-0.39, -0.06)	---
p-value[b]	0.008	---
Number of Daily Retching Episodes		
N	131	125
Baseline Mean (±SD)[a]	2.7 (1.1)	2.6 (1.2)
Day 15 (± 1 day) Mean[a]	1.2 (0.5)	1.4 (0.7)
Mean Change from Baseline (SD) to Day 15 [b]	-1.37	-1.1
Difference (95% CI) vs. placebo[b]	-0.28 (-0.46, -0.09)	---
p-value[b]	0.004	---

[a]Sponsor analyses
[b]Statistical Reviewer's analyses
Source: Adapted from MOR Table 7, Statistical Reviewer's Table 6 and the Sponsor's response to November 8, 2012 request for information.

Dr. Dwyer's analyses confirm that subjects treated with DICLEGIS had a small but statistically significant improvement vs. placebo in the change from baseline to Day 15 in the PUQE score. Dr. Dwyer also performed sensitivity analyses evaluating the PUQE

score and its individual components in the Completer Population (subjects without major protocol violations having baseline values for the PUQE and PUQE values for 7 of 14 days of collection from the 2nd day of maximum tablet intake through Day 15), FDA's Revised Completer Population (subjects with baseline values for the PUQE and PUQE values for 7 of 14 days of collection from the 2nd day of maximum tablet intake through Day 15) and Per Protocol Populations (subjects without major protocol violations having baseline values for the PUQE and PUQE values for 7 of 14 days of collection from the 2nd day of maximum tablet intake through Day 15 and who completed the study with between 80% - 120% of prescribed study medication applications). In the sensitivity analyses of the Revised Completer Population, only the evaluation of retching showed a statistically significant difference vs. placebo. In the sensitivity analyses of the PUQE score in the Completer and Per Protocol Populations, the Per Protocol showed a statistically significant treatment difference of 0.49, but no statistically significant difference was seen in the analysis of the Completer Population. Another sensitivity analysis to explore the sensitivity of imputation for missing values was requested by the Statistical Reviewer and performed by the Sponsor (submitted December 05, 2012) using a mixed model repeated measures (MMRM) model (using daily measure from day 1 to day 14 without imputation)/ The results showed that there were significant treatment improvements in PUQE score (p-value = 0.0003) and its components (number of hours or nausea p-value = 0.0069, number of times of vomiting p-value 0.0014 and number of episodes of retching p = 0.0029). This post hoc-analysis without imputation supports the efficacy of DICLEGIS. Refer to the Statistical Review of Dr. Dwyer for complete discussion of the statistical analyses of primary and secondary efficacy parameters.

To consider the clinical significance of the small treatment effect of DICLEGIS (-0.73) in the primary efficacy analysis and to put the treatment effect in perspective clinically, Dr. van der Vlugt looked at the clinical overview, dated March 14, 1975, from the original application (NDA 21876) for the revised formulation of Bendectin®. Effectiveness of the revised Bendectin formulation was studied in a randomized, double-blind, multi-center, 8-arm, parallel placebo-controlled study in 2,308 women with NVP. The treatment arms were as follows:

1. Bendectin® 1956 original formulation (10 mg doxylamine and 10 mg dicyclomine HCL and 10 mg pyridoxine)
2. 10 mg doxylamine and 10 mg pyridoxine (revised Bendectin® formulation)
3. 10 mg dicyclomine HCL and 10 mg doxylamine
4. 10 mg doxylamine alone
5. 10 mg dicyclomine HCL and 10 mg pyridoxine
6. 10 mg pyridoxine alone
7. 10 mg dicyclomine HCL alone
8. Placebo

Each subject was instructed to take 2 tablets at bedtime for 7 nights, and if necessary, 1 additional tablet in the morning and/or mid-afternoon (the same regimen as for DICLEGIS. Evaluations (not specifically defined in the report document) by the investigators were performed at the initial visit and again following completions of the 7 days of treatment. Subjects completed a diary card at baseline and on each study day. Efficacy was evaluated and included: 1) hours of nausea as reported on the diary card, 2) frequency of vomiting as

reported on the diary card, and 3) an overall effectiveness of medication judgment completed by the investigator. Per the clinical review, a total of 1599 subjects with nausea and/or vomiting reported that they took medication on each of the 6 successive study days and supplied diary cards on each of these 6 days. Adverse reactions volunteered by the subject were recorded. Efficacy analyses were done for both the "physician evaluation" and the "patient's diary card." The efficacy summary for the 8-arm study based on the subject's diary card is presented in Table 10. The efficacy summary based on the "physician evaluation" is reproduced in Dr. van der Vlugt's review.

Table 10 Summary Table; Based Upon the Enrolled Subject's Diary Card

Treatment	Nausea		Vomiting[1]	
	Percent reduction from pretreatment	P[2]	Percentage with no vomiting on 5 or more treatment days	P
Bendectin®	57	<.01	46	<.01
Doxylamine and pyridoxine	64	<.01	48	<.01
Dicyclomine and doxylamine	50	<.01	49	<.01
Doxylamine	56	<.01	54	<.01
Dicyclomine and pyridoxine	44	.03	39	.08
Pyridoxine	35	.09	29	.08
Dicyclomine	36	.25	30	.26
Placebo	31	-	28	-

[1]The analysis of vomiting includes only those patients with vomiting symptoms pretreatment.
[2]The p values are one sided probabilities based on tests of each active medication vs. placebo.
Source: Adapted from MOR Table 9 and NDA 21876, Clinical Overview, 1975 FDA Review dated 3/14/75.

Per the 1975 reviewer:

"The control of nausea by doxylamine alone and by each of the 3 combination which contain doxylamine was consistently statistically significantly ($p<0.01$) superior to placebo by both physician's records and patient's records. Additionally, the control of vomiting favored all formulations containing doxylamine by a statistical significance, as compared to placebo, of $p<0.01$ by the patient's records and in 2 of the 4 doxylamine formulations (i.e., doxylamine alone and Bendectin) of $p\leq0.03$ by the physician's records. By factorial analysis, all medications with doxylamine alone or in combination (4 medications) were, by physician's records and patient's records, more effective in controlling nausea and vomiting than those which did not contain this ingredient (4 medications) with a statistical probability of <0.01"

"Pyridoxine alone excelled over placebo ($p<0.01$) in the reduction of nausea as demonstrated by physician's records; the patient's records of nausea favored pyridoxine with $p=0.09$. Greater efficacy for treatment of nausea by doxylamine/pyridoxine over doxylamine alone was supported marginally with p values of 0.12 and 0.26 by the patient's records and physician record's, respectively. Factorial analysis of the 4 medications with vs. without pyridoxine indicated effectiveness in the control of nausea with p values of 0.01 by patient's records and 0.08 by physician' records."

"Dicyclomine alone had marginal efficacy over placebo by both physician's records and patient's records in the treatment of nausea (p=0.07 by physician's records; p=0.25 by patient's records). Dicyclomine combined with pyridoxine was superior to placebo) -0.03) for control of nausea by both patient's records and physician's evaluations. The contribution of dicyclomine to the efficacy of dicyclomine when given in combination was not measurable in this study."

Conclusions of the 1975 review include:

1. *"This "8-way" study confirms the previous findings that Bendectin is effective in the control of nausea and vomiting of pregnancy."*
2. *"This "8-way" study confirms the previous findings that doxylamine and the combinations containing doxylamine (including Bendectin) are effective in the control of nausea and vomiting of pregnancy."*
3. *"The rationale for providing pyridoxine as a nutritional supplement during pregnancy and in the dosage employed, plus the evidence of its efficacy for control of nausea as well as its contribution to the efficacy of the combination as demonstrated in this study, indicates that pyridoxine is a clinically important component of the anti-nausea/anti-emetic product, Bendectin."*

The reformulated Bendectin® received approval on November 4, 1976. I concur with Dr. van der Vlugt that the Agency's 1976 findings of effectiveness for Bendectin® is supportive of the effectiveness of DICLEGIS in the treatment of nausea and vomiting of pregnancy.

Secondary efficacy outcome analyses (with last observation carried forward) from Study DIC-301 for DICLEGIS are supportive of an effect on the individual parameters of the number of times vomiting per day alone and number of episodes of retching per day, but not the number of hours of nausea alone (See previous Table 9). The reason for the latter finding on hours of nausea is unclear. The 1976 revised formulation of Bendectin® (10 mg doxylamine succinate and 10 mg pyridoxine hydrochloride, as in DICLEGIS) was statistically significantly different from placebo in reducing nausea.

Per the Sponsor's analysis, there was a statistically significant difference in mean change from baseline to Day 15 (± 1 day) for DICLEGIS vs. placebo in a Global Assessment of Well Being score (data not shown). No other secondary endpoint assessment was reported as statistically significantly different. One *post-hoc* analysis of "the request to continue study medication" revealed 49.9% of DICLEGIS-treated subjects vs. 32.8% of placebo treated subjects (p=0.009) requested continuation of study medications at the completion of Study DIC-301. This *post-hoc* analysis supports that the primary efficacy endpoint analysis is clinically meaningful.

This reviewer offers one final comment regarding the clinical significance of the primary endpoint in the years since the voluntary withdrawal of Bendectin® (1983 – present) obstetricians continue to recommend that their patients suffering from nausea and vomiting of pregnancy use a combination of doxylamine (10 mg as ½ of a Unisom tablet) and pyridoxine with over-the-counter preparations for therapy. The professional society that

issues guidelines for the clinical practice of obstetrics and gynecology, the American College of Obstetricians and Gynecologists [(ACOG) in Practice Bulletin, Nausea and Vomiting of Pregnancy, Number 52, April 2004], recommends based on good and consistent scientific evidence (level A), that "treatment of nausea and vomiting of pregnancy with vitamin B6 or B6 plus doxylamine is safe and effective and should be considered first-line pharmacotherapy."

8. Safety

Support for the safety of DICLEGIS is obtained from the data in the application from four Phase 1 studies, the Phase 3 Study DIC-301 and the 120-Day Safety Update (received October 5, 2012). The Agency's August 9, 1999 determination of safety of the RLD, Bendectin® (10 mg doxylamine succinate and 10 mg pyridoxine HCL) and safety data for Diclectin (10 mg doxylamine succinate and 10 mg pyridoxine HCL), manufactured by Duchesnay Inc. in Canada, are considered supportive only.

No maternal deaths were noted during the DICLEGIS development programs. Serious adverse events were collected in Study DIC-301 beginning with the first dose until 30 days after discontinuation or beginning of compassionate use of DICLEGIS. There were a total of 9 serious adverse events (SAEs) reported including four in DICLEGIS-treated subjects (3.0%) and five in placebo (3.9%). There was one case of a bile duct stone in placebo, assessed as not related to study drug. Remaining SAEs in both treatment groups were related to fetal outcomes. There was one case of missed abortion in DICLEGIS (0.8%), assessed as unlikely related to study drug and one case in placebo (0.8%), assessed as not related. There were two cases of spontaneous abortion in DICLEGIS (1.5%), both assessed as not related, and one case in placebo (0.8%), assessed as not related to study drug. There was one case of a fetal disorder (premature rupture of membranes approximately 16 weeks of gestation) in placebo (0.8%), assessed as not related to study drug, and one intrauterine death with possible cystic hygroma at 9.6 weeks in DICLEGIS (0.8%), assessed as not related to study drug. Four (4) of the 9 reported serious adverse events occurred during Study DIC-301 (one case of missed abortion in DICLEGIS, one case of spontaneous abortion in DICLEGIS, one case of spontaneous abortion in placebo and the case of bile duct stone in placebo) and resulted in discontinuation from this study. Three cases occurred during compassionate use of DICLEGIS outside of the window of study and two cases occurred after study drug administration, but within the 30 day safety assessment period in subjects who had taken placebo.

Eleven subjects discontinued study drug in Study DIC-301 due to an adverse event. Four of these were serious and are accounted for in the previous paragraph. The remaining 7 subjects (4 in the DICLEGIS group and 3 in placebo) discontinued because of the non-serious adverse events of somnolence, syncope, dizziness and abdominal pain. These cases were noted as definitely related (one case) probably related (one case) and possibly related (5 cases) to study drug. Refer to Dr. van der Vlugt's review for a complete description of these cases.

Treatment-emergent adverse events (TEAEs) were defined as AEs experienced by the subjects that occurred on or after Day 1 (first dose administered) through Day 15 or the

Early Termination Visit. For subjects who continued to receive medication for compassionate use after Day 15, TEAEs were collected for the 30 days following compassionate dispensation of the study drug. The most common TEAEs occurring in Study DIC-301 are listed in Table 11

Table 11 Common Treatment Emergent Adverse Events (≥2 %) in Study DIC-301

Adverse Event System Organ Class - Preferred Term	DICLEGIS N=133 n (%)	Placebo N=128 n (%)
Gastrointestinal Disorders	**23 (17.3)**	**22 (17.2)**
- Abdominal pain	5 (3.8)	8 (6.3)
- Abdominal pain upper	3 (2.3)	5 (3.9)
- Diarrhea	4 (3.0)	2 (1.6)
- Dry mouth	4 (3.0)	1 (0.8)
- Dyspepsia	5 (3.8)	2 (1.6)
- Nausea	2 (1.5)	3 (2.3)
General Disorder and Administration Site Cond.	**13 (9.8)**	**12 (9.4)**
- Fatigue	9 (6.8)	8 (6.3)
Infections and Infestations	**8 (6.0)**	**10 (7.8)**
- Nasopharyngitis	3 (2.3)	5 (3.9)
Musculoskeletal and Connective Tissue Disorders	**11 (8.3)**	**4 (3.1)**
- Back pain	7 (5.3)	4 (3.1)
- Pain in extremity	4 (3.0)	0 (0.0)
Nervous System Disorder	**42 (31.6)**	**37 (28.9)**
- Dizziness	8 (6.0)	8 (6.3)
- Headache	17 (12.8)	20 (15.6)
- Somnolence	19 (14.3)	15 (11.7)
Reproductive System and Breast Disorders	**8 (6.0)**	**6 (4.7)**
- Vaginal hemorrhage	5 (3.8)	3 (2.3)
Respiratory, Thoracic and Mediastinal Disorders	**6 (4.5)**	**3 (2.3)**
- Cough	3 (2.3)	1 (0.8)

Source: Adapted from MOR Table 23, and NDA 21876, Clinical Study Report for DIC-301, Table 14.52 in 14.3 Safety Summary Tables and Figures, page 64 of 84..

The percentage of subjects experiencing common TEAEs (≥2%) is not substantially different between DICLEGIS and placebo. A 1982 Bendectin® label notes, "The adverse reactions that may occur are those of the individual ingredients. Doxylamine succinate may cause drowsiness, vertigo, nervousness, epigastric pain, headaches, palpitations, diarrhea, disorientation, or irritability. Pyridoxine hydrochloride is a vitamin that is generally recognized as having no adverse effects." Drowsiness or somnolence the first listed adverse reaction occurs in 14.3% of DICLEGIS-treated subjects vs. 11.7% of placebo subjects in Study DIC-301 for DICLEGIS. From the clinical review related to the 1976 approval of Bendectin, 5.7% of Bendectin subjects reported somnolence vs. 3.0% of placebo.

The Sponsor provided six Diclectin® PSURs in the application that cover the period 1983 to January 31, 2012. Post-marketing safety data for Diclectin® for the period February 1, 2012 to September 1, 2012 is included in the 120-Day Safety Update Report. Based on the information available in the six PSURs, Diclectin® has been used by over an estimated (b) (4) women in Canada. The six PSURs submitted in the application were reviewed in their entirety by Dr. van der Vlugt. She notes 15 cumulative cases under the System Organ Class (SOC) of: "Congenital, Familial and Genetic Disorders" and 8 cumulative cases under the SOC of "Pregnancy, Puerperium and Perinatal Conditions."

Post-marketing safety data for the Canadian-marketed Diclectin® for the period February 1, 2012 to September 1, 2012, as included in the 120-Day Safety Update Report, notes two serious and unexpected adverse drug reactions both related to drug ineffectiveness. There were 16 non-serious adverse drug reaction cases reported (four unexpected and 11 expected). In an ongoing study (Study 0020010091 - Part 2) to determine the effects of nausea and vomiting of pregnancy and its treatment with Diclectin® on early child neurodevelopment (45 children of mothers with nausea and vomiting of pregnancy and previous Diclectin® use during the involved pregnancy, 47 children of mothers with nausea and vomiting of pregnancy and no Diclectin® use during the involved pregnancy, and 29 children whose mothers did not have nausea and vomiting during the involved pregnancy), no adverse drug reactions were reported between February 1, 2012 and September 1, 2012. A 2001 publication from Study 0020010091 - Part I study notes that 32% of subjects (31/97) receiving a supradose of Diclectin® (5-12 tablets per day) reported sleepiness, tiredness and/or drowsiness compared with 35% (42/122) among the standard dose recipients. Two cases of major malformations [(1.6%), which is within the background rate of 2% seen in the general population] were noted in the group receiving standard dosing of Diclectin®. The reader is referred to Dr. van der Vlugt's review for a complete discussion of post marketing information on Diclectin®.

Bendectin® has been the subject of many epidemiologic studies (case-control and cohort) and FDA reviews intended to determine whether or not Bendectin is associated with teratogenicity. Overall, a review of the results of these studies leads to the conclusion that the existing data do not demonstrate an association between Bendectin® use and birth defects.

In support of the safety of the combination of 10 mg doxylamine and 10 mg pyridoxine, with or without 10 mg dicyclomine HCl, given during the first trimester of pregnancy, the Sponsor provided two separate meta-analyses in the application. McKeigue et al. (1994) conducted a meta-analysis of 16 cohort and 11 case-control studies published between 1963 and 1991. No increased risk for malformations was found in first trimester exposures to doxylamine and pyridoxine, with or without dicyclomine hydrochloride.[1]

The second meta-analysis, conducted by Einarson et al. (1988) incorporated 12 cohort and 5 case control studies conducted between 1963 and 1985. No statistically significant relationships were found between first trimester use of the combination doxylamine and pyridoxine, with or without dicyclomine HCl, and fetal abnormalities.[2]

One other published literature report on the human reproductive and teratogenic effects of Bendectin® was instructive. Brent (1995), in a publication which addresses the Bendectin® litigation ongoing at that time, reviewed the published literature including epidemiologic studies, animal studies, in vitro studies, basic science articles, review articles, meta-analyses, and case reports. His publication presents analyses of epidemiologic studies,

[1] McKeigue PM et al. Bendectin and birth defects: I. A meta-analysis of the epidemiologic studies. Teratology. 1994;50:27-37.
[2] Einarson TR et al. A method for meta-analysis of epidemiological studies. Drug Intell Clin Pharm. 1988; 22:8130824.

secular trend analysis, animal studies, dose-response relationships, and biologic plausibility. The publication concludes that "therapeutic use of Bendectin® has no measurable teratogenic effect."[3]

One fatal case of overdose of doxylamine alone is reported in the 120-Day Safety Update Report dated (b) (6). A 13 month old girl with no previous history of disease was prescribed an OTC drug (Sedaplus® Saft) containing 250 mg doxylamine/100 mL by her private doctor for teething problems. She was found lifeless the day after receiving 3.5 ml of the OTC product. An autopsy reported "aspiration of stomach contents" to be the cause of death. Per the Sponsor, other fatalities have been reported from doxylamine overdose. These overdose cases are characterized by coma, grand mal seizure and cardiorespiratory arrest. In particular, children appear to be at high risk for cardiorespiratory arrest. "A toxic dose for children of more than 1.8 mg/kg has been reported." Information on children and the risk of overdose is proposed for inclusion in labeling, section 8 USE IN SPECIFIC POPULATIONS, subsection 8.4 Pediatric Use. Two postmarketing overdose reports have been reported to the Canada Vigilance Program for products containing doxylamine. However the dosage ingested and the blood concentrations of doxylamine were not reported. In the medical literature, the lethal dose of doxylamine in human is reported as 25-250 mg/kg body weight.

The application does not include any information on (b) (4). The following information is provided in the Diclectin® Product Monograph, however, regarding (b) (4): (b) (4) This information is also provided in the proposed DICLEGIS labeling. The Sponsor has not proposed language to explain what is meant by (b) (4) The Sponsor was requested to provide recommendations (as well as data to support the recommendations) for labeling. If data supporting the Sponsor's recommendation are not provided, we will recommend removal of instructions (b) (4) from labeling.

I concur with Dr. van der Vlugt that the safety profile and the benefit:risk ratio for DICLEGIS is acceptable. There is no compelling evidence presented to date that there is an increased risk for teratogenicity with the use of the combination of 10 mg doxylamine succinate and 10 mg pyridoxine hydrochloride.

9. Advisory Committee Meeting

Advisory Committee input was not sought for the decision on this NDA.

10. Pediatrics

A full pediatric waiver for ages 0-11 years 11 months was requested by Duchesnay with the rationale that the condition of pregnancy does not apply to premenarchal girls which is generally inclusive of these ages. DRUP concurs with the Sponsor's rationale, but the correct designation is a partial waiver when not all pediatric age groups are covered.

[3] Brent RL. Bendectin: review of the medical literature of a comprehensively studied human nonteratogen and the most prevalent tortogen-litigen. Reprod Toxical. 1995 Jul-Aug:9(4):337-334.

Duchesnay requested a deferment for age range 12-17 years 11 months and proposed a study in non-pregnant adolescent girls to satisfy the Pediatric plan. Duchesnay's requests were discussed at the March 06, 2013 Pediatric Research Committee (PeRC)/Pediatric Research Equity Act (PREA) subcommittee meeting. The committee determined that waiver for premenarchal girls, ages 0-11years 11 months is appropriate. The committee agreed with the deferral for adolescent pregnant girls, ages 12-17 years 11 months. A PREA postmarketing requirement for a study to assess efficacy and safety will be a part of the decisional letter.

11. Other Relevant Regulatory Issues

Inspections by the Office of Scientific Investigations (OSI)

The Division requested an inspection by the OSI for the following clinical sites for the single Phase 3 Study DIC-301:

1. Site # 20 for Study DIC-301; Stanley "Steve" Caritis, MD, Magee-Women's Hospital, Pittsburg, PA 15213.
2. Site # 11 for Study DIC-301; Gary Hankins, MD, University of Texas Medical Branch (UTMB) OB Regional Maternal Clinic, Pasadena, TX 77502.
3. Site # 30 for Study DIC-301; Menachen Miodovick, MD, Washington Hospital Center, Washington, DC 20010.

Ten (10) of the 13 cartons used to store the research records for Site 30 (storage facility - (b) (4)) were destroyed in a roof collapse in (b) (4). In that same accident, all records (CRFs, ICFs, etc.) for Site # 31 (Dr. Menachen Miodovick, Georgetown Medical University) were also destroyed. Site 31 was not included in the Division's request for OSI inspection, but was included by OSI as part of their verification process. In light of the difficulties for complete inspection of Site 30, the Division requested inspection of Site # 10, Investigator - Gary Hankins, MD; UTMB Regional Maternal & Child Health Program Clinic, Galveston, TX 77502.

On February 15, 2013, a Form FDA 483 was issued at the conclusion of the inspection of Site # 20 (Dr. Steve Caritis) because of:

1. failure to complete one or more protocol procedures in 7 of 31 subject records reviewed Example include: the completion visit for Subject 20-013 was completed 3 days outside the established window; ultrasound performed for Subject 20-0232 was completed outside the established window: Day 1 hematology for Subject 20-038 and a urinalysis for Subject 20-025 were not completed; Day 4 blood sampling was not performed for Subject 20-052; Day 15 final study completion visit for Subject 20-052 occurred outside the established window; there was no documentation of the informed consent process for Subject 20-004; and physical exams were not completed by the authorized study personnel for Subjects 20-037 and 20-032.

   Dr. Caritis agreed with the findings.

2. Failure to prepare or maintain adequate and accurate case histories with respect to observations and data pertinent to the investigation.
    - Four (4) subjects reported active history of migraines (Subjects 20-009, 20-023, 20-025, and 20-032). Study records did not rule-out migraines as cause of NVP

      Dr. Caritis disagreed with this assessment, stating that women with nausea and vomiting associated with migraines have a different clinical presentation of their symptoms than women with NVP.
    - Absence of recorded concomitant medication use within 30 days prior to baseline, for example, B6/Unisom use prescribed by private MD prior to study enrollment (Subjects 20-006, 20-007, and 20-032 with no documentation to confirm that the subject did or did not take medication), Compazine prescribed prior to study (Subject 20-036 without documentation of use), and Reglan anti-emetic use (Subject 20-071).

      Dr. Caritis agreed with these findings
    - Twenty-nine (29) of the 31 study records did not document if the subjects tried conservative therapies prior to enrollment.

      Dr. Caritis agreed that there was no documentation that subjects tried conservative therapies prior to enrollment

Dr. Caritas responded to the items listed on the Form FDA in a letter dated January 31, 2013 and outlined his commitment and specific actions for improving study practice to prevent such observations from occurring in future studies. Per the OSI, the audit of Site # 20 "did not indicate serious deviations/findings that would impact the validity or reliability of the submitted data. However, the review division may wish to consider the impact, if any, regarding the fact that 29 of 31 study records reviewed do not document if the subjects tried conservative therapies prior to enrollment and the impact of the potential use of B6/Unisom, Compazine, and Reglan in the subjects listed above. The other deviations noted appear to be isolated in nature and are unlikely to significantly impact safety of efficacy analyses." "With the exception of issues noted above, the study appears to have been conducted adequately, and the data generated by this site appear acceptable in support of the respective indication." Even though the primary outcome measure was change from baseline in the PUQE score and all subjects needed a PUQE minimum of 6 to be randomized, this reviewer remains concerned about the failure of Dr. Caritas to document that the subjects met this criteria of "failing conservative management". The indication is narrowly focused to this group of pregnant women, as it is recognized by ACOG and others that pharmacologic agents should not be first line therapy. A *post-hoc* protocol violation analyses that excluded women who had no documentation of previous attempts to manage symptoms with conservative measures demonstrated that there was still a statistically significant treatment difference in the improvement in the PUQE score for DICLEGIS vs. placebo.

Per OSI, data from Dr. Dr. Gary Hankins Sites # 10 (Galveston, TX) and Site # 11 (Pasadena, TX) are acceptable. The audit did not indicate serious deviations/findings that would impact the validity or reliability of the submitted data.

There have been no inspection summary addendum reports generated for Site 20, 10 or 11, as of the date of this review.

Financial Disclosure

The Sponsor certified on FDA Form 3454 (10/09), dated June 8, 2012, that they "have not entered into any financial arrangement with the listed clinical investigators" "whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a)." The Sponsor also certified "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." Further, the Sponsor certified "that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f)." The 4 Phase 1 principle investigators in Canada and the 4 Phase 3 principle investigators in the U.S. are included.

Tradename Review

In a review entered and signed on September 20, 2012, the Division of Medication Error Prevention and Analysis (DMEPA) concluded that the tradename "DICLEGIS" was acceptable. The Sponsor was notified of the acceptability of the name in a regulatory letter dated October 09, 2012. The proprietary name, DICLEGIS, was reevaluated on April 04, 2013. The reviewer found no vulnerabilities that would result in medication errors with any newly approved names since the last review. DMEPA concluded that the name DICLEGIS was acceptable.

12. Labeling

The Physician's Insert (PI) agreed to by the Agency reviewers [all review disciplines and Safety Endpoints and Labeling Development Team (SEALD)] and the Sponsor is attached to this Review.

The Patient Package Insert (PPI) crafted by the Division of Medical Policy Programs (DMPP), DMEPA and DRUP is attached to this review.

ONDQA and DMEPA accepted the revised container and carton labeling received from the Sponsor on February 27, 2013.

13. Conclusions/Recommendations/Risk Benefit Assessment

I concur with the Biopharmaceutics, Chemistry, Nonclinical Pharmacology, Clinical Pharmacology, Clinical and Statistical Reviewers that NDA 21876 for DICLEGIS can receive an Approval action.

A Pediatric Research Equity Act (PREA) postmarketing requirement to conduct a study to support the efficacy and safety of DICLEGIS in postmenarchal girls, ages 12-17 years 11 months is recommended as part of the Approval letter should the application be approved.

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

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

/s/

SHELLEY R SLAUGHTER
04/08/2013