CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-325

SUMMARY REVIEW

NDA 22-325 Nexterone (amiodarone hydrochloride) Injection
RHPM Overview
December 24, 2008

Sponsor: **Prism Pharmaceuticals**
Type: **505(b)(2)/3S**
Receipt Date: **February 25, 2008**
Goal Date: **December 25, 2008**

Action: **Approval**
Action Date: **December 24, 2008**

Background
Amiodarone injection was originally approved in 1995 (as Cordarone Intravenous). All currently approved applications use a formulation that includes the excipients polysorbate 80 and benzyl alcohol. Some clinicians believe that those excipients contribute to the adverse effects (primarily hypotension) of injectable amiodarone, so the current sponsor has developed a formulation that does not include polysorbate 80 or benzyl alcohol. Instead, this formulation uses Captisol, a proprietary cyclodextrin (sulfobutylether β-cyclodextrin), as a solubilizing agent.

b(4)

During development the sponsor referred to their product as PM101. The sponsor's proposed tradename Nexterone was approved by DMEPA.

Division Director's Memo (12/19/08)
Reviewer: Norman Stockbridge, M.D., Ph.D.
Recommendation: Approval
Summary: The Nexterone Captisol-based formulation was intended

b(4)

The sponsor used a non-inferiority design to compare, in normal volunteers, blood pressure responses to usual bolus infusions of 150 mg as Nexterone over 2 s, Cordarone over 15 s, Cordarone over 10 min, and placebo. Nexterone was similar to Cordarone (95% CI of -1.8 mmHg), but the two infusions of Cordarone were also indistinguishable, so the study lacked assay sensitivity, perhaps because it was conducted in normal volunteers. Adverse events were similar in active treatment groups.

A study in anesthetized dogs suggested less blood pressure effects with Captisol containing Nexterone than with Cordarone, but this is insufficient to obtain preferential labeling.

Relative bioavailability was assessed (and considered adequate) in a 2-period crossover study with an (inadequate!) 42-day washout. Such a study is not ordinarily required of an intravenous drug. However, amiodarone is not in solution, and the Division has required a study to show that its kinetics are similar to those of the reference drug.

The Microbiology review notes that

b(4)

so that the total endotoxin limit may need to be lowered slightly. This effect is trivial, and the program established no basis for Therefore, the limit applicable to Cordarone is sufficient here.

As a result, Nexterone can be approved with labeling that is very similar to Cordarone's.

CDTL Review (11/25/08)
Reviewer: Karen Hicks, M.D.
Recommendation: Approval
Summary: Dr. Hicks recommends:

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. [redacted]

b(4)

Medical Review (11/24/08)
Medical Reviewer: Rob Fiorentino, M.D.
Recommendation: Approval
Summary: I recommend approval of Nexterone IV for initiation of treatment and prophylaxis of frequently recurring ventricular fibrillation (VF) and hemodynamically unstable ventricular tachycardia (VT) in patients refractory to other therapy, as follows:

- Initial Loading Dose: 150 mg/100 mL (in D5W or Normal Saline) infused over 10 minutes
- Followed by: 1 mg/min for 6 hours
- Followed by: 0.5 mg/min for 18 hours

In the event of breakthrough episodes of VF or hemodynamically unstable VT, a repeat loading dose may be administered.

I do not recommend approval of [redacted]. The sponsor has submitted a pharmacodynamic study (Study 102) that was intended to demonstrate [redacted]. The primary endpoint of this study was the change in systolic blood pressure from baseline to the lowest value through 15 minutes postdose. The primary comparison was to the placebo arm, however, additional subjects were also randomized to one of two other active controls arms that included an amiodarone 10 minute rapid IV load or a 15 second rapid IV load.

b(4)

Although this study demonstrated that rapid bolus of Nexterone IV was comparable to placebo with respect to the primary endpoint, the study only investigated bolus administration of Nexterone IV in healthy subjects. This is relevant in that IV amiodarone has been associated with hypotension in the intended patient population, which is expected to have significant cardiac disease. Additionally, data submitted in this NDA suggest that rapid administration of either Nexterone or amiodarone IV in healthy subjects results in an acute increase in heart rate that appears to be associated with the early onset of specific, albeit non-serious, adverse events (e.g., hot flushes, injection site reactions). The observed hemodynamic changes and adverse events in the Nexterone IV bolus arm were most similar to the amiodarone 15 second IV loading dose. Significant decreases in blood pressure were not observed in any of the treatment groups and the data failed to demonstrate that [redacted]

b(4)

Statistics Review (6/11/08)
Reviewer: Fanhui Kong, Ph.D.
Recommendation: Approval
Summary: Study 102 was conducted between July 3, 2007 and November 2, 2007 in Montreal, Canada. The primary objective of the study was to compare the effect of PM101 administered as an immediate intravenous (I.V.) bolus push versus placebo on systolic blood pressure.

Analysis of the primary endpoint in this study showed that the change from baseline was comparable between placebo and PM101, with PM101 being non-inferior to placebo.

Clinical Pharmacology and Biopharmaceutics Review (12/18/08)
Reviewer: Angelica Dorantes, Ph.D.
Recommendation: Approval
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] In addition, while currently approved amiodarone products are labeled for a bolus dose to be diluted and administered over 10 minutes, [redacted] b(4)

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 [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. b(4)

[redacted] The labeling for Nexterone should be basically the same as Cordarone IV. b(4)

Pharmacology/Toxicology Review (10/23/07)
Reviewer: John Koerner, Ph.D.
Recommendation: Approvable, pending resolution of several issues
Summary: Amiodarone is a marketed drug and the need for a new drug application is dictated by the new dosing formulation and dosing regime. The currently marketed amiodarone (Cordarone IV), the reference listed drug product for this 505(b)(2) application, produces hypotension in patients that is attributed to the co-solvents used in its formulation (polysorbate 80 and benzyl alcohol). The dosage and administration section of the Cordarone IV labeling recommends infusing the product over 10 minutes to minimize the potential for hypotension. The sponsor believes that [redacted] b(4)

b(4)

The sponsor provided nonclinical pharmacology data supporting this distinction. Captisol-Enabled Amiodarone (PM101) at the recommended human dose (2.14 mg/kg over 2 seconds + 0.014 mg/kg/min iv) did not produce hypotension in anesthetized dogs, whereas the positive comparator, Cordarone IV given at a dose of 2.14 mg/kg over 10 minutes + 0.014 mg/kg/min produced hypotension in this study. A 10-fold higher dose of either Captisol-Enabled Amiodarone or Cordarone IV produced hypotension secondary to drug-related reductions in cardiac output and cardiac contractility. This distinction could not be made in conscious telemeterized monkeys, in which both Captisol-Enabled Amiodarone and Cordarone IV given intravenously at a dose of 5 mg/kg over 3 minutes were without effects on blood pressure. In these studies (anesthetized dogs and conscious telemeterized monkeys), neither Captisol-Enabled Amiodarone nor Cordarone IV affected ECGs.

In another study, Captisol-Enabled Amiodarone and Amiodarone IV given intravenously at 2.14 mg/kg over 2 seconds +/- 0.014 mg/kg/min for 20 minutes tested negative for electrophysiological effects in anesthetized open chest dogs. 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), as well as an increase in atrial effective refractory period. Fatal AV block was observed with both drug products at the 10-fold higher bolus dose, and the 50-fold higher maintenance dose. The LOAEL (bolus dose) for this effect was 21.4 mg/kg over 2 seconds for both drug products. Additionally, both drug products were associated with pacing-induced ventricular tachycardia degenerating into VF. The 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 sec for Amiodarone IV, respectively. Intermediate doses were not evaluated; therefore the LOAEL could be lower than the present estimate. This highlighted the potential for life-threatening arrhythmias with rapid administration of either drug product.

The sponsor evaluated Captisol-Enabled Amiodarone and Cordarone IV in a 2 week canine intravenous toxicology study. There were no adverse effects observed at the dose administered (5 mg/kg + 10.3 mg/kg/day for 14 days). The steady state plasma amiodarone concentrations observed in this study were similar between these 2 treatment groups, and therefore independent of the change in formulation.

In no study did the sponsor compare plasma amiodarone concentrations following a 2 sec vs a 10 minute initial dosing regime. Therefore, there is no nonclinical pharmacokinetic data comparing these 2 dosing regimes.

Captisol-Enabled amiodarone produced hemolysis in vitro in human blood, but only at a concentration of 50 mg/ml, which suggest this is not an issue clinically. Captisol-Enabled amiodarone appeared to precipitate in plasma and pH 7.63 buffer, similar to Cordarone IV. The precipitating concentrations were as low as 1.0 mg/ml and 1.5 mg/ml, respectively, for Captisol-Enabled amiodarone and Cordarone IV concentrations. Given similar findings with these 2 formulations, and abundant clinical experience with Cordarone IV, this finding also seems clinically irrelevant.

Chemistry Review (12/10/08)
Reviewer: Prafull Shiromani, Ph.D.
Recommendation: Approval
Summary: 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.

Microbiology Review (11/20/08)
Reviewer: Bryan Riley, Ph.D.
Recommendation: Approval,
Summary: This submission is approvable, pending resolution of a product quality microbiology deficiency:

- The proposed maximum dose of [redacted] would translate to the potential administration of [redacted] based on the proposed endotoxin limit of [redacted] and the drug product concentration of 50 mg/mL. This potential endotoxin administration is too high; therefore the endotoxin limit should be lowered to NMT [redacted] (based on a 70 kg patient and NMT [redacted]. b(4)

The deficiency noted in Dr. Riley's review does not apply since the [redacted] is not included in the labeling. The endotoxin limit of [redacted] is acceptable if the bolus dose is infused over 10 minutes. This has been noted in Dr. Shiromani's second CMC review (dated 12/10/08). b(4)

DSI: There were no inspections of the clinical study sites.

Pediatric Rule: PREA does not apply as this application does not include a new dosage form, indication, route of administration or dosing regimen.

Labeling: Labeling is similar to the most recently approved Cordarone label. The major differences are in the How Supplied and Dosage and Administration sections:

- Nexterone may be mixed in D_5W or normal saline, and may be mixed in plastic (PVC) bags (Cordarone and its generic equivalents must be mixed in D_5W in either glass or polyolefin bags). These changes are noted in the Dosage and Administration section.

- The How Supplied section has been revised to describe the formulation changes; Nexterone contains sulfbutyl ether β-cyclodextrin in place of benzyl alcohol and polysorbate 80.

This is the first amiodarone product whose label is in the new PLR format. In addition to the major structural changes related to the new format, some minor content changes were made in an effort to modernize the label (in terms of language and format). SEALD participated in a Division labeling meeting, and the Division discussed the labeling with the sponsor in a 12/22/08 teleconference, during which agreement on the labeling content was reached.

Advisory Committee: N/A