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APPLICATION NUMBER:

021876Orig1s000

SUMMARY REVIEW

Summary Review for Regulatory Action

Date	(electronic stamp)
From	Hylton V. Joffe, M.D., M.M.Sc.
Subject	Division Director Summary Review
NDA/BLA #	021876
Applicant Name	Duchesnay, Inc.
Date of Submission	June 8, 2012
PDUFA Goal Date	April 8, 2013
Proprietary Name / Established (USAN) Name	Diclegis (doxylamine succinate and pyridoxine hydrochloride) delayed-release tablets
Dosage Forms / Strength	10 mg of doxylamine succinate, USP and 10 mg of pyridoxine hydrochloride, USP
Proposed Indication(s)	Treatment of nausea and vomiting of pregnancy in women who do not respond to conservative management
Action	<i>Approval</i>

Material Reviewed/Consulted	Names of discipline reviewers
OND Action Package, including:	
Medical Officer Review	Theresa van der Vlugt, MD
Statistical Review	Kate Dwyer, Ph.D. and Mahboob Sobhan, Ph.D.
Pharmacology Toxicology Review	Kimberly Hatfield, PhD and Alexander Jordan, PhD
CMC Review	Gene Holbert, PhD and Moo Jhong Rhee, PhD
Biopharmaceutics Review	Karen Riviere, PhD and Angelica Dorantes, PhD
Clinical Pharmacology Reviews	Sayed Al Habet, RPh, PhD, Myong-Jin Kim, PharmD, LaiMing Lee, PhD and CAPT E Dennis Bashaw, PharmD
OSI	Cynthia Kleppinger, MD and Janice Pohlman, MD, MPH
CDTL Review	Shelley Slaughter, MD, PhD
DMEPA	Manizheh Siahpoushan, PharmD and James Schlick, RPh, MBA
DMPP	Sharon Williams, RN, BSN, MSN, Robin Duer, RN, BSN, MBA and LaShawn Griffiths, MSHS-PH, BSN, RN
OPDP	Carrie Newcomer, PharmD
SEALD	Abimbola Adebowale, PhD and Laurie Burke, MD

OND=Office of New Drugs
 CDTL=Cross-Discipline Team Leader
 DMEPA=Division of Medication Error Prevention and Analysis
 DMPP=Division of Medical Policy Programs
 OPDP=Office of Prescription Drug Promotion
 OSI=Office of Scientific Investigations
 SEALD=Study Endpoints and Labeling Development

Signatory Authority Review

1. Introduction

Duchesnay, Inc. has submitted this 505(b)(2) new drug application (NDA) for Diclegis delayed-release tablets (originally proposed tradename, (b) (4)). The Applicant is seeking an indication for the treatment of nausea and vomiting of pregnancy after conservative management has failed. Diclegis is a fixed-dose combination tablet that contains 10 mg of doxylamine succinate (a sedating antihistamine) and 10 mg of pyridoxine hydrochloride (a vitamin B₆ analog). If approved, this will be the only FDA-approved treatment for nausea and vomiting of pregnancy.

This document serves as the decisional memorandum for the application.

2. Background

Doxylamine succinate and pyridoxine hydrochloride are marketed separately as non-prescription products. Examples include the Unisom sleep aid, which contains 25 mg of doxylamine succinate taken 30 minutes prior to sleep and Nyquil, which contains 12.5 mg of doxylamine succinate taken up to four times each day. Pyridoxine hydrochloride is available in 25-500 mg dosage strengths.

Currently doxylamine succinate and pyridoxine hydrochloride are used off-label to treat nausea and vomiting of pregnancy. Compounding pharmacies prepare the combination or patients are instructed to take pyridoxine and one-half of a 25 mg Unisom sleep aid. Such use is recommended in the 2004 clinical management guidelines issued by the American College of Obstetricians and Gynecologists. As explained below, there is a long regulatory history that forms the basis for using these products for the treatment of nausea and vomiting of pregnancy. This regulatory history is summarized below. See the clinical review by Dr. Theresa van der Vlugt and the Cross-Discipline Team Leader (CDTL) review by Dr. Shelley Slaughter for further details.

In the 1950s, the FDA approved Bendectin for the treatment of nausea and vomiting of pregnancy. The original formulation contained 10 mg of doxylamine succinate, 10 mg of pyridoxine hydrochloride and 10 mg of dicyclomine hydrochloride. In the 1970s, Bendectin was reformulated without dicyclomine hydrochloride because the DESI (Drug Efficacy Study Implementation) review found dicyclomine to be ineffective for treating nausea and vomiting of pregnancy. There were subsequently several hundred lawsuits alleging that Bendectin caused birth defects, particularly limb defects, which led the company to voluntarily stop marketing Bendectin in 1983, citing financial burden of litigation and adverse publicity.

Two citizen petitions – one submitted in 1992 and another submitted in 1997 – requested that FDA determine whether Bendectin was indeed withdrawn from sale for reasons of safety or effectiveness. FDA reviewed all available data and published a Federal Register Notice in 1999 confirming that Bendectin was not withdrawn from sale for reasons of safety or effectiveness (for further details see <http://www.gpo.gov/fdsys/pkg/FR-1999-08-09/pdf/99-20362.pdf>). Bendectin was relisted in the “Discontinued Drug Products List” section of the Orange book, permitting approval of an abbreviated new drug application (ANDA).

[REDACTED] (b) (4)

The Applicant [REDACTED] (b) (4) filed a 505(b)(2) NDA in 2005, proposing to rely on FDA’s findings of safety and/or effectiveness for Bendectin.

However, FDA refused to file this 505(b)(2) NDA citing lack of a scientific bridge between Diclegis and Bendectin. As mentioned previously, Bendectin was removed voluntarily from the market in 1983 so there were no tablets available for use in a bioequivalence study. In addition, the Applicant was not able to locate pharmacokinetic data for doxylamine and pyridoxine following administration of Bendectin. The Applicant chose to conduct a phase 3 trial to provide new clinical data to support Diclegis for the proposed indication. The FDA and the Applicant reached agreement on the design of this phase 3 trial, which is summarized in Sections 7 and 8 of this memorandum.

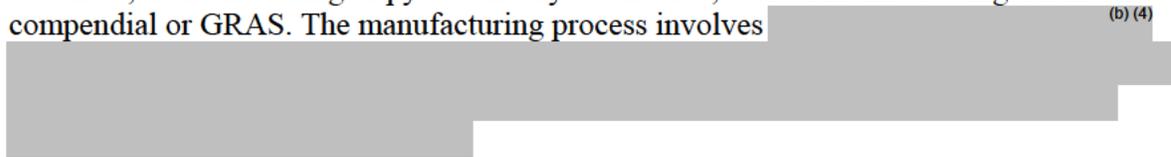
In June 2012, the Applicant resubmitted a 505(b)(2) NDA that included this new phase 3 study, a new single-dose and multiple dose pharmacokinetic study and a new food effect study. In this submission, the Applicant again proposed to rely on FDA’s findings of safety and/or effectiveness for Bendectin. Although these new studies in-and-of-themselves still cannot scientifically bridge Diclegis to Bendectin, we have determined that other available data provide a sufficient scientific bridge between the two products to support a 505(b)(2) NDA. This is important because it allows the Applicant to abbreviate its nonclinical pharmacology/toxicology program and rely on clinical data that confirm no association with teratogenicity.

The scientific basis supporting a bridge to Bendectin is summarized in two clinical pharmacology review addenda, one by Dr. Sayed Al Habet and the other by CAPT E. Dennis Bashaw, Director, Division of Clinical Pharmacology-3. The scientific bridge is reasonable and takes into account the totality of available data, including physical chemistry (both doxylamine succinate and pyridoxine hydrochloride are highly soluble), the fact that Bendectin was not designated as a bioproblem drug during the DESI review and the available pharmacokinetic data for Diclegis, doxylamine succinate and pyridoxine hydrochloride [REDACTED] (b) (4)

[REDACTED]

3. CMC

Diclegis delayed-release tablets contain two active drug substances – 10 mg of doxylamine succinate, USP and 10 mg of pyridoxine hydrochloride, USP. The inactive ingredients are compendial or GRAS. The manufacturing process involves (b) (4)



The Chemistry/Manufacturing/Controls (CMC) reviewers have concluded that the NDA contains sufficient information to assure the identity, strength, purity and quality of the drug product. All Drug Master Files were found to be adequate. In addition, the Office of Compliance has issued an “Acceptable” recommendation for all facilities involved in the manufacturing and testing of the drug substance and drug product.

The CMC reviewers and the Applicant have agreed to a 24-month expiry date for the tablets based on available stability data. In addition, the CMC reviewers are granting the Applicant’s request for a categorical exclusion from environmental assessment, because this application does not increase the use of the active moiety.

All outstanding CMC issues, including labeling, have been adequately addressed. The CMC reviewers recommend approval. See the reviews by Drs. Gene Holbert and Donna Christner for further details.

4. Nonclinical Pharmacology/Toxicology

The Nonclinical Pharmacology/Toxicology reviewers recommend approval of the NDA.

The NDA does not contain new nonclinical pharmacology/toxicology studies. Instead, the Applicant has submitted literature and is relying on FDA’s nonclinical findings pertaining to Bendectin through the 505(b)(2) approval pathway. The findings are briefly summarized below. See the review by Dr. Kimberly Hatfield for details.

Note that there are no pharmacokinetic data in animals for the combination of doxylamine and pyridoxine. Therefore, it is not possible to compare the extent of exposure (AUC) in animals to that achieved in humans. However, as explained below, animal toxicity from doxylamine and pyridoxine occur at many dose multiples above the proposed clinical dose and there is vast clinical experience with these products to conclude that Diclegis is expected to have minimal toxicity in humans.

With regard to general toxicity, repeat-dose studies showed large safety margins for doxylamine, with toxicity occurring in mice at ~180 times the proposed clinical dose and toxicity occurring in rats at ~240 times the proposed clinical dose. The only available repeat-

dose toxicity study for pyridoxine showed a large safety margin, with toxicity occurring in dogs at ~120 times the proposed clinical dose.

FDA has previously determined that doxylamine is not likely to have human carcinogenic potential. Pyridoxine, a vitamin B₆ analog, is not expected to have carcinogenic potential.

Reproductive toxicity in rats given doxylamine occurred with co-existing maternal toxicity at doses 48 times the highest proposed clinical dose. When Bendectin was administered to rats, there was a 24-fold safety margin for maternal and fetal toxicity based on the No Observed Adverse Effect Level (NOAEL). Observations with higher doses (~100-times the clinical dose) included reduced fetal weight, reduced fetal ossification of limbs, increased resorptions, and increased malformations (short 13th rib), although many of these findings were attributed to co-existing maternal toxicity.

When pregnant monkeys were treated with doxylamine succinate and pyridoxine hydrochloride during fetal organogenesis, there were no observed malformations at birth, and no evidence of embryo, fetal or maternal toxicity at doses up to ~3 times the highest proposed clinical dose based on body surface area. Another study in pregnant cynomolgus and rhesus monkeys and baboons, showed ventricular septal defects in the preterm fetuses but no ventricular septal defects in infant monkeys at term. Doses used in this study were 0.5-20 times higher than the clinical dose based on body surface area, with no relationship between dose and incidence of ventricular septal defect. These findings will be labeled but Diclegis will be listed as Pregnancy Category A based on the extensive clinical data that have not confirmed a human risk of teratogenicity with doxylamine and pyridoxine.

5. Clinical Pharmacology/Biopharmaceutics

The clinical pharmacology reviewers find the NDA acceptable. See the reviews by Dr. Sayed Al Habet for further details.

The NDA contains a pivotal pharmacokinetic study (Study 70381) and a single-dose food-effect study (Study 70294). Both studies used the to-be-marketed formulation of Diclegis.

Study 70281 evaluated the single-dose and multiple-dose pharmacokinetics of Diclegis in non-pregnant, healthy women. The single-dose phase involved administration of two Diclegis tablets at bedtime on Days 1 and 2. The multiple-dose phase involved administration of four Diclegis tablets daily (one in the morning, one mid-afternoon and two at bedtime) on Days 3-18. The timing of administration over the course of the day is consistent with how Diclegis was dosed in the phase 3 trial. Tablets were taken on an empty stomach (subjects fasted for at least 2 hours prior to each dose). This study showed that doxylamine accumulates with multiple-dose administration: mean C_{max} increased about 2-fold and mean AUC increased about 2-4-fold. There was no impact on T_{max}. Steady state was achieved after 9 days. The main adverse effect of doxylamine succinate is somnolence, which could conceivably worsen with drug accumulation, although the overall extent of somnolence in the 2-week phase 3 trial was not substantially increased with Diclegis compared to placebo (see Section 8). Dr. Al

Habet notes that the pharmacokinetics of pyridoxine and its metabolites (pyridoxal, pyridoxal 5'-phosphate, pyridoxamine and pyridoxamine 5'-phosphate) is complex due to variability in the data and low concentrations. It appears that pyridoxine does not appreciably accumulate (which is consistent with its short half-life of 30 minutes) but its active metabolites do. No safety concerns are anticipated for the pyridoxine component, which is often taken at doses considerably higher than that found in Diclegis.

The food effect study (70294) evaluated the impact of a standard high-fat, high-calorie meal on the pharmacokinetics of Diclegis in healthy, non-pregnant women. Food delayed the T_{max} for doxylamine by about 7 hours and lowered its C_{max} without affecting the overall extent of absorption (AUC). Similarly, food delayed the T_{max} and lowered the C_{max} for pyridoxine and most of its metabolites. Food also lowered the AUC for pyridoxine and some of its metabolites, although these AUC findings may be limited due to variability in the data. Based on the overall findings, the clinical pharmacology reviewers recommend that Diclegis be taken on an empty stomach, if feasible.

The Biopharmaceutics reviewers have determined that the Applicant's proposed dissolution method and revised dissolution acceptance criteria are acceptable and recommend approval of the NDA. See the review by Dr. Kareen Riviere for details.

6. Clinical Microbiology

Not applicable.

7. Clinical/Statistical-Efficacy

The NDA contains a single phase 3 clinical trial (Study DIC-301). This section briefly summarizes the study design and key efficacy results. See the clinical review by Dr. van der Vlugt, the statistical review by Dr. Kate Dwyer and the CDTL review by Dr. Slaughter for additional details.

Study DIC-301 was a double-blind trial conducted across 6 centers that randomized 280 pregnant women with nausea and vomiting of pregnancy to 14 days of treatment with either Diclegis (the to-be-marketed formulation) or placebo. Participants were to be at least 18 years old with a confirmed singleton gestation of 7-14 weeks and were to have failed non-pharmacologic treatment for nausea and vomiting.

Patients took two tablets of study medication at bedtime on Day 1. If nausea and vomiting was controlled on Day 2, patients continued taking two tablets daily at bedtime. However, if symptoms had persisted into the afternoon of Day 2, patients were to take 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 controlled symptoms on Day 4, the patient was to continue taking three tablets daily. Otherwise, the patient was instructed to take four

tablets starting on Day 4 (one tablet in the morning, one tablet mid-afternoon and two tablets at bedtime).

During the treatment period, about 20% of Diclegis-treated patients remained on 2 tablets daily, 20% required 3 tablets daily and 60% required 4 tablets daily.

The agreed-upon primary efficacy endpoint was the change from baseline in the Pregnancy Unique Quantification of Emesis (PUQE) score at Day 15. Drs. van der Vlugt and Slaughter explain the rationale for using the PUQE score in their reviews. The PUQE score is a composite endpoint that captures the duration of nausea during the preceding 24 hours, the number of times the patient vomited during the preceding 24 hours, and the number of times the patient had retching without vomiting during the preceding 24 hours. Table 1 shows how each of the components of the composite endpoint were scored. These data were captured on diaries that patients completed every morning. The scores for the individual components of the composite endpoint were added to yield an overall score that ranged from 3 (no symptoms) to 15 (most severe). Patients were to have a PUQE score ≥ 6 at enrollment to be eligible for the trial.

**Table 1. Scoring system for each component of the PUQE score
(Based on symptoms during the preceding 24 hours)**

	Not at all (1)	1 hour or less (2)	2-3 hours (3)	4-6 hours (4)	More than 6 hours (5)
Duration of nausea					
Vomiting	7 or more times (5)	5-6 (4)	3-4 (3)	1-2 (2)	I did not throw up (1)
Retching/dry heaves	No time (1)	1-2 (2)	3-4 (3)	5-6 (4)	7 or more (5)

The primary efficacy analysis was conducted on a modified intent-to-treat population (randomized patients who took at least one dose of study medication and had at least one post-baseline PUQE measurement) with last-observation-carried-forward for missing data.

The study participants had a mean age of ~25 years. About 60% were Caucasian and 38% were black. At enrollment, the median gestational age was 9 weeks and the mean PUQE score was 9.

About 80% of Diclegis-treated patients and 65% of placebo-treated patients completed the trial, with this difference in completion rates driven by withdrawal of consent (6% with Diclegis vs. 13% with placebo) and loss-to-follow-up (5% with Diclegis vs. 14% with placebo).

Table 2 summarizes the key efficacy findings. Diclegis results in a statistically significant improvement in symptoms of nausea and vomiting compared to placebo, as assessed using the PUQE score. However, the treatment effect is small. The individual components of the PUQE score all have favorable point estimates, with two of the three components reaching nominal

statistical significance. The consistency of point estimates for each component is reassuring; there is no requirement that each component reach statistical significance when evaluating a composite endpoint (usually, there is not sufficient power to show statistical significance on components of a composite endpoint).

The statistical reviewer summarized the findings from four sensitivity analyses – two prespecified analyses (using a per protocol population and a completer population) and two *post-hoc* analyses (using a revised completer population that did not exclude protocol violators and a mixed-model repeated measures analysis). See Dr. Dwyer’s review for details. Here I focus on the prespecified sensitivity analyses. The treatment effect for the prespecified per protocol population (n=182 or 70% of the treated patients) was -0.5 (95% confidence interval -1.0, -0); p=0.04. The treatment effect for the completer population (n=176 or 67% of treated patients) was -0.4 (95% confidence interval -0.9, 0.1); p=0.15. These results, which are based on a smaller subset of randomized patients and numerically favor Diclegis, are supportive of the primary efficacy endpoint.

The Combination Rule states that “Two or more drugs may be combined in a single dosage form when each component makes a contribution to the claimed effects...” Study DIC-301 did not include monotherapy arms, precluding an ability to assess the contribution of each component to the claimed effects of the combination. However, the DESI review already determined that there is sufficient evidence to support the combination of doxylamine succinate and pyridoxine hydrochloride for the treatment of nausea and vomiting of pregnancy. See the reviews by Drs. van der Vlugt and Slaughter, which summarize the factorial clinical trial reviewed by the FDA in the 1970s that included monotherapy treatment arms and formed the basis for approval of reformulated Bendectin containing doxylamine succinate and pyridoxine hydrochloride.

Table 2. Efficacy Results			
(Adapted from Table 6 in Dr. Dwyer’s statistical review)			
	Baseline Mean ± SD	Change from Baseline Mean	Treatment Difference (95% CI) p-value
PUQE score – composite primary endpoint			
Diclectin (n=131)	9.0 ± 2.1	-4.7	-0.7 (-1.3, -0.2)
Placebo (n=125)	8.8 ± 2.1	-3.9	p<0.01
Individual components of the PUQE score			
Duration of nausea (see scoring in Table 1)			
Diclectin (n=131)	4.0 ± 1.0	-2.4	-0.2 (-0.5, 0.1)
Placebo (n=125)	4.1 ± 0.9	-2.1	p=0.13
Vomiting episodes (see scoring in Table 1)			
Diclectin (n=131)	2.2 ± 1.2	-1.0	-0.2 (-0.4, -0.1)
Placebo (n=125)	2.1 ± 1.2	-0.7	p<0.01
Retching episodes (see scoring in Table 1)			
Diclectin (n=131)	2.7 ± 1.1	-1.4	-0.3 (-0.5, -0.1)
Placebo (n=125)	2.6 ± 1.2	-1.1	p<0.01

8. Safety

Drs. van der Vlugt and Slaughter discuss the safety data in detail. Key findings from Study DIC-301 are summarized below:

- There were no maternal deaths
- There was no concerning signal for serious adverse events. Dr. van der Vlugt notes that the treatment groups were similar with regard to serious adverse events related to pregnancy and perinatal outcomes
- There was no concerning signal for discontinuations due to adverse events
- There were no clinically meaningful effects of Diclegis on vital signs or laboratory parameters

In addition, there is no safety signal based on review of available postmarketing safety data for Diclectin (the Canadian version of Diclegis marketed by the Applicant since 1983 that has been used by an estimated (b) (4) women). Dr. van der Vlugt reviewed these data covering the period of 1983 through September 1, 2012. She notes that the reports of fetal malformation occur below the background rate in the general population.

Doxylamine succinate is a sedating antihistamine. Safety concerns with Diclegis are expected to be primarily related to this component. These safety concerns are well known and already labeled for non-prescription products that contain doxylamine succinate as well as for other products containing other sedating antihistamines. In Study DIC-301, somnolence occurred at a higher incidence among Diclegis-treated patients (14.3%) compared to placebo-treated patients (11.7%) although the different completion rates may account for some of this difference. No serious adverse events of somnolence were reported. A total of two Diclegis-treated patients and one placebo-treated patient discontinued due to somnolence, numbers that are too low to draw meaningful conclusions.

The following safety concerns will be incorporated into the Diclegis package insert based on what is already known for doxylamine succinate and sedating antihistamines:

- A Contraindication against coadministration with a monoamine oxidase inhibitor (MAOI) because of the potential for the MAOI to prolong and intensify the anticholinergic effects of the antihistamine
- A Warning and Precaution about avoiding activities requiring complete mental alertness, such as driving or operating heavy machinery until cleared to do so by a healthcare provider
- A Warning and Precaution to avoid concomitant use with alcohol or other central nervous system depressants because of a risk of severe drowsiness
- A Warning and Precaution to use caution in patients who may be susceptible to anticholinergic effects (e.g., those with narrow angle glaucoma, urinary bladder-neck obstruction)

Teratogenicity

As discussed previously, FDA concluded in 1999 that Bendectin is not associated with teratogenicity. A search today in PubMed¹ did not identify new clinical studies published after 1999 that could potentially contradict FDA's determination of safety.

9. Advisory Committee Meeting

This NDA was not taken to advisory committee. We did not identify efficacy or safety issues that needed input from an advisory panel.

10. Pediatrics

This NDA triggers the Pediatric Research Equity Act (PREA). The review team discussed the Applicant's proposed pediatric plan with the Pediatric Review Committee (PeRC). We agree to grant a deferral for children ≥ 12 years old (the NDA is ready for approval and pediatric studies have not yet been conducted). We agree to grant a waiver for children < 12 years old (pregnancy does not apply to premenarchal girls and the number of postmenarchal girls < 12 years old is too small to practically study). (b) (4)

(b) (4) based on discussions with PeRC, we will require the Applicant to (b) (4) conduct a safety and efficacy study in pregnant adolescents. We have reached an agreement on timelines for such a study, which will be included in the Approval letter.

11. Other Relevant Regulatory Issues

Financial Disclosures: Drs. van der Vlugt and Slaughter noted no concerns related to financial disclosures or potential conflicts of interest.

Office of Scientific Investigations: Some regulatory violations were noted at all four sites inspected for Study DIC-301. However, the Clinical Inspection Summary notes that these violations are unlikely to significantly impact primary safety and efficacy analyses. Two noteworthy findings are summarized below. See the review by Dr. Cynthia Kleppinger for details.

- Not all study records reviewed by OSI documented whether patients had tried conservative therapy prior to enrollment. Dr. Slaughter notes that a *post-hoc* analysis that excluded such women still yielded a statistically significant treatment difference.

¹The PubMed search was limited to human studies in English and included the following terms: "Bendectin AND teratogen", "Bendectin AND malformation", "Diclectin and teratogen", "Diclectin and malformation", "doxylamine AND teratogen", "doxylamine AND malformation", "pyridoxine AND teratogen" and "pyridoxine AND malformation"

This is reassuring given that Diclegis will be only indicated for patients who have failed conservative management.

- Site 30 randomized 35 patients into Study DIC-301 (13% of the total number of randomized patients). Complete records were only available for 15 of these 35 patients – the remainder was destroyed when the roof collapsed at the storage facility. In the same incident, all the records for the 19 patients (7%) randomized at Site 31 were destroyed. OSI determined that the available records for review did not indicate serious deviations or findings that would impact validity or reliability of the submitted data. After learning about the missing source documents, OSI expanded inspections to include another site (Site 10), which randomized 40 patients (14%) into Study DIC-301. OSI determined that data from this site are acceptable.

Tradename review: On April 4, 2013, the Division of Medication Error Prevention and Analysis (DMEPA) confirmed that the proposed tradename, Diclegis, is acceptable. See the review by Dr. Manizheh Siahpoushan for details.

There are no other unresolved relevant regulatory issues.

12. Labeling

Key aspects of the physician labeling include the following:

- Compliance with the Physician's Labeling Rule (PLR) format
- Clear dosing instructions that reflect how Diclegis was studied in the clinical trial
- Labeling safety concerns related to doxylamine (e.g., somnolence, anticholinergic effects, contraindicated concomitant use with monoamine oxidase inhibitors) that are consistent with how other sedating antihistamines are labeled
- A statement reminding healthcare providers to reassess the patient for continued need for Diclegis as pregnancy progresses
- A Limitation of Use stating that Diclegis has not been studied in women with hyperemesis gravidarum
- Pregnancy Category A classification with labeling of the nonclinical reproductive toxicity findings and a summary of the available clinical data that support lack of teratogenicity in humans

The package insert has been finalized, incorporating input from the various review disciplines as well as input from the Office of Prescription Drug Promotion (OPDP) and the Study Endpoints and Labeling Development (SEALD) group. See the reviews by Dr. Carrie Newcomer (OPDP) and Dr. Abimbola Adebawale (SEALD) for details.

Diclegis also has a patient package insert that includes information on contraindications, the dosing regimen, breastfeeding, side effects, and storage instructions. The language in this leaflet has been optimized for the layperson with input from the Division of Medical Policy Programs (DMPP). See the review by Ms. Sharon Williams for details.

13. Decision/Action/Risk Benefit Assessment

- Regulatory Action

APPROVAL

- Risk Benefit Assessment

I agree with all review disciplines that this 505(b)(2) NDA supports approval of Diclegis for the treatment of nausea and vomiting of pregnancy when conservative measures have failed. There is a sufficient scientific bridge to FDA's findings of safety and effectiveness for Bendectin, a prior determination by FDA that Bendectin was not withdrawn for reasons of safety or effectiveness, and a new clinical trial that shows the Diclegis formulation provides a small, but statistically significant improvement in nausea and vomiting of pregnancy. Safety concerns are predominantly related to the somnolence and anticholinergic effects of the doxylamine succinate component and are well-known and can be adequately labeled. Importantly, the available evidence shows that first trimester exposure to the combination of doxylamine succinate and pyridoxine hydrochloride is not associated with teratogenicity. Although the treatment effect is small, there are no other FDA-approved treatments for nausea and vomiting of pregnancy. This approval will provide an important treatment option for these patients.

- Recommendation for Postmarketing Risk Evaluation and Mitigation Strategies

None.

- Recommendation for other Postmarketing Requirements and Commitments

None, other than the required pediatric postmarketing trial described in Section 10.

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/s/

HYLTON V JOFFE
04/08/2013