

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**021876Orig1s000**

**CLINICAL PHARMACOLOGY AND  
BIOPHARMACEUTICS REVIEW(S)**

**Final**  
**(April 5, 2013)**  
**Addendum Review**  
**Clinical Pharmacology Review**  
**Office of Clinical Pharmacology (OCP)**

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<b>NDA: 021876</b>	<b>Date of Submission:</b> June 8, 2012 (cover letter)
<b>Generic Name:</b>	Doxylamine succinate 10 mg/Pyridoxine 10 mg
<b>Proposed Brand Name:</b>	Diclegis™
<b>Formulation:</b>	Delayed Release Tablet
<b>OCP Division:</b>	Division of Clinical Pharmacology 3
<b>Office of New Drugs (OND):</b>	Division of Reproductive and Urologic Products
<b>Route of Administration:</b>	Oral
<b>Indication:</b>	Treatment of Nausea and Vomiting of Pregnancy in Women who do not Respond to Conservative Management
<b>Dosage and Administration:</b>	Two tablets daily at bedtime. If symptoms are not adequately controlled, the dose can be increased to a maximum recommended dose of four tablets daily (one in the morning, one mid-afternoon and two at bedtime) as described in the full prescribing information.
<b>Type of Submission:</b>	505(b)(2)
<b>Sponsor:</b>	Duchesnay, Inc. Quebec, Canada
<b>Reviewer:</b>	Sayed (Sam) Al Habet, RPh, PhD
<b>Secondary Reviewer/Signer:</b>	LaiMing Lee, PhD

## Synopsis:

This is an addendum to the original clinical pharmacology review for this application (DARRTS date March 4, 2013). The primary purpose of this addendum is to review the *in vivo* bioavailability study comparing the Diclegis Delayed Release Tablet to an oral solution. This study was not originally reviewed as part of the NDA as it was not felt to be necessary to the application due to the presence of both a single and multiple dose study and a comparative food effect study that are of a more recent vintage with the to-be-marketed formulation. However, since the date of the original review, the importance of this study vis a vis the establishment of a 505(b)(2) “bio-bridge” [REDACTED] (b) (4)

[REDACTED]. It should also be noted that this study (02163) was analyzed at [REDACTED] (b) (4) during the time period where their analytical deviations were noted. This issue was dealt with by both attention to the review of the analytical method and in consideration that the approval of this application depends on this information in a qualitative and not a quantitative sense.

In order to tie this review to the previous review, this review also contains an assessment of the bioavailability of the single dose data from the solution study (02163) to the fasted arm of the food effect study 70294 (in our review dated March 4, 2013). This is being done NOT to establish bioequivalence across the two studies (that would be impossible for a multitude of reasons) but to demonstrate the relative performance in a qualitative way, i.e., that the resulting profiles are similar and of a nature that would be expected.

The issue of a 505(b)(2) “bio-bridge” is dealt with in a memo from Dr. Bashaw, Dir. Division of Clinical Pharmacology-3 to Dr. Hylton Joffe, Dir. Division of Reproductive and Urologic Drug Products. Due to the existence of this memo which lays out the ground work for the bridge, this issue will not be included in this review.

### **Summary of Study 02163:**

**Title:** “Radomized, 2-way crossover, relative bioavailability study of Diclectin delayed release tablets and a combination of doxylamine succinate 10 mg/10 mL and pyridoxine hydrochloride 10 mg/10 mL oral solutions administered as 2 x 10 mg-10 mg delayed release tablets or 1 x 20 mL + 1 x 20 mL of oral solutions in healthy adult females under fasting conditions.”

**Final Report Date:** June 17, 2003

**Objective:** The objective of this study was to compare the rate and extent of absorption of Diclectin delayed release tablet versus a combination of reference doxylamine succinate and pyridoxine oral solutions, administered under fasting conditions. This study will provide overnight plasma-concentration time profiles of the components of Diclectin and the solution.

**Study Design:**

The study was conducted in 18 non-pregnant female subjects. The study was randomized, single dose, 2-way crossover, under fasting condition with a washout period of 28 days. After a supervised fast for at least 8 hours, subjects were dosed at bedtime in the evenings at approximately 22:00 hours as follows:

**Treatment A:** 2 x Diclectin tablets (total dose of 20 mg of each component, doxylamine and Pyridoxine)

**Treatment B:** 20 mL x 10mg/mL doxylamine succinate oral solution + 20 mL x 10 mg/mL Pyridoxine oral solution (total dose is 20 mg of each component)

Subject fasted an additional 8 hours. The formulations used in this study are listed in **Table 1**.

**Table 1. Study Formulation (Study 02163)**

Code	on Market/Description		
A	Duchesnay, Canada (Diclectin <sup>®</sup> ), doxylamine succinate-pyridoxine hydrochloride 10 mg-10 mg delayed-release tablet: white, biconvex tablet, printed with a drawing of a pregnant woman in purple ink.	Lot No.: 1018	N/AV  Packaging Date: (b) (4)
		Lot No.: C0046A001  Product No.: C0046A/S	Manufacturing Date: (b) (4)
B	Duchesnay, Canada (Diclectin), pyridoxine hydrochloride powder to be reconstituted to a 10 mg/10 mL oral solution: white powder that reconstituted to a clear liquid.	Lot No.: F0829A001  Product No.: F0829A/S	Packaging Date: (b) (4)

**Blood Sampling:**

Blood samples for PK analysis were collected at the following time points:

Pre-dose (0), 0.25, 0.5, 0.75, 1, 1.5, 2, 2.33, 2.67, 3, 3.33, 3.67, 4, 4.5, 5, 5.5, 6, 8, 10, 12, 24, 48, 72, and 120 h.

### **Summary of Study 70294 (food effect study):**

This study was reviewed in the original review dated March 4, 2013. Briefly, the following is a brief summary of the study design.

**Objective:** To assess the effect of food on the bioavailability of [REDACTED]<sup>(b) (4)</sup>, administered as a 2 x 10 mg-10 mg delayed-release tablet (for a total dose of 20 mg-20 mg), under fasting and fed conditions

**Design:** Single-dose, randomized, 2-way crossover study

**Subjects:** 44 healthy females

**Method:** All subjects fasted at least 10 hours prior to drug administration and those in the fed group received a standard high-fat, high-caloric meal within 30 minutes before drug administration (2 eggs fried in butter, 2 slices of toast with butter, 2 strips of bacon, approximately 128 g of hash brown potatoes, and 200 mL of whole milk).

After dosing, subjects were subsequently fasted for a period of at least 4 hours. The treatment phases (fasting and fed conditions) were separated by a washout period of 27 days.

#### **Blood Sampling:**

PK blood samples were collected at the following time points: pre-dose (0), 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 16, 24, 36, 48, 96, 144, 192, and 216 h.

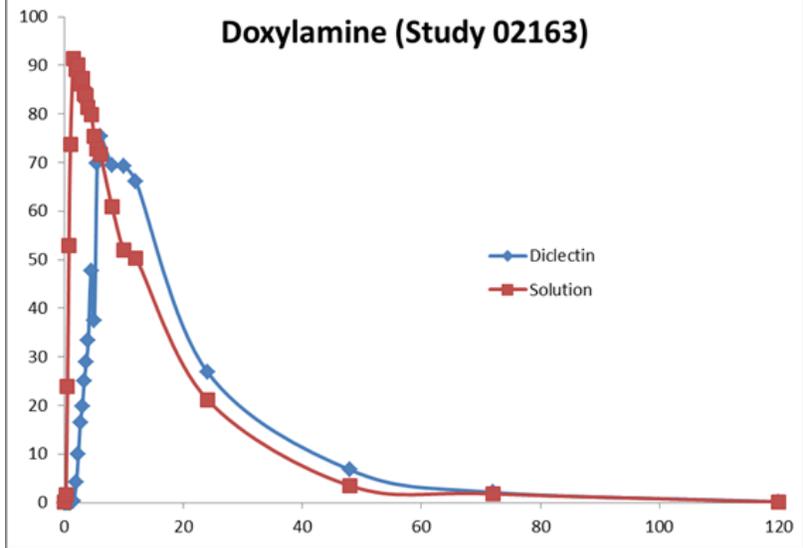
#### **Integrated Results of Studies 02163 and 70294:**

For this memo, it was essential to integrate the data from the two studies: 02163 that was associated with [REDACTED]<sup>(b) (4)</sup> and the new PK study 70294 using only the fasting arm (see review dated March 4, 2013). As stated above, both studies were conducted after a single dose. The data from these two studies are summarized in **Figures 1-4 and Tables 2 and 3.**

The mean C<sub>max</sub> of doxylamine and pyridoxine in studies 02163 is comparable to that observed in Study 70294. Also, as expected, the C<sub>max</sub> following oral solution is higher than the delayed release tablet. The mean AUC following the tablet and oral solution is comparable in both studies, as would be expected.

It should be noted that the timing of plasma sampling are not similar in both studies.

**Figure 1. Mean Doxylamine Plasma concentration-Time Profiles Following Diclectin and Oral Solution (Study 02163, (b) (4))**



**Figure 2. Mean Doxylamine Plasma concentration-Time Profiles in Fasting Condition (Study 70294)**

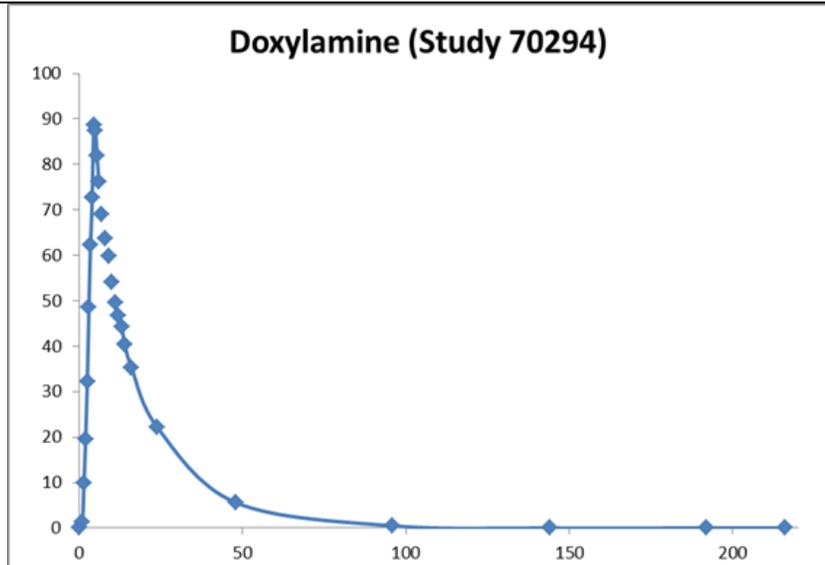


Figure 3. Mean Pyridoxine Plasma concentration-Time Profiles (Study 02163, (b) (4))

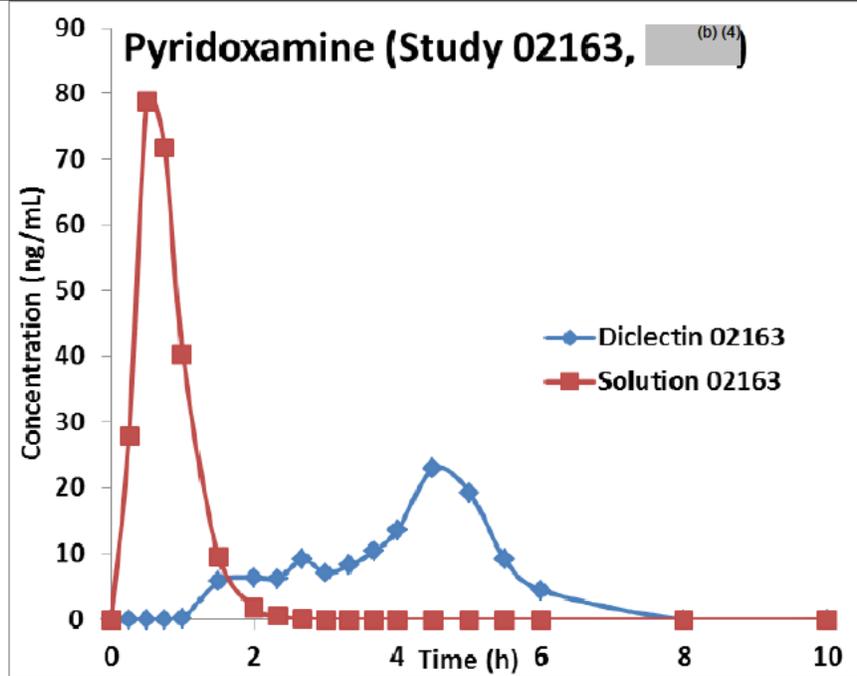
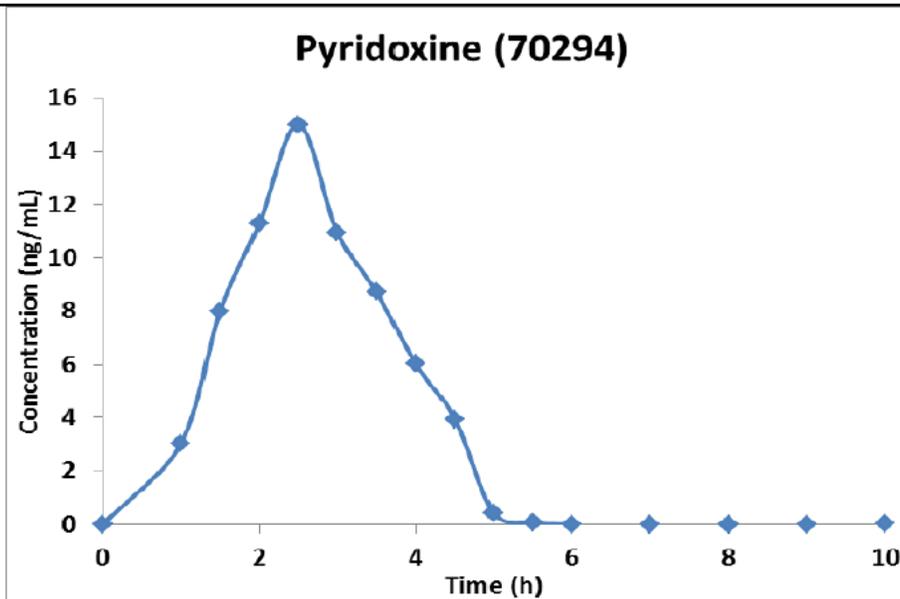


Figure 4. Mean Pyridoxine Plasma concentration-Time Profiles (Study 70294)



**Table 2. Mean ( $\pm$  SD) Doxylamine PK Parameters Following Diclectin and Oral Solution in Studies 02163 and 70294:**

<b>Parameters</b>	<b>Diclectin (Study 02163)</b>	<b>Solution (Study 02163)</b>	<b>Diclegis (Fasting) (Study 70294)</b>
AUC (0-inf) (ng.h/mL)	1729 $\pm$ 571	1659 $\pm$ 469	1448 $\pm$ 332
Cmax (ng/mL)	90 $\pm$ 13.1	97 $\pm$ 18	95 $\pm$ 18
F (%) vs solution	104.51 $\pm$ 15		
Ratio (AUC) (%)	103.53		
90% CI (%)	97.96-109.42		

**Table 3. Mean ( $\pm$  SD) Pyridoxine PK Parameters Following Diclectin and Oral Solution in Studies 02163 and 70294:**

<b>Parameters</b>	<b>Diclectin (Study 02163)</b>	<b>Solution (Study 02163)</b>	<b>Diclegis (fasting) (Study 70294)</b>
AUC (0-inf) (ng.h/mL)	59 $\pm$ 22	66 $\pm$ 26	39 $\pm$ 13
Cmax (ng/mL)	50 $\pm$ 31	96 $\pm$ 46	35 $\pm$ 14
F (%) vs solution	92 $\pm$ 22		
Ratio (AUC) (%)	89.93		
90% CI (%)	79.33-101.96		

**Conclusions:**

From these data it can be concluded the following:

- Compared to an oral solution, the Cmax is lower and the Tmax is longer after tablet. This is a confirmatory of the delayed release characteristic of the delayed release tablet.
- The AUC after oral solution is comparable to that for doxylamine. For pyridoxine the data is more complex, but this is due to the relatively short half-life of pyridoxine and the sampling schedule used. A higher degree of concordance is seen with the longer half-lived metabolites across the studies, as would be expected
- It should also be noted that due to the delayed release character of this dosage form, there is a high degree of variability present in the data with the CV% at individual timepoints in the profiles ranging from 46-280% for doxylamine and 119-412% for pyridoxine in study 02163.
- Overall, the Cmax and AUC for both components from study 02163 are comparable to that observed in Study 70294

Please refer to the Division Directors memo regarding the 505(b)(2) bridging aspects of this product.

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SAYED AL HABET  
04/05/2013

LAI M LEE  
04/05/2013



## Memorandum

Food and Drug Administration  
5600 Fishers Lane  
Rockville, MD 20857

**DATE:**

**FROM:** CAPT E. Dennis Bashaw, Pharm.D.  
Director, Division of Clinical Pharmacology-3  
Office of Clinical Pharmacology (OCP)  
Office of Translational Sciences  
Center for Drug Evaluation and Research, FDA

**To:** Hylton Joffe, M.D.  
Director, Division of Reproductive and Urologic Drug Products  
Office of Drug Evaluation-3  
Center for Drug Evaluation and Research, FDA

**SUBJECT:** OCP Approach to Bridging for the 505(b)(2) application for NDA 021876

### **Background**

DICLEGIS® is a combination product of doxylamine succinate, an antihistamine, and pyridoxine hydrochloride, a Vitamin B6 analog, indicated for the treatment of nausea and vomiting of pregnancy in women who do not respond to conservative management. It was originally approved in the late 1950s by Merril National under the tradename BENDECTIN® and subsequently removed from the market in 1983 due to an association with a specific type of birth defect. During this time it has continued to be marketed in other countries, such as Canada under the trade name, DICLECTIN®.

Since its removal from the market a number of studies, both epidemiological and animal (reproductive) have been done to demonstrate the teratogenic potential of this combination. It should be noted that both entities are available OTC as separate products. Subsequently the additional research has conclusively demonstrated that the teratogenic risk posed by this combination has not been demonstrated. One of the lead investigators who published some of the original teratogenic findings in animals was subsequently dismissed from his academic position due to allegations of data fabrication regarding this drug.

The product is now pending approval at the FDA by the Canadian sponsor (Duchesnay, Inc. Quebec, Canada).

### **Approval Route**

In order to re-introduce this combination into the market, the sponsor elected to use the 505(b)(2) approval route. This route was chosen for a number of reasons including the

ability to then access the large published literature on the lack of teratogenic potential of this combination that exists.

(b) (4)

(b) (4)

(b) (4)

lack of bridging between (b) (4) and the RLD, BENDECTIN®. Following meetings with the FDA, the sponsor agreed to conduct Phase III study (DIC-301) and two PK studies: effect of food study (70294) and multiple dose study (70381).

**Bio-Bridge**

Operationally, under a 505(b)(2) rubric a sponsor need NOT show bioequivalence to the RLD. They must, however, show the relative bioavailability and from that comparison undertake additional in vivo clinical studies to demonstrate either the safety (if the levels are higher than the RLD) or efficacy (if the levels are lower than the RLD). In this case it is impossible to have a comparison to the RLD as the last lots of it were produced over 29yrs ago.

(b) (4) represents the (fortunately) rare situation where a product, long removed from the market is attempting to be re-introduced. Unfortunately the FDA does not have a published policy or guidance document on these situations, most likely due to its rarity. Even so, the FDA does have a mandate to decrease the amount of unnecessary research in both human and animals when possible. In this situation, to require this sponsor to reproduce the vast amount of experience with the original product and with the active pharmaceutical ingredient (API) would be an extreme approach.

Turning to the situation at hand, it is the opinion of the Division of Clinical Pharmacology-3 that the submitted data in this NDA is sufficient for approval under a 505(b)(2) approach for the following reasons:

-At the time of withdrawal, 1983, the FDA had only been requiring in vivo biopharmaceutic studies since 1977, and there was not a mandate to do such studies in products that were already approved.

-When BENDECTIN® went through the Drug Efficacy and Safety Implementation (DESI) process in 1962, it was not designated a bioproblem drug and no additional studies were required-as were required by other drugs that were classified as such.

-Both entities in this product are highly soluble (doxylamine 1gm/1mL, pyridoxine 0.1mg/mL).

-While BENDECTIN® was not a compendial product itself, both single entity doxylamine and pyridoxine tablets did have entries in the USP and the NF in the time period of BENDECTIN's® removal (1975 and 1980 editions-available at the White Oak Library). These compendia recommended disintegration testing as a quality control test, a test that is known to be insensitive but would be indicative of a low level of concern about these products.

(b) (4)

(b) (4)

-The newly generated pharmacokinetic information is vastly superior to that which was available at the time BENDECTIN® was either approved (with no data) or at the time of removal from the market.

**Conclusion**

Thus we are in the situation where we have a drug that cannot, for valid reasons, do a direct head-to-head comparison. A combination product that is composed of two highly soluble drugs that are marketed as single entities at doses much higher than those used here available over the counter (doxylamine at 2.5x dose, pyridoxine at 25x dose.)

(b) (4)



Additional OCP/OND requested studies

- ⇒ A multiple dose pk trial of the to be marketed product (including parent and metabolite pk data for both entities)
- ⇒ A phase 3 clinical trial

Given the situation it is our conclusion that, *in toto*, the combination of physical chemistry (solubility), <sup>(b) (4)</sup>, and additional *in vivo* pharmacokinetic data and clinical studies requested by OCP/OND represents an appropriate level due diligence by the Agency for approval via the 505(b)(2) provisions.

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/s/  
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EDWARD D BASHAW

04/05/2013

This version of the Clin Pharm Memo is identical to the one submitted into the DARRTS system previously with the exception that it does not have the DRAFT watermark that was mistakenly left on the previous document

**BIOPHARMACEUTICS REVIEW**  
**Office of New Drug Quality Assessment**

<b>Application No.:</b>	NDA 21-876	<b>Reviewer:</b> Kareen Riviere, Ph.D.	
<b>Submission Date:</b>	6/8/2012; 11/19/2012; 2/26/2013		
<b>Division:</b>	DRUP	<b>Team Leader:</b> Angelica Dorantes, Ph.D.	
<b>Sponsor:</b>	Duchesnay Inc.	<b>Acting Supervisor:</b> Richard Lostritto, Ph.D.	
<b>Trade Name:</b>	Diclegis	<b>Date Assigned:</b>	7/5/2012
<b>Generic Name:</b>	doxylamine succinate and pyridoxine hydrochloride	<b>Date of Review:</b>	3/4/2013
<b>Indication:</b>	Treatment of nausea and vomiting of pregnancy in patients who do not respond to conservative management	<b>Type of Submission:</b> 505(b)(2) Resubmission	
<b>Formulation/strengths:</b>	DR Tablet; 10mg/10mg		
<b>Route of Administration:</b>	Oral		

**SUMMARY:**

This submission is a 505(b)(2) New Drug Application for delayed release (DR) tablets containing the drug combination of doxylamine succinate and pyridoxine hydrochloride at the 10mg/10mg strength. The proposed indication is for the treatment of nausea and vomiting of pregnancy in patients who do not respond to conservative management.

The Biopharmaceutics information in this NDA includes a drug product development section with the proposed dissolution method and acceptance criteria. The Biopharmaceutics review for this NDA is focused on the evaluation and acceptability of the proposed dissolution methodology and acceptance criteria.

**A. Dissolution Method**

The proposed dissolution method is:

Acid Stage				
USP Apparatus	Rotation Speed	Media Volume	Temp	Medium
II	100 rpm	1000 mL	37°C	0.1N HCl
Buffer Stage				
USP Apparatus	Rotation Speed	Media Volume	Temp	Medium
II	100 rpm	1000 mL	37°C	pH 6.8 buffer

The provided data support the proposed dissolution method and it is deemed acceptable.

**B. Dissolution Acceptance Criteria**

The proposed dissolution acceptance criteria are:

<b>Acid Stage Acceptance Criterion</b>
NMT (b) (4) in 120 minutes
<b>Buffer Stage Acceptance Criterion</b>
Q = (b) (4) at 15 minutes

Based on the provided data, the proposed dissolution acceptance criterion for the buffer stage was considered less than appropriate. Therefore, in an IR letter addressed to the Applicant dated February 14, 2013, ONDQA Biopharmaceutics recommended a dissolution acceptance criterion of  $Q = (b) (4)$  at 15 minutes for the buffer stage based on the mean in-vitro dissolution profiles from the clinical and primary stability batches at release and under long term stability. In a submission dated February 26, 2013, the Applicant accepted FDA's recommendation.

### **C. In vitro Alcohol Interaction Studies**

In an email dated August 8, 2012, Dr. Hylton Joffe from the clinical division deemed it unnecessary to request the Applicant to conduct an in vitro drug-alcohol interaction study since the patient population is pregnant women who are always strongly advised not to drink any alcohol during pregnancy because of adverse effects of alcohol on the fetus. Although this reviewer disagrees with this conclusion, this reviewer defers to the Clinical Team's decision.

### **RECOMMENDATION:**

1. Diclegis DR 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:***  $Q = \text{NMT } (b) (4)$  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.

#### **Kareen Riviere, Ph.D.**

Biopharmaceutics Reviewer  
Office of New Drug Quality Assessment

#### **Angelica Dorantes, Ph.D.**

Biopharmaceutics Team Leader  
Office of New Drug Quality Assessment

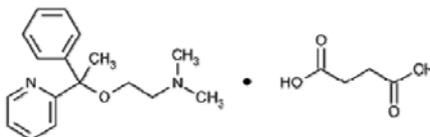
cc: Dr. Richard Lostritto

# ASSESSMENT OF BIOPHARMACEUTICS INFORMATION

## 1. Background

### Drug Substance

Doxylamine succinate is an antihistamine. Figure 1 shows the structure of doxylamine succinate.



**Figure 1.** Chemical structure of doxylamine succinate

The aqueous solubility of doxylamine succinate is presented in Table 1.

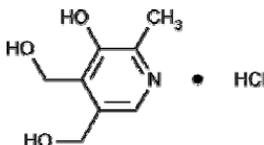
**Table 1.** Solubility Profile of Doxylamine Succinate

pH	Solubility of Doxylamine Succinate (g/mL)
1.83	> 0.91
2.80	>1.0
4.01	>1.1
5.20	>1.3
6.20	>1.1
7.94	0.76

#### Reviewer's Assessment:

*Table 1 indicates that doxylamine succinate has a solubility of ~1 g/mL in the pH range of 2.8 to 6.2. Based on this table, at pH 6.8 the solubility of doxylamine succinate should be between 0.76 g/ml and 1.1 g/mL. Therefore, the proposed dissolution medium for the buffer stage at pH 6.8 (1000 mL) provides adequate sink conditions for the 10 mg strength of doxylamine succinate, because a solubility of 30 mg/mL is needed to achieve sink conditions.*

Pyridoxine hydrochloride is vitamin B6. It has a pKa of 5.0. Figure 2 shows the structure of pyridoxine hydrochloride.



**Figure 2.** Chemical structure of pyridoxine hydrochloride

The Applicant did not measure the aqueous solubility of pyridoxine hydrochloride. However, the Applicant claimed that pyridoxine hydrochloride is freely soluble in water.

#### Reviewer's Assessment:

*According to the 14th edition of The Merck Index, 1 g of pyridoxine hydrochloride is soluble in about 4.5 mL of water (which is >200 mg/mL). Therefore, the proposed dissolution medium for the buffer stage at pH 6.8 (1000 mL) provides adequate sink conditions for the 10 mg strength of pyridoxine hydrochloride, because a solubility of 30 mg/mL is needed to achieve sink conditions.*

**Drug Product**

The composition of the proposed drug product is shown in Table 2.

**Table 2. Composition of the Proposed Drug Product**

Component and Quality Standard	Function	Quantity per unit (mg)	(b) (4)
(b) (4)			
Doxylamine Succinate, USP	API	10.0	(b) (4)
Pyridoxine HCl, USP	API	10.0	(b) (4)
Microcrystalline Cellulose (b) (4)102, NF	(b) (4)		(b) (4)
Magnesium Trisilicate, USP			(b) (4)
Croscarmellose Sodium, NF			(b) (4)
Magnesium Stearate, NF (b) (4)			(b) (4)
Colloidal Silicon Dioxide, NF			(b) (4)
(b) (4)			(b) (4)
(b) (4)			(b) (4)
(b) (4)			(b) (4)

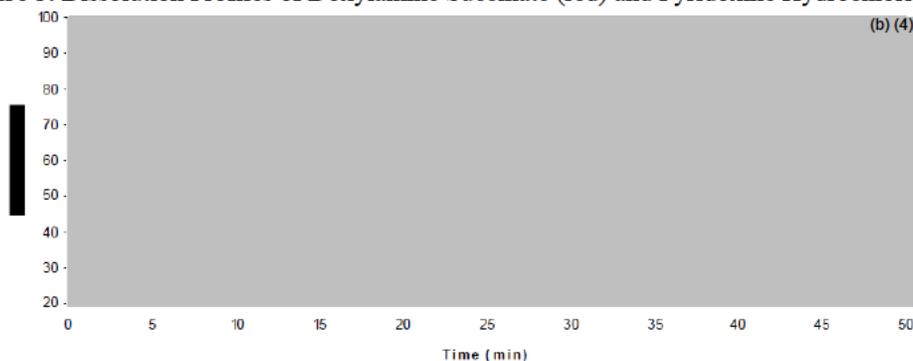
**2. Dissolution Method**

The proposed two-stage dissolution method is shown below.

Acid Stage				
USP Apparatus	Rotation Speed	Media Volume	Temp	Medium
II	100 rpm	1000 mL	37°C	0.1N HCl
Buffer Stage				
USP Apparatus	Rotation Speed	Media Volume	Temp	Medium
II	100 rpm	1000 mL	37°C	pH 6.8 buffer

The dissolution profiles for the two active ingredients are illustrated in Figure 3.

**Figure 3.** Dissolution Profiles of Doxylamine Succinate (red) and Pyridoxine Hydrochloride (blue)



**Reviewer's Assessment:**

*The data in Figure 3 shows that both APIs have similar dissolution profiles. However, it is not apparent what dissolution method was used. Furthermore, this sole figure is not adequate to support the selection of the proposed dissolution testing conditions. Additionally, the Applicant did not provide dissolution profiles in the acid and buffer stage. Thus, the following Biopharmaceutics IR comment was conveyed to the Applicant on August 21, 2012.*

**Communication with the Applicant**

**FDA Request**

There is insufficient data to support the adequacy of the proposed dissolution method (b) (4). Include the dissolution method report supporting the selection of the proposed dissolution test. The dissolution report should include the following information:

Detailed description of the dissolution test being proposed for the evaluation of your product and the developmental parameters supporting the proposed dissolution method as the optimal test for your product (i.e., selection of the equipment/apparatus, in vitro dissolution/release media, agitation/rotation speed, pH, assay, sink conditions, etc.). The testing conditions used for each test should be clearly specified. The dissolution profile should be complete and cover at least (b) (4).

**Applicant's Response**

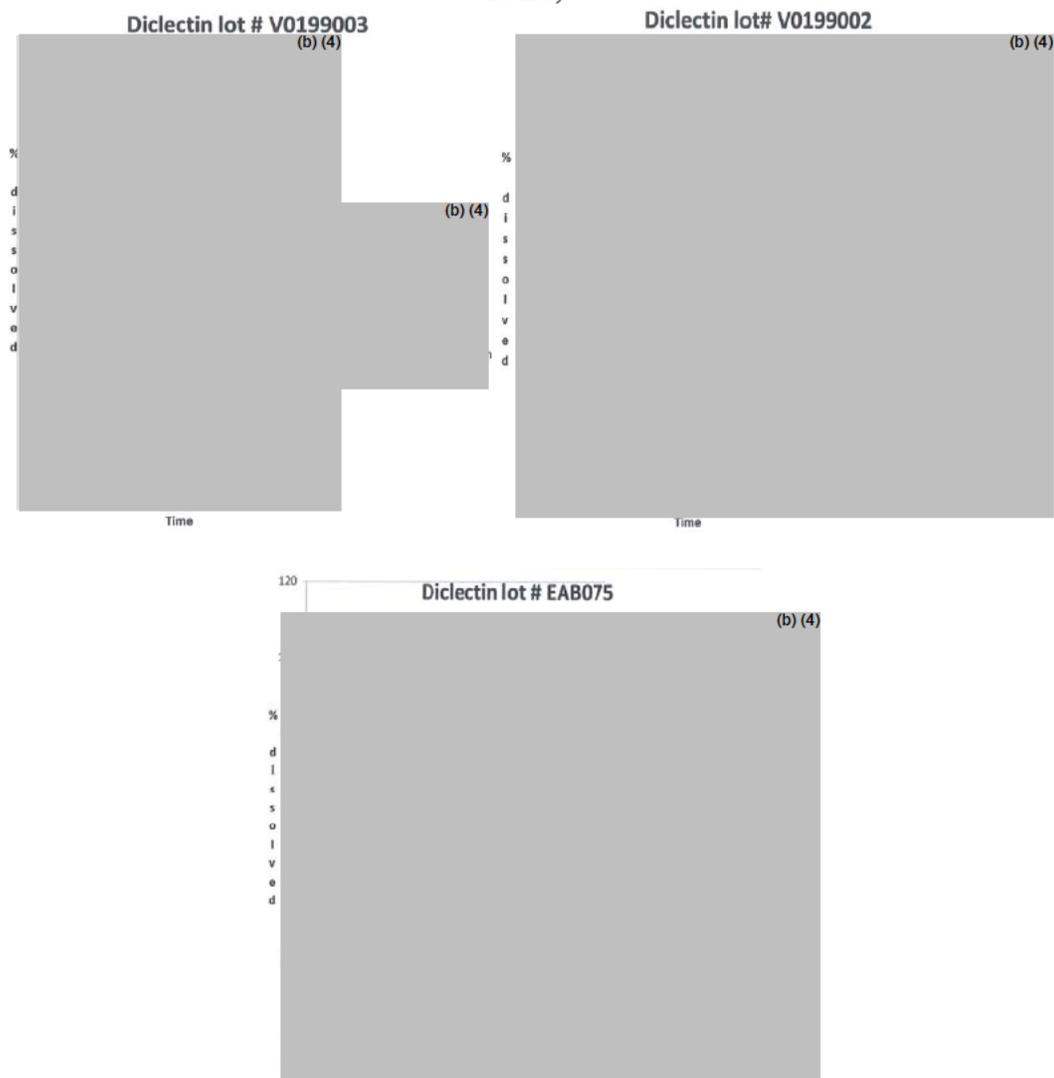
In response to this information request, Duchesnay has provided a Dissolution Method Note to File pertaining to the development of the proposed drug product dissolution method (refer to Module 3 Section 3.2.P.2.2 of this NDA sequence). A detailed description of the dissolution test is included in Part A, sub-section 1 of the Note to File. Justifications of the proposed dissolution parameters as well as developmental dissolution profiles are included in Part A, sub-section 2 of the Note to File.

The Applicant also provided additional data to support their proposed dissolution method in a submission dated November 19, 2012.

**Selection of Dissolution Media, Apparatus, and Rotation Speed**

The Applicant stated that they followed the recommendations outlined in USP <711> for delayed release dosage forms in their selection of 0.1 N HCl as the acidic medium and pH 6.8 buffer as the basic medium. The Applicant selected USP Apparatus II. They did not provide dissolution data using USP Apparatus I. Figure 4 shows the dissolution profiles for drug product lots performed using different paddle speeds.

**Figure 4 a,b, c.** Dissolution Profiles for Various Drug Product Lots Performed using Different Paddle Speeds (pH6.8 Buffer)



**Reviewer's Assessment:**

*The selection of USP Apparatus II is acceptable because it is commonly used for tablet formulations. Also, the selection of 0.1 N HCl and pH 6.8 buffer as the media for the two-stage dissolution method is acceptable since these media are recommended by the USP for delayed release dosage forms.*

(b) (4)

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*The Applicant selected to use a 100 rpm paddle speed. This speed appears quite fast. The Applicant could have selected a paddle speed of 75 rpm to make the method more discriminating. However, the Applicant only has stability data using the 100 rpm paddle speed, and the dissolution method has been validated using the 100 rpm paddle speed. Thus, the 100 rpm paddle speed is acceptable.*

### **Evaluating the Discriminating Ability of the Proposed Dissolution Method**

The original submission did not contain data/information regarding the discriminating ability of the proposed dissolution method. Therefore, the following Biopharmaceutics IR comment was conveyed to the Applicant on August 21, 2012.

#### **Communication with the Applicant**

##### **FDA Request**

There are insufficient data to support the adequacy of the proposed dissolution method (b) (4). Include the dissolution method report supporting the selection of the proposed dissolution test. The dissolution report should include the following information:

- a. Data to support the discriminating ability of the selected method. In general, the testing conducted to demonstrate the discriminating ability of the selected dissolution method should compare the dissolution profiles of the reference (target) product vs. the test products that are intentionally manufactured with meaningful variations for the most relevant critical manufacturing variables (i.e.,  $\pm 10$ -20% change to the specification-ranges of these variables). In addition, if available, submit data showing that the selected dissolution method is able to reject batches that are not bioequivalent.

##### **Applicant's Response**

The (b) (4) drug product is designed to be a delayed release dosage form which has (b) (4) coating to protect the tablet until it has passed through the stomach. Once inside the intestines the product is formulated to immediately release both active ingredients. Dissolution data shows that (b) (4) of each active is released within 15 minutes under buffer conditions. Disintegration testing according to USP using simulated intestinal fluid correlate well with this dissolution data. Additionally, both active ingredients have been shown to have high solubility.

Comparative dissolution profiles has been provided in Part B of the Note to File for different manufacturing changes that had occurred during development (b) (4). Some differences are noticed between these batches in the early part of the dissolution profile.

The Applicant investigated whether their proposed method can detect formulation and manufacturing changes (refer to Table 3 and Figure 5 and b.

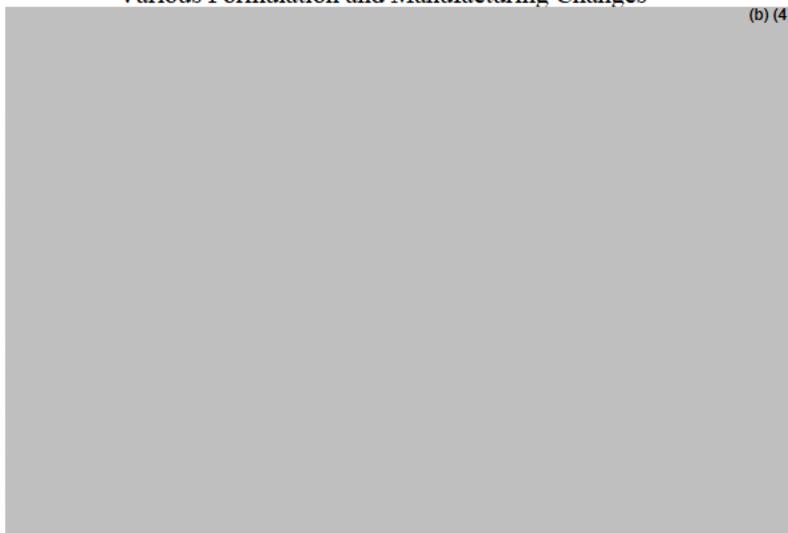
**Table 3. Summary of Formulation and Manufacturing Changes**

(b) (4)

A large rectangular area is completely redacted with a solid grey fill, obscuring the content of Table 3.

**Figure 5 and b. Dissolution Profiles for Drug Product Lots with Various Formulation and Manufacturing Changes**

(b) (4)





**Reviewer's Assessment**

*Figure 5 demonstrates that the proposed dissolution method can only detect very large changes in the manufacturing and formulation variables. However, it cannot discriminate meaningful formulation and manufacturing variations. Nevertheless, the proposed dissolution method has adequate discriminating power.*

*Overall, the proposed dissolution method is acceptable.*

**3. Dissolution Acceptance Criteria**

The proposed dissolution acceptance criteria are shown below.

<b>Acid Stage Acceptance Criterion</b>
NMT (b) (4) in 120 minutes
<b>Buffer Stage Acceptance Criterion</b>
Q = (b) (4) at 15 minutes

**Communication with the Applicant**

The following Biopharmaceutics IR comment was conveyed to the Applicant on August 21, 2012.

**FDA Request**

Provide complete dissolution profile data (raw data and mean values) from the pivotal clinical and primary stability batches supporting the selection of the dissolution acceptance criterion (i.e., specification-sampling time point and specification value) for your proposed product.

**Applicant's Response**

Dissolution profiles for the clinical batch 1120, primary stability batch 1205 as well as production-scale batches 1214V, 1208V and 1226V are included in part B of the Note to File. Corresponding dissolution raw data and mean values for these drug product batches are included in Appendix 4 to the Note to File.

**Reviewer's Assessment**

*Based on the data provided in the November 1 (b) (4) 2012 submission, the buffer stage acceptance criterion is less than acceptable and should be tightened to  $Q =$  (b) (4) at 15 minutes. The following Biopharmaceutics IR comment was conveyed to the Applicant on February 14, 2013.*

**FDA Request**

Based on the mean *in-vitro* dissolution profiles from the clinical and primary stability batches at release and under long term (b) (4) lity, the following dissolution acceptance criterion for the buffer stage is recommended:  $Q =$  (b) (4) at 15 minutes. We recommend that you revise the dissolution acceptance criterion accordingly and submit an updated sheet of specifications for the drug product.

**Applicant's Response (excerpt)**

As per FDA request, the dissolution acceptance criterion has been revised to  $Q =$  (b) (4) at 15 minutes.

**Reviewer's Evaluation: Acceptable**

*In a submission dated February 26, 2013, the Applicant accepted the recommendation to tighten the dissolution buffer stage acceptance criterion.*

**4. Assessment of Alcohol Effect on *In Vitro* Drug Release**

In an email dated August 8, 2012, Dr. Hylton Joffe from the clinical division deemed it unnecessary to request the Applicant to conduct an in vitro drug-alcohol interaction study since the patient population is pregnant women who are always strongly advised not to drink any alcohol during pregnancy because of adverse effects of alcohol on the fetus. Although this reviewer disagrees with this conclusion, this reviewer defers to the Clinical Team's decision.

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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.**  
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/s/  
-----

KAREEN RIVIERE  
03/04/2013

ANGELICA DORANTES  
03/04/2013

**Final**  
**(March 4, 2013)**  
**Clinical Pharmacology Review**  
**Office of Clinical Pharmacology (OCP)**

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<b>NDA: 021876</b>	<b>Date of Submission:</b> June 8, 2012 (cover letter)
<b>Generic Name:</b>	Doxylamine succinate 10 mg/Pyridoxine 10 mg
<b>Proposed Brand Name:</b>	Diclegis™
<b>Formulation:</b>	Delayed Release Tablet
<b>OCP Division:</b>	Division of Clinical Pharmacology 3
<b>Office of New Drugs (OND):</b>	Division of Reproductive and Urologic Products
<b>Route of Administration:</b>	Oral
<b>Indication:</b>	Treatment Nausea and Vomiting of Pregnancy
<b>Dosage and Administration:</b>	Oral, 2 tablets at QHS, 1 QAM, and 1 QPM
<b>Type of Submission:</b>	505(b)(2)
<b>Sponsor:</b>	Duchesnay, Inc. Quebec, Canada
<b>Reviewer:</b>	Sayed (Sam) Al Habet, R.Ph., Ph.D.
<b>Secondary Reviewer/Signer:</b>	Myong-Jin Kim, Pharm.D.

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## 1.0 Executive Summary

### 1.1 Recommendation

From the Clinical Pharmacology perspective, this NDA is acceptable.

### 1.2 Phase 4 Commitments/Requirements

From the Clinical Pharmacology perspective, no post-marketing commitments/requirements are indicated for this NDA.

### 1.3 Summary of Important Clinical Pharmacology Findings:

This is a 505(b)(2) NDA application for a product originally known as Bendectin® which was approved in 1956 for the treatment of nausea and vomiting during pregnancy (NDA 10598). Originally, the product contained three components: 10 mg doxylamine, 10 mg pyridoxine (vitamin B<sub>6</sub>), and 10 mg dicyclomine. The latter component, dicyclomine, was removed from the original formulation in 1976 for the lack of efficacy based on the FDA Drug Efficacy Study Implementation (DESI) assessment. However, in 1983, the product was withdrawn from the US market due adverse publicity associated with its potential teratogenic effect and later in 1999 was negated by the FDA. Since then, the product has been off the US market. Nevertheless, it has continued to be marketed in other countries, such as Canada under the trade name, Diclectin®,

The product contains two active components (doxylamine and pyridoxine). It should be noted that both components of this product are sold in the US *over the counter* (OTC). Doxylamine is available individually as a sleeping aide (e.g., Unisom at 25 mg doxylamine tablet) or in combination with other drugs such as cough preparations (e.g., NyQuil at 6.25 mg doxylamine/15 mL). Similarly, pyridoxine (Vitamin B<sub>6</sub>) is available by several suppliers and sold on-line and retail stores as OTC preparations containing 25, 50, 100, 250, and 500 mg tablets and capsules.

Based on the data submitted in this NDA, following multiple dose administration for 18 days, the drug and its metabolites appear to accumulate. The intake of high calories food reduces the absorption of the drug and its metabolites.

In terms of adverse events, overall the drug was well tolerated in all studies including Phase III study as the most frequently observed adverse events in this study were abdominal pain, fatigue, back pain, dizziness, headache, and somnolence.

In term of safety, Phase III study was conducted in 2009. From this study, no teratogenicity reports were received.

## What is the Content of the NDA Submission?

In this submission the sponsor included two pivotal PK studies, one to characterize the PK after single and multiple doses administration (**Study 70281**) and the other is to investigate the effect of food (**Study # 70294**). In addition to the PK studies, the sponsor conducted a clinical trial to support the safety and efficacy of the product in pregnant women (**Study # DIC-301**). Based on the two PK studies, the following conclusions can be made:

### Single and Multiple Dose Study (Study 70281):

- The parent drugs and metabolites accumulate in the body following multiple doses administration as shown for C<sub>max</sub> and AUC of doxylamine (**Figures 1.3.1-1.3.3 and Tables 1.3.1 and 1.3.2**) and pyridoxine (**Figures 1.3.4 and 1.3.6 and Tables 1.3.1 and 1.3.2**).
- There was high variability in the data which is primarily associated with low and undetectable concentration in the terminal elimination phases. For these reasons the elimination rate constants were not adequately determined or mostly could not be determined in many subjects. Therefore, the determinations of the half-life and the AUC to infinity were not adequate in many situations and should be interpreted carefully.

**Figure 1.3.1. Mean Plasma Concentration-Time Profiles of Doxylamine After Single and Multiple Doses (Study 70381)**

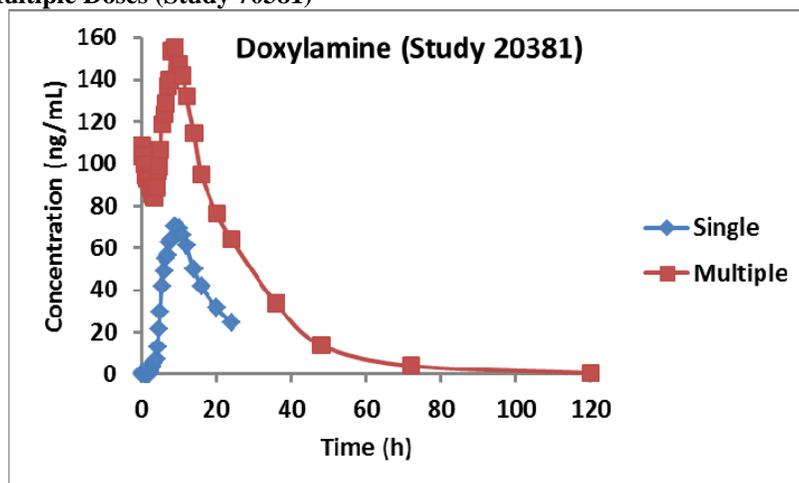


Figure 1.3.2. Mean AUCs of Doxylamine (Study 70381)

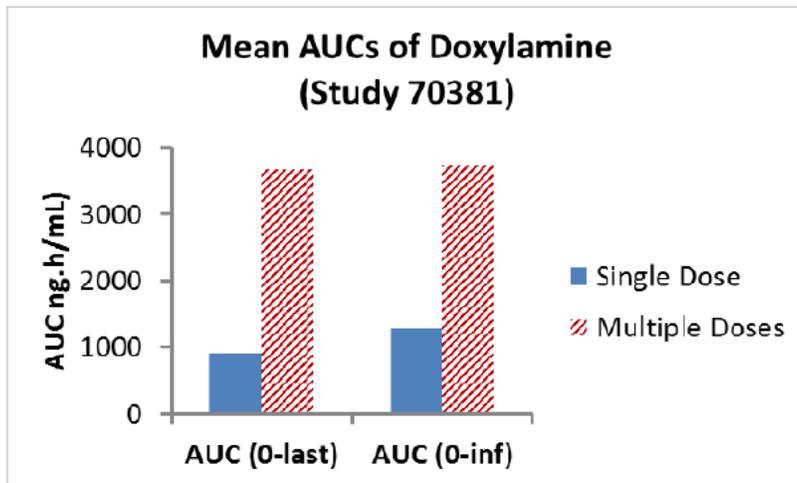


Figure 1.3.3. Mean Cmax of Doxylamine (Study 70381)

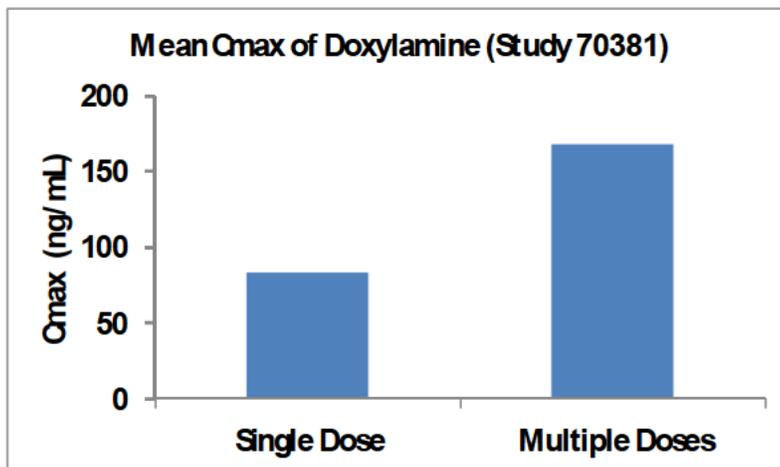


Figure 1.3.4. Mean Plasma Concentration-Time Profiles of Pyridoxine After Single and Multiple Doses (Study 70381)

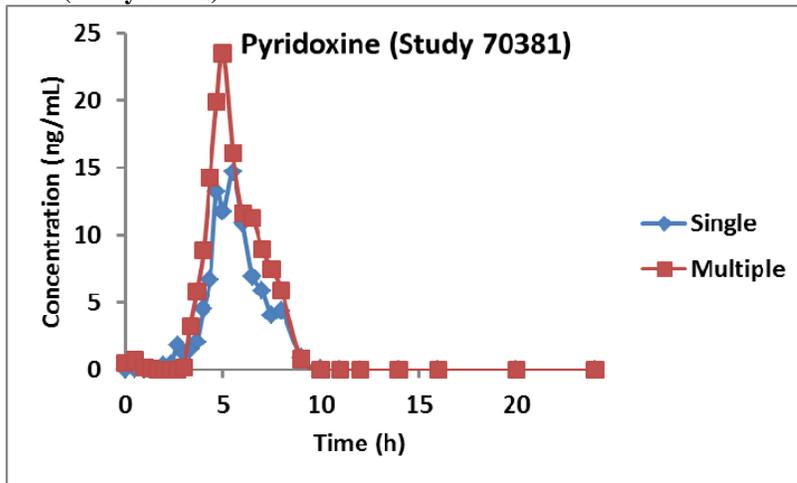
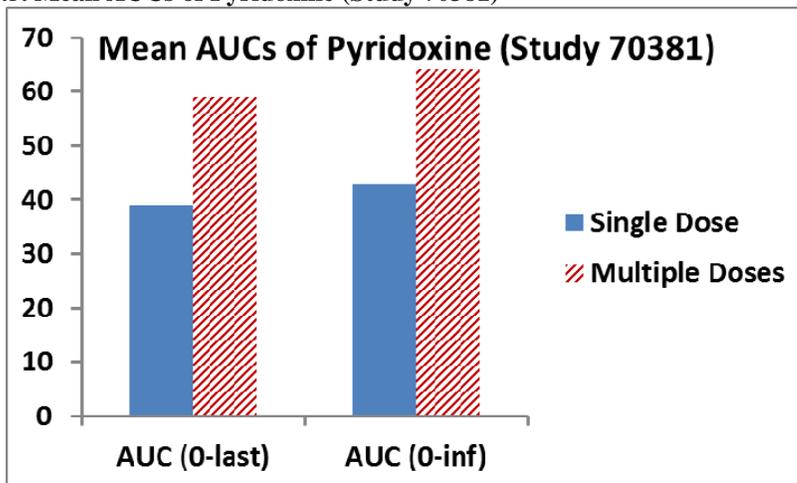
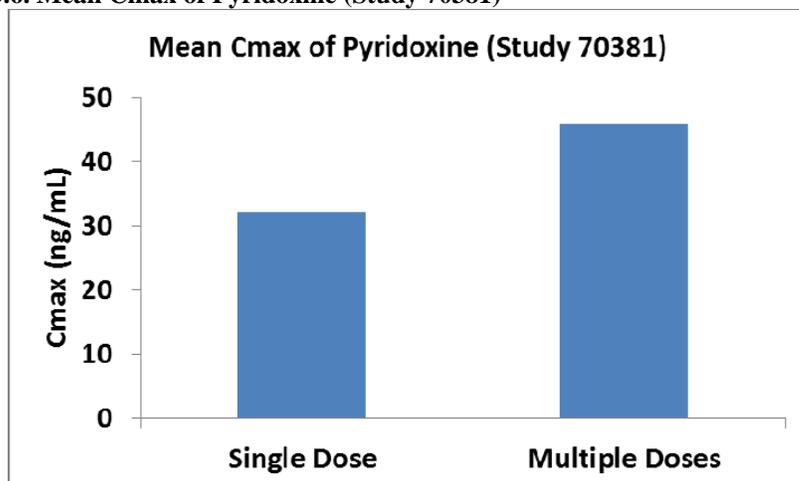


Figure 1.3.5. Mean AUCs of Pyridoxine (Study 70381)



**Figure 1.3.6. Mean Cmax of Pyridoxine (Study 70381)**



**Table 1.3.1. Mean ± SD of AUC (0-last) and AUC 0-inf) (Study 70281)**

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)

**Table 1.3.2. Mean ± SD of Cmax and Half-life (Study 70281)**

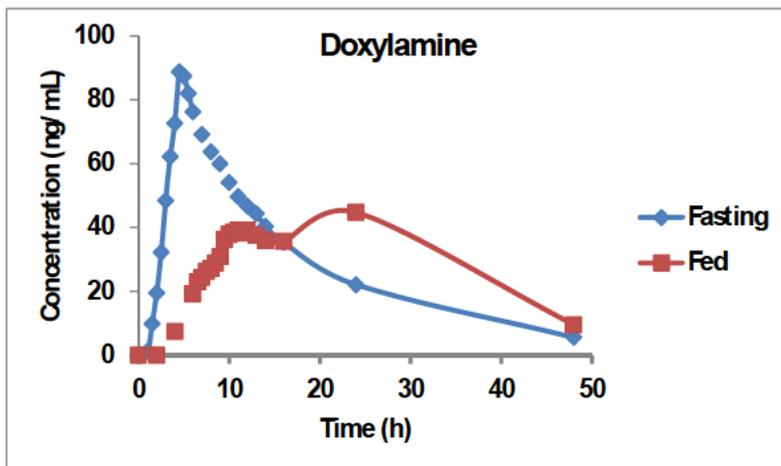
Analytes/Components	Cmax (ng/mL)		Half Life (h)	
	Single	Multiple	Single	Multiple
Doxylamine	83 ± 21	168 ± 38	10.05 ± 2.09	11.91 ± 3.33
Pyridoxine	32.57 ± 15.03	46.05 ± 28.30	0.49 ± 0.23	0.45 ± 0.14
Pyridoxal	74.29 ± 21.80	210.02 ± 54.36	1.29 ± 0.50	19.44 ± 14.46
Pyridoxal 5'-Phosphate	30.01 ± 10.03	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

**Effect of Food (Study 70294)**

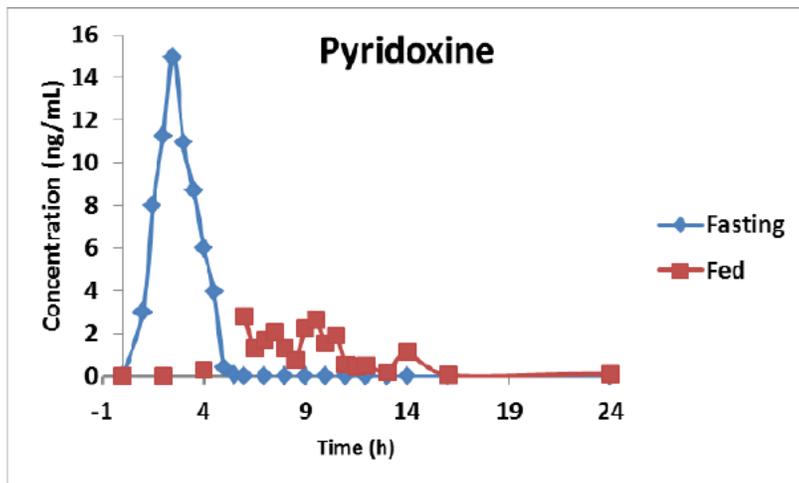
- When taken with food, a delay in Tmax was observed, as well as a reduction in both Cmax and AUC of the parent drugs and pyridoxine metabolites (**Figures 1.3.7 and 1.3.8 and Tables 1.3.3 and 1.3.4**).

- As stated above, there was high variability in the data primarily associated with undetectable plasma levels in many subjects during the terminal elimination phase. For example, the %CV for one of the pyridoxine metabolite, pyridoxamine, was 337.16% (Table 1.3.3).

**Figure 7. Mean Plasma Concentration-Time Profiles (0-48 h only) of Doxylamine in Fed and Fasting Conditions (Study 70294)**



**Figure 8. Mean Plasma Concentration-Time Profiles (0-24 h only) of Pyridoxine in Fed and Fasting Conditions (Study 70294)**



**Table 1.3.3. Mean ± SD of AUC (0-last) and AUC 0-inf) (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 ± <b>19038*</b>	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%**

**Table 1.3.4. Mean ± SD of Cmax and Median Tmax (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

### Conclusions:

Based on these studies, the parent drugs and metabolites accumulate in the body following multiple doses. Based on the PK study, the drug should be taken on empty stomach with water or after light food to ensure adequate absorption. Alternatively, based on Phase III study design, the drug may be given at least 2 hours *prior to or after* meals, if feasible. It is recognized that pregnant women may need to consume some light food and/or snacks to reduce the nausea and vomiting. This may not have any major consequences on the PK of the drug compared to high fat/calorie meals.

## 2.0 Question Based Review (QBR)

### What is the History of the Product?

#### What is the Original Product?

A similar product was originally approved in 1956 for the treatment of nausea and vomiting during pregnancy under a trade name, **Bendectin®** (NDA 10598, Hoechst Marion Russel, Inc). At that time, the product contained **three** active ingredients: 10 mg doxylamine succinate, 10 mg pyridoxine hydrochloride, and 10 mg dicyclomine hydrochloride. In the mid 60s, the tablet coat was modified as delayed release. Subsequently in 1976 and based on FDA Drug Efficacy Study Implementation (**DESI**), dicyclomine was removed from the formulation as it was shown not to contribute to the efficacy. Later it was reformulated and then listed in the FDA Orange Book as a Reference Listed Drug (RLD). Therefore, now the product contains **two** active ingredients, 10 mg doxylamine succinate and 10 mg pyridoxine hydrochloride.

It appears that due to litigation and other reasons including but not limited to teratogenic reports, the sponsor at that time (Merrel Dow) withdrew the product from the market on June 9, 1983. However, on June 9, 1999, the FDA determined that Bendectin® was not withdrawn for safety or efficacy reasons.

Since its withdrawal in 1983, **Bendectin®** has not been in the US market. However, a combination of doxylamine succinate and pyridoxine hydrochloride remains marketed by different sponsors in other countries such as Canada under the trade name, **Diclectin®** with the same **two** ingredients (10 mg doxylamine succinate and 10 mg pyridoxine hydrochloride).

It should be noted that, after the submission of this NDA on June 8, 2012, the sponsor requested and proposed new name on August 3, 2012. The proposed new name is "**Diclegis**". The name (b) (4) will be used throughout this review to avoid confusion as the name (b) (4) is (b) (4) impeded in all Figures, Tables, and texts submitted in this NDA as (b) (4)

#### What are the Relevant Sponsor's Correspondences with the FDA?

(b) (4)

(b) (4)

Subsequently, the sponsor submitted an NDA for (b) (4) (NDA # 021876) on April 18, 2005. A **Refuse-to-File** letter was issued on June 16, 2005 for the following reasons:

- From a clinical pharmacology perspective, the 505(b)(2) application is not fileable because it does not contain information necessary to establish a link between the proposed formulation of (b) (4) and the 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 (b) (4).
- From a clinical perspective, the 505(b)(2) application is not fileable because the application is seeking an indication (b) (4). For example, the proposed indication (b) (4) is not supported by substantive data on safety and efficacy.

At the meeting held on August 9, 2005, the sponsor was advised to conduct a safety and efficacy study to qualify for 505(b)(2) application. Based on this, the sponsor submitted a clinical protocol on November 22, 2005 (Protocol # DIC-301) and received FDA comments on February 2, 2006.

At the meeting held on April 17, 2007, the sponsor confirmed that the two PK studies (02163 and 02191) were subject to audit due to the (b) (4) bioanalytical quality issues at the facility located in (b) (4). At that meeting, the sponsor also confirmed the plan to conduct a food effect study (Study 70294) and a single and multiple dose PK study (Study # 70381) in addition to a phase 3 clinical study (Study # DIC-301).

At the Pre-NDA meeting held on December 14, 2009, the sponsor confirmed that the PK studies as well as the clinical study (DIC-301) were conducted using the final-to-be marketed formulation. Furthermore, it was agreed that the two old PK studies that were associated with (b) (4) will be submitted with the NDA for completeness only.

## What Was Submitted in this NDA?

In addition to the clinical study (DIC-301) and several literature articles, the sponsor submitted the following PK studies:

Study No	Description	Notes
02163	Relative bioavailability study versus oral solution. Submitted for safety data only in agreement with FDA.	There were no significant or serious adverse events in this study.
02191	Food effect study using an obsolete formulation. Submitted for safety data only in agreement with FDA	There were no significant or serious adverse events in this study.
70294	Food effect study using the commercial formulation	For relevant serious adverse events (serious adverse events leading to withdrawal and other serious adverse events), events are linked to the source data in the report.
70381	Single and multidose pharmacokinetics study using the commercial formulation	For relevant serious adverse events (serious adverse events leading to withdrawal and other serious adverse events), events are linked to the source data in the report.

As indicted above, studies 02163 and 02191 are submitted for completeness only. They are not reviewed due to the data integrity issue with the analytical laboratory (b) (4). The following is the summary of the two pivotal PK studies (70294 and 70381). **The focus of this review and the summary is on the PK characteristics of the parent drugs, doxylamine and pyridoxine.** The detail reviews of the parent drugs and pyridoxine metabolites for these two studies are shown in **Appendix/Section 4.2.**

### Is There a Food Effect?

The sponsor conducted one study to investigate the effect of food (Study 70294). This study is summarized below:

**Objective:** To assess the effect of food on the bioavailability of (b) (4), administered as a 2 x 10 mg-10 mg delayed-release tablet (for a total dose of 20 mg-20 mg), under fasting and fed conditions

**Design:** Single-dose, randomized, 2-way crossover study

**Subjects:** 44 healthy females

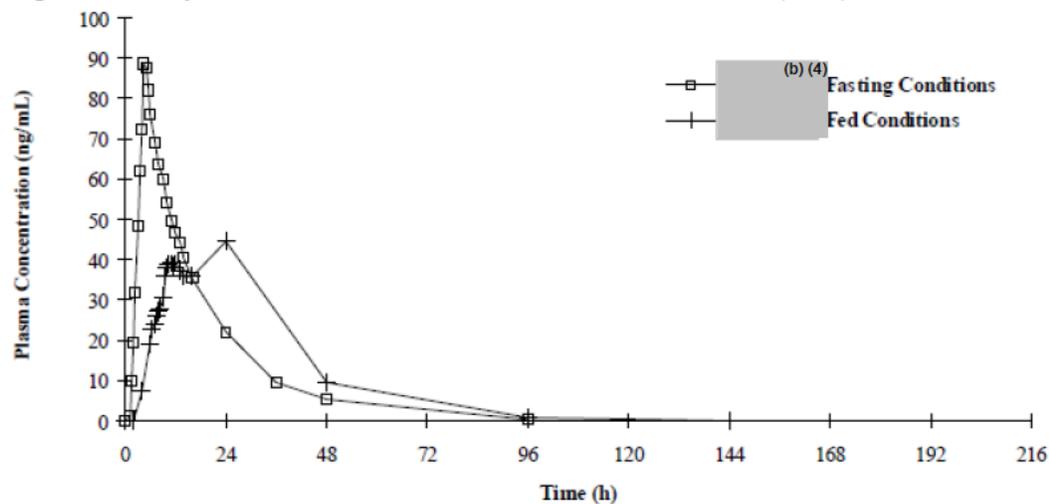
**Method:** All subjects fasted at least 10 hours prior to drug administration and those in the fed group received a standard high-fat, high-caloric meal within 30 minutes before drug administration (2 eggs fried in butter, 2 slices of toast with butter, 2 strips of bacon, approximately 128 g of hash brown potatoes, and 200 mL of whole milk).

After dosing, subjects were subsequently fasted for a period of at least 4 hours. The treatment phases (fasting and fed conditions) were separated by a washout period of 27 days.

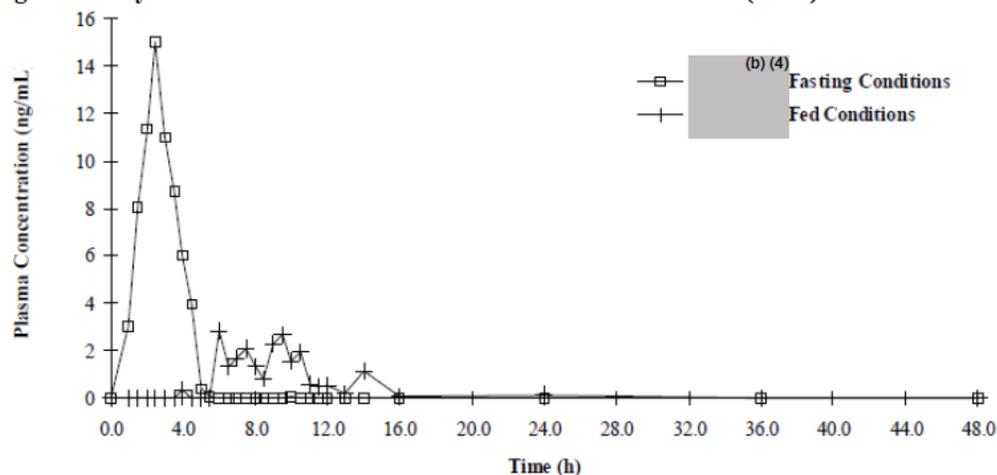
## Results:

- The plasma concentration-time profiles of parent drugs, doxylamine and pyridoxine are shown in **Figures 2.1 and 2.2**. The PK parameters for all analyzed components, including the metabolites of pyridoxine are shown in **Tables 2.1-2.4**.
- Food delayed the C<sub>max</sub> of both doxylamine and pyridoxine by approximately 7 hours when compared to administration under fasting conditions (based on median T<sub>max</sub> results). The same trend was also observed for the pyridoxine metabolites.
- The C<sub>max</sub> of doxylamine and pyridoxine as well as pyridoxine metabolites were also reduced with food. However, the effect of food on the pyridoxine metabolites was more complex (see **Appendix 4.2**)
- The half-life of doxylamine is approximately 12 hours. However pyridoxine half-life is very short (<30 minutes).

**Figure 2.1. Doxylamine Mean Plasma-Concentration Time Profiles (n=42)**



**Figure 2.2. Pyridoxine Mean Plasma-Concentration Time Profiles (n=42)**



**Table 2.1. Comparison of AUC (0-t) in Fed and Fasting Condition**

AUC <sub>0-t</sub>	(b) (4) under fasting conditions (A) (2 x 10 mg-10 mg)	(b) (4) under fed conditions (B) (2 x 10 mg-10 mg)
Doxylamine	1407.20 ± 336.94	1488.03 ± 463.21
Pyridoxine	33.75 ± 13.71	18.32 ± 14.52
Pyridoxal	193.66 ± 53.95	138.40 ± 70.85
Pyridoxal 5'-phosphate	1975.12 ± 881.98	2096.63 ± 916.50
Pyridoxamine	5646.73 ± 19038.59	342.15 ± 399.55
Pyridoxamine 5'-phosphate	51967.10 ± 41092.51	52045.43 ± 47013.65

**Table 2.2. Comparison of AUC (0-inf) in Fed and Fasting Condition**

AUC <sub>0-inf</sub>	(b) (4) under fasting conditions (A) (2 x 10 mg-10 mg)	(b) (4) under fed conditions (B) (2 x 10 mg-10 mg)
Doxylamine	1447.89 ± 332.18	1579.01 ± 422.72
Pyridoxine	39.48 ± 12.85	24.18 ± 13.99
Pyridoxal	231.20 ± 71.75	197.11 ± 76.34
Pyridoxal 5'-phosphate	2415.23 ± 1087.78	2838.60 ± 1469.78
Pyridoxamine	1530.63 ± 822.85	3239.49
Pyridoxamine 5'-phosphate	47527.96 ± 28290.13	184751.02 ± 259063.79

**Table 2.3. Comparison of C<sub>max</sub> in Fed and Fasting Condition**

C <sub>max</sub>	(b) (4) under fasting conditions (A) (2 x 10 mg-10 mg)	(b) (4) under fed conditions (B) (2 x 10 mg-10 mg)
Doxylamine	94.90 ± 18.40	75.74 ± 16.59
Pyridoxine	35.54 ± 21.40	13.71 ± 10.77
Pyridoxal	85.39 ± 21.53	45.63 ± 25.00
Pyridoxal 5'-phosphate	29.75 ± 10.93	34.16 ± 11.88
Pyridoxamine	487.32 ± 651.49	367.37 ± 381.33
Pyridoxamine 5'-phosphate	1325.08 ± 745.22	994.09 ± 652.73

**Table 2.4. Comparison of T<sub>max</sub> in Fed and Fasting Condition**

T <sub>max</sub>	(b) (4) under fasting conditions (A) (2 x 10 mg-10 mg)	(b) (4) under fed conditions (B) (2 x 10 mg-10 mg)
Doxylamine	5.13 ± 3.39	14.9 ± 7.4
Pyridoxine	2.50 ± 0.94	9.25 ± 3.96
Pyridoxal	3.23 ± 0.95	12.7 ± 6.6
Pyridoxal 5'-phosphate	11.8 ± 7.3	17.8 ± 5.7
Pyridoxamine	9.66 ± 21.68	9.34 ± 4.60
Pyridoxamine 5'-phosphate	28.5 ± 62.2	47.4 ± 64.6

**Reviewer's Comments:**

The objective of the study was to characterize the PK profiles of (b) (4) following fed and fasting conditions. There was high variability in the data. This made the determination of the terminal elimination rate constant difficult and inadequate. Therefore, in some situations the determination of AUC (0-infinity) as well as the terminal elimination half-lives was not possible and could not be determined.

Overall and even after considering the high variability in the data, the AUC zero to the last measurable concentration (i.e., AUC<sub>0-t</sub>) and AUC zero to infinity (AUC<sub>0-inf</sub>) for almost all the analytes were lower in fed conditions compared to fasting conditions (**Figures 2.1 and 2.2 and Tables 2.1-2.4**). The same conclusion can be drawn for C<sub>max</sub> (**Table 2.3**). The most affected PK parameter was the T<sub>max</sub> as it was significantly delayed for some of the analytes and in particular for doxylamine and pyridoxine (**Table 2.4**).

Food delayed and reduced C<sub>max</sub> for almost all the analyzed components in this study. The most complex data were observed for pyridoxine metabolites. Overall, food reduced the C<sub>max</sub> and

AUC for these metabolites. However, the clinical significance of the high variability in the data is unknown.

The study clearly demonstrated delay in T<sub>max</sub> and reduction in C<sub>max</sub> and AUC of the parent drugs and its known metabolites when given with food. Due to the high variability and impact on the PK parameters described above when administered with food, (b) (4) should be administered on empty stomach with water, if feasible. Alternatively, based on Phase III study design, the drug may be given at least 2 hours *prior to or after* meals, if feasible. It is recognized that pregnant women may need to consume some light food and/or snacks to reduce the nausea and vomiting. This may not have any major consequences on the PK of the drug compared to high fat/calorie meals.

### **Does the Drug Accumulate?**

The sponsor conducted one study to investigate the PK profiles and potential of accumulation after single and multiple doses as summarized below (Study 70381).

**Objective:** To assess the PK profile of the active ingredients of (b) (4) delayed-release tablets after single and multiple doses in healthy non-pregnant female volunteers

**Design:** This was a single and multiple-dose study in 18 non-pregnant females. Subjects remained in clinic for 20 days throughout the study.

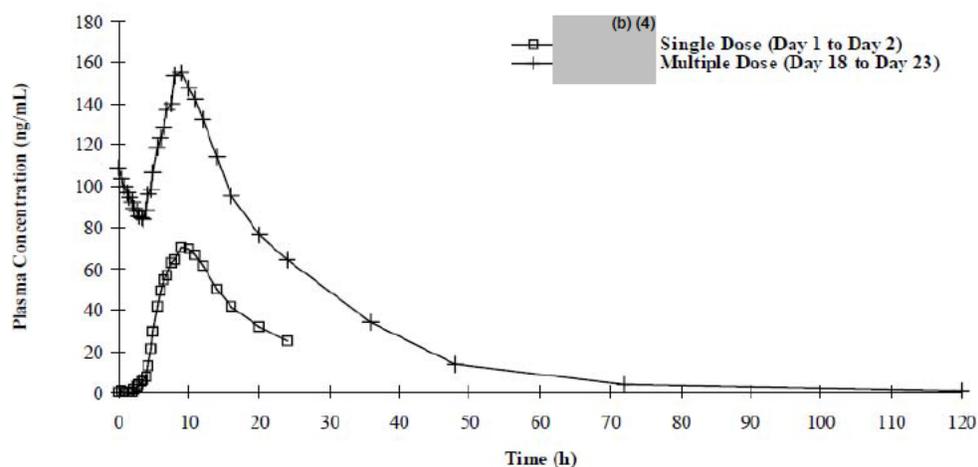
**Methods:** Subjects were administered a single oral dose of (b) (4), as 2 tablets at 22:00 h on Days 1 and 2, and were administered multiple oral doses from Days 3 through 18, according to the following schedule: 1 tablet at 09:00 and 16:00, and 2 tablets at 22:00, under empty-stomach conditions (defined as at least 2 hours after eating).

### **Results:**

#### **Doxylamine:**

- Following multiple dose administrations the exposure of doxylamine (C<sub>max</sub> and AUC) was significantly increased compared to single dose (**Figure 2.3 and Table 2.5**).
- The mean accumulation index (ratio of AUC<sub>0-24</sub> Day 18/AUC<sub>0-24</sub> Day 1) was more than unity (2.76) suggesting that doxylamine accumulates following multiple dosing (**Table 2.5**)
- Steady-state appears to be achieved after Day 9.

**Figure 2.3. Doxylamine Mean Plasma-Concentration Time Profiles (n=18)**



**Table 2.5. Mean PK Parameters of Doxylamine (n=18)**

Parameters	Single Dose Administration			Multiple Dose Administration			P-Value
	Mean	SD	CV (%)	Mean	SD	CV (%)	
AUC <sub>0-1st</sub> (ng·h/mL)	911.40	205.62	22.56	3661.27	1279.16	34.94	-
AUC <sub>0-inf</sub> (ng·h/mL)	1280.90	369.32	28.83	3721.46	1318.50	35.43	<0.0001 <sup>§</sup>
AUC <sub>0-24</sub> (ng·h/mL)	911.40	205.62	22.56	2531.40	719.47	28.42	<0.0001 <sup>§</sup>
C <sub>max</sub> (ng/mL)	83.26	20.62	24.76	168.58	38.49	22.83	<0.0001 <sup>§</sup>
C <sub>min0-24</sub> (ng/mL)	-	-	-	62.00	23.49	37.89	-
T <sub>max</sub> (h)	7.23	1.87	25.90	7.82	1.62	20.70	0.2808 <sup>£</sup>
T <sub>max</sub> <sup>*</sup> (h)	7.50	1.88	-	8.00	2.25	-	-
K <sub>el</sub> (h <sup>-1</sup> )	0.0719	0.0152	21.15	0.0615	0.0133	21.61	0.0028 <sup>£</sup>
T <sub>½ el</sub> (h)	10.05	2.09	20.79	11.91	3.33	27.99	0.0016 <sup>£</sup>
C <sub>ave</sub> (ng/mL)	-	-	-	105.47	29.98	28.42	-
AI	-	-	-	1.33	0.18	13.30	-
AI <sup>†</sup>	-	-	-	2.76	0.30	10.86	-
CL (mL/h)	-	-	-	8448.94	2094.06	24.78	-
Vd <sub>ss</sub> (mL)	-	-	-	138565.90	24649.17	17.79	-

(-) = Calculation not applicable

\* Medians and interquartile ranges are presented.

<sup>§</sup> Paired t-test was used on ln transformed data

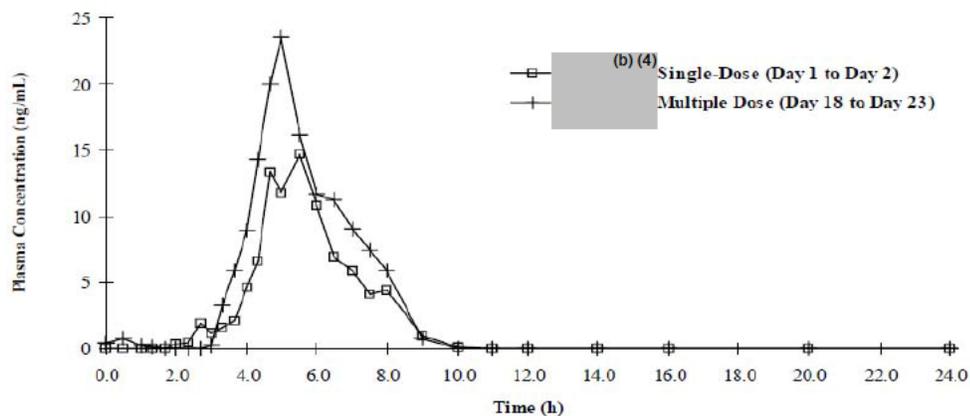
<sup>£</sup> Wilcoxon Signed-Rank test was used on untransformed data

<sup>†</sup> Calculated as AUC<sub>0,24</sub> day 18 / AUC<sub>0,24</sub> day 1

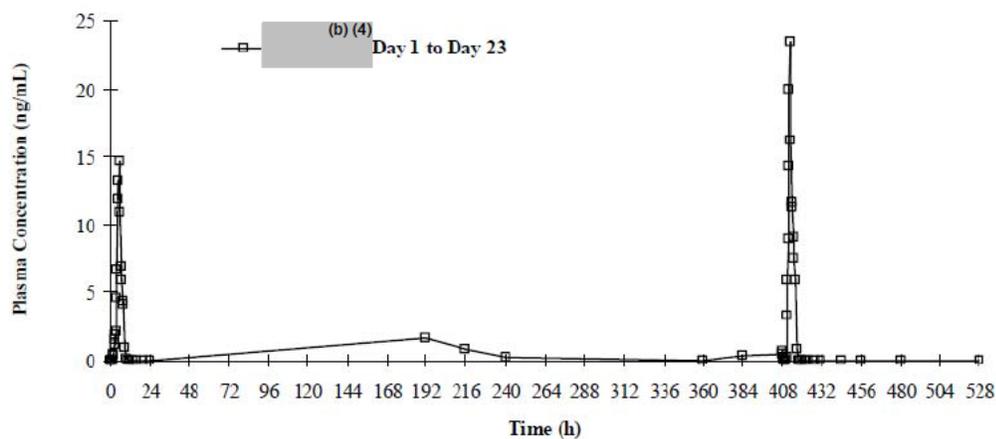
## Pyridoxine:

The data for pyridoxine and specifically for its metabolites are complex due to the variability and low concentrations (see **Appendix 4.2**). Overall, the concentration of pyridoxine was higher after multiple dose administration than after a single dose (**Figures 2.4.-2.5 and Table 2.6**).

**Figure 2.4. Pyridoxine Mean Plasma-Concentration Time Profiles (n=18)**



**Figure 2.5. Pyridoxine Mean Concentration Throughout the Study (n=18)**



**Table 2.6. Mean PK Parameters of Pyridoxine (n=18)**

Parameters	Single Dose Administration			Multiple Dose Administration			P-Value
	Mean	SD	CV (%)	Mean	SD	CV (%)	
AUC <sub>0-last</sub> (ng·h/mL)	39.34	16.53	42.01	59.30	33.90	57.17	-
AUC <sub>0-inf</sub> ** (ng·h/mL)	43.39	16.46	37.93	64.45	36.36	56.42	0.0008 <sup>§</sup>
AUC <sub>0-24</sub> *** (ng·h/mL)	40.70	16.45	40.41	62.74	33.68	53.68	<0.0001 <sup>§</sup>
C <sub>max</sub> (ng/mL)	32.57	15.03	46.14	46.05	28.30	61.45	0.0533 <sup>§</sup>
C <sub>min0-24</sub> (ng/mL)	-	-	-	0.00	0.00	-	-
T <sub>max</sub> (h)	5.71	1.53	26.69	5.62	1.25	22.21	0.6781 <sup>£</sup>
T <sub>max</sub> * (h)	5.50	1.83	-	5.25	1.62	-	-
K <sub>el</sub> ** (h <sup>-1</sup> )	1.7604	0.8190	46.52	1.6590	0.4872	29.37	0.7869 <sup>£</sup>
T <sub>1/2 el</sub> ** (h)	0.49	0.23	47.43	0.45	0.14	30.03	0.8926 <sup>£</sup>
C <sub>ave</sub> (ng/mL)	-	-	-	2.54	1.40	55.28	-
AI <sup>ψ</sup>	-	-	-	1.00	0.00	-	-
AI <sup>‡</sup> ***	-	-	-	1.59	0.51	31.69	-
CL*** (mL/h)	-	-	-	383966.86	155137.87	40.40	-
Vd <sub>ss</sub> <sup>¥</sup> (mL)	-	-	-	237378.42	136320.45	57.43	-

(-) = Calculation not applicable

\* Medians and interquartile ranges are presented.

\*\* For few subjects, the elimination rate constant could not be calculated.

\*\*\* For this parameter, N = 17 for the multiple dose administration.

ψ For this parameter, N = 15.

¥ For this parameter, N = 14.

§ Paired t-test was used on ln transformed data

£ Wilcoxon Signed-Rank test was used on untransformed data

‡ Calculated as AUC<sub>0-24</sub> day 18 / AUC<sub>0-24</sub> day 1

### Summary of Phase III Study (Study # DIC-301):

#### What is the Efficacy Profile?

As mentioned earlier, the sponsor conducted a Phase III study for the duration of 15 days in 256 pregnant women over 18 years of age with a gestational age of 7-14 weeks. The enrolled women had nausea and vomiting due to pregnancy with a Pregnancy Unique-Quantification of Emesis (PUQE) score >6 and not responding to conservative management. The drug was administered as follows:

- Day 1: **2** tablets at bedtime
- Day 2 and 3: If symptoms of nausea and vomiting persisted into the afternoon hours of Day 2 (i.e., PUQE Score above 3), the subject was directed to take her usual dose of **2** tablets ( (b) (4) or placebo) at bedtime and an additional tablet the next morning on Day 3.
- Day 4: Based upon assessment in the clinic on Day 4 (± 1 day), the subject may have been directed to take an additional 4th tablet mid-afternoon to control evening symptoms.
- The minimum assigned study medication was 2 tablets daily at bedtime, increasing when indicated to the maximal dosage of 4 tablets per day according to the timing, duration, severity, and frequency of the symptoms experienced by the subject.

**Duration:** The duration of study was 15 days with 14 days dosing period.

**Evaluation:** Clinical evaluations were conducted on Day 4 ( $\pm 1$  day), Day 8 ( $\pm 1$  day), and Day 15 ( $\pm 1$  day). Also, during these visits, one blood sample was collected. These samples were collected to explore the relationship between plasma concentration (trough) and PUQE score.

From this study, there was some change from baseline of PUQE score compared to placebo (**Table 2.7**). The difference between treatments was not that large. However, statistically it reaches a significant level. For detail on the clinical significance of these findings, please see the Medical Officer's review.

**Table 2.7. Primary Efficacy Analysis: Change from Baseline on Day 15 in PUQE Score.**

Data/ Category	Statistics	Treatment Group		P value for comparison
		Diclectin <sup>®</sup> (N = 131)	Placebo (N = 125)	
ITT-E via LOCF				
Baseline	N	131	125	
	Mean $\pm$ SD	9.0 $\pm$ 2.1	8.8 $\pm$ 2.1	
	Median	9.0	8.0	
	Min, Max	6, 15	6, 15	
Day 15 ( $\pm 1$ day)	N	131	125	
	Mean $\pm$ SD	4.2 $\pm$ 1.9	4.9 $\pm$ 2.3	
	Median	3.0	4.0	
	Min, Max	3, 11	3, 12	
Change from Baseline	N	131	125	
	Mean $\pm$ SD	-4.8 $\pm$ 2.7	-3.9 $\pm$ 2.6	0.006 <sup>1</sup>
	Median	-5.0	-4.0	
	Min, Max	-11, 3	-11, 2	

**Is there a Relationship between the concentration of doxylamine, pyridoxine, or pyridoxine metabolites and PUQE Score?**

As stated earlier, the sponsor attempted to explore the relationship between plasma concentration and PUQE score. Overall, the exposure-response analysis could not demonstrate any correlation between pyridoxine levels and doxylamine and change in PUQE scores on Days 4, 8, and 15 (**Table 2.8**).

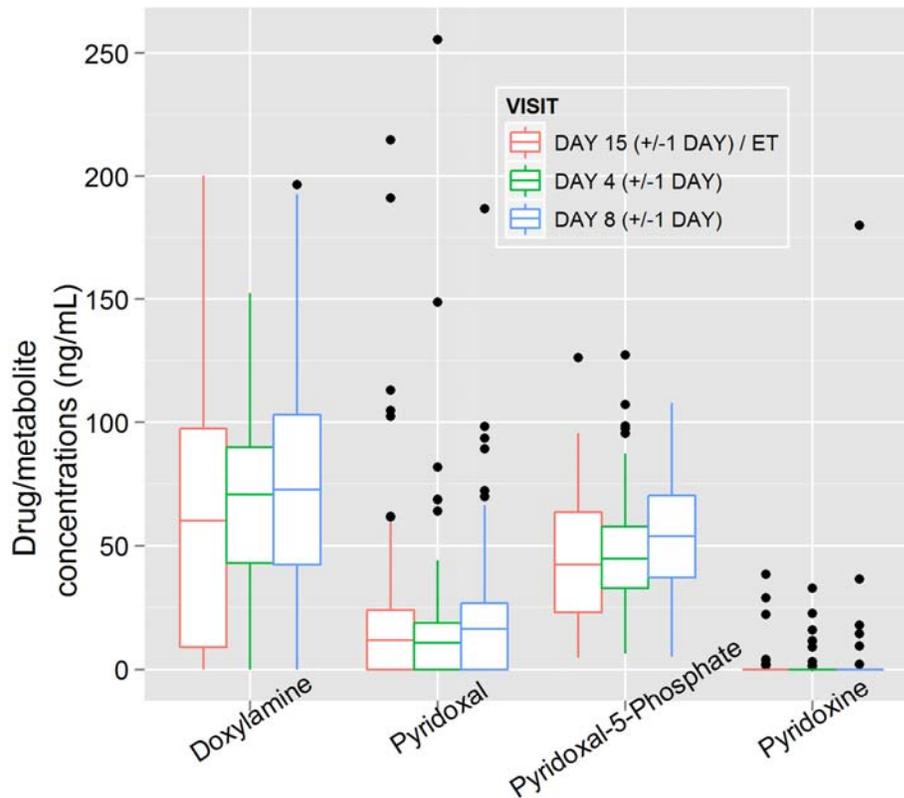
**Table 2.8. Exploratory Efficacy Analysis: Relationship between Change from Baseline in PUQE Score and Plasma Level of Pyridoxine and Doxylamine (source DIC-301 study report, Table 14.4.6).**

Visit	Statistics	Change from Baseline in PUQE Score	Plasma Level of Vitamin B <sub>6</sub>				
			Pyridoxine	Pyridoxal 5' -Phosphate	Pyridoxal	Doxylamine	Total Vitamin B <sub>6</sub>
DAY 4	N	126	117	121	120	121	121
	Means SD	-3.6 ± 2.6	0.946 ± 4.252	47.221 ± 21.703	15.559 ± 29.804	66.032 ± 33.598	63.567 ± 44.839
	Median	-4.0	0.000	44.720	10.790	70.680	55.650
	Min,Max	-11, 4	0.00, 32.78	6.50, 127.42	0.00, 255.55	0.00, 152.43	6.50, 365.50
	PCC(P-value) <sup>1</sup>		-0.090(0.340)	-0.015(0.871)	0.062(0.502)	-0.113(0.222)	0.024(0.793)
DAY 8	N	120	107	113	110	112	113
	Means SD	-4.6 ± 2.6	2.432 ± 17.832	53.379 ± 23.909	21.073 ± 26.162	75.152 ± 46.570	76.195 ± 53.206
	Median	-5.0	0.000	53.700	16.445	72.660	71.870
	Min,Max	-11, 3	0.00, 179.96	5.13, 107.83	0.00, 186.83	0.00, 196.53	5.13, 448.60
	PCC(P-value) <sup>1</sup>		0.187(0.055)	-0.070(0.466)	0.119(0.219)	-0.120(0.210)	0.092(0.333)
DAY 15	N	101	120	120	120	120	121
	Means SD	-5.2 ± 2.5	0.861 ± 4.817	44.968 ± 25.741	20.005 ± 32.904	61.844 ± 52.802	65.290 ± 52.706
	Median	-5.0	0.000	42.440	11.820	60.105	57.610
	Min,Max	-11, 3	0.00, 38.45	4.77, 126.28	0.00, 214.71	0.00, 200.38	4.77, 297.20
	PCC(P-value) <sup>1</sup>		0.019(0.849)	-0.007(0.947)	0.182(0.072)	-0.114(0.263)	0.106(0.293)

As noted in **Table 2.8** and **Figure 2.6**, there was high variability in the data, which is in agreement with the observations from the PK studies. In addition, only a single concentration measurement was obtained on the listed days which hinder evaluation of other potential PK parameters (i.e., AUC). Finally, these exploratory analyses are 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 is expected given pyridoxine's short half-life (i.e., ~30 min).

A full concentration time-course profile in this Phase III study is unavailable due to the implement sampling scheme; however, a summary of the mean exposures for doxylamine, pyridoxine, and pyridoxine metabolites is presented below in **Figure 2.6**.

**Figure 2.6. Pre-Dose (Trough) Plasma Concentrations on Days 4, 8, and 15 (Phase III study, DIC-301)**



**What are the Adverse Events in Phase III?**

Overall the drug was well tolerated as the most frequently observed adverse events in this study were abdominal pain, fatigue, back pain, dizziness, headache, and somnolence.

**What is the Pregnancy Outcome in Phase III?**

The study was conducted in 2009. No teratogenicity reports were received (see Medical Officer’s review). Based on ultrasound readings, there were no observed abnormalities at the end of the study, except subchorionic hemorrhage in one subject and a cyst in another subject. These observations do not appear to be related to the drug (see Medical Officer’s review).

## Reviewer's Comments:

Although it is not the same but comparable product, Bendectin®, has a long history with the FDA. Also, it has been marketed since 1956, the volume of utilization since it was originally marketed is questionable as it was discontinued from the US market for over 3 decades. It appears that its voluntary discontinuation from the market by the sponsor was due to litigation and the unfavorable publicity at that time in reference to teratogenic potential and other issues. Therefore, from the clinical pharmacology perspective, the duration of exposure can be critical for optimizing efficacy and minimizing any potential risk to the mother and fetus. This will be addressed carefully in the label.

According to the label, the sponsor is proposing three times daily administration of the drug as two tablets at night, one in the morning and one in mid-day for unlimited duration. In addition, the proposed label states that this drug is not to be administered on as needed basis (i.e., PRN). Furthermore, according to the patient's package insert, patients will be instructed to continue treatment with the drug without stopping, unless instructed by their health care provider (i.e., requires tapering). This dosing regimen will be addressed in the label to minimize extensive and unnecessarily lengthy exposure. As shown above, the drug and its active metabolites are accumulated in the body after multiple dosing (**see also Appendix 4.2**).

From the regulatory and clinical pharmacology perspective, the sponsor conducted three studies per the Agency's recommendations over the years. In the absence of the RLD, the critical study to qualify for 505(b)(2) and the approvability of the drug is the safety and efficacy study (DIC-301). This is a pivotal study that was conducted to justify for the proposed dosing regimen. It appears that the drug was administered during the clinical trial within 2 hours with respect to food intake.

The old two studies conducted in association with (b) (4) are questionable and have not been reviewed.

## Overall Conclusions:

The sponsor conducted two studies to characterize the PK of (b) (4) following multiple doses and the effect of food. The multiple doses study demonstrates accumulation of the drug and its metabolites. Food intake has been shown to significantly delay the Tmax and reduced the Cmax and AUC. Based on these studies the following conclusions can be made;

- Since the drug and its metabolite accumulate in the body, patients may need to be monitored and/or self-monitor for any signs of adverse events. Patients should be instructed to not abruptly stop the therapy without consulting their health-care provider.
- The drug should be taken on empty stomach with water or at least 2 hours *prior to or after* meals, if feasible. The 2 hours' time frame is to represent the Phase III study design. However, it is recognized that pregnant women may need to consume some light meals and/or snacks to reduce the nausea and vomiting. This may not have any major consequences on the PK of the drug compared to high fat/calories meals.

## 2.1 Bipharmaceutics

### What is the Formulation?

(b) (4) is a delayed release tablet containing 10 mg of doxylamine succinate and 10 mg of pyridoxine hydrochloride.

As stated in this review, originally, the combination of 10 mg doxylamine succinate, 10 mg pyridoxine hydrochloride and 10 mg dicyclomine hydrochloride was sold by Merrell Dow as Bendectin®. This three ingredient combination was launched in the United States in 1956. In 1976, Bendectin was reformulated and the ingredient, dicyclomine hydrochloride, was removed because it did not contribute to the antiemetic effectiveness. In Canada, the product Diclectin was approved in 1975 as a three-ingredient combination consisting of 10 mg doxylamine succinate, 10 mg pyridoxine hydrochloride and 10 mg dicyclomine hydrochloride. Similarly, the product was reformulated in 1979 to the two-ingredient combination of 10 mg doxylamine succinate and 10 mg pyridoxine hydrochloride (Table 2.3.1). For more discussion on the formulation, see ONDQA review.

**Table 2.3.1** (b) (4) **Formulation Composition**

<b>Strength (label claim):</b> Doxylamine Succinate 10 mg, Pyridoxine HCl 10 mg	
(b) (4)	<b>Quantity per Tablet</b>
Doxylamine Succinate USP	10.0 mg
Pyridoxine HCl USP	10.0 mg
Microcrystalline Cellulose 102 NF	(b) (4)
Magnesium Trisilicate USP	(b) (4)
Croscarmellose Sodium NF	(b) (4)
Magnesium Stearate NF (b) (4)	(b) (4)
Colloidal Silicon Dioxide NF	(b) (4)

## 2.2 Analytical Methods

### Are the Analytical Methods Adequate?

A validated LC/MS analytical method was used to determine the concentrations of doxylamine, pyridoxine and metabolites. As example of the validation, the following are the quality control (QC) parameters for measurement of doxylamine and pyridoxine.

### QC Parameters for Doxylamine:

Linearity:  $r^2 \geq 0.9978$

Calibration Curve Range: 0.51 to 253.60 ng/mL

Between-Run Accuracy: QC % nominal concentrations: 93.35 to 99.12%

Between-Run Precision: QC coefficients of variation: 2.18 to 4.15%

Within-Run Accuracy: QC % nominal concentrations: 95.18 to 101.78%

Within-Run Precision: QC coefficients of variation: 0.94 to 3.39%

Recovery of Analyte: QC means: 97.85, 98.35 and 98.08%

Recovery of Internal Standard: Mean: 111.00%

Matrix Selectivity: No significant interference observed in tested matrices for doxylamine and internal standard

Potentially Interfering Drugs: No effect on analyte quantitation

Interference Evaluation of Pyridoxine, Pyridoxal and Pyridoxal-5-phosphate:

No effect on analyte quantitation

Lower Limit of Quantitation (LLOQ): 0.51 ng/mL with a signal to noise ratio of 14

Dilution Integrity Accuracy: QC % nominal concentrations: 102.11 and 103.92%

Dilution Integrity Precision: QC coefficients of variation: 1.06 and 1.23%

### QC Parameters of Pyridoxine:

Linearity:  $r^2 \geq 0.9908$

Calibration Curve Range: 1.00 to 199.84 ng/mL

Between-Run Accuracy: QC % nominal concentrations: 100.43 to 103.07%

Between-Run Precision: QC coefficients of variation: 5.00 to 5.71%

Within-Run Accuracy: QC % nominal concentrations: 97.50 to 117.67%

Within-Run Precision: QC coefficients of variation: 4.27 to 14.77%

Recovery of Analyte: QC means: 92.49, 91.32 and 91.55%

Recovery of Internal Standard: Mean: 95.89%

Matrix Selectivity: No significant interference observed in tested matrices for pyridoxine and internal standard

Potentially Interfering Drugs: No effect on the quantitation of the analyte

Lower Limit of Quantitation (LLOQ): 1.00 ng/mL with a signal to noise ratio of 89

Dilution Integrity Accuracy: QC % nominal concentrations: 101.50 and 99.66%

Dilution Integrity Precision: QC coefficients of variation: 5.95 and 8.56%

### 3.0 Detailed Labeling Recommendations

Labeling comments will be made directly into the label during the internal labeling meetings and discussion with the sponsor.

#### **Dosing Instruction:**

#### **Bendectin (From PDR 1982):**

“2 Bendectin tablets at bedtime. In severe cases or when nausea occurs during the day. 1 additional Bendectin tablet in the morning and another in mid afternoon”

(b) (4) **(Sponsor Proposed):**



#### **General Labeling Comment:**

Based on the discussion at the Pre-NDA meeting held on December 14, 2009, the sponsor was advised to provide information from the literature on ADME (absorption, distribution, metabolism, and excretion) and the effect of intrinsic and extrinsic factors. Therefore, the clinical pharmacology section of the proposed label is largely associated with the old label, literature reports, and the data from the new submitted PK studies.

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

## 4.2. Individual Study Review

### 4.2.1 Study 70381 (Single and Multiple Doses PK):

**Title:** Single and Multiple Dose Safety and Pharmacokinetic Study of (b) (4) in Healthy Non-pregnant Female Subjects.

#### Objectives:

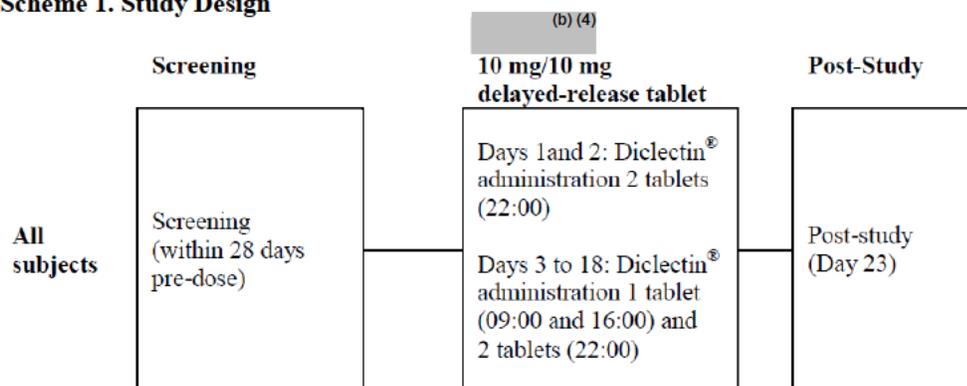
- The primary objective was to assess the pharmacokinetic profile of (b) (4) delayed-release tablets as a single and as multiple doses in healthy non-pregnant female volunteers.
- The secondary objective was to assess the safety and tolerability of (b) (4) in healthy non-pregnant female volunteers.

#### Design:

The study was conducted in 18 healthy female subjects between the ages of 18 to 45 years (Scheme 1). The drug was administered after overnight fast as follows:

- **Single Dose:** 2 tablets at 22:00 hours at two consecutive days (Days 1 and 2)
- **Multiple Doses:** 1 tablet at 09:00 and 16:00 and 2 tablets at 22:00 for 16 consecutive days (Days 3 to 18).

#### Scheme 1. Study Design



#### Drug Administration:

##### Days 1 and 2:

Subjects fasted for at least 2 hours before tablet administration. Tablets were administered with 240 mL water at approximately 22:00 hour. Then subjects were served snack at approximately 30 minutes later.

**Days 3 through 18:**

Subjects were dosed after fasting for at least 2 hours before dosing on 09:00, 16:00 and 22:00 hours. The tablets were administered with 240 mL water.

**Food and Fluid Intake:**

Subjects were served standardized meals at approximately 18:00, with a snack given at approximately 22:30 on Day -1, at approximately 06:00, 12:00, and 18:00 on Days 1 and 18, at approximately 06:00, 12:00, and 18:00, with a snack given at approximately 22:30 on Days 2 to 17 and on Day 19, and at approximately 06:00 on Day 20.

With the exception of the volume administered at the time of dosing, fluids were not permitted from 1 hour before dosing to 1 hour after the dosing on Days 1 and 18 for the 22:00 dosing, but water was permitted *ad libitum* at all other times.

**PK Samples:**

PK blood samples were collected for the determination of doxylamine, pyridoxine, pyridoxamine, pyridoxamine 5'-phosphate, pyridoxal, and pyridoxal 5'-phosphate as follows:

**Day -1:** 22:00; Day 1: 10:00 & 22:00 (Pre-Dose);

**Day 1 and 2:** 0.50, 1, 1.33, 1.67, 2, 2.33, 2.67, 3, 3.33, 3.67, 4, 4.33, 4.67, 5, 5.50, 6, 6.50, 7, 7.50, 8, 9, 10, 11, 12, 14, 16, 20, 24 hours post-dose (Prior to Day 2 dose);

**Days 9, 10, 11, 16, 17 and 18:** Trough levels prior to 22:00 dose;

**Day 18-23:** Pre-dose, 0.50, 1, 1.33, 1.67, 2, 2.33, 2.67, 3, 3.33, 3.67, 4, 4.33, 4.67, 5, 5.50, 6, 6.50, 7, 7.50, 8, 9, 10, 11, 12, 14, 16, 20, 24, 36, 48, 72, and 120 hours post-dose.

**Subjects:**

All subjects were non-pregnant females as shown in the following Table.

Category	Statistic	Diclectin <sup>®</sup>
Age (years)	Mean ± SD	33 ± 9
	Range	20 - 45
	Median	30
	N	18
Age Groups	<18	0
	18-40	13 (72.2 %)
	41-64	5 (27.8 %)
	65-75	0
	>75	0
Race	White	18 (100.0 %)
	Black	0
	Asian	0
	Other	0
Ethnicity	Not Hispanic	17 (94.4 %)
	Hispanic	1 (5.6 %)
Height (cm)	Mean ± SD	163.2 ± 5.4
	Range	153.0 - 172.0
	Median	162.5
	N	18
Weight (kg)	Mean ± SD	66.4 ± 8.9
	Range	53.5 - 83.6
	Median	64.9
	N	18
BMI (kg/m <sup>2</sup> )	Mean ± SD	24.9 ± 2.6
	Range	20.1 - 29.4
	Median	24.7
	N	18

All subjects were females.

### Results:

The results of the study are summarized in **Figures 4.2.1.1-12** and **Tables 4.2.1.1-6**.

It should be noted that the terminal elimination phase following a single dose administration is not adequately characterized for some of the analytes over 24 hours sampling period. Therefore, the data after multiple dosing are more adequate to characterize the PK profiles of the drug product than after single dose. Pyridoxal 5'-phosphate and pyridoxamine 5'-phosphate concentrations were corrected for baseline. Based on the data the following conclusions can be made:

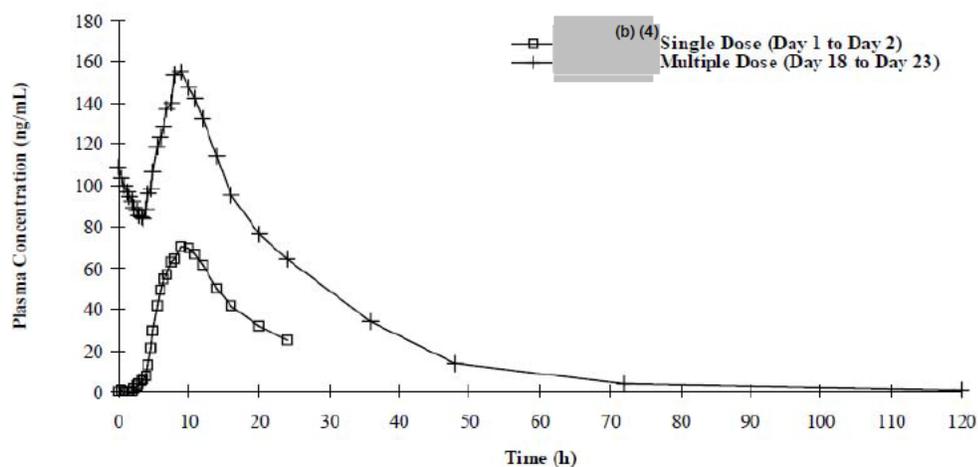
- Doxylamine exposure (C<sub>max</sub> and AUC) increased after multiple dosing relative to single dose administration. The T<sub>max</sub> was not affected by multiple doses.
- Unlike doxylamine and other components, pyridoxine did not appear to accumulate following multiple dosing. This is consistent with its short half-life (~30 min).
- Overall, there was high variability in the data and in particular for pyridoxine and all pyridoxine metabolites.
- Overall, the PK pyridoxine and pyridoxine metabolites (pyridoxal, pyridoxal 5'-phosphate, pyridoxamine and pyridoxamine 5'-phosphate) is complex.

The following is brief summary of the PK information for each component of the product.

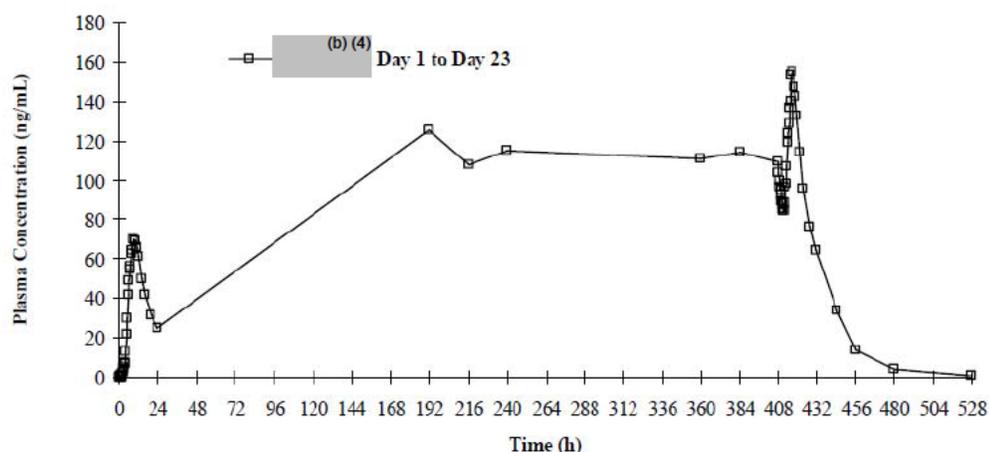
#### Doxylamine PK Data:

The concentration-time profiles for doxylamine demonstrated an increase in plasma concentrations after multiple doses compared to a single-dose administration (**Figures 4.2.1.1 and 4.2.1.2**). The C<sub>max</sub> and AUC were increased by approximately 2 and 3 fold after multiple doses compared to single dose, respectively (**Table 4.2.11**). The T<sub>max</sub> was comparable after single and multiple-dose administrations (**Table 4.2.1.1**). Also, the half-life did not change much with frequency of dosing as it was approximately 10 h and 12 h after single and multiple dose administration, respectively (**Table 4.2.1.1**).

**Figure 4.2.1.1. Doxylamine Mean Plasma-Concentration Time Profiles (n=18)**



**Figure 4.2.1.2. Doxylamine Mean Concentration Throughout the Study (n=18)**



**Table 4.2.1.1. Mean PK Parameters of Doxylamine (n=18)**

Parameters	Single Dose Administration			Multiple Dose Administration			P-Value
	Mean	SD	CV (%)	Mean	SD	CV (%)	
AUC <sub>0-18h</sub> (ng·h/mL)	911.40	205.62	22.56	3661.27	1279.16	34.94	-
AUC <sub>0-24h</sub> (ng·h/mL)	1280.90	369.32	28.83	3721.46	1318.50	35.43	<0.0001 <sup>§</sup>
AUC <sub>0-24h</sub> (ng·h/mL)	911.40	205.62	22.56	2531.40	719.47	28.42	<0.0001 <sup>§</sup>
C <sub>max</sub> (ng/mL)	83.26	20.62	24.76	168.58	38.49	22.83	<0.0001 <sup>§</sup>
C <sub>min0-24h</sub> (ng/mL)	-	-	-	62.00	23.49	37.89	-
T <sub>max</sub> (h)	7.23	1.87	25.90	7.82	1.62	20.70	0.2808 <sup>£</sup>
T <sub>max</sub> * (h)	7.50	1.88	-	8.00	2.25	-	-
K <sub>el</sub> (h <sup>-1</sup> )	0.0719	0.0152	21.15	0.0615	0.0133	21.61	0.0028 <sup>£</sup>
T <sub>½ el</sub> (h)	10.05	2.09	20.79	11.91	3.33	27.99	0.0016 <sup>£</sup>
C <sub>ave</sub> (ng/mL)	-	-	-	105.47	29.98	28.42	-
AI	-	-	-	1.33	0.18	13.30	-
AI <sup>†</sup>	-	-	-	2.76	0.30	10.86	-
CL (mL/h)	-	-	-	8448.94	2094.06	24.78	-
Vd <sub>ss</sub> (mL)	-	-	-	138565.90	24649.17	17.79	-

(-) = Calculation not applicable

\* Medians and interquartile ranges are presented.

<sup>§</sup> Paired t-test was used on ln transformed data

<sup>£</sup> Wilcoxon Signed-Rank test was used on untransformed data

<sup>†</sup> Calculated as AUC<sub>0,24</sub> day 18 / AUC<sub>0,24</sub> day 1

### Pyridoxine PK Data:

In contrary to doxylamine, the concentration-time profiles for pyridoxine demonstrated a slight increase in plasma concentrations after multiple doses compared to a single-dose administration (Figure 4.2.1.3 and 4.2.1.4). The C<sub>max</sub> was increased from 32 to 46 ng/mL and AUC increased from 43 to 64 ng h/mL after single and multiple dose administration, respectively (Table

4.2.1.2). However, the T<sub>max</sub> was similar under both conditions of administration for single- and multiple administrations (Table 4.2.1.2).

Pre-dose concentrations observed on Days 9, 10, 11, 16, 17 and 18 for pyridoxine were near or lower than the limit of quantitation, suggesting that pyridoxine did not accumulate after multiple dose administrations. This is expected considering the rapid absorption and the short elimination half-life of pyridoxine as it was approximately 30 min after single and multiple dose administration (Table 4.2.1.2).

Figure 4.2.1.3. Pyridoxine Mean Plasma-Concentration Time Profiles (n=18)

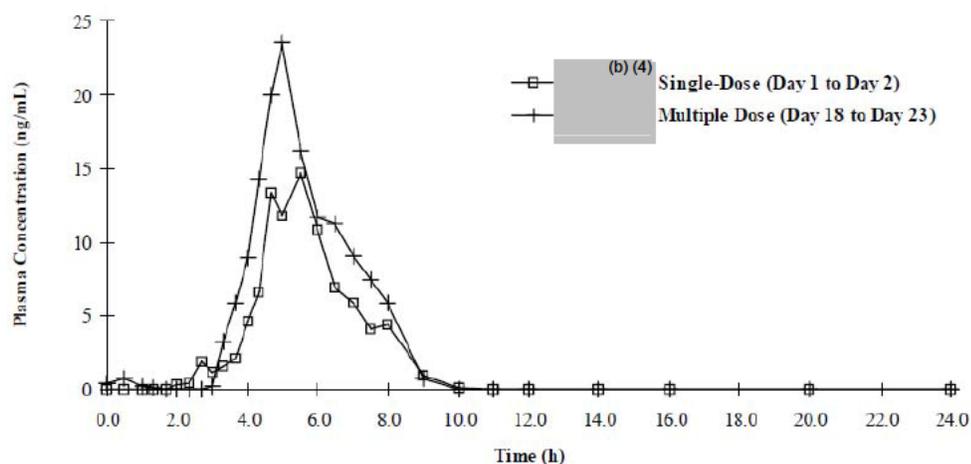
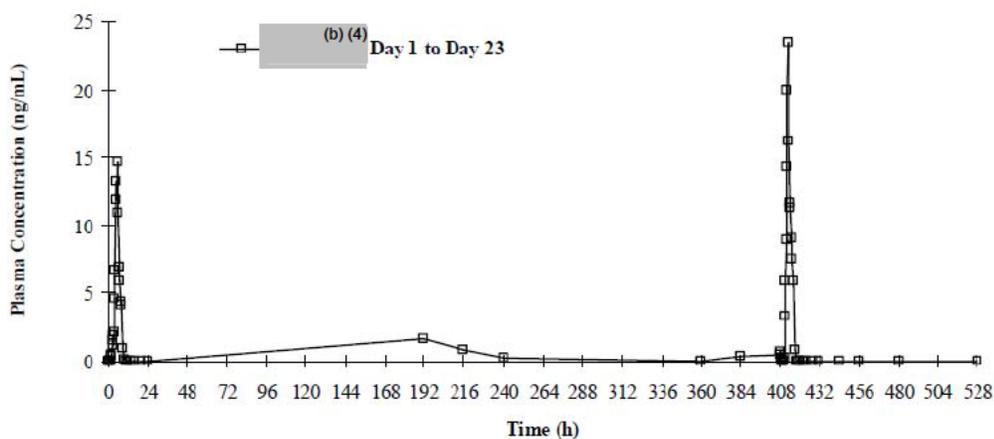


Figure 4.2.1.4. Pyridoxine Mean Concentration Throughout the Study (n=18)



**Table 4.2.1.2. Mean PK Parameters of Pyridoxine (n=18)**

Parameters	Single Dose Administration			Multiple Dose Administration			P-Value
	Mean	SD	CV (%)	Mean	SD	CV (%)	
AUC <sub>0-last</sub> (ng·h/mL)	39.34	16.53	42.01	59.30	33.90	57.17	-
AUC <sub>0-inf</sub> ** (ng·h/mL)	43.39	16.46	37.93	64.45	36.36	56.42	0.0008 <sup>§</sup>
AUC <sub>0-24</sub> *** (ng·h/mL)	40.70	16.45	40.41	62.74	33.68	53.68	<0.0001 <sup>§</sup>
C <sub>max</sub> (ng/mL)	32.57	15.03	46.14	46.05	28.30	61.45	0.0533 <sup>§</sup>
C <sub>min0-24</sub> (ng/mL)	-	-	-	0.00	0.00	-	-
T <sub>max</sub> (h)	5.71	1.53	26.69	5.62	1.25	22.21	0.6781 <sup>£</sup>
T <sub>max</sub> * (h)	5.50	1.83	-	5.25	1.62	-	-
K <sub>el</sub> ** (h <sup>-1</sup> )	1.7604	0.8190	46.52	1.6590	0.4872	29.37	0.7869 <sup>£</sup>
T <sub>1/2 el</sub> ** (h)	0.49	0.23	47.43	0.45	0.14	30.03	0.8926 <sup>£</sup>
C <sub>ave</sub> (ng/mL)	-	-	-	2.54	1.40	55.28	-
AI <sup>ψ</sup>	-	-	-	1.00	0.00	-	-
AI <sup>‡</sup> ***	-	-	-	1.59	0.51	31.69	-
CL*** (mL/h)	-	-	-	383966.86	155137.87	40.40	-
Vd <sub>ss</sub> <sup>¥</sup> (mL)	-	-	-	237378.42	136320.45	57.43	-

(-) = Calculation not applicable

\* Medians and interquartile ranges are presented.

\*\* For few subjects, the elimination rate constant could not be calculated.

\*\*\* For this parameter, N = 17 for the multiple dose administration.

ψ For this parameter, N = 15.

¥ For this parameter, N = 14.

§ Paired t-test was used on ln transformed data

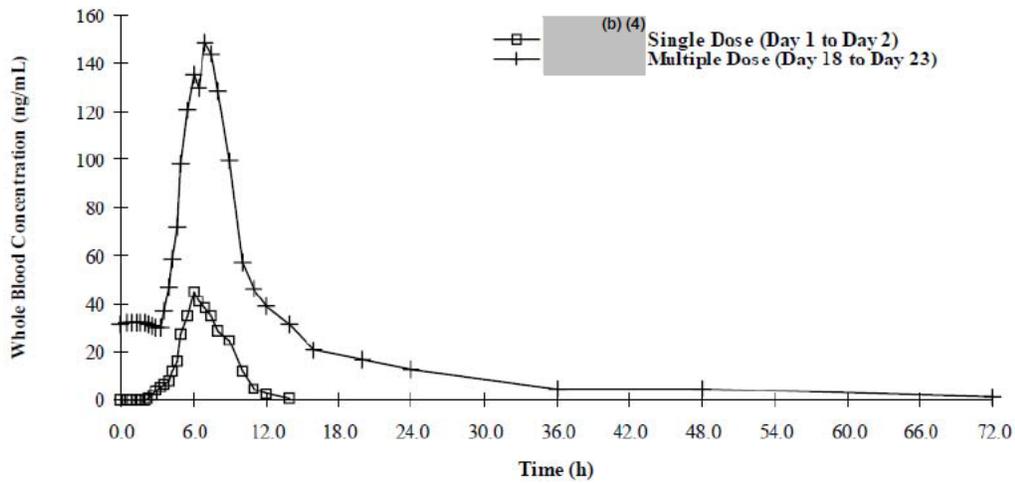
£ Wilcoxon Signed-Rank test was used on untransformed data

‡ Calculated as AUC<sub>0-24</sub> day 18 / AUC<sub>0-24</sub> day 1

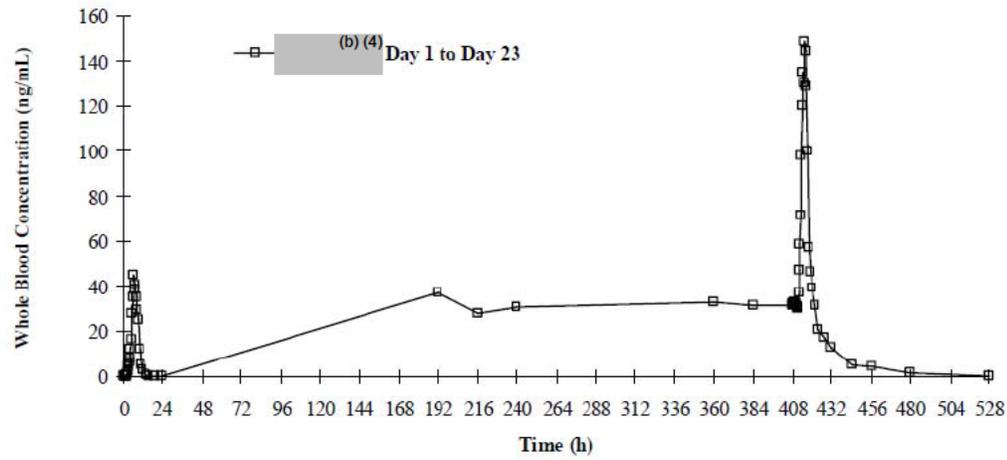
### Pyridoxal PK Data:

The concentration-time profiles for pyridoxal demonstrated a marked increase in concentrations after multiple doses compared to a single-dose administration (**Figures 4.2.1.5 and 4.2.1.6**). The C<sub>max</sub> was increased by approximately 2.8 fold and AUC (0-inf) was increased by approximately 7.5 fold (i.e., from 211.60 to 1587.22 ng/h/mL, **Table 4.2.1.3**). The half-life was also markedly increased from 1.29 h after single dose to 19.44 h after multiple dose administration (i.e., ~15 fold, **Table 4.2.1.3**). The T<sub>max</sub> was similar under both conditions of administration with mean values of 6.50 h and 6.75 h for single- and multiple-dose administrations, respectively.

**Figure 4.2.1.5. Pyridoxal Mean Plasma-Concentration Time Profiles (n=18)**



**Figure 4.2.1.6. Pyridoxal Mean Concentration Throughout the Study (n=18)**



**Table 4.2.1.3. Mean PK Parameters of Pyridoxal (n=18)**

Parameters	Single Dose Administration			Multiple Dose Administration			P-Value
	Mean	SD	CV (%)	Mean	SD	CV (%)	
AUC <sub>0-last</sub> (ng·h/mL)	187.46	44.69	23.84	1296.71	363.05	28.00	-
AUC <sub>0-inf</sub> ** (ng·h/mL)	211.60	46.09	21.78	1587.22	550.04	34.65	<0.0001 <sup>§</sup>
AUC <sub>0-24</sub> (ng·h/mL)	195.13	46.18	23.67	1147.19	241.34	21.04	<0.0001 <sup>§</sup>
C <sub>max</sub> (ng/mL)	74.29	21.80	29.34	210.02	54.36	25.88	<0.0001 <sup>§</sup>
C <sub>min0-24</sub> (ng/mL)	-	-	-	12.55	1.54	12.28	-
T <sub>max</sub> (h)	6.50	1.37	21.07	6.75	1.18	17.46	0.5173 <sup>£</sup>
T <sub>max</sub> * (h)	6.00	1.00	-	6.75	1.50	-	-
K <sub>el</sub> ** (h <sup>-1</sup> )	0.6004	0.1739	28.96	0.0538	0.0304	56.55	<0.0001 <sup>£</sup>
T <sub>½ el</sub> ** (h)	1.29	0.50	39.27	19.44	14.46	74.37	<0.0001 <sup>‡</sup>
C <sub>ave</sub> (ng/mL)	-	-	-	47.80	10.06	21.04	-
AI**	-	-	-	1.77	0.82	46.39	-
AI <sup>‡</sup> (-)	-	-	-	6.09	1.55	25.53	-
CL (mL/h)	-	-	-	18171.26	3762.68	20.71	-
Vd <sub>ss</sub> ** (mL)	-	-	-	463221.19	288763.33	62.34	-

(-) = Calculation not applicable

\* Medians and interquartile ranges are presented.

\*\* For few subjects the elimination rate constant could not be calculated.

<sup>§</sup> Paired t-test was used on ln transformed data

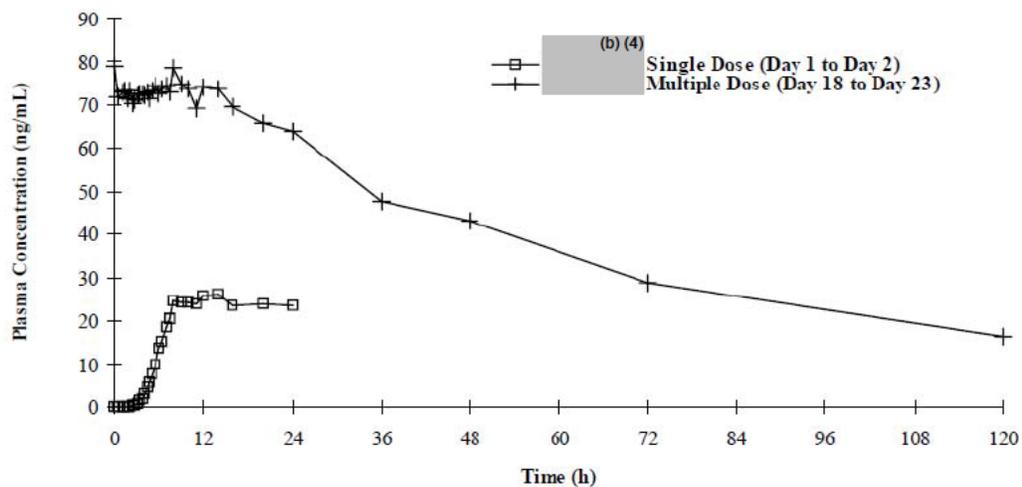
<sup>£</sup> Wilcoxon Signed-Rank test was used on untransformed data

<sup>‡</sup> Calculated as AUC<sub>0-24</sub> day 18 / AUC<sub>0-24</sub> day 1

### Pyridoxal 5'-Phosphate:

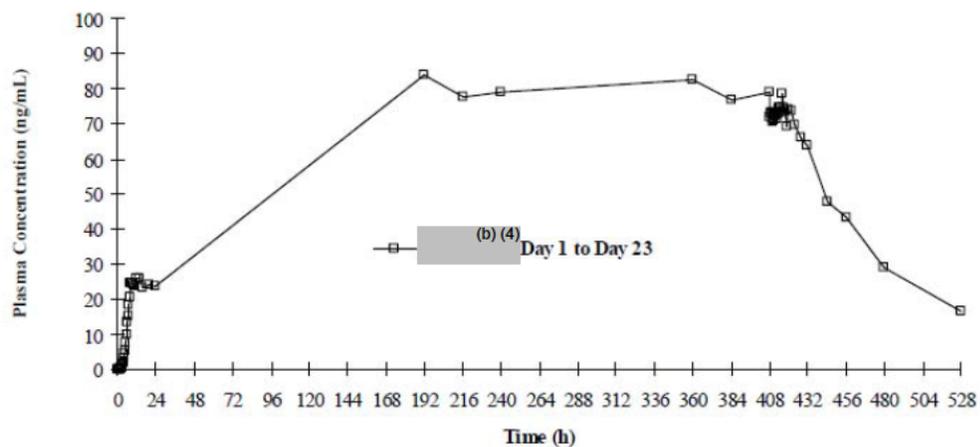
The concentration-time profiles for baseline corrected data of pyridoxal 5'-phosphate demonstrated an increase in plasma concentrations after multiple doses compared to a single-dose administration (**Figures 4.2.1.7 and 4.2.1.8**). The C<sub>max</sub> was increased by approximately 3.8 fold from 30 ng/L to 85 ng/mL and the AUC (0-inf) by approximately 4 fold from 1536 to 6070 ng h/mL after single and multiple dose administration respectively (**Table 4.2.1.4**). The half-life was also increased from approximately 37 h to 53 h after single and multiple doses, respectively. In contrary to other analytes, the T<sub>max</sub> was decreased after multiple administrations compared to single dose administration, with mean values of 11.7 h and 6.28 h for single- and multiple-dose administrations, respectively. It should be noted, however, that there was a wide variability in T<sub>max</sub> data with a %CV of 105%.

**Figure 4.2.1.7. Baseline Corrected Pyridoxal 5'-Phosphate Mean Plasma-Concentration Time Profiles (n=18)**



**Figure 4.2.1.8. Baseline Corrected Pyridoxal 5'-Phosphate Mean Concentration Throughout the Study (n=18)**

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**Table 4.2.1.4. Mean PK Parameters of Pyridoxal 5'-Phosphate (n=18)**

Parameters	Single Dose Administration			Multiple Dose Administration			P-Value
	Mean	SD	CV (%)	Mean	SD	CV (%)	
AUC <sub>0-last</sub> (ng·h/mL)	442.01	155.63	35.21	4766.31	1137.10	23.86	-
AUC <sub>0-inf</sub> ** (ng·h/mL)	1536.39	721.51	46.96	6099.69	1383.66	22.68	-
AUC <sub>0-24</sub> *** (ng·h/mL)	442.01	155.63	35.21	1725.01	358.01	20.75	0.1231 <sup>§</sup>
C <sub>max</sub> (ng/mL)	30.01	10.03	33.42	84.91	16.85	19.85	<0.0001 <sup>§</sup>
C <sub>min0-24</sub> (ng/mL)	-	-	-	59.24	14.70	24.81	-
T <sub>max</sub> (h)	11.7	5.3	44.99	6.28	6.64	105.77	0.0133 <sup>§</sup>
T <sub>max</sub> * (h)	11.5	6.0	-	4.92	8.76	-	-
K <sub>el</sub> ** (h <sup>-1</sup> )	0.0204	0.0078	38.35	0.0139	0.0035	25.16	-
T <sub>½ el</sub> ** (h)	36.99	12.01	32.48	53.46	15.30	28.62	-
C <sub>ave</sub> (ng/mL)	-	-	-	70.37	15.82	22.49	-
AI	-	-	-	3.74	0.91	24.41	-
AI <sup>†</sup> ***	-	-	-	3.98	0.67	16.76	-
CL*** (mL/h)	-	-	-	12034.64	2324.43	19.31	-
V <sub>d<sub>ss</sub></sub> *** (mL)	-	-	-	973426.44	448586.78	46.08	-

(-) = Calculation not applicable

\* Medians and interquartile ranges are presented.

\*\* For many subjects the elimination rate constant could not be calculated.

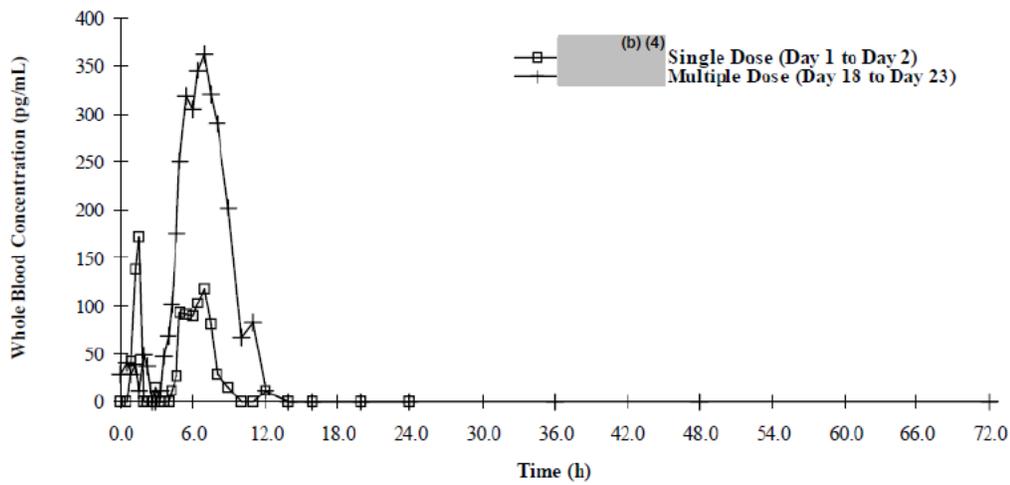
\*\*\* For this parameter, N = 17.

<sup>§</sup> Paired t-test was used on ln transformed data<sup>†</sup> Wilcoxon Signed-Rank test was used on untransformed data<sup>‡</sup> Calculated as AUC<sub>0-24</sub> day 18 / AUC<sub>0-24</sub> day 1**Pyridoxamine PK Data:**

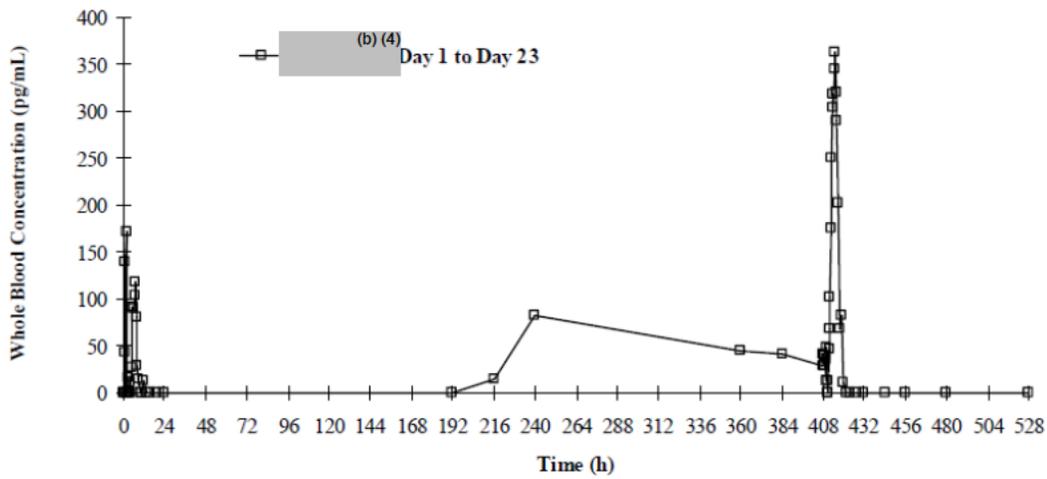
The concentration-time profiles for pyridoxamine demonstrated increased concentrations after multiple doses compared to a single-dose administration (**Figures 4.2.1.9 and 4.2.1.10**). The increase was mainly observed within the first 24 hours of administration (**Figure 4.2.1.9 and Table 4.2.1.5**). It should be noted that due to variability in the data, the terminal elimination phase was not adequately determined in many subjects and hence the AUC (0-inf) value are not adequately determined either. Therefore, the comparison should be based on the data for AUC (0-last) and AUC (0-24 h) (**Table 4.2.1.5**). This also affected the terminal elimination half-life values which was longer after a single dose administration (10.98h) than after multiple dose administration (2.90h).

The T<sub>max</sub> was similar under both conditions of administration with mean values of 5.88 h and 6.58 h for single- and multiple-dose administrations, respectively.

**Figure 4.2.1.9. Pyridoxamine Mean Plasma-Concentration Time Profiles (n=18)**



**Figure 4.2.1.10. Pyridoxamine Mean Concentration Throughout the Study (n=18)**



**Table 4.2.1.5. Mean PK Parameters of Pyridoxamine (n=18)**

Parameters	Single Dose Administration			Multiple Dose Administration			P-Value
	Mean	SD	CV (%)	Mean	SD	CV (%)	
AUC <sub>0-inf</sub> (pg·h/mL)	467.28	514.41	110.09	1607.17	696.39	43.33	-
AUC <sub>0-inf</sub> ** (pg·h/mL)	4121.04	2712.73	65.83	2607.78	824.65	31.62	-
AUC <sub>0-24</sub> *** (pg·h/mL)	565.61	527.50	93.26	1786.34	683.05	38.24	<0.0001 <sup>§</sup>
C <sub>max</sub> (pg/mL)	532.21	736.88	138.46	535.57	157.72	29.45	0.0737 <sup>§</sup>
C <sub>min0-24</sub> (pg/mL)	-	-	-	0.00	0.00	-	-
T <sub>max</sub> (h)	5.88	2.13	36.23	6.58	1.39	21.05	0.4348 <sup>£</sup>
T <sub>max</sub> * (h)	6.00	2.03	-	7.00	2.00	-	-
K <sub>el</sub> ** (h <sup>-1</sup> )	0.0932	0.0749	80.33	0.2913	0.1182	40.58	-
T <sub>½ el</sub> ** (h)	10.98	8.82	80.33	2.90	1.52	52.33	-
C <sub>ave</sub> (pg/mL)	-	-	-	72.13	29.28	40.60	-
AI **	-	-	-	1.01	0.02	2.45	-
AI <sup>‡</sup> †	-	-	-	6.17	6.87	111.41	-
CL <sup>‡</sup> (mL/h)	-	-	-	12813737.20	4826116.19	37.66	-
Vd <sub>ss</sub> ** † (mL)	-	-	-	58551283.79	42569754.90	72.71	-

<sup>†</sup> For the calculation of the PK parameters, N = 15 for the single dose administration.

(-) = Calculation not applicable

\* Medians and interquartile ranges are presented.

\*\* For many subjects, the elimination rate constant could not be calculated.

\*\*\* For this parameter, N = 15 for the single dose administration and N = 17 for the multiple dose administration.

† For this parameter, N = 14.

‡ For this parameter, N = 17.

§ Paired t-test was used on ln transformed data

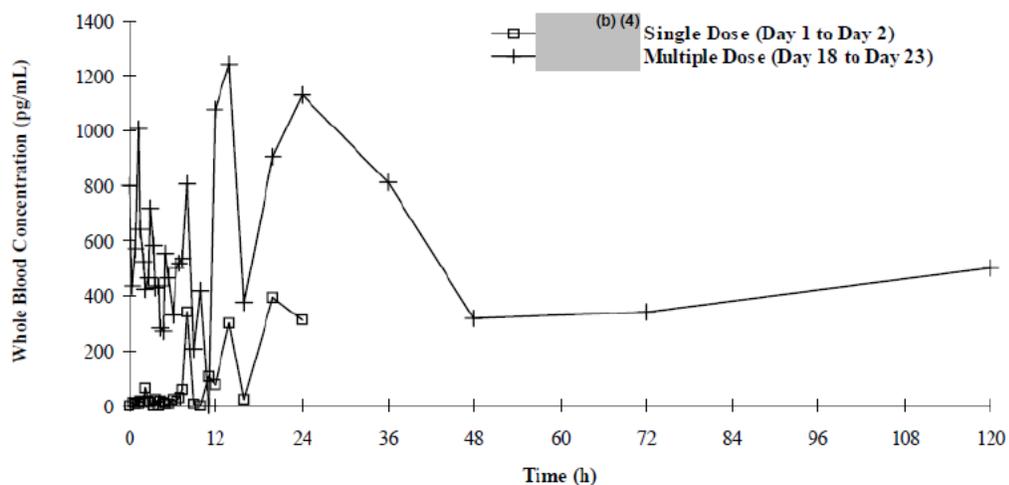
£ Wilcoxon Signed-Rank test was used on untransformed data

† Calculated as AUC<sub>0-24</sub> day 18 / AUC<sub>0-24</sub> day 1

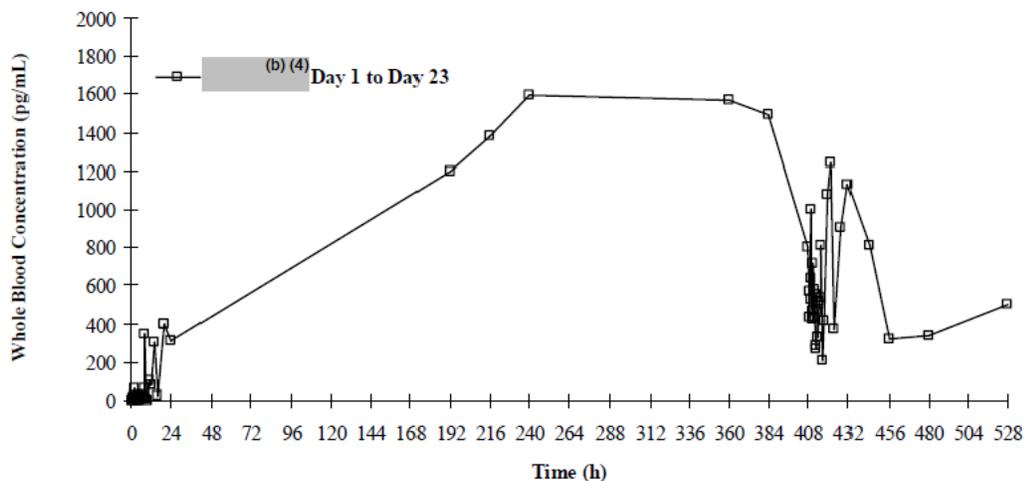
#### Pyridoxamine 5'-Phosphate PK Data:

The concentration-time profiles for baseline corrected data of pyridoxamine 5'-phosphate data demonstrated a marked increase in concentrations after multiple doses compared to a single-dose administration (**Figures 4.2.1.11 and 4.2.1.12**). The C<sub>max</sub> was increased by approximately 3 fold from 739 to 2291 ng/mL and AUC (0-inf) by 18 fold from 522 to 94459 ng h/mL after single and multiple dose, respectively (**Table 4.2.1.6**). The half-life was also increased from 5.42 h after a single dose to 44 h after multiple dose administration (**Table 4.2.1.6**). The T<sub>max</sub> was similar under both conditions of administration with mean values of 14.8 h and 12.4 h for single- and multiple-dose administrations, respectively.

**Figure 4.2.1.11. Baseline Corrected Pyridoxamine 5'-Phosphate Mean Plasma-Concentration Time Profiles (n=18)**



**Figure 4.2.1.12. Baseline Corrected Pyridoxamine 5'-Phosphate Mean Concentration Throughout the Study (n=18)**



**Table 4.2.1.6. Mean PK Parameters of Pyridoxamine 5'-phosphate (n=18)**

Parameters	Single Dose Administration			Multiple Dose Administration			P-Value
	Mean	SD	CV (%)	Mean	SD	CV (%)	
AUC <sub>0-last</sub> (pg·h/mL)	3457.82	2393.20	69.21	58859.26	58292.60	99.04	-
AUC <sub>0-inf</sub> ** (pg·h/mL)	5231.93	3839.39	73.38	94459.22	58010.53	61.41	-
AUC <sub>0-24</sub> (pg·h/mL)	3503.62	2385.10	68.08	17085.23	14937.64	87.43	<0.0001 <sup>§</sup>
C <sub>max</sub> (pg/mL)	739.29	450.99	61.00	2290.90	1703.36	74.35	<0.0001 <sup>§</sup>
C <sub>min0-24</sub> (pg/mL)	-	-	-	109.94	253.47	230.54	-
T <sub>max</sub> (h)	14.8	6.6	44.54	12.4	11.2	90.58	0.2257 <sup>‡</sup>
T <sub>max</sub> * (h)	14.0	11.2	-	11.0	11.0	-	-
K <sub>el</sub> ** (h <sup>-1</sup> )	0.1584	0.0985	62.19	0.0189	0.0097	51.38	-
T <sub>1/2 el</sub> ** (h)	5.42	3.37	62.19	44.33	21.70	48.95	-
C <sub>ave</sub> (pg/mL)	-	-	-	711.88	622.40	87.43	-
AI**	-	-	-	3.20	1.29	40.18	-
AI <sup>ψ</sup>	-	-	-	6.67	6.18	92.58	-
CL (mL/h)	-	-	-	3463120.15	4554498.98	131.51	-
Vd <sub>ss</sub> ** <sup>ψ</sup> (mL)	-	-	-	195291598.15	269782002.87	138.14	-

(-) = Calculation not applicable

\* Medians and interquartile ranges are presented.

\*\* For many subjects the elimination rate constant could not be calculated.

<sup>ψ</sup> For this parameter, N = 4.

<sup>§</sup> Paired t-test was used on ln transformed data

<sup>‡</sup> Wilcoxon Signed-Rank test was used on untransformed data

<sup>‡</sup> Calculated as AUC<sub>0-24</sub> day 18 / AUC<sub>0-24</sub> day 1

### Reviewer's Comments:

The objective of the study was to characterize the PK profiles of (b) (4) following single and multiple dose administration. There was high variability in the data. This made the determination of the terminal elimination rate constants difficult and inadequate. Therefore, in some situations the determination of AUC (0-infinity) as well as the terminal elimination half-lives could not be determined.

Based on this study, all components demonstrated increase in exposure (C<sub>max</sub> and AUC) following multiple doses compared to single dose. All components demonstrated accumulation, after multiple doses, except pyridoxine which exhibits a rapid absorption and a short half-life of approximately 30 min. All other components have a long half-life ranging from approximately 1 hour after a single dose to approximately 50 hours after multiple doses.

### Conclusion:

The study clearly demonstrates accumulation of the parent drugs and its known metabolites after multiple doses. Due to the high variability in plasma concentrations, the generated PK parameters should be interpreted carefully.

#### 4.2.2. Study 70294 (Effect of Food):

**Title:** “Randomized, open-label, 2-way crossover, relative bioavailability study of doxylamine-pyridoxine 10 mg-10 mg ( (b) (4) ) delayed-release tablets following a 2 x 10 mg-10 mg dose in healthy adult females under fasting and fed conditions”

##### **Objectives:**

The objective of this study was to assess the effect of food on the bioavailability of 2 (b) (4) tablets under fasting and fed conditions.

##### **Design:**

This was a single dose 2-way crossover comparative bioavailability performed under fed and fasting conditions with a washout period of 27 days. The study was conducted in 42 non-pregnant healthy female subjects between the ages of 18 to 45 years. The drug was administered after overnight fast as follows:

- **Treatment A (Fasting):** 2 tablets were administered after overnight fast in the morning. Subjects continued fasting for 4 hours post dosing.
- **Treatment B (Fed):** 2 tablets were administered after overnight fast and 30 minutes after high-fat, high-calorie breakfast. Subjects continued fasting for 4 hours post dosing.

##### **Drug Administration:**

Subjects fasted overnight prior to each treatment arm. In the fed arm, subjects consumed breakfast 30 minutes before drug administration.

##### **Food and Fluid Intake:**

Subjects were served a high-fat, high-caloric breakfast of between 800 to 1000 calories (approximately 150 calories from protein, 250 calories from carbohydrates, and 500 to 600 calories from fat). The breakfast consisted of two eggs fried in butter, 2 slices of toast with butter, 2 strips of bacon, approximately 128 g of hash brown potatoes, and 200 mL of whole milk. Subjects were required to completely consume this breakfast prior to drug administration. Subjects were dosed as specified in the protocol, and were subsequently fasted for a period of at least 4 hours. Tablets were administered with 240 mL water in each treatment.

With the exception of the volume administered at the time of dosing and with the pre-dose breakfast given to the subjects who received treatment B only, fluids were not permitted from 1 hour before dosing to 1 hour after dosing, but water was permitted *ad libitum* at all other times.

### PK Samples:

PK blood samples were collected for the determination of doxylamine, pyridoxine, pyridoxamine, pyridoxamine 5'-phosphate, pyridoxal, and pyridoxal 5'-phosphate at -1 hour, -0.5 hour and 5 minutes before drug administration and at 1, 1.50, 2, 2.50, 3, 3.50, 4, 4.50, 5, 5.50, 6, 7, 8, 9, 10, 11, 12, 13, 14, 16, 24, 36, 48, 96, 144, 192 and 216 hours post-dose.

### Results:

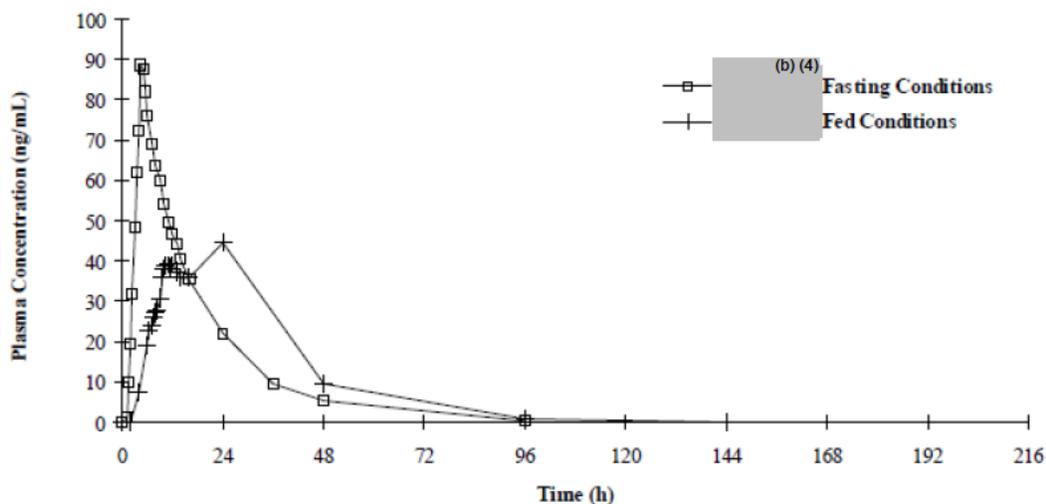
As in the previous study, there was high variability in the data that limit adequate determination the terminal elimination phase, half-lives, and AUC 0-inf. Several subjects had no detectable concentration in the terminal phase.

However, overall impression from this study is that food delayed the T<sub>max</sub> and reduced C<sub>max</sub> and AUC for all components. The following is a brief summary of the data for each component.

### Doxylamine PK Data:

The concentration-time profiles for doxylamine demonstrate a delayed T<sub>max</sub> and a reduced C<sub>max</sub> when (b) (4) is taken under fed conditions as compared when taken under fasting conditions (Figure 4.2.2.1 and Table 4.2.2.1).

Figure 4.2.2.1. Doxylamine Mean Plasma-Concentration Time Profiles (n=42)



**Table 4.2.2.1. Mean PK Parameters of Doxylamine (n=42)**

Parameters	(b) (4) Fasting Conditions (A) N = 42			(b) (4) Fed Conditions (B) N = 42		
	Mean	SD	CV (%)	Mean	SD	CV (%)
AUC <sub>0-t</sub> (ng·h/mL)	1407.20	336.94	23.94	1488.03	463.21	31.13
AUC <sub>0-inf</sub> * (ng·h/mL)	1447.89	332.18	22.94	1579.01	422.72	26.77
AUC <sub>t/inf</sub> * (%)	97.02	1.75	1.80	96.08	4.22	4.39
C <sub>max</sub> (ng/mL)	94.90	18.40	19.39	75.74	16.59	21.90
T <sub>max</sub> (h)	5.13	3.39	66.09	14.9	7.4	49.22
T <sub>max</sub> ** (h)	4.50	0.50	-	11.8	14.9	-
K <sub>el</sub> * (h <sup>-1</sup> )	0.0586	0.0147	25.07	0.0581	0.0118	20.25
T <sub>1/2 el</sub> * (h)	12.64	3.43	27.15	12.48	2.88	23.11

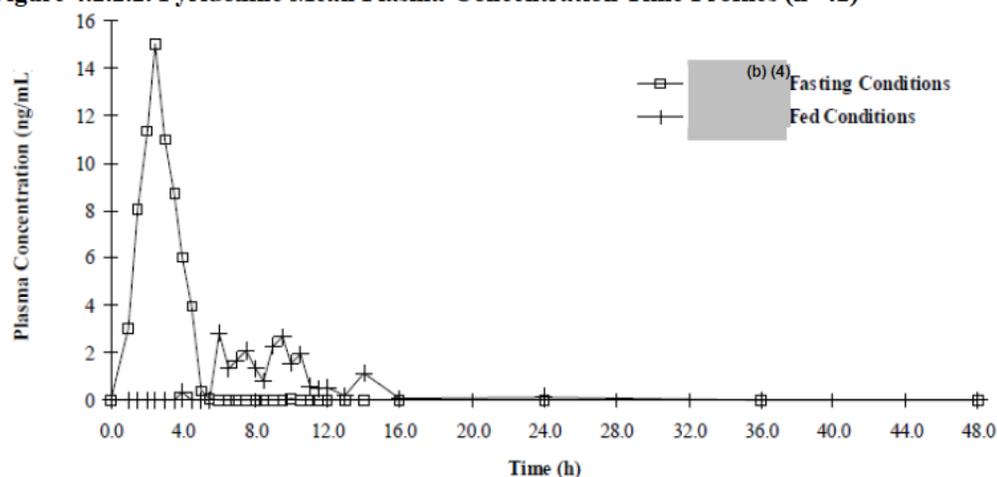
\* For these parameters, N = 37 for Treatment B.

\*\* Medians and interquartile ranges are presented.

**Pyridoxine and Pyridoxal PK Data:**

The concentration-time profiles of pyridoxine and pyridoxal under fasting and fed conditions demonstrated a significantly delayed in T<sub>max</sub> as well as a reduced C<sub>max</sub> when (b) (4) is taken under fed conditions compared when taken under fasting conditions (Figure 4.2.2.2 and Figure 4.2.2.3 and Tables 4.2.2.2 and 4.2.2.3.). There was no detectable concentration during the first 6 hours during the fed arm, especially for pyridoxine, whereas there were substantially detectable concentrations during the fasting arm.

**Figure 4.2.2.2. Pyridoxine Mean Plasma-Concentration Time Profiles (n=42)**



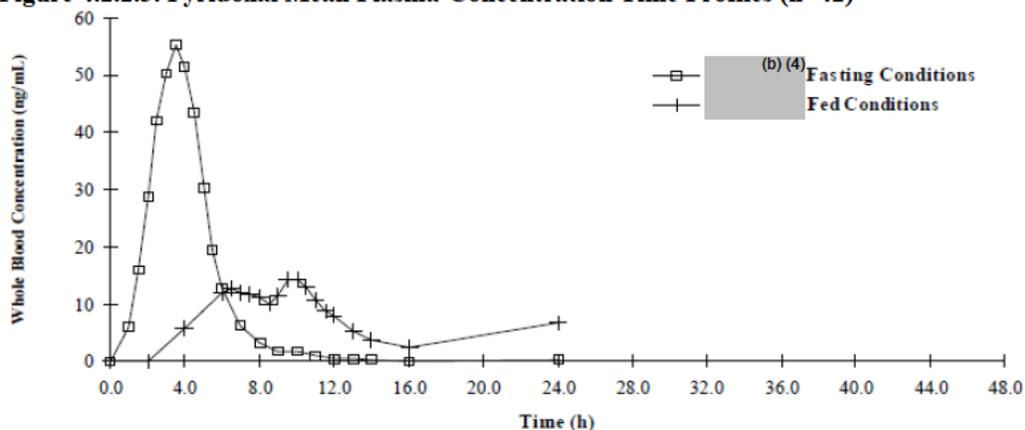
**Table 4.2.2.2. Mean PK Parameters of Pyridoxine (n=42)**

Parameters	(b) (4) Fasting Conditions (A) N = 42			(b) (4) Fed Conditions (B) N = 33		
	Mean	SD	CV (%)	Mean	SD	CV (%)
AUC <sub>0-t</sub> (ng·h/mL)	33.75	13.71	40.61	18.32	14.52	79.26
AUC <sub>0-inf</sub> * (ng·h/mL)	39.48	12.85	32.55	24.18	13.99	57.88
AUC <sub>t/inf</sub> * (%)	95.51	5.26	5.51	92.61	6.28	6.78
C <sub>max</sub> (ng/mL)	35.54	21.40	60.22	13.71	10.77	78.60
T <sub>max</sub> (h)	2.50	0.94	37.73	9.25	3.96	42.83
T <sub>max</sub> ** (h)	2.50	1.00	-	9.00	4.48	-
K <sub>el</sub> * (h <sup>-1</sup> )	2.1215	0.7242	34.14	1.6606	0.5901	35.53
T <sub>½el</sub> * (h)	0.37	0.16	42.25	0.48	0.21	42.84

\* For these parameters, N = 31 for Treatment A and N = 18 for Treatment B.

\*\* Medians and interquartile ranges are presented.

**Figure 4.2.2.3. Pyridoxal Mean Plasma-Concentration Time Profiles (n=42)**



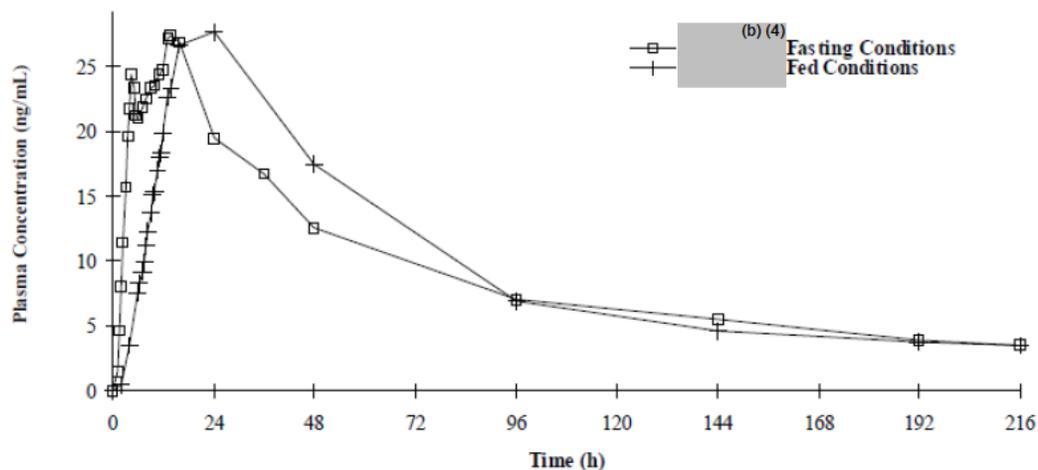
**Table 4.2.2.3. Mean PK Parameters of Pyridoxal (n=18)**

Parameters	(b) (4) Fasting Conditions (A) N = 42			(b) (4) Fed Conditions (B) N = 41		
	Mean	SD	CV (%)	Mean	SD	CV (%)
AUC <sub>0-t</sub> (ng·h/mL)	193.66	53.95	27.86	138.40	70.85	51.19
AUC <sub>0-inf</sub> * (ng·h/mL)	231.20	71.75	31.03	197.11	76.34	38.73
AUC <sub>t/inf</sub> * (%)	86.01	8.68	10.10	81.23	13.94	17.16
C <sub>max</sub> (ng/mL)	85.39	21.53	25.21	45.63	25.00	54.79
T <sub>max</sub> (h)	3.23	0.95	29.41	12.7	6.6	51.96
T <sub>max</sub> ** (h)	3.03	1.50	-	10.0	8.0	-
K <sub>el</sub> * (h <sup>-1</sup> )	0.5337	0.2804	52.53	0.4662	0.2323	49.84
T <sub>½el</sub> * (h)	2.14	2.18	101.92	2.01	1.25	62.31

### Pyridoxal 5'-Phosphate:

The concentration-time profiles for baseline corrected data of pyridoxal 5'-phosphate demonstrates delayed in  $T_{max}$  under fed conditions. However, the observed  $C_{max}$  appears to be comparable in in both arms (**Figure 4.2.2.4 and Table 4.2.2.4**).

**Figure 4.2.2.4. Baseline Corrected Pyridoxal 5'-Phosphate Mean Plasma-Concentration Time Profiles (n=42)**



**Table 4.2.2.4. Mean PK Parameters of Pyridoxal 5'-Phosphate (n=42)**

Parameters	<sup>(b) (4)</sup> Fasting Conditions (A) N = 42			<sup>(b) (4)</sup> Fed Conditions (B) N = 42		
	Mean	SD	CV (%)	Mean	SD	CV (%)
$AUC_{0-t}$ (ng·h/mL)	1975.12	881.98	44.65	2096.63	916.50	43.71
$AUC_{0-inf}^*$ (ng·h/mL)	2415.23	1087.78	45.04	2838.60	1469.78	51.78
$AUC_{v_{inf}}^*$ (%)	83.50	13.03	15.60	82.03	13.53	16.50
$C_{max}$ (ng/mL)	29.75	10.93	36.73	34.16	11.88	34.78
$T_{max}$ (h)	11.8	7.3	61.84	17.8	5.7	31.87
$T_{max}^{**}$ (h)	13.0	9.4	-	16.0	10.0	-
$K_{el}^*$ ( $h^{-1}$ )	0.0115	0.0084	73.48	0.0126	0.0161	127.64
$T_{1/2 el}^*$ (h)	81.60	42.17	51.68	94.61	56.93	60.18

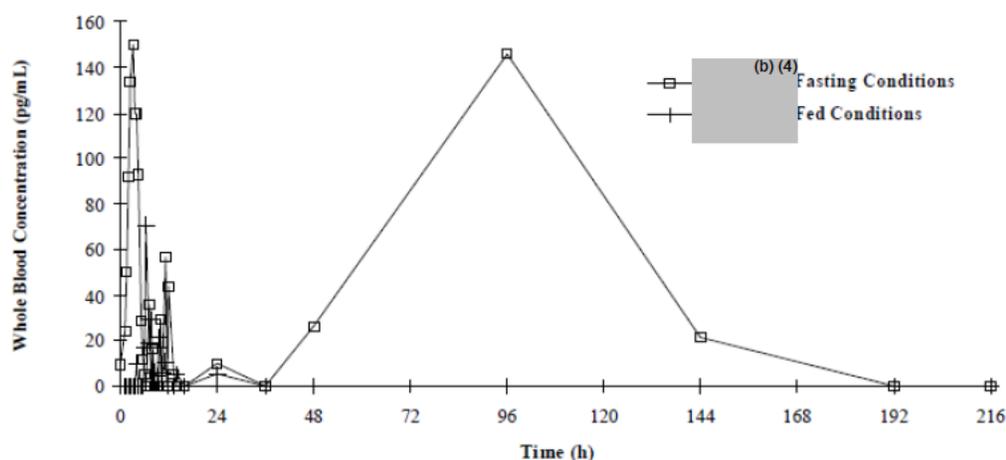
\* For these parameters, N = 36 for Treatment A and N = 29 for Treatment B.

\*\* Medians and interquartile ranges are presented.

### Pyridoxamine PK Data:

The concentration-time profiles for pyridoxamine is strange as there was a peak at 96 hours in fasting arm (**Figure 4.2.2.5 and Table 4.2.2.5**). Such a peak is unexplainable. Nevertheless, the concentrations in fed arms were very low and undetectable after 24 hour of administration.

**Figure 4.2.2.5. Pyridoxamine Mean Plasma-Concentration Time Profiles (n=42)**



**Table 4.2.2.5. Mean PK Parameters of Pyridoxamine (n=42)**

Parameters	(b) (4) Fasting Conditions (A) N = 39			(b) (4) Fed Conditions (B) N = 16		
	Mean	SD	CV (%)	Mean	SD	CV (%)
AUC <sub>0-t</sub> (pg·h/mL)	5646.73	19038.59	337.16	342.15	399.55	116.78
AUC <sub>0-inf</sub> * (pg·h/mL)	1530.63	822.85	53.76	3239.49	-	-
AUC <sub>t/inf</sub> * (%)	41.73	15.09	36.16	27.19	-	-
C <sub>max</sub> (pg/mL)	487.32	651.49	133.69	367.37	381.33	103.80
T <sub>max</sub> (h)	9.66	21.68	224.49	9.34	4.60	49.19
T <sub>max</sub> ** (h)	3.00	2.01	-	8.75	3.63	-
K <sub>el</sub> * (h <sup>-1</sup> )	0.3213	0.1569	48.84	0.0936	-	-
T <sub>1/2 el</sub> * (h)	3.08	2.54	82.68	7.40	-	-

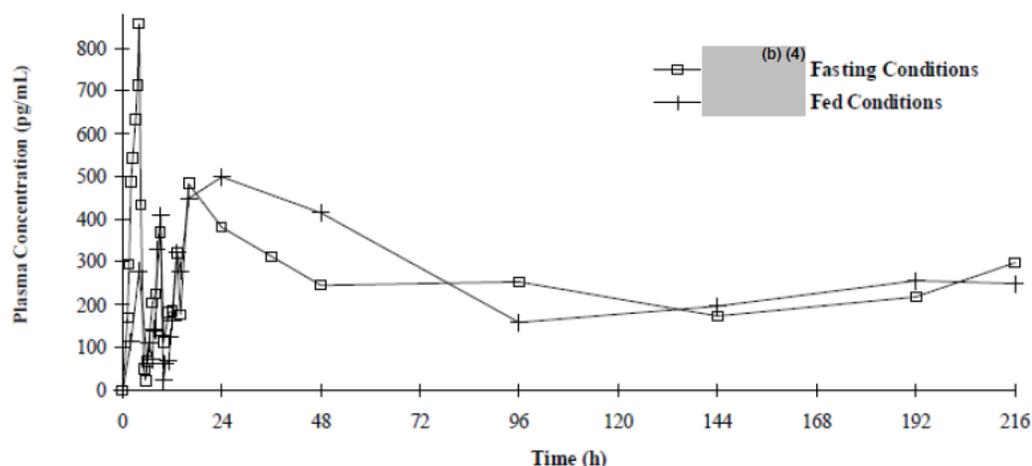
\* For these parameters, N = 6 for Treatment A and N = 1 for Treatment B.

\*\* Medians and interquartile ranges are presented.

**Pyridoxamine 5'-Phosphate PK Data:**

The concentration-time profiles for baseline corrected data of pyridoxamine 5'-phosphate data demonstrated a delayed T<sub>max</sub> as well as a reduced C<sub>max</sub> when (b) (4) was administered under fed conditions compared to fasting conditions (Figure 4.2.2.6. and Table 4.2.2.6).

**Figure 4.2.2.6. Baseline Corrected Pyridoxamine 5'-Phosphate Mean Plasma-Concentration Time Profiles (n=42)**



**Table 4.2.2.6. Mean PK Parameters of Pyridoxamine 5'-phosphate (n=18)**

Parameters	(b) (4) Fasting Conditions (A) N = 42			(b) (4) Fed Conditions (B) N = 42		
	Mean	SD	CV (%)	Mean	SD	CV (%)
AUC <sub>0-t</sub> (pg·h/mL)	51967.10	41092.51	79.07	52045.43	47013.65	90.33
AUC <sub>0-inf</sub> * (pg·h/mL)	47527.96	28290.13	59.52	184751.02	259063.79	140.22
AUC <sub>t-inf</sub> * (%)	72.50	21.34	29.43	70.94	26.84	37.83
C <sub>max</sub> (pg/mL)	1325.08	745.22	56.24	994.09	652.73	65.66
T <sub>max</sub> (h)	28.5	62.2	218.47	47.4	64.6	136.33
T <sub>max</sub> ** (h)	4.00	12.50	-	20.0	39.0	-
K <sub>el</sub> * (h <sup>-1</sup> )	0.0534	0.1136	212.61	0.0294	0.0395	134.05
T <sub>1/2 el</sub> * (h)	66.47	51.29	77.17	105.49	147.79	140.10

\* For these parameters, N = 8.

\*\* Medians and interquartile ranges are presented.

**Overall Summary of PK Parameters:**

Considering the high variability in the data, overall the AUC zero to the last measurable concentration (AUC 0-t) and AUC zero to infinity (AUC 0-inf) for almost all the analytes are lower in fed conditions compared to fasting conditions (Tables 4.2.2.7 and 4.2.2.8). The same conclusion can be drawn for C<sub>max</sub> (Table 4.2.2.9). The most affected PK parameters was the T<sub>max</sub> as it was significantly delayed for some of the analytes and in particular for doxylamine and pyridoxine (Table 4.2.2.10).

**Table 4.2.2.7. Comparison of AUC (0-t) in Fed and Fasting Condition**

AUC <sub>0-t</sub>	<sup>(b) (4)</sup> under fasting conditions (A) (2 x 10 mg-10 mg)	<sup>(b) (4)</sup> under fed conditions (B) (2 x 10 mg-10 mg)
Doxylamine	1407.20 ± 336.94	1488.03 ± 463.21
Pyridoxine	33.75 ± 13.71	18.32 ± 14.52
Pyridoxal	193.66 ± 53.95	138.40 ± 70.85
Pyridoxal 5'-phosphate	1975.12 ± 881.98	2096.63 ± 916.50
Pyridoxamine	5646.73 ± 19038.59	342.15 ± 399.55
Pyridoxamine 5'-phosphate	51967.10 ± 41092.51	52045.43 ± 47013.65

**Table 4.2.2.8. Comparison of AUC (0-inf) in Fed and Fasting Condition**

AUC <sub>0-inf</sub>	<sup>(b) (4)</sup> under fasting conditions (A) (2 x 10 mg-10 mg)	<sup>(b) (4)</sup> under fed conditions (B) (2 x 10 mg-10 mg)
Doxylamine	1447.89 ± 332.18	1579.01 ± 422.72
Pyridoxine	39.48 ± 12.85	24.18 ± 13.99
Pyridoxal	231.20 ± 71.75	197.11 ± 76.34
Pyridoxal 5'-phosphate	2415.23 ± 1087.78	2838.60 ± 1469.78
Pyridoxamine	1530.63 ± 822.85	3239.49
Pyridoxamine 5'-phosphate	47527.96 ± 28290.13	184751.02 ± 259063.79

**Table 4.2.2.9 Comparison of C<sub>max</sub> in Fed and Fasting Condition C<sub>max</sub>**

C <sub>max</sub>	<sup>(b) (4)</sup> under fasting conditions (A) (2 x 10 mg-10 mg)	<sup>(b) (4)</sup> under fed conditions (B) (2 x 10 mg-10 mg)
Doxylamine	94.90 ± 18.40	75.74 ± 16.59
Pyridoxine	35.54 ± 21.40	13.71 ± 10.77
Pyridoxal	85.39 ± 21.53	45.63 ± 25.00
Pyridoxal 5'-phosphate	29.75 ± 10.93	34.16 ± 11.88
Pyridoxamine	487.32 ± 651.49	367.37 ± 381.33
Pyridoxamine 5'-phosphate	1325.08 ± 745.22	994.09 ± 652.73

**Table 4.2.2.10. Comparison of Tmax in Fed and Fasting Condition:**

$T_{max}$	(b) (4) under fasting conditions (A) (2 x 10 mg-10 mg)	(b) (4) under fed conditions (B) (2 x 10 mg-10 mg)
Doxylamine	5.13 ± 3.39	14.9 ± 7.4
Pyridoxine	2.50 ± 0.94	9.25 ± 3.96
Pyridoxal	3.23 ± 0.95	12.7 ± 6.6
Pyridoxal 5'-phosphate	11.8 ± 7.3	17.8 ± 5.7
Pyridoxamine	9.66 ± 21.68	9.34 ± 4.60
Pyridoxamine 5'-phosphate	28.5 ± 62.2	47.4 ± 64.6

**Reviewer's Comments:**

The objective of the study was to characterize the PK profiles of (b) (4) following fed and fasting conditions. There was high variability in the data. This made the determination of the terminal elimination rate constant difficult and inadequate. Therefore, in some situations the determination of AUC (0-infinity) as well as the terminal elimination half-lives could not be determined.

Based on this study, food delayed and reduced Cmax for almost all the analyzed components in this study. The most complex data was observed for pyridoxine metabolites. However, overall food reduced the Cmax and AUC for these metabolites. However, the clinical significance of these highly variable data is unknown.

**Conclusion:**

The study clearly demonstrated a delay in Tmax and reduction in Cmax. There was also some reduction in AUC of the parent drugs and its known metabolites when given with food. Due to the high variability and unpredictability in blood levels caused by food, (b) (4) may need to be given on empty stomach with water. This is also recommended in the sponsor's proposed label which states that (b) (4) take (b) (4) on an empty stomach with a glass of water".

However, the sponsor's recommendation in reference to food intake may not be practically feasible. It is recognized that pregnant women may need to consume some light food and/or snacks to reduce the nausea and vomiting. The use of these light meals is not expected to have any major consequences on the PK of the drug compared to high fat/calories meals. Alternatively, based on Phase III study design, the drug may be given at least 2 hours *prior to or after* meals, if feasible.

### 4.3 Filing Memo

## Final (August 13, 2012)

<b>Office of Clinical Pharmacology</b>			
<i>New Drug Application Filing and Review Form</i>			
<u>General Information About the Submission</u>			
	Information		Information
NDA/BLA Number	021876	Brand Name	Diclegis (submitted August 3, 2012)
OCP Division (I, II, III, IV, V)	III	Generic Name	Doxylamine succinate/ pyridoxine HCl (10mg/10mg)
Medical Division	DRUP	Drug Class	Antihistamine/ Vitamin
OCP Reviewer	Sayed (Sam,) Al Habet, R.Ph., Ph.D.	Indication	Treatment of Nausea and Vomiting of Pregnancy
OCP Secondary Reviewer/Signer	Myong-Jin Kim, Pharm.D.	Dosage Form	Delayed Release tablets (10 mg/10mg)
Pharmacometrics Reviewer		Dosing Regimen	2 tablets QHS, 1 tablet QAM, and 1 tablet QPM
Date of Submission	June 8, 2012 (cover letter)	Route of Administration	Oral
Estimated Due Date of OCP Review	December 2012	Sponsor	Duchesnay/ Quebec, Canada and OptumInsight, Baskin Ridge, NJ
Medical Division Due Date	January 2013	Priority Classification	Standard
PDUFA Due Date	March 30, 2013		

<i>Clin. Pharm. and Biopharm. Information</i>				
	<b>“X” if included at filing</b>	<b>Number of studies submitted</b>	<b>Number of studies reviewed</b>	<b>Critical Comments If any</b>
<b>STUDY TYPE</b>		X		
<b>Table of Contents present and sufficient to locate reports, tables, data, etc.</b>		X		
<b>Tabular Listing of All Human Studies</b>		X		
<b>HPK Summary</b>		X		
<b>Labeling</b>		X		
<b>Reference Bioanalytical and Analytical Methods</b>				
<b>I. Clinical Pharmacology</b>	X			
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -	X	1		
<b>Healthy Volunteers-</b>				
single dose:	X	1		
multiple dose:	X	1		
<b>Patients-</b>				
single dose:				
multiple dose:				
<b>Dose Proportionality</b>				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
<b>Drug-drug interaction studies</b>				
-				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
<b>Subpopulation studies -</b>				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				

hepatic impairment:				
<b>PD -</b>				
Phase 2:				
Phase 3:				
<b>PK/PD -</b>				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
<b>Population Analyses -</b>				
Data rich:				
Data sparse:				
<b>II. Biopharmaceutics</b>				
<b>Absolute bioavailability</b>				
<b>Relative bioavailability -</b>	x	1		
solution as reference:		1		
alternate formulation as reference:				
<b>Bioequivalence studies -</b>				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
<b>Food-drug interaction studies</b>		2		
<b>Bio-waiver request based on BCS</b>				
<b>BCS class</b>				
<b>Dissolution study to evaluate alcohol induced dose-dumping</b>				
<b><i>In vitro</i> Penetration Studies</b>				
<b>Genotype/phenotype studies</b>				
<b>Chronopharmacokinetics</b>				
<b>Pediatric development plan</b>		1		
<b>Literature References</b>		1		
<b>Total Number of Studies</b>				

On **initial** review of the NDA/BLA application for filing:

	<b>Content Parameter</b>	<b>Yes</b>	<b>No</b>	<b>N/A</b>	<b>Comment</b>
<b>Criteria for Refusal to File (RTF)</b>					
1	Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?			X	Relative bioavailability to oral solution
2	Has the applicant provided metabolism and drug-drug interaction information?			X	
3	Has the sponsor submitted bioavailability data satisfying the CFR requirements?	X			
4	Did the sponsor submit data to allow the evaluation of the validity of the analytical assay?	X			
5	Has a rationale for dose selection been submitted?	X			
6	Is the clinical pharmacology and biopharmaceutics section of the NDA organized, indexed and paginated in a manner to allow substantive review to begin?	X			
7	Is the clinical pharmacology and biopharmaceutics section of the NDA legible so that a substantive review can begin?	X			
8	Is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work?	X			
<b>Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)</b>					
<b>Data</b>					
9	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?	X			
10	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?			X	
<b>Studies and Analyses</b>					
11	Is the appropriate pharmacokinetic information submitted?	X			
12	Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?			X	
13	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?			X	

14	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?			X	
15	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?			X	<12 years old waived (Per meeting dated December 14, 2009, IND 072300). Deferral for 12 to (b) <sub>(4)</sub> years.
16	Did the applicant submit all the pediatric exclusivity data, as described in the WR?			X	Proposal filed for 12 to (b) <sub>(4)</sub> years on April 13, 2012 (IND 72,300, Serial # 0029)
17	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?	X			
<b>General</b>					
18	Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	X			
19	Was the translation (of study reports or other study information) from another language needed and provided in this submission?			X	

**IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE? \_\_\_\_\_ Yes\_**

**Executive Filing Summary:**

**Historical Perspective of the Product:**

Bendectin was approved for the treatment of nausea and vomiting during pregnancy (NDA 10598, Hoechst Marion Russel, Inc) in 1956. At that time, the product contained three active ingredients: 10 mg doxylamine succinate, 10 mg pyridoxine hydrochloride, and 10 mg dicyclomine hydrochloride. In the mid 60s, the tablet coat was modified as delayed release. Subsequently in 1976 and based on FDA Drug Efficacy Study Implementation (DESI), dicyclomine was removed from the formulation as it was shown not to contribute to the efficacy. Later it was reformulated and then listed in the FDA Orange Book as a Reference Listed Drug (RLD).

It appears that due to litigation and other reasons including but not limited to teratogenic reports, the sponsor at that time (Merrel Dow) withdrew the product from the market on June 9, 1983. However, in June 9, 1999, the FDA determined that Bendectin was not withdrawn for safety or efficacy reasons.

Since it was withdrawn in 1983, Bendectin has not been in the US market. However, it remains marked in other countries such as Canada under the trade name, Diclectin with the same ingredients (10 mg doxylamine succinate and 10 mg pyridoxine hydrochloride).

It should be noted that, after the submission of this NDA on June 8, 2012, the sponsor requested and proposed new name on August 3, 2012. The proposed new name is "Diclegis". (b) (4)

**Historical Perspective of FDA Correspondence and Submissions:**

(b) (4)

(b) (4)

Subsequently, the sponsor submitted an NDA for (b) (4) (NDA # 021876, i.e., the same current NDA number) on April 18, 2005. A Refuse-to-File letter was issued on June 16, 2005 for the following reasons:

- From a clinical pharmacology perspective, the 505(b)(2) application is not fileable because it does not contain information necessary to establish a link between the proposed formulation of (b) (4) and the 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 Diclectin.
- From a clinical perspective, the 505(b)(2) application is not fileable because the application is seeking an indication (b) (4). For example, the proposed indication (b) (4) is not supported by substantive data on safety and efficacy.

At the meeting held on August 9, 2005, the sponsor was advised to conduct a safety and efficacy study to qualify for 505(b)(2) application. Based on this, the sponsor submitted a clinical protocol on November 22, 2005 (Protocol # DIC-301) and received FDA comments on February 2, 2006.

At the meeting held on April 17, 2007, the sponsor confirmed that the two PK studies (02163 and 02191) were subject to audit due to the (b) (4) bioanalytical quality issues at the facility located in (b) (4). At that meeting, the sponsor also confirmed the plan to conduct a food effect study (Study 70294) and a single and multiple dose PK study (Study # 70381) in addition to a phase 3 clinical study (Study # DIC-301).

At the Pre-NDA meeting held on December 14, 2009, the sponsor confirmed that the PK studies as well as the clinical study (DIC-301) were conducted using the final-to-be marketed formulation. Furthermore, it was agreed that the two old PK studies that were associated with (b) (4) will be submitted with the NDA for completeness only.

**Dosing Instruction:**

**Bendectin (From PDR 1982):**

“2 Bendectin tablets at bedtime. In severe cases or when nausea occurs during the day. 1 additional Bendectin tablet in the morning and another in mid afternoon”

(b) (4) **(Sponsor Proposed):**



### General Labeling Comment:

Based on the discussion at the Pre-NDA meeting held on December 14, 2009, the sponsor was advised to provide information from the literature on ADME (absorption, distribution, metabolism, and excretion) and the effect of intrinsic and extrinsic factors. Therefore, the clinical pharmacology section of the proposed label is largely associated with the old label, literature reports, and the data from the new submitted PK studies.

### What Is Submitted in this NDA?

In addition to the clinical study (DIC-301) and several literature articles, the sponsor submitted the following PK studies:

Study No	Description	Notes
02163	Relative bioavailability study versus oral solution. Submitted for safety data only in agreement with FDA.	There were no significant or serious adverse events in this study.
02191	Food effect study using an obsolete formulation. Submitted for safety data only in agreement with FDA	There were no significant or serious adverse events in this study.
70294	Food effect study using the commercial formulation	For relevant serious adverse events (serious adverse events leading to withdrawal and other serious adverse events), events are linked to the source data in the report.
70381	Single and multidose pharmacokinetics study using the commercial formulation	For relevant serious adverse events (serious adverse events leading to withdrawal and other serious adverse events), events are linked to the source data in the report.

It should be noted that sparse PK samples were collected in Phase III study (DIC-301). As indicated above, studies 02163 and 02191 are submitted for completeness only. They may not be reviewed due to the data integrity issue with the analytical laboratory, (b) (4). The following is the summary of the two pivotal PK studies (70294 and 70381):

#### Study 70294 (Food Effect Study):

**Objective:** To assess the effect of food on the bioavailability of (b) (4), administered as a 2 x 10 mg-10 mg delayed-release tablet (for a total dose of 20 mg-20 mg), under fasting and fed conditions

**Design:** Single-dose, randomized, 2-way crossover study

**Subjects:** 44 healthy females

**Method:** All subjects fasted at least 10 hours prior to drug administration and those in the fed group received a standard high-fat, high-caloric meal within 30 minutes before drug administration. After dosing, subjects were subsequently fasted for a period of at least 4 hours. The treatment phases (fasting and fed conditions) were separated by a washout period of 27 days.

**Results:**

- Food delayed the C<sub>max</sub> of both doxylamine and pyridoxine by approximately 7 hours when compared to administration under fasting conditions (based on median T<sub>max</sub> results).
- The C<sub>max</sub> of doxylamine and pyridoxine was also reduced with food.
- The effect of food on the pyridoxine metabolites was more complex (data not shown here, pending review)
- The half life of doxylamine is approximately 12 hours. However pyridoxine half life is very short (<30 minutes).

**Study 70381 (Single and Multiple Doses):**

**Objective:** To assess the PK profile of the active ingredients of (b) (4) delayed-release tablets after single and multiple doses in healthy non-pregnant female volunteers

**Design:** This was a single and multiple-dose study in 18 non-pregnant females. Subjects remained in clinic for 20 days throughout the study.

**Methods:** Subjects were administered a single oral dose of (b) (4), as 2 x 10 mg/10 mg delayed-release tablets at 22:00 h on Days 1 and 2, and were administered multiple oral doses from Days 3 through 18, according to the following schedule: 1 x 10 mg/10 mg delayed-release tablet at 09:00 and 16:00, and 2 x 10 mg/10 mg delayed-release tablets at 22:00, under empty-stomach conditions (defined as at least 2 hours after eating).

**Results:****Doxylamine:**

- Following multiple dose administrations the exposure of doxylamine (C<sub>max</sub> and AUC) was significantly increased compared to single dose.
- The mean accumulation index (ratio of AUC<sub>0-24</sub> Day 18/AUC<sub>0-24</sub> Day 1) was more than unity (2.76) suggesting that doxylamine accumulates following multiple dosing.
- Steady-state appears to be achieved after Day 9.

**Pyridoxine:**

- The data for pyridoxine is complex due to the variability and low concentrations. Overall, the concentration of pyridoxine was higher after multiple dose administration than after a single dose.
- The accumulation index reflects 1.5 fold increases after multiple dose administration compared to single dose.

**Reviewer's Comments:**

Bendectin has a long history with the FDA. Although, it has been marketed since 1956, the volume of utilization over these decades is questionable as it was discontinued from the US market for over 3 decades. It appears that its voluntary discontinuation from the market by the sponsor was due to litigation and the unfavorable publicity at that time in reference to teratogenic potential and other issues. Therefore, from the clinical pharmacology perspective, an attempt will be made to assess the duration of exposure to optimize dosing regimen and minimize any potential associated risk to the mother and fetus. The labeling will be carefully reviewed.

According to the label, the sponsor is proposing three times daily administration of the drug as two tablets at night, one in the morning and one in mid day for unlimited duration. In addition, the proposed label states that this drug is not to be administered on as needed basis (i.e., PRN). Furthermore, according to the patient's package insert, patients will be instructed to continue treatment with the drug without stopping, unless instructed by their health care provider (i.e., requires tapering). This dosing regimen will be reviewed carefully to minimize extensive and unnecessarily lengthy exposure. As shown above, the drug and its active metabolites (pending review) are accumulated in the body after multiple dosing.

From the regulatory and clinical pharmacology perspective, the sponsor conducted three studies per the Agency's recommendations over the years. In the absence of the RLD, the critical study to qualify for 505(b)(2) and the approvability of the drug is the clinical safety and efficacy study (DIC-301). This is a pivotal study that was conducted to justify the proposed dosing regimen. However, it is not clear how the drug was administered relative to food intake in this study (pending review).

The two PK studies are also critical to characterize the exposure after multiple doses and the effect of food on the absorption. Both of these two studies are also important for the optimization of dosing regimen and labeling.

The old two studies conducted in association with (b) (4) are questionable and may not be of value to this NDA.

**Recommendation:**

The NDA can be filed from the clinical pharmacology perspective.

Sayed (Sam) Al Habet, RP.h., Ph.D.

Reviewing Clinical Pharmacologist

Date

Myong-Jin Kim, Pharm.D.

Secondary Reviewer

Date

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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.**  
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/s/  
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SAYED AL HABET  
03/04/2013

MYONG JIN KIM  
03/04/2013