CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-325

CHEMISTRY REVIEW(S)

CMC BRANCH CHIEF MEMORANDUM

To:	NDA 22-325
From:	Ramesh Sood, Ph.D., Branch Chief, ONDQA
Date:	10-Dec-2008
Drug:	Nexterone (amiodarone hydrochloride) injection
Route of administration:	Intravenous injection
Strength:	[redacted] b(4)
Subject:	**"Approval"** recommendation for NDA 22-325

Introduction: Nexterone is indicated for the treatment and prophylaxis of frequently recurring ventricular fibrillation (VF) and hemodynamically unstable ventricular tachycardia (VT) 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. Nexterone is an alternative formulation of intravenous amiodarone to the currently approved CORDARONE IV (and its generic equivalents). Nexterone does not contain polysorbate 80 or benzyl alcohol. These excipients are present in the Cordarone formulation. The current formulation contains Captisol® (sulfobutylether β-cyclodextrin, SBECD) which increases the solubility of amiodarone. The applicant states that this excipient does not possess undesirable features [redacted] of polysorbate 80. b(4)

Nexterone will be available in two distinct packaging configurations. The product is packaged in [redacted] glass vials [redacted] A 50 mg/ml solution is filled in single-use, [redacted] glass vials with fill volumes of [redacted] respectively. In addition, a 50 mg/ml concentration solution will also be available in [redacted] ml [redacted] glass syringes containing [redacted] duct. b(4)

Drug Substance: Amiodarone HCl is a white to almost white, fine, crystalline powder which is slightly soluble in water. The drug substance is manufactured by [redacted] in [redacted] The chemistry, manufacturing and control (CMC) information for Amiodarone HCl was provided by reference to U.S. DMF [redacted] for which Prism Pharmaceuticals has provided a Letter of Authorization (dated 18-Jan-08) from [redacted] is the US agent for [redacted] This DMF was recently updated (amendment 11-Jan-08) and found acceptable by Drs. Quan Zhang/ Ubrani Venkataram (26-Feb-08) of OGD. There is a monograph for amiodarone HCl in the European Pharmacopoeia, but not in USP/NF. The drug substance has been demonstrated to be stable for up to 60 months when stored at 25°C/75% RH in the designated commercial package, i.e. stored in a [redacted] b(4) b(4) b(4)

The quality of the drug substance is assured through drug substance specification by the applicant. The drug substance acceptance specification established by the applicant includes testing for Description, solubility in methylene chloride, appearance of solution, identification (by IR) ——— residue on ignition, heavy metals, water, pH. ———, impurities by TLC and HPLC, assay by titration, residual solvents by ——— b(4)

Drug product: The drug product is a sterile, free-flowing clear, colorless to slightly yellow solution. The aqueous solubility of the DS has been increased at least ——— by complexing with Captisol, a complex, which when administered intravenously, dissociates instantaneously due to its dilution by blood. Captisol is currently used in three approved human parenteral products in the US: Vfend®, Geodon® and Abilify®. The final formulation is composed of amiodarone HCl ———, Captisol ———, citric acid monohydrate ———, sodium citrate dihydrate ——— in WFI, with pH adjusted to ——— with either citric acid monohydrate or NaOH. The sponsor's formulation development efforts indicated that ——— ——— was not a viable option for this product. Hence, they have resorted to an ——— ——— technique and ——— b(4) b(4)

The drug product manufacturing is fairly simple which involves ——— ——— The quality of the drug product is assured through appropriate in-process controls and the final product specification. The final drug product specification include tests and limits for appearance, identification (by HPLC and UV), fill volume, pH, assay, impurities, osmolarity, sterility, particulate matter and bacterial endotoxins. All analytical methods used for drug product testing have been adequately described and validated. b(4)

Based on the provided long term stability data and 6 months of accelerated stability data for the drug product, an expiration period of 24 months, as proposed by the applicant, has been assigned to the product packaged in vials and pre-filled syringes when stored at 25 °C (77 °F) with excursions permitted to 15-30 °C (59-86 °F) (USP Controlled Room Temperature).

The microbiology reviewer has also provided "approval" recommendation.

An overall acceptable recommendation was made by the Office of Compliance for all manufacturing sites on December 4, 2008.

Recommendation: The application is recommended for **"Approval"** from a CMC perspective.

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

/s/

Ramesh Sood
12/10/2008 09:00:47 AM
CHEMIST

CHEMISTRY REVIEW

NDA 22-325

NEXTERONE™ (amiodarone HCl) Injection

PRISM PHARMACEUTICALS

b(4)

Review No. 2

Prafull Shiromani, Ph.D.

Division of Pre-Marketing Assessment I
Office of New Drug Quality Assessment

Table of Contents

Chemistry Review Data Sheet

1. NDA 22-325

2. REVIEW #: 2

3. REVIEW DATE: 09-Dec-2008

4. REVIEWER: Prafull Shiromani, Ph.D.

5. PREVIOUS DOCUMENTS: N/A

Previous Documents	Document Date
ND22-325-Original Submissions and Several Updated Stability Amendments	21-Feb-2008 – Original Submission (see Review1)

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
NDA 22-325:	
Amendment 0015: Responses to FDA IR Letter	
Amendment 0016 – Nexterone Syringes – Stability Update	09-Oct-2008
Amendment 0017: Response to FDA IR Letter-Label	14-Oct-2008
Amendment 0018: Response to FDA IR Letter-Label	24-Nov-2008 25-Nov-2008

7. NAME & ADDRESS OF APPLICANT:

Name: Prism Pharmaceuticals, Inc.

Address: 1150 First Avenue, Suite 1050, King of Prussia, PA 19406
Representative: Daniel J. Cushing, Ph.D., Vice President, Drug Development & Regulatory Affairs
Telephone: 610-986-1024

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: NEXTERONE™ IV
b) Non-Proprietary Name (USAN): Amiodarone HCl
c) Code Name/# (ONDC only):
d) Chem. Type/Submission Priority (ONDC only):
- Chem. Type: 3
- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 505(b)(2)

10. PHARMACOL. CATEGORY: Treatment and prophylaxis of frequently recurring ventricular fibrillation and hemodynamically unstable ventricular tachycardia, for patients who are unable to take oral medication.

11. DOSAGE FORM: Injection

12. STRENGTH/POTENCY: 50 mg/mL

13. ROUTE OF ADMINISTRATION: Parenteral

14. Rx/OTC DISPENSED: _x__Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
_____SPOTS product – Form Completed
__x___Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

b(4)

Molecular formula: $C_{25}H_{29}I_2NO_3 \cdot HCl$

Molecular weight: 681.78

Chemical Abstracts Service (CAS) registry number: b(4)

Chemical Name:

b(4)

United States Adopted Name (USAN), free base: Amiodarone

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
					N/A		
10304	V	Baxter Pharmaceutical Solutions	Syringe - Sterile Processing Facility in Bloomington, Indiana	1	Adequate	20-Nov-2008	Bryan Riley-Microbiology
					N/A		
					Adequate	10-Jul-008	Lisa Shelton-Microbiology

b(4)

b(4)

Chemistry Review Data Sheet

					Adequate	26-Feb-2008	Reviewer: Dr. U. Venkataram of OGD
					Adequate	06-Jul-2006	Dr. R. Lu of ONDQA
20732	IV	CyDex	Captisol®	1	Adequate	23-Sep-2008	P. Shiromani
4030-Amendment	V	HollisterStier Laboratories	Vial	1	Adequate	04-Sep-2007	Robert Mello
					N/A		
					N/A		
					N/A		
					Adequate	15-Oct-2007	Reviewer Dr. M. Salazar Driver, ONDQA.
					Adequate	25-Aug-2008	Rona LeBlanc-Microbiology

b(4)

b(4)

b(4)

b(4)

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted

6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents: N/A

DOCUMENT	APPLICATION NUMBER	DESCRIPTION

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	Adequate	10-Jun-2008	Fanhui Kong
EES	Acceptable	04-Dec-2008	S. Adams
Pharm/Tox	Completed	12-Nov-2008	John Koerner
Biopharm	pending		Angelica Dorantes
LNC			
Methods Validation	Samples not sent to the laboratory since conventional methods		
DMEPA	Completed	06-Nov-2008	Richard Abate
EA	Categorical Exclusion claimed - Accepted		Prafull Shiromani
Microbiology	Adequate	21-Nov-2008	Bryan Riley

The Chemistry Review for NDA 22-325

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The applicant has provided adequate responses to the FDA IR letter sent on 15-Sep-2008, the Microbiology Consult reviewer has recommended approval (see details in this review), and the Office of Compliance has issued an "ACCEPTABLE" Overall Recommendation (summary report in this review); accordingly, this NDA is recommended for approval from a CMC perspective.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

N/A

II. Summary of Chemistry Assessments

CMCC Review #2 focuses on the applicants response (Amendment 0015, 0017, and 0018) to the Deficiencies delineated in CMC Review #1 and on the updated stability data for the syringes on one lot provided in Amendment 0016. The applicants responses to the FDA CMC IR Letter have been reviewed to be adequate. This review also mentions the Microbiology recommendation.

A. Description of the Drug Product(s) and Drug Substance(s)

NEXTERONE IV is an alternative formulation of intravenous amiodarone to CORDARONE IV (and its generic equivalents). NEXTERONE IV does not contain polysorbate 80 or benzyl alcohol which are employed in the competitive drug products.

Drug Substance

Amiodarone HCl is the subject of U.S. DMF ——— for which Prism Pharmaceuticals has provided a Letter of Authorization (dated 18-Jan-08) from ———, which permits FDA to access ———, DMF ——— in support of Prism Pharmaceuticals' application. ——— is the US agent for ———, the drug substance is manufactured by the latter company in ———. This DMF was recently updated (amendment 11-Jan-08) and found acceptable by Drs. Quan Zhang/ Ubrani Venkataram (26-Feb-08) of OGD. b(4)

There is a monograph for amiodarone HCl in the European Pharmacopoeia, but not in USP/NF. The drug substance has been demonstrated to be stable for up to 60 months when stored at 25°C/75% RH in the designated commercial package, i.e. [redacted] b(4)

Drug Product

NEXTERONE is an alternative formulation of intravenous amiodarone to CORDARONE IV (and its generic equivalents). CORDARONE IV (amiodarone HCl), and generic Amiodarone HCl Injection, contain 50 mg/mL of amiodarone HCl, 20.2 mg/mL of benzyl alcohol, 100 mg/mL of polysorbate 80 and water for injection. NEXTERONE does not contain polysorbate 80 or benzyl alcohol and is instead comprised of a complex of amiodarone HCl and Captisol® (sulfobutylether β-cyclodextrin, SBECD); the latter solubilizer does not possess the undesirable features (potential side effects, interactions with plastic infusion system components) of polysorbate 80 [redacted] b(4) The DP is indicated for the treatment and prophylaxis of frequently recurring ventricular fibrillation (VF) and hemodynamically unstable ventricular tachycardia (VT) in patients refractory to other therapy. NEXTERONE IV also can be used to treat patients with VT/VF for whom oral amiodarone is indicated, but who are unable to take oral medication.

This formulation is bioequivalent to the currently marketed Amiodarone IV Reference Listed Drug (RLD) formulation. In addition, while Amiodarone IV is labeled for the loading dose (150 mg) to be diluted in 100 mL D5W and administered over 10 minutes [redacted] b(4)

Two discrete DP sections are provided within Module 3 of this application. One 3.2P section describes the drug product manufacturing and controls for NEXTERONE vials (manufactured by HollisterStier Laboratories LLC, Spokane, WA) and a separate 3.2.P section is provided for NEXTERONE pre-filled syringes (manufactured by Baxter Pharmaceutical Solutions, LLC, Bloomington, IN). The same drug product is used in both cases.

The drug product is a sterile, free-flowing clear, colorless to slightly yellow solution. The aqueous solubility of the DS has been increased at least [redacted] by complexing with Captisol, a complex, which when administered intravenously, dissociates instantaneously due to its dilution by blood. Captisol is currently used in three approved human parenteral products in the US: Vfend®, Geodon® and Abilify®.

The product is packaged in [redacted] glass [redacted] vials [redacted] b(4) The sponsor studied the stability of twelve lots of the DP vials. Based on the satisfactory 12/18-month stability data provided and in accordance with ICH Q1E the sponsor's proposed shelf life of 24 months for the drug product in vials is justified.

NEXTERONE , 50 mg/mL, is also packaged with a 3 mL fill volume into a 5 mL [redacted] glass syringe composed of [redacted] and 5 mL [redacted] b(4) that are all manufactured by [redacted] Based on the current twelve-month satisfactory stability data provided for the syringes and in accordance with ICH Q1E a

shelf life of 24 months for the drug product in syringes is justified as proposed by the sponsor.

In **Amendment 0015** the applicant has provided adequate responses to the FDA CMC IR letter, which include revised specification for the drug product, validation data for specified impurities, commitment to add the descriptor 'Injection' to the dosage form description, etc.

In **Amendment 0016** the applicant has provided updated 12-month stability information on lot 907770 in pre-filled syringes. This data supports the satisfactory 12-month stability data provided in previous amendments on the additional three stability batches in pre-filled syringes.

In **Amendments 0017 and 0018** the applicant has provided labels of the container and carton, which contain the NDC number and composition of the product (in response to our IR letter). Additionally, DMEPA (Division of Medication Error Prevention and Analysis) has objected to the inclusion of the modifier, 'IV', as a part of the proposed proprietary name; the removal of this modifier is reflected in the labels presented in these amendments.

The Microbiology Consult by Dr. Bryan Riley concludes that there are no microbiology associated issues with this NDA.

B. Description of How the Drug Product is Intended to be Used

The recommended starting dose of NEXTERONE IV is about 1000 mg over the first 24 hours of therapy, delivered by the following infusion regimen:

Loading infusions	***First* Rapid:**	b(4)
		OR
		150 mg over the FIRST 10 minutes (15 mg/min). Add 3 mL of NEXTERONE IV (150 mg) to 100 mL D_5W 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 IV (900 mg) to 500 mL D_5W 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.

All proposed doses can be achieved using the proposed commercial strength of the drug product and its presentation in vials and syringes, (Note: The Medical Reviewer has disallowed [redacted] b(4)

C. Basis for Approvability or Not-Approval Recommendation

The applicant has provided adequate responses to the FDA IR letter sent on 15-Sep-2008, the Microbiology Consult reviewer has recommended approval (see details in this review), and the Office of Compliance has issued an "ACCEPTABLE" Overall Recommendation (summary report in this review); accordingly, this NDA is recommended for approval from a CMC perspective.

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

ChemistName/Date: Prafull Shiromani, Ph.D.
ChemistryTeamLeaderName/Date: Ramesh Sood, Ph.D.
ProjectManagerName/Date: Russell Fortney

C. CC Block

11 Page(s) Withheld

✓ Trade Secret / Confidential (b4)

_____ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

CHEMISTRY REVIEW

Chemistry Review Data Sheet

FDA CDER EES

ESTABLISHMENT EVALUATION REQUEST

SUMMARY REPORT

Application : NDA 22325/000
Org Code : 110
Priority : 3S

Sponsor: PRISM PHARMS
528 FAYETTE ST
CONSHOHOCKEN, PA 19428

Stamp Date : 25-FEB-2008
PDUFA Date : 25-DEC-2008
Action Goal :
District Goal: 26-OCT-2008

Brand Name : NEXTERONE IV (AMIODARONE HCL) 50MG/ML
Estab. Name:
Generic Name: AMIODARONE HCL 50MG/ML
Dosage Form: (INJECTION)
Strength : 50 MG/ML

FDA Contacts:			
	R. FORTNEY	Project Manager	301-796-1068
	D. LU	Review Chemist (HFD-150)	301-796-2059
	T. OLIVER	Team Leader	301-796-1728

3 Overall Recommendation: ACCEPTABLE on 04-DEC-2008by S. ADAMS (HFD-325) 301-796-31

Establishment : CFN : 1833527 FEI : 1000115571
BAXTER PHARMACEUTICAL SOLUTIONS LLC
927 SOUTH CURRY PIKE
BLOOMINGTON, IN 47403
DMF No: AADA:

Responsibilities: FINISHED DOSAGE MANUFACTURER

Profile : SVS
Last Milestone: CC RECOMMENDATION OAI Status: NONE
Milestone Date: 08-MAY-08

CHEMISTRY REVIEW

Chemistry Review Data Sheet

Decision : ACCEPTABLE

Reason : DISTRICT RECOMMENDATION

Establishment : CFN : [redacted] FEI : [redacted]

[redacted] b(4)

DMF No: [redacted]

AADA:

b(4)

Responsibilities: DRUG SUBSTANCE MANUFACTURER

Profile : [redacted]

Last Milestone: OC RECOMMENDATION OAI Status: NONE b(4)

Milestone Date: 04-DEC-08

Decision : ACCEPTABLE

Reason : DISTRICT RECOMMENDATION

Establishment : CFN [redacted] FEI : [redacted]

[redacted] b(4)

DMF No:

AADA: b(4)

Responsibilities: FINISHED DOSAGE RELEASE TESTER

Chemistry Review Data Sheet

ESTABLISHMENT EVALUATION REQUEST

SUMMARY REPORT

Profile : CTL OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 24-MAR-08
Decision : ACCEPTABLE
Reason : BASED ON PROFILE

Establishment : CFN : 3010477 FEI : 3010477
HOLLISTER STIER LABORATORIES LLC
3525 N REGAL ST
SPOKANE, WA 992075788
DMF No:
AADA:

Responsibilities: FINISHED DOSAGE MANUFACTURER

Profile : [redacted] b(4)
Last Milestone: OC RECOMMENDATION OAI Status: NONE
Milestone Date: 24-JUL-08
Decision : ACCEPTABLE
Reason : DISTRICT RECOMMENDATION

Establishment : CFN : [redacted] FEI [redacted] b(4)
DMF No: AADA: b(4)

Responsibilities: FINISHED DOSAGE RELEASE TESTER

Profile : CTL OAI Status: NONE

CHEMISTRY REVIEW

Chemistry Review Data Sheet

Last Milestone: OC RECOMMENDATION
Milestone Date: 24-MAR-08
Decision : ACCEPTABLE
Reason : BASED ON PROFILE

Establishment : CFN : [redacted] FEI : [redacted]

[redacted] b(4)

DMF No: AADA:

Responsibilities: FINISHED DOSAGE RELEASE TESTER

Profile : CTL OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 24-MAR-08
Decision : ACCEPTABLE
Reason : BASED ON PROFILE

Establishment : CFN : [redacted] FEI : [redacted]

[redacted] b(4)

DMF No: AADA:

Chemistry Review Data Sheet

ESTABLISHMENT EVALUATION REQUEST

SUMMARY REPORT

Responsibilities: FINISHED DOSAGE RELEASE TESTER

Profile :	CTL	OAI Status:	NONE
Last Milestone:	OC RECOMMENDATION		
Milestone Date:	24-MAR-08		
Decision :	ACCEPTABLE		
Reason :	BASED ON PROFILE		

****

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/s/

Prafull Shiromani
12/10/2008 08:56:37 AM
CHEMIST

Ramesh Sood
12/10/2008 08:58:21 AM
CHEMIST

CHEMISTRY REVIEW

NDA 22-325

NEXTERONE™ IV (amiodarone HCl) Injection

PRISM PHARMACEUTICALS

b(4)

Prafull Shiromani, Ph.D.

Division of Pre-Marketing Assessment I
Office of New Drug Quality Assessment

Table of Contents

Chemistry Review Data Sheet

1. NDA 22-325

2. REVIEW #: 1

3. REVIEW DATE: 30-Jul-2008

4. REVIEWER: Prafull Shiromani, Ph.D.

5. PREVIOUS DOCUMENTS: N/A

Previous Documents	Document Date

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
NDA 22-325	
Amendment - Nexterone Vials-Stability Update	25-Feb-2008
Amendment - Nexterone Syringes-Stability Update	16-Apr-2008
Amendment – Nexterone Syringes-Stability Update	02-Jul-2008 10-Jul-2008
Amendment (0014) – Nexterone Syringes – Stability Update	11-Sep-2008

7. NAME & ADDRESS OF APPLICANT:

Name: Prism Pharmaceuticals, Inc.

Chemistry Review Data Sheet

Address:	1150 First Avenue, Suite 1050, King of Prussia, PA 19406
Representative:	Daniel J. Cushing, Ph.D., Vice President, Drug Development & Regulatory Affairs
Telephone:	610-986-1024

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: NEXTERONE™ IV
b) Non-Proprietary Name (USAN): Amiodarone HCl
c) Code Name/# (ONDC only):
d) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: 3
- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 505(b)(2)

10. PHARMACOL. CATEGORY: Treatment and prophylaxis of frequently recurring ventricular fibrillation and hemodynamically unstable ventricular tachycardia, for patients who are unable to take oral medication.

11. DOSAGE FORM: Injection

12. STRENGTH/POTENCY: 50 mg/mL

13. ROUTE OF ADMINISTRATION: Parenteral

14. Rx/OTC DISPENSED: _x__Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
_____SPOTS product – Form Completed

___x___Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

[redacted] b(4)

Molecular formula: $C_{25}H_{29}I_2NO_3 \cdot HCl$

Molecular weight: 681.78

Chemical Abstracts Service (CAS) registry number: [redacted]

Chemical Name: [redacted] b(4)

United States Adopted Name (USAN), free base: Amiodarone

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
[redacted]					N/A		b(4)
10304	V	Baxter Pharmaceutical Solutions	Syringe - Sterile Processing Facility in Bloomington, Indiana				**Micro consult** Sterile processing facility (previous review by micro-adequate 03-Sep-2004-Bryan Riley)
[redacted]					N/A		b(4)

Chemistry Review Data Sheet

							Microbiology deficiency-OGD-Neil Sweeney-4/11/2008
					Adequate	26-Feb-2008	Reviewer: Dr. U. Venkataram of OGD
					Adequate	06-Jul-2006	Dr. R. Lu of ONDQA
20732	IV	CyDex	Captisol®	1	Adequate	23-Sep-2008	P. Shiromani
4030-Amendment	V	HollisterStier Laboratories	Vial				**MICRO CONSULT** DMF Section [redacted]
					N/A		
							MICRO CONSULT
					N/A		
					Adequate	15-Oct-2007	Reviewer Dr. M. Salazar Driver, ONDQA.
							MICRO CONSULT Section 5:

b(4)

b(4)

b(4)

b(4)

Chemistry Review Data Sheet

							Study and Section 6:

b(4)

b(4)

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type I DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents: N/A

DOCUMENT	APPLICATION NUMBER	DESCRIPTION

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A	N/A	None
EES	pending		
Pharm/Tox	pending		
Biopharm	pending		
LNC			
Methods Validation	Samples not sent to the laboratory since conventional methods		
DMETS	pending		

Chemistry Review Data Sheet

EA	Categorical Exclusion claimed - Accepted		Prafull Shiromani
Microbiology	pending		

The Chemistry Review for NDA 22-325

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

This NDA in its present form cannot be recommended for approval from a CMC perspective. The approval of this application, from a CMC perspective, depends on the applicants response to the FDA IR letter sent to the applicant on 15-Sep-2008. Additionally, the overall Compliance and Microbiology recommendations have not been received at this time.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

N/A

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

NEXTERONE IV is an alternative formulation of intravenous amiodarone to CORDARONE IV (and its generic equivalents). NEXTERONE IV does not contain polysorbate 80 or benzyl alcohol which are employed in the competitive drug products.

Drug Substance

Amiodarone HCl is the subject of U.S. DMF ——— for which Prism Pharmaceuticals has provided a Letter of Authorization (dated 18-Jan-08) from ——— which permits FDA to access ———, DMF ——— in support of Prism Pharmaceuticals' application. ——— is the US agent for ——— the drug substance is manufactured by the latter company in ———. This DMF was recently updated (amendment 11-Jan-08) and found acceptable by Drs. Quan Zhang/ Ubrani Venkataram (26-Feb-08) of OGD. b(4) b(4)

There is a monograph for amiodarone HCl in the European Pharmacopoeia, but not in USP/NF.

The API is a white to almost white fine crystalline powder, which is very slightly soluble in water. It has unusual solubility behavior, which is attributed to its ability to form micelles.

Since the anionic environment has an effect on the CMC (critical micelle concentration) of the drug substance selection of the proper excipients/buffer and their concentration is vital in formulating the compound.

One concern arose during this review regarding the potential genotoxicity of the chemical, [redacted] b(4)
[redacted]. An IR was sent to the NDA sponsor (since the [redacted] was presented in the NDA) to limit the presence of this impurity to an acceptance criterion that would result in a daily exposure of NMT [redacted] in the drug product. The b(4)
sponsor responded citing literature that a higher TTC value of [redacted] would be acceptable for a genotoxic impurity in pharmaceuticals dosed for </= 1 month [redacted] approach), as is the case here. This response was considered to be acceptable by the FDA Pharm. Tox. reviewer.

The drug substance has been demonstrated to be stable for up to 60 months when stored at 25°C/75% RH in the designated commercial package, i.e [redacted] b(4)

Drug Product

NEXTERONE IV is an alternative formulation of intravenous amiodarone to CORDARONE IV (and its generic equivalents). CORDARONE IV (amiodarone HCl), and generic Amiodarone HCl Injection, contain 50 mg/mL of amiodarone HCl, 20.2 mg/mL of benzyl alcohol, 100 mg/mL of polysorbate 80 and water for injection. NEXTERONE IV does not contain polysorbate 80 or benzyl alcohol and is instead comprised of a complex of amiodarone HCl and Captisol® (sulfobutylether β-cyclodextrin, SBECD); the latter solubilizer does not possess the undesirable features [redacted] b(4)
[redacted] of polysorbate 80. [redacted] The DP is indicated for the treatment and prophylaxis of frequently recurring ventricular fibrillation (VF) and hemodynamically unstable ventricular tachycardia (VT) in patients refractory to other therapy. NEXTERONE IV also can be used to treat patients with VT/VF for whom oral amiodarone is indicated, but who are unable to take oral medication.

This formulation is bioequivalent to the currently marketed Amiodarone IV Reference Listed Drug (RLD) formulation. In addition, while Amiodarone IV is labeled for the loading dose (150 mg) to be diluted in 100 mL D5W and administered over 10 minutes. [redacted] b(4)

Two discrete DP sections are provided within Module 3 of this application. One 3.2P section describes the drug product manufacturing and controls for NEXTERONE IV vials (manufactured by HollisterStier Laboratories LLC, Spokane, WA) and a separate 3.2.P section is provided for NEXTERONE IV pre-filled syringes (manufactured by Baxter Pharmaceutical Solutions, LLC, Bloomington, IN). The same drug product is used in both cases.

The drug product is a sterile, free-flowing clear, colorless to slightly yellow solution. The preclusion of [redacted] has not adversely affected the sterility of the product to date, since all the 12 stability batches passed the sterility test at the 12-month time point. The aqueous solubility of the DS has been increased at least [redacted] by complexing with Captisol, a complex, which when administered intravenously, dissociates instantaneously due to its dilution by blood. Captisol is currently used in three approved human parenteral products in the US: Vfend®, Geodon® and Abilify®. The final formulation, based on extensive development efforts, is composed of amiodarone HCl [redacted] Captisol [redacted] citric acid monohydrate [redacted] sodium citrate dihydrate [redacted] in WFI, with pH adjusted to [redacted] with either citric acid monohydrate or NaOH. The sponsor states that amiodarone is well known to form and associate with micellar phases in aqueous solution. The micelles are submicron in size and represent an association of multiple molecules in solution (an organized aggregation). Some cyclodextrins have also been implicated in micelle-like formation and association. Thus in the NEXTERONE IV formulation, the sponsor claims that [redacted] though no hard evidence is provided to substantiate their claim. The sponsor asserts that [redacted]

b(4)

b(4)

b(4)

The sponsor's formulation development efforts indicated that [redacted] was not a viable option for this product. Hence, they have resorted to an [redacted] technique [redacted]

b(4)

The product is packaged in [redacted] glass [redacted] vials [redacted] The sponsor studied the stability of twelve lots of the DP vials. Based on the satisfactory 12/18-month stability data provided and in accordance with ICH Q1E the sponsor's proposed shelf life of 24 months for the drug product is justified. The level of the degradant [redacted] was much lower [redacted] than it's acceptance criterion of NMT [redacted], even at 40°C/75% RH/12 months; accordingly, the sponsor has been requested to lower it's acceptance criterion.

b(4)

NEXTERONE IV, 50 mg/mL, is also packaged with a 3 mL fill volume into a 5 mL [redacted] glass syringe composed of [redacted], and 5 mL [redacted] Based on the current twelve-month satisfactory stability data provided for the syringes and in accordance with ICH Q1E a shelf life of 24 months for the drug product in syringes is justified as proposed by the sponsor.

b(4)

B. Description of How the Drug Product is Intended to be Used

The recommended starting dose of NEXTERONE IV is about 1000 mg over the first 24 hours of therapy, delivered by the following infusion regimen:

Loading infusions	*First* Rapid:	[redacted] b(4)
	OR	
		150 mg over the FIRST 10 minutes (15 mg/min). Add 3 mL of NEXTERONE IV (150 mg) to 100 mL D_5W 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 IV (900 mg) to 500 mL D_5W 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.

All proposed doses can be achieved using the proposed commercial strength of the drug product and its presentation in vials and syringes.

C. Basis for Approvability or Not-Approval Recommendation

Approvability will be based on the sponsor's response to FDA comments submitted through an IR-letter dated 15-Sep-2008 . These comments are the following:

Drug Product-Vials and Syringes

i. P.2.1.2 Excipients

The CMC information for Captisol was referenced to the DMF # 20732. DMF # 20732 was reviewed and found to be deficient and the deficiencies have been conveyed to the DMF holder.

ii. P.5.1 Specification

a. In accordance with USP <1> Injections, include "essentially free of visible particles" as part of your acceptance criterion for Appearance in the drug product specification.
b. Incorporate an identity test for the counterion, chloride.
c. Include a test and acceptance criterion for osmolarity.

iii. P.5.3 Validation of Analytical Procedure

Provide validation data for the specified identified degradants [redacted] and [redacted], similar to that provided for the [redacted] b(4)

iv. P.8.1 Stability Summary and Conclusions

Reduce the acceptance criterion for the specified degradan[redacted] in the drug product specification, as the stability data indicate that it's level remains consistently at [redacted] even after 12 months at 40°C/75% RH, for all stability lots. b(4)

v. P.8.2 –SYRINGES

Since the syringe submission does not include stability data on production batches you should, as per ICH Q1A(R2), commit to placing the first three production batches on accelerated stability studies for 6 months, in addition to placing them on long term conditions.

vi. II. Review Of Common Technical Document-Quality (Ctd-Q) Module 1, A. Labeling & Package Insert

a. In the Dosage and Administration section (#2), the statement [redacted] does not conform to the compatibility study presented in P.2.6 – Compatibility, Diluent and Container (glass, polyolefin, PVC) Compatibility (CyDex Report N108-1, Study II) [redacted] Accordingly, please clarify this inconsistency. b(4) b(4)

b. In the description section of the Package Insert (#11) include the other inactive ingredients i.e. 3.8 mg citric acid monohydrate, 2.1 mg sodium citrate dihydrate and that sodium hydroxide or citric acid monohydrate may be added to adjust pH.

c. In the How Supplied section (#16) provide the NDC numbers for the vials and the prefilled syringe. These NDC numbers should also be provided in the container and carton labels.

d. Include the dosage form injection on the container and carton labels as shown below:

Nexterone™ IV(amiodarone HCl) Injection.

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

ChemistName/Date: Prafull Shiromani, Ph.D.
ChemistryTeamLeaderName/Date: Ramesh Sood, Ph.D.
ProjectManagerName/Date: Russell Fortney

C. CC Block

127 Page(s) Withheld

✓ Trade Secret / Confidential (b4)

_____ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

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

/s/

Prafull Shiromani
9/24/2008 11:47:39 AM
CHEMIST

Ramesh Sood
9/26/2008 09:06:07 AM
CHEMIST

Initial Quality Assessment
Branch I

OND Division:	Division of Cardio-Renal Products
NDA:	**22-325**
Applicant:	**Prism Pharmaceuticals**
Letter Date:	22-FEB-08
Stamp Date:	25-FEB-08
PDUFA Date:	25-DEC-08
Trademark:	Nexterone™ IV
Established Name:	amiodarone hydrochloride
Dosage Form:	Injectable solution
Route of Administration:	Intravenous
Indication:	Ventricular tachycardia, ventricular fibrillation
Assessed by:	**Thomas F. Oliver, Ph.D.**

Summary and Critical Issues:

Nexterone™ IV (amiodarone hydrochloride) was developed for the treatment of ventricular tachycardia and ventricular fibrillation. Prism Pharmaceuticals has investigated the use of Nexterone™ IV (amiodarone hydrochloride) under IND 72,383 (AT 06-JUN-06). The applicant had a pre-IND meeting (06-JAN-06) to discuss a number of issues including the stability protocol, definition of —— batch scale, and definition of a single-use unit. The applicant had a CMC pre-NDA meeting (06-NOV-07) to discuss the: drug product specification, DS supplier's release specification, biological safety of extractables, and validation of the manufacturing process. In addition, the applicant had a pre-NDA meeting (20-NOV-07) where the pre-filled syringe configuration and the excipient, Captisol, were discussed. Minutes for all of these meetings can be found in DFS and should be reviewed by the assigned reviewer. b(4)

Drug Substance

Amiodarone hydrochloride is white to almost-white fine crystalline powder. It is very slightly soluble in water (0.0007 g/mL). It has been reported (Ravin et al., J. Pharm Sci., 1975; 64: 1830-1833) that anions such as chloride, sulfate, acetate, tartrate and citrate significantly affect the equilibrium solubility of amiodarone hydrochloride; that its solubility was depressed by the addition of increasing amounts of acetate ions; and that its solubility showed a dramatic temperature dependency. Some of this unusual solubility behavior has been attributed by Ravin et al. to the compound's ability to form micelles. The same authors also reported Amiodarone HCl solubility increases as the temperature is increased.

The drug substance will be manufactured at the ———— site in ————. The applicant has referred all drug substance details to DMF ——— A LoA (dated 18-JAN-06) was provided from ——— which allows cross-reference to their DMF ———for amiodarone hydrochloride. The DMF was recently updated (amendment 11-JAN-08) and found acceptable by Dr. Ubrani Venkataram (26-FEB-08). The applicant submitted a dossier from ——— as part of their NDA. Amiodarone hydrochloride is sensitive to light. b(4)

b(4)

Drug Product

Nexterone IV (amiodarone HCl) will be supplied as a [redacted] The recommended starting dose is about 1000 mg over the first 24 hours of therapy, delivered by the following infusion regimen: 1) Initial Load: [redacted] 2) Followed by: 1 mg/min for 6 hours, and 3) Followed by: 0.5 mg/min for the remaining 18 hours. The drug product is a sterile, free-flowing solution with a clear, colorless to slightly yellow appearance. b(4)

The drug product is comprised of amiodarone HCl, Captisol® (sulfobutylether β-cyclodextrin sodium salt), citric acid, sodium citrate, and water for injection (sodium hydroxide and citric acid monohydrate may be added as needed for pH adjustment). The applicant states that Nexterone IV is not compatible with [redacted] methods b(4)

The drug product (Nexterone IV in vials) will be manufactured by HollisterStier laboratories LLC (Spokane, WA) as a sterile [redacted] solution. The vials are of [redacted] glass [redacted] are of identical composition for all fill sizes. [redacted] The manufacturing process consists of the following steps: [redacted] b(4)

[redacted] The registration lots have been manufactured at the full batch size. b(4)

The drug product (Nexterone IV in pre-filled syringes) will be manufactured by Baxter Pharmaceutical Solutions, LLC (Bloomington, IN) as a sterile parenteral product. The glass syringes are composed of [redacted] glass [redacted] The filled syringe is packaged in a blister package, and [redacted] The manufacturing process consists of the following steps: [redacted] The solution is [redacted] b(4)

The applicant has requested a 24 month expiry for the drug product (in vials and in syringes) utilizing [redacted] until use.

Critical Issues for Review

- The applicant submitted a technical dossier for amiodarone hydrochloride as part of the NDA. It appears that [redacted] utilizes the [redacted] As this compound is an alkylating agent (potentially genotoxic), the reviewer will need to work with the pharm/tox reviewer to determine whether the compound is controlled to an acceptable level. b(4)

· The applicant has proposed a NMT ——impurity specification limits for compound ——— as part of the drug substance release testing. It will need to be determined whether this specification limit is acceptable in conjunction with the pharm/tox reviewer (i.e., adequately qualified). b(4)

·The applicant has stated that amiodarone hydrochloride is sensitive to light. It will need to be determined whether the drug substance is adequately packaged and labeled accordingly.

· The applicant utilizes Captisol® (sulfbutylether-β-cyclodextrin sodium salt, DMF #20732, CyDex Inc., LoA dated 23-JAN-08) as a solubilizing agent for the drug substance, amiodarone HCl. The proposed patient exposure levels to excipient, Captisol®, will need to be evaluated in the context of what has been approved previously and the proposed patient population. As amiodarone HCl has limited solubility, the adequacy of the formulation should be closely evaluated (e.g., compatibility studies, stability data). In addition, how the formulation performance is related to the degree of substitution on the β-cyclodextrin, and whether there are sufficient controls in place to ensure future batch performance will need to be determined.

· The applicant stated that Nexterone IV was not compatible with ——— methods and ——— The two drug product manufacturing processes (in glass vials by HollisterStier and in syringes by Baxter) utilizes ——— As a result, the manufacturing process at both sites and the associated validations should be consulted to the Microbiology group. b(4)

· The compatibility of the excipients used in the drug product will need to be evaluated.

· It will need to be determined the importance of temperature on the drug product manufacturing process and whether there are controls in place to adequately control the temperature.

· It will need to be determined whether the applicant has adequately justified their hold times for pre-filtered and filtered drug product solutions.

· The applicant utilizes ——— The reviewer will need to determine how critical the manufacturing process is to ——— and whether there are adequate safeguards in place to control ——— exposure. b(4)

· The applicant has proposed a drug product pH specification limit of——— The acceptability of this range will need to be determined (i.e., product manufactured with these limits can perform adequately and meet specifications at expiry). b(4)

· The applicant has proposed an impurity specification limit of ——— for degradant ——— It will need to be determined whether this specification limit is acceptable in conjunction with the pharm/tox reviewer (i.e., adequately qualified). b(4)

• The adequacy of the syringe and its components is important for drug product performance. The information (including DMFs) used to support the use of the designated syringe will need to be evaluated. In addition, the compatibility of the Nexterone IV with the syringe components will need to be determined (e.g., adequacy of extractable and leachable studies).

• Each syringe will need to be evaluated in terms of the amount of liquid each can hold and whether that corresponds to the manufacturing procedure. In addition, the calibration of the syringe will need to be defined such that the appropriate amount of liquid can be withdrawn and injected as prescribed.

• As amiodarone hydrochloride is very slightly soluble, the loss of active (i.e., assay changes) due to adsorption onto glass or other components may be critical. The reviewer will need to evaluate any factors which may accentuate this loss (e.g., temperature, time, pH, etc.).

• The applicant has indicated amiodarone hydrochloride is sensitive to light. It will need to be determined the extent of degradation due to exposure with light (i.e., photostability data) in both the vials and syringes and whether the sponsor utilizes packaging that provides adequate protection in each case. It will also need to be determined whether the product can be administered as directed in the label or whether additional measures will need to described or included to prevent degradation during the infusion itself. In addition, the labeling will need to need to sufficiently describe the photosensitive nature of the drug product.

• Nexterone IV is an alternate formulation compared to Cordarone IV and a number of approved generics, all of which utilize 20.2 mg/mL of benzyl alcohol. Nexterone IV is monitored for sterility and bacterial endotoxins as part of release and stability testing. It will need to be determined whether this formulation [redacted] will be able to perform as outlined in the label and meet the specification out to the proposed expiry. b(4)

• The label lists amiodarone HCl, and it appears the sponsor utilizes 50 mg of amiodarone HCl per mL, however, the reviewer should verify.

Comments and Recommendation:

The NDA appears to be fileable from a CMC perspective. Since Dr. Donghao (Robert) Lu performed the original IND review (07-JUL-06, ANDA 76924 formulated product) and a second review (20-AUG-07, Prism's formulated product), he would be a prudent choice as the CMC reviewer for this NDA.

The applicant has claimed a categorical exclusion to the environmental assessment as the action does not increase the use of the active moiety; 21 CFR 25.31 (a). The applicant noted that other FDA-approved formulations and dosage forms amiodarone HCL are currently marketed with the identical strength (50 mg/mL), route of administration (intravenous), indications for use, and intended patient population.

The microbiology sections of the drug product, and should be consulted to the Microbiology group by the project manger. This action should be verified by the CMC reviewer.

The manufacturing and testing sites were submitted into EES (24-MAR-08 by T.Oliver), however, the reviewer will need to confirm that these are the correct and only sites.

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/s/

Thomas Oliver
3/24/2008 02:07:03 PM
CHEMIST

Ramesh Sood
3/27/2008 12:53:35 PM
CHEMIST