CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-325

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

CLINICAL PHARMACOLOGY REVIEW

NDA	22-325
IND	72,383
NDA Type	Original New drug Application
Submission Date	February 21, 2008
Brand Name	NEXTERONE®
Generic Name	Amiodarone Hydrochloride
Sponsor	PRISM Pharmaceuticals
Dosage Form; Strength	Injection for intravenous administration; 50 mg/mL
Proposed Indication	Antiarrhythmic agent indicated for initiation of treatment and prophylaxis of frequently recurring ventricular fibrillation and hemodynamically unstable ventricular tachycardia in patients refractory to other therapy.
Proposed Dosage Regimen	[redacted], alternatively, add 3 mL Nexterone (150 mg) to 100 ml D5W or normal saline infused over 10 minutes; either of these regimens (loading infusions) are followed by 1 mg/min for 6 hours (slow infusion) and 0.5 mg/min (maintenance infusion) thereafter
Reviewer	Angelica Dorantes, Ph.D. & Ganesh Iyer, Ph.D.
Team Leader (Acting)	Robert Kumi, Ph.D.
OCP Division	Clinical Pharmacology 1
OND Divisions	Division of Cardiovascular & Renal Products

b(4)

TABLE OF CONTENTS

CLINICAL PHARMACOLOGY REVIEW

1 Executive Summary

In this Original NDA submission, PRISM Pharmaceuticals is seeking approval of Nexterone (amiodarone HCl), as an antiarrhythmic agent indicated for initiation of treatment and prophylaxis of frequently recurring ventricular fibrillation and hemodynamically unstable ventricular tachycardia in patients refractory to other therapy. Currently, there are multiple approved intravenous amiodarone products, including Cordarone IV that has been discontinued.

This is a 505 (b)(2) NDA application for a new formulation of injectable amiodarone that does not include benzyl alcohol or polysorbate 80; instead it is comprised of a complex of amiodarone and Captisol® in water for injection. Captisol, a sulfbutyl ether β-cyclodextrin, has been shown to solubilize amiodarone in water at the 50 mg/mL (approved Cordarone® IV) concentration. The sponsor suggests that [redacted] b(4)
[redacted] In addition, while currently approved amiodarone products are labeled for a bolus dose to be diluted and administered over 10 minutes, [redacted]

PRISM Pharmaceuticals submitted the following two studies to support the approval of the proposed amiodarone formulation.

- **Study PM-101;** conducted to determine the bioequivalence of their product (PM101) to the Amiodarone IV reference listed drug, when given at the same rate of infusion. The results of this study showed that their product met the bioequivalence criteria.
- **Study PM-102;** a blood pressure study designed to show that [redacted] b(4)
  [redacted] This study was reviewed by Dr. Robert Fiorentino, medical reviewer from the DCaRP. He concluded that the results from Study 102 did not show any clinical difference between their product (Nexterone) and Cordarone IV. Therefore, t[redacted] b(4)
  [redacted] The labeling for Nexterone should be basically the same as Cordarone IV.

1.1 Recommendation

Bioequivalence

The Office of Clinical Pharmacology/Division of Clinical Pharmacology has reviewed NDA 22-325 dated February 21, 2008 for Nexterone and finds the bioequivalence information submitted to support the approval of Nexterone acceptable.

Labeling

Detailed labeling recommendations are presented on page 13 of this review. The proposed labeling is included in Attachment 1.

Reviewer Comments:

1. *Due to the fact that the results from clinical study PM-102 did not show a difference between their product (Nexterone) and Cordarone IV,* [redacted] b(4)
   [redacted] *Therefore, they should modify as*

appropriate the proposed labeling for Nexterone to be similar to that of the approved product, Cordarone IV, but maintain the new SPL format.

1.2 Phase 4 Commitments

Not applicable.

Angelica Dorantes, Ph.D. _____
Office of Clinical Pharmacology

FR Signed by Robert Kumi, Ph.D. _____
OCP Acting Team Leader

CC list: HFD-110: NDA 22-325; HFD 860 (Mehta, Uppoor)

1.3 Summary of Important Clinical Pharmacology & Biopharmaceutical Findings

This application is supported by one bioequivalence study (PM-101) and one clinical blood pressure study (PM-102) designed to show [redacted] The clinical study (PM-102) was evaluated by Dr. Robert Fiorentino, medical reviewer of the DCaRP. b(4)

Demonstration of Bioequivalence:

The sponsor conducted one bioavailability/bioequivalence study (PM101 IV) to demonstrate the bioequivalence between their product (Nexterone) and the commercial Cordarone IV product.

Study PM101 IV was a randomized, double-blind, 2-way cross over study conducted in healthy subjects to establish the bioequivalence of Nexterone (amiodarone hydrochloride) and Cordarone IV Generic reference listed drug. The results for the assessment of bioequivalence are summarized in the following table.

PK Measure *	Geometric Least Squares Mean (n = 78)		Geometric Mean Ratio	90% CI
	Nexterone	Cordarone IV		
Amiodarone				
Cmax	6038.62	6024.26	1.00	95 - 106%
AUCt	8055.94	7836.94	1.03	100 - 106%
AUC0-inf,	9398.57	9153.87	1.03	100 -106%
Desethylamiodarone				
Cmax	19.88	19.81	1.00	98 - 103%
AUCt	1199.66	1187.09	1.01	99 - 103%
AUC0-inf	4623.71	4496.10	1.03	90 – 118%

Truncated PK sampling up to 72 hours were utilized for the estimation of the PK parameters, AUCt and AUC.

The results of the study indicate that the 90% CI for amiodarone AUCt, AUC0-inf, and Cmax are within the Agency's bioequivalence criteria of 80 to 125%. Therefore, this study shows that Nexterone is bioequivalent to Cordarone IV.

Analytical Method: A validated high performance liquid chromatography method using tandem mass spectrometry detection was used for the determination of plasma amiodarone and desethylamiodarone. The limit of detection was 5.02 ng/ml for amiodarone and 1.97 ng/ml for desethylamiodarone. The assay performance was acceptable.

DSI AUDIT REPORT:

Bioequivalence study PM-101 was audited by the Division of Scientific Investigations (DSI). DSI reported no significant findings following inspection of the clinical site. However, for the analytical site a Form FDA-483 was issued. DSI recommends that the data from the analytical Study M06-830 be accepted for review, however, it is mentioned that OCP's reviewer should be aware of the significant pre-dose DEA concentrations observed in all subjects in study period two.
The Form FDA-483 observations are as follow:

<u>Anapharm, 2500 rue Einstein, Quebec City, Quebec, Canada (Anapharm-Quebec City)</u>

1. **The effect of preparing and processing standard curves and quality control samples (QCs) containing amiodarone (A) and desethylamiodarone (DEA) separately vs. those containing A and DEA concomitantly was not evaluated. Specifically, during method validation and production runs, standard curves and QCs of A and DEA were prepared and then processed by spiking each analyte and internal standard in to separate blank human plasma, but A and DEA were present concomitantly in study plasma samples.**

   Anapharm-Quebec City acknowledged this observation and conducted an experiment during the inspection to investigate the issue raised in the 483 observation. The results of the experiment showed that data generated from QC samples containing either A or DEA, and QC samples containing both A and DEA concomitantly (Attachment 2) were accurate (within 8% of the nominal values)

2. **Significant DEA concentrations (>5% Cmax) were found in pre-dose human plasma samples of all subjects in study period two. This finding was not discussed in the analytical report.**
   DPC1 reviewer should be aware of the significant (>5% Cmax) pre-dose DEA concentrations observed in study period two (likely due to inadequate wash-out period). During the inspection, Anapharm - Quebec City said that the sponsor did not contract Anapharm-Quebec City to conduct the pharmacokinetic data analysis and they were not sure if the DEA data reported by the Sponsor were corrected for the pre-dose DEA concentrations.

<u>Reviewer Comment:</u>

1. The DSI concern can be resolved easily by re-analyzing the DEA data corrected by pre-dose levels. However, the re-analysis of the DEA metabolite data will not change the Agency's bioequivalence conclusion, which is based on the parent entity (amiodarone). Additionally, the use of a highly specific LC/MS/MS assay ensures that the pre-dose DEA concentrations do not have any interference or influence on amiodarone's PK and bioequivalence results.

QUESTION BASED REVIEW

An abbreviated Question Based Review was adopted for this NDA application.

2.1 General Attributes

2.1.1. ***What are the highlights of the chemistry and physical-chemical properties of the drug substances, and the formulation of the drug product?***

Formulation: Nexterone is a sterile clear, colorless to slightly yellow solution visually free from particulates. The concentration of Nexterone (amiodarone HCl) is 50 mg/mL and is available in 5, 10 and 20 mL vials with fill volumes of 3 mL, 9 mL, or 18 mL respectively. The table below summarizes the composition on Nexterone.

Composition of Nexterone (amiodarone HCl), 50 mg/mL, Pre-filled Syringes

Description	Quality Standard	Function	Quantity g/L	Quantity % w/v	Quantity in Pre-Filled Syringe (mg)
Amiodarone HCl	Ph. Eur.	Drug Substance	50.0	[redacted]	150.0
Captisol® (sulfobutylether β-cyclodextrin)	CyDex, Inc. DMF #20732	[redacted]	225.0	[redacted]	[redacted]
Citric Acid Monohydrate	USP	[redacted]	[redacted]	[redacted]	[redacted]
Sodium Citrate Dihydrate	USP	[redacted]	2.10	[redacted]	[redacted]
Sodium Hydroxide	NF/Ph.Eur./JP	pH adjuster	[redacted]	[redacted]	[redacted]
Citric Acid Monohydrate	USP	pH adjuster	[redacted]	[redacted]	[redacted]
Water For Injection	USP/Ph.Eur./JP	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

b(4)

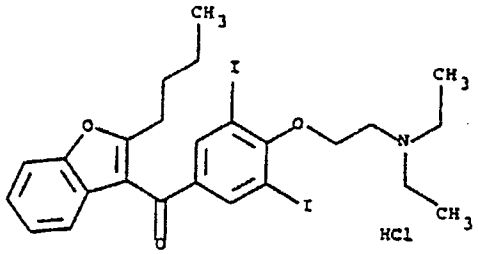
b(4)

b(4)

b(4)

Physical-Chemical Properties: Nexterone, for intravenous use, contains amiodarone HCl ($C_{25}H_{29}I_2NO_3$•HCl), a class III antiarrhythmic drug. Amiodarone HCl is (2-butyl-3- benzofuranyl)[4-[2-(diethylamino)ethoxy]-3,5-diiodophenyl] methanonehydrochloride.

Amiodarone HCl has the following structural formula:



Amiodarone HCl is a white to slightly yellow crystalline powder, and is very slightly soluble in water. It has a molecular weight of 681.78 and contains 37.3% iodine by weight.

2.1.2 *What is the proposed mechanism of drug action and therapeutic indications?*

Mechanism of Action: Amiodarone is generally considered a class III antiarrhythmic drug, but it possesses electrophysiological characteristics of all four Vaughan Williams classes. Like class I drugs, amiodarone blocks sodium channels at rapid pacing frequencies, and like class II drugs, it exerts a noncompetitive antisympathetic action. One of its main effects, with prolonged administration, is to lengthen the cardiac action potential, a class III effect. The negative chronotropic effect of amiodarone in nodal tissues is similar to the effect of class IV drugs. In addition to blocking sodium channels, amiodarone blocks myocardial potassium channels, which contributes to slowing of conduction and prolongation of refractoriness. The antisympathetic action and the block of 14 calcium and potassium channels are responsible for the negative dromotropic effects on the sinus node and for the slowing of conduction and prolongation of refractoriness in the atrioventricular (AV) node. Its vasodilatory action can decrease cardiac workload and consequently myocardial oxygen consumption.

Pharmacodynamics: Intravenous amiodarone has been reported to produce negative inotropic and vasodilatory effects in animals and humans. In clinical studies of patients with refractory VF or hemodynamically unstable VT, treatment-emergent, drug-related hypotension occurred in 288 of 1836 patients (16%) treated with intravenous amiodarone. No correlations were seen between the baseline ejection fraction and the occurrence of clinically significant hypotension during infusion of intravenous amiodarone. Hemodynamic studies in animals compared the human-equivalent dose of NEXTERONE with placebo. NEXTERONE did not affect blood pressure and was devoid of negative inotropic and vasodilatory effects.

Proposed Indications: Nexterone is indicated for initiation of treatment and prophylaxis of frequently recurring ventricular fibrillation and hemodynamically unstable ventricular tachycardia in patients refractory to other therapy. Nexterone also can be used to treat patients with VT/VF for

whom oral amiodarone is indicated, but who are unable to take oral medication. During or after treatment with Nexterone, patients may be transferred to oral amiodarone therapy

Nexterone should be used for acute treatment until the patient's ventricular arrhythmias are stabilized. Most patients will require this therapy for 48 to 96 hours, but Nexterone may be safely administered for longer periods if necessary.

2.1.3 What is the proposed dosage and route of administration?

The following information was extracted from the proposed labeling. The recommended starting dose of Nexterone is about 1000 mg over the first 24 hours of therapy, delivered by the following infusion regimen:

NEXTERONE DOSE RECOMMENDATIONS – FIRST 24 HOURS		
Loading infusions	***First* Rapid:**	[redacted] b(4) **OR** **150 mg over the FIRST 10 minutes (15 mg/min).** Add 3 mL of Nexterone (150 mg) to 100 mL D5W or normal saline (concentration = 1.5 mg/mL). Infuse 100 mL over 10 minutes.
	***Followed by* Slow:**	**360 mg over the NEXT 6 hours (1 mg/min).** Add 18 mL of Nexterone (900 mg) to 500 mL D5W or normal saline (concentration = 1.8 mg/mL)
Maintenance infusion		**540 mg over the REMAINING 18 hours (0.5 mg/min).** Decrease the rate of the slow loading infusion to 0.5 mg/min.

After the first 24 hours, the maintenance infusion rate of 0.5 mg/min (720 mg/24 hours) should be continued utilizing a concentration of 1 to 6 mg/mL (Nexteroneconcentrations greater than 2 mg/mL should be administered via a central venous catheter). In the event of breakthrough episodes of VF or hemodynamically unstable VT, a 150-mg supplemental loading infusion given either [redacted] mixed in 100 mL of D_5W or normal saline may be administered. Such infusions should be administered over intervals of not less than 10 minutes. The rate of the maintenance infusion may be increased to achieve effective arrhythmia suppression. b(4)

The first 24-hour dose may be individualized for each patient; however, in controlled clinical trials, mean daily doses above 2100 mg were associated with an increased risk of hypotension.

Based on the experience from clinical studies of intravenous amiodarone, a maintenance infusion of up to 0.5 mg/min can be cautiously continued for 2 to 3 weeks regardless of the patient's age, renal function, or left ventricular function. There has been limited experience in patients receiving intravenous amiodarone for longer than 3 weeks.

2.2 General Clinical Pharmacology

2.2.1 *What clinical studies were conducted to support this NDA?*

This is a 505 (b) (2) application. Two human clinical trials were submitted in support of this NDA.

Study PM-101 was a randomized, double-blind, 2-way cross over study to evaluate the bioequivalence of Nexterone (amiodarone hydrochloride) vs. Cordarone IV Generic reference listed drug in healthy subjects.

Study PM-102 was a randomized, double-blind, double-dummy, placebo-controlled trial to determine the relative effect of PM 101 administered as an IV bolus push versus placebo on systolic blood pressure (SBP) in healthy adult subjects. This study was evaluated by the medical reviewer.

2.2.2 *Were the active moieties in the plasma appropriately identified and measured to assess pharmacokinetic parameters?*

Yes, amiodarone and its major metabolite desethylamiodarone were measured in human plasma. The pharmacokinetic parameters AUC0-72 hrs, AUC0-inf, Cmax, Tmax, and T1/2 were estimated following infusion of 150 mg of Nexterone and Cordarone IV over 10 minutes.

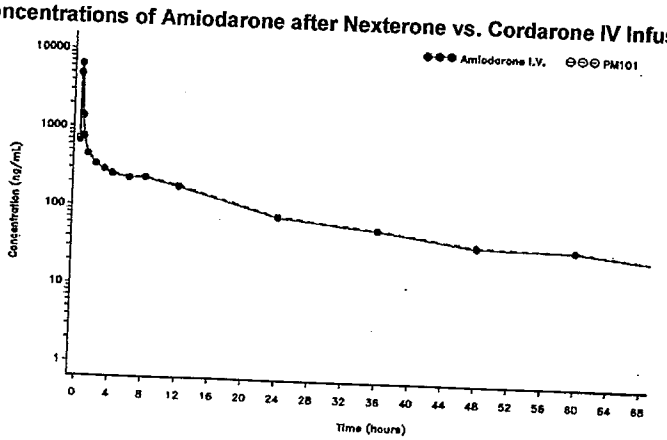
2.2.3 *Were Exposure-Response relationships established with Nexterone in terms of efficacy?*

NO, there is no established relationship between amiodarone concentration and therapeutic response for short-term intravenous use. However, steady-state amiodarone concentrations of 1 to 2.5 mg/L have been associated with antiarrhythmic effects and acceptable toxicity following chronic oral amiodarone therapy.

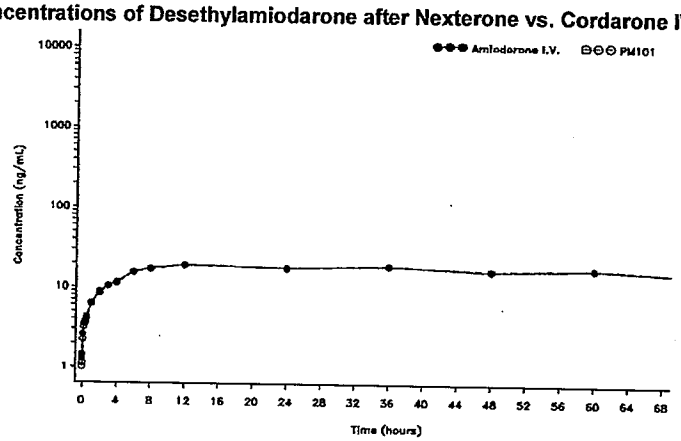
2.2.4 *What are the PK characteristics of the Nexterone product?*

The amiodarone and desethylamiodarone pharmacokinetic parameters were estimated following infusion of 150 mg of Nexterone (PM101) and Cordarone IV over 10 minutes: AUC0-72 hrs, AUC0-inf, Cmax, Tmax, and T1/2.

Mean Plasma Concentrations of Amiodarone after Nexterone vs. Cordarone IV Infusion:



Mean Plasma Concentrations of Desethylamiodarone after Nexterone vs. Cordarone IV Infusion



The following table summarizes the PK parameters.

Summary of Amiodarone and Desethylamiodarone Pharmacokinetic Results Following Nexterone and Cordarone I.V. administration

	Amiodarone (n=78)	
	Arithmetic Mean (SD)	
Parameter	**Nexterone**	**Cordarone**
C_{max} (ng/ml)	6445 (2387)	6378 (2172)
T_{max} (hours)	0.083-0.317	0.083-0.183
$AUC_{0\text{-}72hrs}$ (ng.hr/ml)	8416 (2528)	8225 (2515)
$AUC_{0\text{-}inf}$ (ng.hr/ml)	9809 (2946)	9607 (2950)
T½ (hours)	37.3 (9.1)	38.1 (10)
	Desethylamiodarone (n=78)	
	Arithmetic Mean (SD)	
Parameter	**Nexterone**	**Cordarone**
C_{max} (ng/ml)	20.3 (4.2)	20.4 (4.7)
T_{max} (hours)	30 (6-72)	24 (6-60.1)
$AUC_{0\text{-}72hrs}$ (ng.hr/ml)	1222 (245)	1223 (271)
$AUC_{0\text{-}inf}$ (ng.hr/ml)	5419 (2669)*	5075 (2339)**
T½ (hours)	183 (95.5)*	182 (98.3)**
	* n=54	** n=53

2.3 General Biopharmaceutics

2.3.1 Does the formulation change (complex of amiodarone with cyclodextrin and exclusion of benzyl alcohol or polysorbate 80) affect the PK of amiodarone?

The data indicate that the formulation change does not affect the pharmacokinetics of amiodarone. The BE study (Nexterone vs. Cordarone IV) showed that the 90% CI for both AUC and Cmax were within the Agency's bioequivalence acceptance criteria of 80 - 125% as shown in the following table.

Measure*	Nexterone (test)	Amiodarone IV (Reference)	Geometric mean ratio[a]	90% CI	Intrasubject %CV
Cmax	6039	6024	1.00	95-106	21.11
AUC_T	8056	7837	1.03	100-106	10.50

[a]test/reference * Geometric mean

2.3.2 *Does the formulation change affect the PD of amiodarone?*

The PD information provided in study PM-102 was reviewed by Dr. Robert Fiorentino, medical reviewer from DCaRP. His review indicates that the results of the primary pharmacodynamic (PD) endpoint for Study PM-102 showed that the change from baseline was comparable between placebo and Nexterone, with Nexterone being non-inferior to placebo. The following Table shows these results.

SBP change from baseline to lowest value within 15 minutes post-dose

	Change from baseline (mm Hg)		Treatment effect (vs. placebo)	
	Placebo (n = 111)	PM101 (n =104)	Mean difference	Lower limit of 90% CI
Mean (SD)	-4.25 ± 4.43	-4.83± 5.01	-0.57	-1.64
Median	-3.50	-4.00		
Min, Max	-22.0, 5.0	-25.0, 3.5		

Additional analyses by Dr. Kong (statistician) using the modified intent-to-treat population are shown in the next table. The statistical analyses also confirmed the sponsor's results.

Parameter, mmHg	Placebo (N=112)	PM101 (N=112)	Amiodarone I.V. 10 min (N=57)	Amiodarone I.V. 15 sec (N=57)
Mean SBP at Baseline	108.16	106.91	107.53	107.54
Mean Lowest SBP within 15 Minutes Post-Dose	103.85	102.08	102.49	102.65
Mean Change from Baseline to Lowest SBP with 15 Minutes Post-Dose	-4.31	-4.83	-5.04	-4.89
Standard Deviation	4.45	6.10	5.11	5.76
Minimum, Maximum	-22.0, 5.0	-38.5, 14.5	-21.0, 5.0	-24.0, 6.5
Mean Difference, PM101 - Plbo		-0.51		
Lower Limit of 90% CI of Mean Difference		-1.69		
Lower Limit of 95% CI of Mean Difference		-1.92		

Source: FDA statistical reviewer, Fanhui Kong.

Based on the results from Study PM102, Dr. Fiorentino recommended approval of Nexterone for initiation of treatment and prophylaxis of frequently recurring ventricular fibrillation (VF) and hemodynamically unstable ventricular tachycardia (VT) in patients refractory to other therapy. He did not recommend approval of Nexterone [redacted] Dr. Fiorentino mentions that the study demonstrated that rapid bolus of Nexterone IV was comparable to placebo with respect to the primary endpoint, however, the study only investigated bolus administration of Nexterone in healthy subjects. This is relevant in that Cordarone IV has been associated with hypotension in the intended patient population, which is expected to have

b(4)

significant cardiac disease. The data failed to demonstrate that Nexterone administered as a rapid bolus provides any hemodynamic advantage compared to Cordarone IV. There is insufficient evidence to support the conclusion that an [redacted] b(4)

2.4 Bioanalytical

2.4.1 Were the analytical methods used to determine Nexterone in biological fluids adequately validated?

Yes, the method was properly validated. The concentrations of amiodarone and desethylamiodarone were determined from the plasma samples using a validated liquid chromatography with tandem mass spectrometer detection (LC/MS/MS).

LABELING RECOMMENDATIONS

Pharmacokinetic Information

1. *Regarding section 12.3 of the proposed labeling, the following changes are recommended:*

[redacted] b(4)

b(4)

2. *Note that the half-life for amiodarone in the labeling of the approved CORDARONE IV product is much longer than the half-life reported in this submission (i.e., t1/2 = 20-47 days vs. 27-48 hrs). However, in study PM-101 the PK samples were collected for only 72 hrs (less than one half-life). Therefore, the results from this study are limited.*

3. *Also, note that the labeling committee accepted the NEXTERONE name, but without the IV part. Therefore, the "IV" words should be removed from the NEXTERONE product's name throughout the text of the proposed labeling.*

4. APPENDICES

4.1. Appendix I: Proposed Labeling
4.2. Appendix II: Individual Studies
4.3 Appendix III: Division of Scientific Investigations Reviewer's Memo
4.4 Appendix IV: OCP Filing and Review Form

17 Page(s) Withheld

_____ Trade Secret / Confidential (b4)

__✓__ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

4.2. APPENDIX II

Individual Study Review

Study No. 101 IV

Study Title: A randomized, double-blind, 2-way cross over study to determine the relative bioavailability of PM 101 IV (amiodarone hydrochloride) and Cordarone IV Generic reference listed drug in healthy subjects

Study Period: 18 December 2006 to 23 April 2007

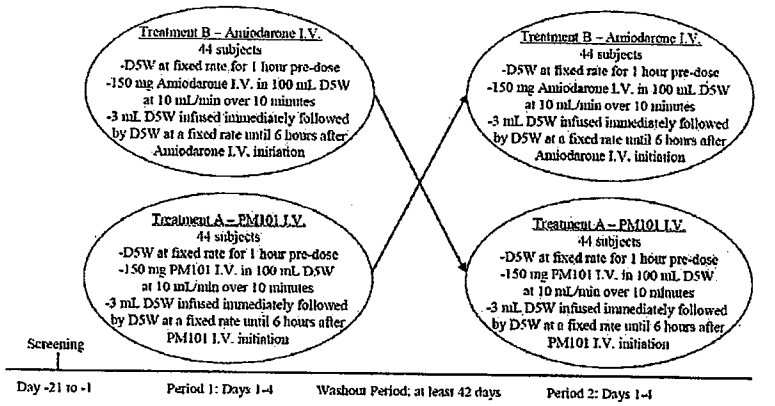
Principal Investigator/Study Site: Richard Larouche, MD/ Anapharm- Montreal, 5160, boul. Decarie, suite 800, Montreal (Quebec), Canada, H3X 2H9

Analytical Site: Anapharm, 2050 boul. Rene-Levesque Ouest, Quebec, QC, Canada, G1V 2K8

Objective: The primary objective of this study was to compare the relative bioavailability of the test (PM101 I.V., amiodarone hydrochloride) and reference (Amiodarone I.V., Reference Listed Drug [RLD], amiodarone hydrochloride—Cordarone® I.V. is no longer sold in the U.S.) products following intravenous injection.

Study Design: In this randomized, single-center, double-blind, 2-period crossover study designed to evaluate the relative bioavailability of PM101 I.V. (test) and Amiodarone I.V. (reference), 88 subjects were randomized to one of two treatment sequences—test drug followed by reference drug or reference drug followed by test drug. The two periods of each treatment sequence were separated by a washout period of at least 42 days (from the first dose to the second dose).

Figure 1 Study Design Schematic



Note: Subjects entered the clinic on Day -1 of the first treatment period, and following the washout period of at least 42 days (from first dose to second dose), subjects entered the study on Day -1 of the second treatment period, the day before study medication administration.

Study medication was administered after a 10-hour overnight fast as follows:

Treatment A:	PM101 I.V. (amiodarone hydrochloride)
-1 hr to 0 hr:	Intravenous infusion (I.V.) of 5% dextrose in water (D5W) at a fixed rate to keep vein open
0 hr to 10 min:	150 mg PM101 I.V. in 100 mL D5W at 10 mL/min
11 min to 6 hrs:	3 mL D5W flush to clean line followed by D5W infused at a fixed rate to keep vein open
Treatment B:	Amiodarone I.V. (amiodarone hydrochloride)
-1 hr to 0 hr:	Intravenous infusion of D5W at a fixed rate to keep vein open
0 hr to 10 min:	150 mg Amiodarone I.V. in 100 mL D5W at 10 mL/min
11 min to 6 hrs:	3 mL D5W flush to clean line followed by D5W infused at a fixed rate to keep vein open

Number of Subjects Planned and Analyzed:

A total of 88 subjects were planned and randomized to sequence; 82 subjects received PM101 I.V. and 87 subjects received Amiodarone I.V. Of the 88 subjects enrolled, 80 subjects completed the PM101 I.V. treatment period and 79 subjects completed the Amiodarone I.V. treatment period. All subjects were included in the safety analyses, and 78 subjects were included in the pharmacokinetic analyses.

Diagnosis and Main Criteria for Inclusion:

Healthy male and non-pregnant, non-breast-feeding female volunteers 18 to 59 years of age

Test Product, Dose and Mode of Administration, Batch Number:

PM101 I.V. (50 mg/mL) administered by intravenous injection as 150 mg PM101 I.V. in 100 mL of 5% dextrose in water (D5W) at 10 mL/min for 10 minutes; Lot No.: 7043 (expiration date: June 2007)

Reference Therapy, Dose and Mode of Administration, Batch Numbers:

Amiodarone I.V. Reference Listed Drug (50 mg/mL) administered by intravenous injection as 150 mg of Amiodarone I.V. in 100 mL of D5W at 10 mL/min for 10 minutes; Lot No.: 402554 (expiration: October 2007))

Duration of Treatment:

Subjects remained in the clinic during the two treatment periods: Day -1 to Day 4 of Period 1, and following a washout period of at least 42 days, Day -1 to Day 4 of Period 2. On the morning of Day 1 for both treatments, subjects were infused with 5% dextrose in water (D5W) for 1 hour prior to treatment followed by infusion with PM101 I.V. or Amiodarone I.V. for 10 minutes and then D5W until 6 hours after study drug initiation.

Criteria for Evaluation:

- **Blood Samples:** Samples of venous blood were obtained in 4 mL EDTA K2 tubes within 30 minutes prior to dose administration (0 hour, pre-dose) and 1, 5, 10, 20 and 30 minutes, and 1, 2, 3, 4, 6, 8, 12, 24, 36, 48, 60, and 72 hours after the start of the study drug infusion. The 10-minute sample was obtained at the end of the infusion of the study drug. The PK blood samples for amiodarone and desethylamiodarone were obtained.

- **Analytical Methodology:** The concentration of amiodarone and desethylamiodarone were determined from the plasma samples using a validated liquid chromatography with tandem mass spectrometer detection (LC/MS/MS) method. The bioanalytical report is provided.

- ***Pharmacokinetics:*** Pharmacokinetic parameters were estimated from concentrations of amiodarone and desethylamiodarone in plasma samples. The following parameters were estimated for plasma samples: maximum plasma concentration (Cmax), time Cmax was observed (Tmax), last measured plasma concentration (Clast), area under the concentration versus time curve from time 0 to infinity (AUC), area under the concentration versus time curve from time 0 to Clast (AUCT), terminal elimination rate constant (.z), and terminal elimination half-life (T½). The actual time was used for the calculation of pharmacokinetic parameters.

- ***Efficacy:*** Efficacy was not evaluated in this study.

- ***Safety:*** Safety was evaluated through the assessment of adverse events, clinical laboratory tests, vital signs, 12-lead electrocardiograms, and physical examinations.

Statistical Methods:

- ***Pharmacokinetics:*** Pharmacokinetic parameters for amiodarone and desethylamiodarone were calculated from the plasma concentration data using standard, non-compartmental methods. Pharmacokinetic parameters were calculated using WinNonlin. Pharmacokinetic analyses were performed using SAS. All statistical tests were two-sided with a significance level of 0.05 unless specified otherwise. Following log transformation, AUC, AUCT, and Cmax results for amiodarone and desethylamiodarone were compared between treatment groups using the average bioequivalence approach and an analysis of variance (ANOVA) model. The 90% confidence interval (CI) of ratios of the least-squares-geometric-means was calculated based on results from the ANOVA. If the 90% CI for the amiodarone AUCT and Cmax fell within the limit of 80 and 125%, the PM101 I.V. (test) and Amiodarone® I.V. products were considered bioequivalent.
- ***Safety:*** All adverse events (AEs) were coded by system organ class and preferred term using the Medical Dictionary for Regulatory Activities (MedDRA®), Hematology, blood chemistry, and urinalysis laboratory results were summarized by time point for each sequence and overall. Vital signs data and changes from pre-dose on Day 1 of each treatment period were summarized by treatment group and time point for each sequence and overall.

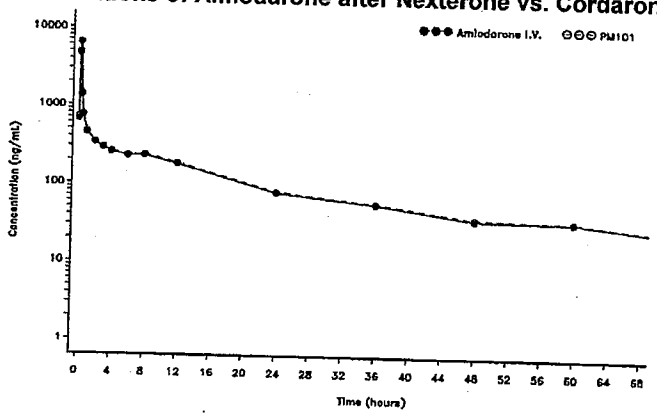
RESULTS

Pharmacokinetics: Mean plasma concentrations of amiodarone and desethylamiodarone following 150 mg of PM101 I.V. and Amiodarone I.V. infused over 10 minutes appeared superimposable throughout the 72-hour collection interval (Figures on following page). The PK results for PM101 I.V. and Amiodarone I.V. demonstrated similar peak exposure and total exposure values for amiodarone and desethylamiodarone. The PK parameters are listed in the following table.

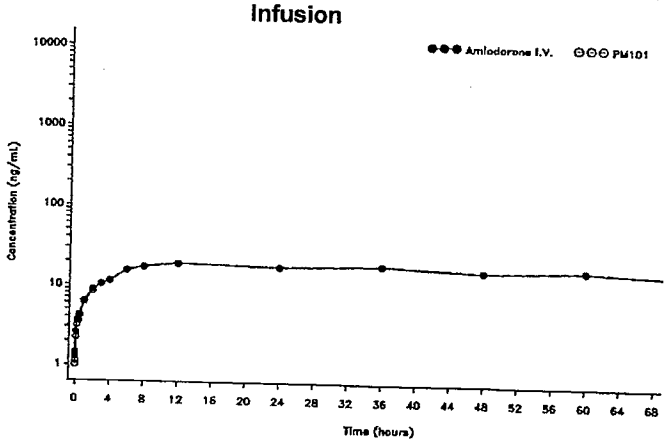
Mean (SD) Pharmacokinetic Results for Amiodarone and Desethylamiodarone in Nexterone I.V. and Cordarone I.V.

Parameter	Amiodarone (n=78)	
	Nexterone	**Cordarone**
C_{max} (ng/ml)	6445 (2387)	6378 (2172)
T_{max} (hours)	0.083-0.317	0.083-0.183
$AUC_{0-72hrs}$ (ng.hr/ml)	8416 (2528)	8225 (2515)
AUC_{0-inf} (ng.hr/ml)	9809 (2946)	9607 (2950)
T½ (hours)	37.3 (9.1)	38.1 (10)
	Desethylamiodarone (n=78)	
	Nexterone	**Cordarone**
C_{max} (ng/ml)	20.3 (4.2)	20.4 (4.7)
T_{max} (hours)	30 (6-72)	24 (6-60.1)
$AUC_{0-72hrs}$ (ng.hr/ml)	1222 (245)	1223 (271)
AUC_{0-inf} (ng.hr/ml)	5419 (2669)*	5075 (2339)**
T½ (hours)	183 (95.5)*	182 (98.3)**
	* n=54	** n=53

Mean Plasma Concentrations of Amiodarone after Nexterone vs. Cordarone IV Infusion:



Mean Plasma Concentrations of Desethylamiodarone after Nexterone vs. Cordarone IV Infusion



Bioequivalence Analysis: An analysis of the bioequivalence of amiodarone and desethylamiodarone in Nexterone I.V. and Cordarone I.V. is provided in the table below.

Bioequivalence of Amiodarone and Desethylamiodarone in Nexterone I.V. and Cordarone I.V

Parameter	Geometric LS Means		Geometric Mean Ratio	90% CI %	Intrasubject %CV
	Nexterone (Test)	Cordarone (Reference)			
Amiodarone					
C_{max}	6039	6024	1.00	94.8-106	21.11
$AUC_{0\text{-}72hrs}$	8056	7837	1.03	100-106	10.50
$AUC_{0\text{-}inf}$	9399	9154	1.03	100-106	10.39
Desethylamiodarone					
C_{max}	19.88	19.81	1.00	98-103	8.93
$AUC_{0\text{-}72hrs}$	1200	1187	1.01	99-103	7.71
$AUC_{0\text{-}inf}$	4624	4496	1.03	90-118	37.54

The results of the study showed that Nexterone is bioequivalent to Cordarone I.V. after single dose intravenous administration.

4.3. APPENDIX III

Division of Scientific Investigations Audit Request Memo

DEPARTMENT OF HEALTH & HUMAN SERVICES — Public Health Service

CENTER FOR DRUG EVALUATION AND RESEARCH — Food and Drug Administration

DATE: April 25, 2008

FROM: Ganesh R. Iyer, Ph.D
Division of Pharmaceutical Evaluation I
Office of Clinical Pharmacology and Biopharmaceutics

THROUGH: Norman Stockbridge, MD, Ph.D, Director
Division of Cardiovascular and Renal Products, ODE1
Office of New Drugs

Mehul Mehta, Ph.D, Director
Division of Pharmaceutical Evaluation I, OCP
Office of Translational Sciences

TO: C. T. Viswanathan, Ph.D, Associate Director, Bioequivalence
GLP and Bioequivalence Branch, Division of Scientific Investigations
Office of Medical Policy

ISSUE: Audit Request for NDA No. 22-325 for Nexterone™ IV (amiodarone HCL) dated February 21, 2008, Prism Pharmaceuticals, Inc., Protocol Number 101 (Relative bioavailability of test (PM101, amiodarone hydrochloride) versus Cordarone® I.V. generic listed drug (amiodarone hydrochloride) in healthy subjects.

Background:

On February 21, 2008, Prism Pharmaceuticals submitted new drug application (NDA) for NEXTERONE™ (amiodarone hydrochloride) injection, 50 mg/mL, in 3 mL, 9mL, and 18 mL sterile, single-use vials, as well as 3mL sterile, single-use, pre-filled syringes to the Division of Cardio-Renal Drug Products. The objective of NDA22-325 is to seek approval for the use of Nexterone for initiation of treatment and prophylaxis of frequently recurring ventricular fibrillation, hemodynamically unstable ventricular tachycardia in patients refractory to other therapy and treatment of patients with ventricular tachycardia or ventricular fibrillation for whom oral amiodarone is indicated, but who are unable to take oral medication.

Audit Request:

The Office of Clinical Pharmacology/Division of Pharmaceuticals Evaluation 1, would like to request that the clinical and analytical data associated with the following bioequivalence study (Study ReportPM101-101) be audited by the Division of Scientific Investigations. Please note that this relative BE study is the only study linking the test formulation (Nexterone IV) to the reference generic (Cordarone IV) formulation.

Study Report PM101-101, Phase I Randomized, double-blind, 2-period cross over trial to determine the relative bioavailability of PM101 IV (amiodarone hydrochloride) and Cordarone® IV. Generic listed drug (amiodarone hydrochloride) in healthy adult subjects

Investigator & Study Site,	Richard Larouche, MD Anapharm- Montreal 5160, boul. Decarie, suite 800 Montreal (Quebec), Canada H3X 2H9
Analytical Laboratories	Pharmacokinetic Assessments Anapharm, 2050 boul. Rene-Levesque Quebec, QC, Canada G1V 2K8

Please note that NDA 22-325 was submitted electronically and the files for this submission are located in CDER's Electronic Document Room (EDR). The link is http://edr.fda.gov.

4.3 APPENDIX IV
OCP Filing and Review Form

Office of Clinical Pharmacology and Biopharmaceutics

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA Number	22-325	Brand Name	Nexterone
OCPB Division (I, II, III)	DCP1	Generic Name	Amiodarone HCl
Medical Division	DCaRP	Drug Class	Class III Antiarrhythmic
OCPB Reviewer	Angelica Dorantes & Ganesh Iyer	Indication(s)	Prophylaxis of frequently recurring ventricular fibrillation and hemodinamically unstable ventricular tachycardia
OCPB Team Leader	Angelica Dorantes (Acting)	Dosage Form	IV Injection
		Dosing Regimen	1000 mg over the first 24 hrs therapy
Date of Submission	February 21, 2008	Route of Administration	IV
Estimated Due Date of OCPB Review	November 15, 2008	Sponsor	Prism Pharmaceuticals
PDUFA Due Date	December 25, 2008	Priority Classification	S
Division Due Date	November 21, 2008		

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X	[redacted]		
Tabular Listing of All Human Studies	X			
HPK Summary	X			
Labeling	X			
Reference Bioanalytical and Analytical Methods	X	[redacted]	[redacted]	
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:				
multiple dose:				
Patients-				
single dose:				
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				

Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD:				
Phase 2:				
Phase 3:				
PK/PD:				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability:				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:	X	1	1	
replicate design; single / multi dose:				
Food-drug interaction studies:				
Dissolution:				
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies		2	2	

Filability and QBR comments		
	"X" if yes	Comments
Application filable ?	X	
Comments sent to firm ?		
QBR questions (key issues to be considered)		
Other comments or information not included above		
Primary reviewer Signature and Date		
Secondary reviewer Signature and Date		

CC: NDA 22-325, HFD-110(Russell Fortney), HFD-860(Dorantes, Kumi, Mehta, Uppoor)

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

/s/

Angelica Dorantes
12/18/2008 05:06:43 PM
BIOPHARMACEUTICS

Robert Kumi
12/18/2008 05:18:40 PM
BIOPHARMACEUTICS