

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

***APPLICATION NUMBER:***

**22-325**

**CROSS DISCIPLINE TEAM LEADER REVIEW**

### Cross-Discipline Team Leader Review

<b>Date</b>	November 25, 2008
<b>From</b>	Karen A. Hicks, M.D.
<b>Subject</b>	Cross-Discipline Team Leader Review
<b>NDA/BLA #</b>	NDA 22,325
<b>Supplement#</b>	N (000)
<b>Applicant</b>	Prism Pharmaceuticals
<b>Date of Submission</b>	February 21, 2008
<b>PDÜFA Goal Date</b>	December 25, 2008
<b>Proprietary Name / Established (USAN) names</b>	Nexterone™ IV Amiodarone HCl
<b>Dosage forms / Strength</b>	Loading Dose: _____ or 150 mg/100 mL (in D <sub>5</sub> W or Normal Saline) infused over 10 minutes Followed by: 1 mg/min for 6 hours Followed by: 0.5 mg/min thereafter
<b>Proposed Indication(s)</b>	1. Treatment and prophylaxis of frequently recurring ventricular fibrillation and hemodynamically unstable ventricular tachycardia in patients refractory to other therapy 2. Treatment of patients with ventricular tachycardia/ventricular fibrillation for whom oral amiodarone is indicated, but who are unable to take oral medication.
<b>Recommended:</b>	1. Approval for the treatment and prophylaxis of frequently recurring ventricular fibrillation and hemodynamically unstable ventricular tachycardia in patients refractory to other therapy 2. Approval for the treatment of patients with ventricular tachycardia/ventricular fibrillation for whom oral amiodarone is indicated, but who are unable to take oral medication 3. _____ if _____

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This review was based, in part, on the primary reviews of:

- Chemistry (Pravall Shiromani, Ph.D.), September 24, 2008
- Microbiology (Bryan S. Riley, Ph.D.), November 20, 2008
- Preclinical Pharmacology and Toxicology (John Koerner, Ph.D. and Charles Resnick, Ph.D.), November 12, 2008
- Clinical Pharmacology and Biopharmaceutics (Angelica Dorantes, Ph.D.), Draft review dated November 14, 2008
- Clinical (Robert P. Fiorentino, M.D., M.P.H.), November 24, 2008
- Biostatistics (Fanhui Kong, Ph.D.), June 10, 2008
- Division of Scientific Investigations (Martin K. Yau, Ph.D.), October 2, 2008
- Division of Medication Error Prevention and Analysis (Richard Abate, R.Ph.), November 6, 2008

## 1. Introduction

Nexterone IV is an alternative formulation of intravenous (IV) amiodarone to Cordarone® IV, the reference listed drug product for this 505(b)(2) application, and its generic equivalents. Nexterone IV is submitted as a new drug application based on its new formulation and dosing regime.

In patients, Cordarone® IV (amiodarone HCl) and generic Amiodarone HCl Injection cause hypotension which is attributed to their co-solvents, polysorbate 80 and benzyl alcohol. To minimize the potential for hypotension, the labels recommend that Cordarone® IV and generic Amiodarone HCl injection are administered over 10 minutes.

Nexterone IV does not contain polysorbate 80 or benzyl alcohol and instead contains a complex of amiodarone HCl and Captisol® (sulfobutylether β-cyclodextrin, SBECD). Per the Chemistry Review, SBECD "does not possess the undesirable features (potential side effects, interactions with plastic infusion system components) of polysorbate 80."

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The sponsor seeks the same indications and usage for Nexterone IV as for Amiodarone HCl injection and Cordarone® IV:

"[Tradename] Nexterone IV 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 IV also can be used to treat patients with ventricular tachycardia (VT)/ventricular fibrillation (VF) for whom oral amiodarone is indicated, but who are unable to take oral medication. During or after treatment with Nexterone IV, patients may be transferred to oral amiodarone therapy.

"Nexterone IV 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 IV may be safely administered for longer periods if necessary."

Nexterone IV has similar dosing recommendations to Amiodarone HCl injection and Cordarone® IV

This application included two studies to support the approval of Nexterone IV:

- **Study 101** ("A Randomized, Double-Blind, 2-Period Crossover Trial to Determine the Relative Bioavailability of PM101 I.V. (amiodarone hydrochloride) and Cordarone® I.V. Generic Reference Listed Drug (amiodarone hydrochloride) in Healthy Adult Volunteers" was conducted to determine whether or not PM101 I.V. (Nexterone IV) was bioequivalent to Cordarone® I.V. when administered at the same infusion rate. This study demonstrated that PM101 I.V. (Nexterone IV) was bioequivalent to Cordarone® I.V..
- **Study 102** ("A Randomized, Double-Blind, Double-Dummy, Placebo-Controlled Trial to Determine the Relative Effect of PM101 I.V. versus Placebo on Hemodynamics in Healthy Adult Volunteers") was conducted to compare the effect of PM101 I.V. administered as an immediate intravenous bolus push versus placebo on systolic blood pressure (SBP). The primary endpoint was the change in systolic blood pressure from baseline to the lowest value (peak reduction) within 15 minutes after the start of study drug administration. This study demonstrated that PM 101 I.V. was non-inferior to placebo.

## 2. Background

Although amiodarone is considered to be a class III antiarrhythmic drug, amiodarone has electrophysiological characteristics of all four Vaughan Williams' classes as follows:

- Blocks sodium channels at rapid pacing frequencies (class I)
- Has noncompetitive antisymphathetic action (class II)
- Blocks potassium channels (slows conduction and prolongs the action potential and refractory period)
- Has a negative chronotropic effect in nodal tissues (class IV)

Warnings for intravenous amiodarone include hypotension, bradycardia, atrioventricular block, proarrhythmia, and pulmonary toxicity. Per the label, clinically significant hypotension during intravenous infusion is usually seen within the first several hours of treatment and is associated with the rate of the infusion rather than the dose. Practitioners are advised to treat hypotension initially by slowing the infusion, and if unsuccessful, by using vasopressors drugs, positive inotropic agents, and/or volume expansion.

## 3. CMC

There are no outstanding CMC issues.

In the Chemistry review, there was initial concern about the potential genotoxicity of the chemical, \_\_\_\_\_

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\_\_\_\_\_ A Discipline Review Letter, dated June 10, 2008, asked the sponsor

“to demonstrate that this chemical gives negative results when tested directly in appropriate in vitro genotoxicity assays. Otherwise, you should limit the presence of this impurity to an acceptance criterion that would result in a daily exposure of NMT \_\_\_\_\_ in the drug product. Should you revise the acceptance criterion for this impurity, provide appropriate validation data to demonstrate that the analytical procedure is capable of quantifying this impurity at the revised lower level.”

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According to the Chemistry Review, “the sponsor responded citing literature that a higher TTC value of \_\_\_\_\_ would be acceptable for a genotoxic impurity in pharmaceuticals dosed for  $\leq 1$  month (staged approach), as is the case here. This response was considered to be acceptable by the FDA Pharmacology/Toxicology reviewer.”

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## 4. Nonclinical Pharmacology/Toxicology

There are no outstanding nonclinical issues, unless the sponsor chooses to pursue approval of the \_\_\_\_\_ of Nexterone IV in the future.

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In Study N104 (“An Examination of the Cardiovascular Electrophysiology Effects of PM101, Captisol and Amiodarone HCl IV Reference Listed Drug in Anesthetized Female Beagle Dogs (CorDynamics Study Number 7 98-07 0I),” both drug products were associated with pacing-induced ventricular tachycardia degenerating into ventricular fibrillation (VF), suggesting the proarrhythmic potential of the rapid 2 second bolus. Per Dr. Koerner, “the lowest observed adverse effect level (LOAEL) (bolus dose) for this effect was 2.14 mg/kg over 2 seconds for Captisol-Enabled Amiodarone and 21.4 mg/kg over 2 seconds for Amiodarone IV, respectively. Intermediate doses were not evaluated; therefore, the LOAEL could be lower than the present estimate.” If the sponsor seeks approval \_\_\_\_\_

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Per Dr. Koerner, Study N104 demonstrated no electrophysiological effects in anesthetized open chest dogs after receiving Captisol-Enabled Amiodarone or Amiodarone IV intravenously at 2.14 mg/kg over 2 seconds +/- 0.014 mg/kg/min for 20 minutes. However, increasing the bolus dose 10-fold to 21.4 mg/kg or the maintenance dose 50-fold to 0.7 mg/kg/min for 20 minutes “yielded electrophysiological effects consistent with depression of AV

and sinus nodal function (decreased Wenckebach rate, increased AH and HV intervals, increased sinus nodal recovery time), and increase in atrial effective refractory period.” Fatal atrioventricular (AV) block was noted at these same doses, with a LOAEL (bolus dose) of “21.4 mg/kg over 2 seconds for both drug products.”

In Study N103 (“An Examination of the Cardiovascular Effects of PM101, Captisol, and Cordarone IV on Anesthetized Female Beagle Dogs (CorDynamics Study Number 798-0601)”), the sponsor provided preclinical evidence of hypotension with Cordarone® IV at low doses and with Cordarone® IV and Captisol-Enabled Amiodarone at higher doses. Per Dr. Koerner’s review, in anesthetized dogs, the sponsor demonstrated that Captisol-Enabled Amiodarone (PM101 I.V.) at the recommended human dose (2.14 mg/kg over 2 seconds + 0.014 mg/kg/min IV) did not result in hypotension, in contrast to Cordarone® IV at a dose of 2.14 mg/kg over 10 minutes + 0.014 mg/kg/min. However, Captisol-Enabled Amiodarone or Cordarone® IV given to anesthetized dogs at a 10-fold higher dose “resulted in hypotension related to drug-related reductions in cardiac output and cardiac contractility.” Nevertheless, conscious telemeterized monkeys did not develop hypotension after administration of Captisol-Enabled Amiodarone and Cordarone® administered intravenously at a dose of 5 mg/kg over 3 minutes in Study 1548-166 (“A Crossover, Single-Dose Intravenous Infusion Comparison Study of Captisol-Enabled™ Amiodarone, Cordarone®, and a Benzyl Alcohol-Free Amiodarone Formulation in a Male Cynomolgus Monkey Telemetry Model”). In anesthetized dogs and conscious telemeterized monkeys, there were no significant electrocardiographic changes.

## 5. Clinical Pharmacology/Biopharmaceutics

There are no outstanding Clinical Pharmacology/Biopharmaceutics issues. The results of Study 101 are discussed in detail in Dr. Dorantes’ review and are summarized below.

**Study 101** (“A Randomized, Double-Blind, 2-Period Crossover Trial to Determine the Relative Bioavailability of PM101 I.V. (amiodarone hydrochloride) and Cordarone® I.V. Generic Reference Listed Drug (amiodarone hydrochloride) in Healthy Adult Volunteers” (December 18, 2006 – April 23, 2007)

Study 101 was a randomized, single-center, double-blind, 2-period crossover study conducted to evaluate the relative bioavailability of PM101 I.V. (test) and Amiodarone I.V. (reference). Following screening, 88 healthy subjects, 18 to 59 years of age, were randomized to one of two treatment sequences—test drug followed by reference drug or reference drug followed by test drug. The duration of each treatment period was 4 days, and there was a washout period of at least 42 days from the first to the second dose.

Treatment regimens are summarized in Table 1.

**Table 1. Treatment Regimen (Study 101)**

<b>Treatment A</b>	<b>PM101 I.V. (amiodarone hydrochloride) (Nexterone IV)</b>
-1 hour to 0 hour:	Intravenous infusion (I.V.) of 5% dextrose in water (D <sub>5</sub> W) at a fixed rate to keep vein open
0 hour to 10 minutes	150 mg PM101 I.V. in 100 mL D <sub>5</sub> W at 10 mL/min
11 minutes to 6 hours	3 mL D <sub>5</sub> W flush to clean line followed by D <sub>5</sub> W infused at a fixed rate to keep vein open
<b>Treatment B</b>	<b>Amiodarone I.V. (amiodarone hydrochloride) (Reference Listed Drug)</b>
-1 hour to 0 hour	Intravenous infusion of D <sub>5</sub> W at a fixed rate to keep vein open
0 hour to 10 minutes	150 mg Amiodarone I.V. in 100 mL D <sub>5</sub> W at 10 mL/min
11 minutes to 6 hours	3 mL D <sub>5</sub> W flush to clean line followed by D <sub>5</sub> W infused at a fixed rate to keep vein open

A total of 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 population, and 78 subjects were included in the pharmacokinetic evaluation. Five subjects discontinued the study due to an adverse event, including 4 subjects in the Amiodarone I.V. treatment period (sinus tachycardia and dizziness; erythema on both arms, palpitations, abdominal distension/pain, diarrhea, oral hypoesthesia, nausea, chest discomfort, fatigue, feeling cold; chest pressure, burning sensation in chest, and difficulty breathing; difficulty breathing/hot flush with infusion and subsequent erythema on thighs and back) and 1 subject in the PM101 I.V. treatment period (redness on the infusion arm).

Study 101 demonstrated that PM101 I.V. (Nexterone IV) was bioequivalent to Cordarone® IV. Per Dr. Dorantes, “the 90% CI for amiodarone AUC, AUCt, and Cmax were within the Agency’s bioequivalence criteria of 80 to 125%,” as shown in Table 2.

**Table 2. Bioequivalence Results (Study 101)**

Parameter	Geometric Least Squares Mean		Geometric Mean Ratio	90% CI	Intrasubject % Coefficient of Variation
	Nexterone (PM101)	Cordarone IV			
<b>Amiodarone</b>					
Cmax, ng/mL	6038.62	6024.26	1.00	95 - 106%	21.11
AUCt, ng·hr/mL	8055.94	7836.94	1.03	100 - 106%	10.50
AUC0-inf, ng·hr/mL	9398.57	9153.87	1.03	100 - 106%	10.39
<b>Desethylamiodarone</b>					
Cmax, ng/mL	19.88	19.81	1.00	98 - 103%	8.93
AUCt, ng·hr/mL	1199.66	1187.09	1.01	99 - 103%	7.71
AUC0-inf, ng·hr/mL	4623.71	4496.10	1.03	90 - 118%	37.54

(Reproduced from Clinical Pharmacology Review by Angelica Dorantes, Ph.D., Section 1.3, page 5)

**DSI Audit Report:**

At the request of the Division of Cardiovascular and Renal Products (DCRP) and the Division of Clinical Pharmacology I (DCP1), the Division of Scientific Investigations (DSI) audited the clinical and analytical portions of Study 101. There were no significant findings from inspection of the clinical site at Anapharm-Montreal. However, for the analytical site (Anapharm-Quebec City), a Form FDA-483 was issued. DSI recommended accepting data from the analytical study, M06-830, for review; however, DSI wanted to make the Clinical Pharmacology reviewer aware of the significant pre-dose desethylamiodarone (DEA) concentrations found in all subjects during Study Period Two.

The Form FDA-483 observations are summarized below:

2. During method validation and production runs, standard curves and quality controls (QCs) of amiodarone (A) and desethylamiodarone (DEA) were prepared and then processed by spiking each analyte and internal standard into separate blank human plasma. However, both A and DEA were present concomitantly in study plasma samples. Anapharm-Quebec City acknowledged this observation and performed an experiment during the investigation to further evaluate this issue. The experiment demonstrated that quality control samples containing either A or DEA, and quality control samples containing both A and DEA concomitantly were accurate and within 8% of the nominal values.
3. Significant DEA concentrations (> 5% Cmax) were found in the predose human plasma samples of all subjects in Study Period Two but were not discussed in the analytical report. These significant concentrations were thought to be due to an inadequate wash-out period.

Dr. Dorantes stated the sponsor reported the elevated pre-dose DEA concentrations in Study Period 2, and that DSI’s concern could be “easily resolved by re-analyzing the DEA data corrected by pre-dose levels.” However, the Office of Clinical Pharmacology did not think that re-analysis of the DEA metabolite data “[would] change the Agency’s bioequivalence acceptance criteria outcome, which is based on the parent entity (amiodarone).” Furthermore, the sponsor used a highly specific LC/MS/MS assay; therefore, “the pre-dose DEA concentrations [did] not have any influence on amiodarone’s PK and bioequivalence results.”

**Results of Study 101: PM101 I.V. (Nexterone IV) was bioequivalent to Cordarone® I.V..**

## 6. Clinical Microbiology

Dr. Riley stated the submission was "approvable," pending resolution of a product quality microbiology deficiency as follows:

"The proposed maximum dose of \_\_\_\_\_ would translate to the potential administration of \_\_\_\_\_ based on the proposed endotoxin limit of EU/mL and the drug product concentration of \_\_\_\_\_. This potential endotoxin administration is too \_\_\_\_\_, therefore, the endotoxin limit should be lowered to NMT \_\_\_\_\_ based on a 70 kg patient and NMT 3U/kg/hr."

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However, since we are not recommending approval of Nexterone IV as \_\_\_\_\_ Dr. Riley acknowledges that the endotoxin limit "is acceptable." Therefore, this submission may be approved.

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## 7. Clinical/Statistical- Efficacy/Safety

Study 101 was a bioequivalence study (reviewed in Section 5), and Study 102 was a pharmacodynamic study. Study 102 is discussed in detail in Dr. Fiorentino's review and is summarized below.

**Study 102** ("A Randomized, Double-Blind, Double-Dummy, Placebo-Controlled Trial to Determine the Relative Effect of PM101 I.V. versus Placebo on Hemodynamics in Healthy Adult Volunteers") (July 3, 2007 – November 2, 2007)

Study 102 was a randomized, double-blind double-dummy, placebo-controlled study to compare the effect of PM101 administered as an immediate intravenous (I.V.) bolus push with placebo on systolic blood pressure (SBP).

The primary endpoint was the change in systolic blood pressure from baseline to the lowest value (peak reduction) within 15 minutes after the start of study drug administration in the per protocol (PP) population. The PP population included all randomized subjects who were compliant with study medication administration without major protocol deviations and completed the assessments of the primary efficacy endpoint during the first 15 minutes post-dose. The primary endpoint was analyzed using an ANOVA model.

Per Dr. Kong's review, "noninferiority of PM101 compared to placebo for the primary endpoint was prospectively defined as a SBP decrease of 5 mm Hg from baseline to the lowest value within 15 minutes after the drug administration in the PM101 group compared to placebo."

Blood pressure was measured every 3 minutes in the first hour after dosing and then hourly x 11. A final blood pressure measurement was obtained at 24 hours post-dose.

Approximately 342 healthy male and female volunteers, 18 to 55 years of age, were randomized in a 2:2:1:1 fashion to four treatment arms: 114 to PM101 I.V. (2 second bolus push), 113 to placebo, 57 to Amiodarone I.V. (10 minute loading infusion), and 58 to Amiodarone I.V. (15 second loading infusion). The treatment regimens are summarized in Table 3. Four subjects did not take study drug. A total of 323 subjects completed the study and 338 subjects were included in the safety population and pharmacodynamic analysis. A total of nineteen subjects discontinued the study. Fourteen of these subjects discontinued due to adverse events, including one subject in the placebo group, five subjects in the PM101 I.V. group, one subject in the Amiodarone I.V. (10 minute) group, and seven subjects in the Amiodarone I.V. (15 second) group. One subject each in the PM101 I.V. and Amiodarone I.V. (15 second) groups withdrew due to a vasovagal reaction prior to receiving study drug. Three of the discontinuations in the PM101 I.V. group were due to pain over the infusion site and vein with

induration and redness, compared to one similar event in the Amiodarone I.V. (10 minute) group and six similar events in the Amiodarone I.V. (15 second) group.

**Table 3. Treatment Regimen (Study 102)**

Treatment Group	Study Drug	Regimen
A	Placebo I.V. (D <sub>5</sub> W)	D <sub>5</sub> W immediate intravenous bolus (< 2 seconds) then D <sub>5</sub> W intravenous infusion for 6 hours then D <sub>5</sub> W intravenous infusion for 18 hours
B	PM101 (Nexterone) I.V. (2 second bolus)	150 mg immediate intravenous bolus (< 2 seconds) then 1 mg/minute intravenous infusion for 6 hours then 0.5 mg/minute intravenous infusion for 18 hours
C	Amiodarone I.V. Reference Listed Drug (10 minute Loading Dose)	150 mg/100 mL intravenous infusion over 10 minutes at 10 mL/min then 1 mg/minute intravenous infusion for 6 hours then 0.5 mg/minute intravenous infusion for 18 hours
D	Amiodarone I.V. Reference Listed Drug (15 second Loading Dose)	150 mg intravenous infusion over 15 seconds then 1 mg/minute intravenous infusion for 6 hours then 0.5 mg/minute intravenous infusion for 18 hours

In the PP Population, the lowest SBP within 15 minutes post-dose was similar between treatment groups: Placebo:  $-4.25 \pm 4.42$  mm Hg; PM101 I.V. (2 second bolus):  $-4.83 \pm 5.01$  mm Hg; Amiodarone I.V. (10 minutes):  $-4.81 \pm 4.83$  mm Hg; Amiodarone I.V. (15 seconds):  $-4.80 \pm 5.89$  mm Hg, as shown in Table 4.

Per Dr. Kong, “analysis of the primary endpoint [showed] that the change from baseline was comparable between placebo and PM101 ( $-4.25 \pm 4.42$  vs.  $-4.83 \pm 5.01$  mm Hg, respectively), with a mean difference of  $-0.57$  mm Hg, indicating that PM101 was non-inferior (lower limit of 90% CI was  $-1.64$ ).” Dr. Kong clarified that the two-sided 95% CI and *not* the two-sided 90% CI was used to determine the non-inferiority of PM101 and that the lower limit of the 95% CI was  $-1.84$ ).

**Table 4. Systolic Blood Pressure from Baseline to 15 Minutes Post-Dose: Study 102 (PP Population)**

Parameter, mmHg	Placebo (N=111)	PM101 (N=104)	Amiodarone I.V. 10 min (N=54)	Amiodarone I.V. 15 sec (N=54)
Mean SBP at Baseline	108.16	106.92	107.14	107.89
Mean Lowest SBP within 15 Minutes Post-Dose	103.91	102.10	102.33	103.09
Mean Change from Baseline to Lowest SBP with 15 Minutes Post-Dose	-4.25	-4.83	-4.81	-4.80
Standard Deviation	4.42	5.01	4.83	5.89
Minimum, Maximum	-22.0, 5.0	-25.0, 3.5	-21.0, 5.0	-24.0, 6.5
Mean Difference, PM101 - Plbo		-0.57		
Lower Limit of 90% CI of Mean Difference		-1.64		
Lower Limit of 95% CI of Mean Difference		-1.84		

(Analysis by Fanhui Kong, Ph.D., Statistical Review and Evaluation for NDA 22,325 (Nexterone™ IV (amiodarone HCL) dated June 10, 2008, page 5)

A secondary analysis in the modified intention-to-treat (MITT) population supported the primary analysis, as shown in Table 5. The MITT population included all randomized subjects who received any amount of study medication and had a baseline and at least one on-therapy assessment of SBP.

## 10. Other Relevant Regulatory Issues

N/A

## 11. Labeling

Since Study 102 suggested there is not a significant difference in blood pressure changes between the Nexterone IV bolus and other treatment arms.

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The marked-up label is currently circulating among the review team.

The Division of Medication Error Prevention and Analysis "objects to the inclusion of 'IV' as part of the proprietary name because Nexterone IV will be available only as injection for intravenous use and other medical abbreviations are often misinterpreted as 'IV' including the Roman numeral four and 'IU' meaning international units." However, there is no objection to the use of Nexterone alone.

## 12. Recommendations/Risk Benefit Assessment

In summary, Study 101 demonstrated that PM101 I.V. (Nexterone IV) was bioequivalent to Cordarone® I.V.. Additionally, Study 102 demonstrated that PM101 I.V. was non-inferior to placebo with respect to the primary endpoint, the change in systolic blood pressure from baseline to the lowest value (peak reduction) within 15 minutes after the start of study drug administration.

### 12.1 Recommended Regulatory Action

I recommend approval of Nexterone for the following indications and dosing regimen:

- Initiation of treatment and prophylaxis of frequently recurring ventricular fibrillation and hemodynamically unstable ventricular tachycardia in patients refractory to other therapy
- Treatment of 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 IV DOSE RECOMMENDATIONS - FIRST 24 HOURS -

<b>Loading infusions</b>	<b>First Rapid:</b>	<b>150 mg over the FIRST 10 minutes (15 mg/min).</b> Add 3 mL of NEXTERONE IV (150 mg) to 100 mL D <sub>5</sub> W or normal saline (concentration = 1.5 mg/mL). Infuse 100 mL over 10 minutes.
	<b>Followed by Slow:</b>	<b>360 mg over the NEXT 6 hours (1 mg/min).</b> Add 18 mL of NEXTERONE IV (900 mg) to 500 mL D <sub>5</sub> W or normal saline (concentration = 1.8 mg/mL)
<b>Maintenance infusion</b>		<b>540 mg over the REMAINING 18 hours (0.5 mg/min).</b> Decrease the rate of the slow loading infusion to 0.5 mg/min.

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**12.2 Recommended Comments to Applicant**

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