

CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

022325Orig1s001

Trade Name: NEXTERONE

Generic or Proper Name: amiodarone hydrochloride

Sponsor: Baxter Healthcare Corp.

Approval Date: 11/16/2010

Indication: NEXTERONE is an antiarrhythmic agent indicated for initiation of treatment and prophylaxis of frequently recurring ventricular fibrillation (VF) and hemodynamically unstable ventricular tachycardia (VT) in patients refractory to other therapy.

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APPROVAL LETTER



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 22325/S-001

SUPPLEMENT APPROVAL

Prism Pharmaceuticals, Inc.
Attention: Daniel J. Cushing, Ph.D.
Vice President Drug Development & Regulatory Affairs
Chief Scientific Officer
1150 First Avenue, Suite 1050
King of Prussia, PA 19406

Dear Dr. Cushing:

Please refer to your Supplemental New Drug Application (sNDA) dated May 5, 2010, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Nexterone (amiodarone hydrochloride) Injection.

This "Prior Approval" supplemental new drug application provides for two new premixed bag formulations of Nexterone (150 mg/100 ml and 360 mg/200 ml).

We have completed our review of this supplemental application. It is approved, effective on the date of this letter, for use as recommended in the enclosed, agreed-upon labeling text.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit, using the FDA automated drug registration and listing system (eLIST), the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format, as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>, that is identical to the enclosed labeling and include the labeling changes proposed in any pending "Changes Being Effected" (CBE) supplements. Information on submitting SPL files using eLIST may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As" at <http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf>.

The SPL will be accessible from publicly available labeling repositories.

CARTON AND IMMEDIATE CONTAINER LABELS

Submit final printed carton and container labels that are identical to the carton and immediate container labels submitted via email on November 4, 2010, as soon as they are available, but no more than 30 days after they are printed.

Please submit these labels electronically according to the guidance for industry titled "Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (June 2008)." Alternatively, you may submit 12 paper copies, with 6 of the copies individually mounted on heavy-weight paper or similar material. For

administrative purposes, designate this submission “**Product Correspondence – Final Printed Carton and Container Labels for approved NDA 22325/S-001.**” Approval of this submission by FDA is not required before the labeling is used.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit the following, in triplicate, (1) a cover letter requesting advisory comments, (2) the proposed materials in draft or mock-up form with annotated references, and (3) the package insert(s) to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications
5901-B Ammendale Road
Beltsville, MD 20705-1266

You must submit final promotional materials and package insert(s), accompanied by a Form FDA 2253, at the time of initial dissemination or publication [21 CFR 314.(b)(3)(i)]. Form FDA 2253 is available at <http://www.fda.gov/opacom/morechoices/fdaforms/cder.html>; instructions are provided on page 2 of the form. For more information about submission of promotional materials to the Division of Drug Marketing, Advertising, and Communications (DDMAC), see <http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm>.

LETTERS TO HEALTH CARE PROFESSIONALS

If you decide to issue a letter communicating important safety-related information about this drug product (i.e., a “Dear Health Care Professional” letter), we request that you submit, at least 24 hours prior to issuing the letter, an electronic copy of the letter to this NDA, to CDERMedWatchSafetyAlerts@fda.hhs.gov, and to the following address:

MedWatch Program
Office of Special Health Issues
Food and Drug Administration
10903 New Hampshire Ave
Building 32, Mail Stop 5353
Silver Spring, MD 20993

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, please call Russell Fortney, Regulatory Project Manager, at (301) 796-1068.

Sincerely,

{See appended electronic signature page}

Norman Stockbridge, M.D., Ph.D.

Director
Division of Cardiovascular and Renal Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosure: Agreed-upon Labeling Text

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

/s/

NORMAN L STOCKBRIDGE
11/16/2010

**CENTER FOR DRUG EVALUATION AND
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LABELING

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use NEXTERONE® safely and effectively. See full prescribing information for NEXTERONE.

NEXTERONE (amiodarone HCl) Premixed Injection for intravenous use
Initial U.S. Approval: 2008

INDICATIONS AND USAGE

NEXTERONE is an antiarrhythmic agent indicated for initiation of treatment and prophylaxis of frequently recurring ventricular fibrillation (VF) and hemodynamically unstable ventricular tachycardia (VT) in patients refractory to other therapy. (1)

DOSAGE AND ADMINISTRATION

- The recommended starting dose is about 1000 mg over the first 24 hours of therapy, delivered by the following infusion regimen (2):
 - Initial Load: 150 mg per 100 mL infused over 10 minutes
 - Followed by: 1 mg/min for 6 hours
 - Followed by: 0.5 mg/min thereafter
- In the event of breakthrough episodes of VF or hemodynamically unstable VT (2):
 - Repeat the Initial Load described above as needed (infused over 10 minutes)
- Increase the rate of the maintenance infusion to achieve effective arrhythmia suppression. (2)

DOSAGE FORMS AND STRENGTHS

Injection, 1.5 mg/mL (150 mg/100 mL) Premixed in Dextrose (3)
Injection, 1.8 mg/mL (360 mg/200 mL) Premixed in Dextrose (3)

CONTRAINDICATIONS

NEXTERONE is contraindicated in patients with (4):

- Known hypersensitivity to any of the components of NEXTERONE, including iodine
- Cardiogenic shock
- Marked sinus bradycardia
- Second- or third-degree atrio-ventricular (AV) block unless a functioning pacemaker is available.

WARNINGS AND PRECAUTIONS

- Hypotension: Treat initially by slowing the infusion; additional standard therapy may be needed, including the following: vasopressor drugs, positive inotropic agents, and volume expansion. (5.1)
- Bradycardia and AV block: Treat by slowing the infusion rate or discontinuing NEXTERONE. (5.2)

ADVERSE REACTIONS

- The most common adverse reactions (1-2%) leading to discontinuation of intravenous amiodarone therapy are hypotension, asystole/cardiac arrest/pulseless electrical activity, VT, and cardiogenic shock. (6)
- Other important adverse reactions are, torsade de pointes (TdP), congestive heart failure, and liver function test abnormalities. (6)

To report SUSPECTED ADVERSE REACTIONS, contact Prism Pharmaceuticals at 610-265-7710 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- Since amiodarone is a substrate for CYP3A and CYP2C8, drugs/substances that inhibit these isoenzymes may decrease the metabolism and increase serum concentration of amiodarone.
- Amiodarone inhibits p-glycoprotein and certain CYP450 enzymes, including CYP1A2, CYP2C9, CYP2D6, and CYP3A. This inhibition can result in unexpectedly high plasma levels of other drugs which are metabolized by those CYP450 enzymes or are substrates for p-glycoprotein.
- Fluoroquinolones, macrolide antibiotics, and azoles are known to cause QTc prolongation. There have been reports of QTc prolongation, with or without TdP, in patients taking amiodarone when fluoroquinolones, macrolide antibiotics, or azoles were administered concomitantly.

USE IN SPECIFIC POPULATIONS

- Pregnancy: Use NEXTERONE during pregnancy only if the potential benefit to the mother justifies the risk to the fetus (8.1).
- Nursing mothers: Amiodarone and one of its major metabolites, desethylamiodarone (DEA), are excreted in human milk, suggesting that breast-feeding could expose the nursing infant to a significant dose of the drug. Advise mothers to discontinue breast feeding (8.3).
- Pediatric use: The safety and efficacy of amiodarone in the pediatric population have not been established (8.4).

See 17 for PATIENT COUNSELING INFORMATION

Revised: December/2010

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*Sections or subsections omitted from the full prescribing information are not listed.

1 INDICATIONS AND USAGE

NEXTERONE® is indicated for initiation of 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. During or after treatment with NEXTERONE, patients may be transferred to oral amiodarone therapy [see *Dosage and Administration (2)*].

Use NEXTERONE 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 DOSAGE AND ADMINISTRATION

Amiodarone shows considerable interindividual variation in response. Although a starting dose adequate to suppress life-threatening arrhythmias is needed, close monitoring with adjustment of dose is essential. The recommended starting dose of NEXTERONE is about 1000 mg over the first 24 hours of therapy, delivered by the following infusion regimen:

Table 1: NEXTERONE PREMIXED INJECTION DOSE RECOMMENDATIONS: FIRST 24 HOURS

Loading infusions	First Rapid: 150 mg over the FIRST 10 minutes (15 mg/min).
	Directly infuse NEXTERONE Premixed Injection (150 mg/100 mL; 1.5mg/mL) at a rate of 10mL/min.
	Followed by Slow: 360 mg over the NEXT 6 hours (1 mg/min).
	Directly infuse NEXTERONE Premixed Injection (360 mg/200 mL; 1.8 mg/mL) at a rate of 0.556 mL/min.
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. Directly infuse NEXTERONE Premixed Injection (360 mg/200 mL; 1.8 mg/mL) at a rate of 0.278 mL/min.

After the first 24 hours, continue the maintenance infusion rate of 0.5 mg/min (720 mg per 24 hours) by directly infusing NEXTERONE Premixed Injection (360 mg/200 mL; 1.8 mg/mL) at a rate of 0.278 mL/min. The rate of the maintenance infusion may be increased to achieve effective arrhythmia suppression.

In the event of breakthrough episodes of VF or hemodynamically unstable VT, use 150 mg supplemental infusions of NEXTERONE (infused over 10 minutes to minimize the potential for hypotension).

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. Do not exceed an initial infusion rate of 30 mg/min.

Based on the experience from clinical studies of intravenous amiodarone, a maintenance infusion of up to 0.5 mg/min can be 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.

Administer NEXTERONE, whenever possible, through a central venous catheter dedicated to that purpose. Use an in-line filter during administration.

Intravenous amiodarone loading infusions at much higher concentrations and rates of infusion much faster than recommended have resulted in hepatocellular necrosis and acute renal failure, leading to death [see *Warnings and Precautions (5.3)*].

Intravenous amiodarone concentrations greater than 3 mg/mL have been associated with a high incidence of peripheral vein phlebitis; however, concentrations of 2.5 mg/mL or less appear to be less irritating. Therefore, for infusions longer than 1 hour, do not exceed NEXTERONE concentrations of 2 mg/mL, unless a central venous catheter is used [see *Adverse Reactions (6.2)*].

NEXTERONE Premixed Injection is available in GALAXY® containers as a single-use, ready-to-use, iso-osmotic solution in dextrose for intravenous administration. No further dilution is required. NEXTERONE Premixed Injection should not be combined with any product in the same intravenous line or premixed container. Protect from light until ready to use.

NEXTERONE does not need to be protected from light during administration.

Since the premixed container is for single-use only, any unused portion should be discarded.

NOTE: Inspect parenteral drug products for particulate matter and discoloration prior to administration, whenever solution and container permit. Check for minute leaks prior to use by squeezing the bag firmly. If leaks are detected, discard solution as sterility may be impaired.

CAUTION: Do not use plastic containers in series connections. Such use could result in air embolism due to residual air being drawn from the primary container before the administration of the fluid from the secondary container is complete.

Preparation of NEXTERONE Premixed Injection for administration:

1. Suspend container from eyelet support.
2. Remove protector from outlet port at bottom of container.
3. Attach administration set. Refer to complete directions accompanying set.

Admixture Incompatibility

NEXTERONE in D₅W is incompatible with the drugs shown in Table 2.

Table 2: Y-SITE INJECTION INCOMPATIBILITY

Drug	Vehicle	Amiodarone Concentration	Comments
Aminophylline	D ₅ W	4 mg/mL	Precipitate
Cefamandole Nafate	D ₅ W	4 mg/mL	Precipitate
Cefazolin Sodium	D ₅ W	4 mg/mL	Precipitate
Mezlocillin Sodium	D ₅ W	4 mg/mL	Precipitate
Heparin Sodium	D ₅ W	--	Precipitate

Sodium Bicarbonate	D ₅ W	3 mg/mL	Precipitate
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Intravenous to Oral Transition

Patients whose arrhythmias have been suppressed by NEXTERONE may be switched to oral amiodarone. The optimal dose for changing from intravenous to oral administration of amiodarone will depend on the dose of NEXTERONE already administered, as well as the bioavailability of oral amiodarone. When changing to oral amiodarone therapy, clinical monitoring is recommended, particularly for elderly patients. See package insert for oral amiodarone.

Since grapefruit juice is known to inhibit CYP3A-mediated metabolism of oral amiodarone in the intestinal mucosa, resulting in increased plasma levels of amiodarone, do not drink grapefruit juice during treatment with oral amiodarone [see *Drug Interactions (7)*].

Table 3 provides suggested doses of oral amiodarone to be initiated after varying durations of NEXTERONE administration. These recommendations are made on the basis of a similar total body amount of amiodarone delivered by the intravenous and oral routes, based on 50% bioavailability of oral amiodarone.

Table 3: RECOMMENDATIONS FOR ORAL DOSAGE AFTER INTRAVENOUS INFUSION

Duration of NEXTERONE Infusion [#]	Initial Daily Dose of Oral Amiodarone
< 1 week	800-1600 mg
1-3 weeks	600-800 mg
> 3 weeks*	400 mg

[#] Assuming a 720 mg/day infusion (0.5 mg/min).

* NEXTERONE is not intended for maintenance treatment.

3 DOSAGE FORMS AND STRENGTHS

Injection, 1.5 mg/mL (150 mg/100 mL) Premixed in Dextrose

Injection, 1.8 mg/mL (360 mg/200 mL) Premixed in Dextrose

4 CONTRAINDICATIONS

NEXTERONE is contraindicated in patients with:

- Known hypersensitivity to any of the components of NEXTERONE Premixed Injection, including iodine. Hypersensitivity reactions may involve rash, angioedema, cutaneous/mucosal hemorrhage (bleeding), fever, arthralgias (joint pains), eosinophilia (abnormal blood counts), urticaria (hives), thrombotic thrombocytopenic purpura, or severe periarteritis (inflammation around blood vessels).
- Cardiogenic shock.
- Marked sinus bradycardia.
- Second- or third-degree atrio-ventricular (AV) block unless a functioning pacemaker is available.

5 WARNINGS AND PRECAUTIONS

NEXTERONE should be administered only by physicians who are experienced in the treatment of life-threatening arrhythmias, who are thoroughly familiar with the risks and benefits of amiodarone therapy, and who have access to facilities adequate for monitoring the effectiveness and side effects of treatment.

5.1 Hypotension

Hypotension is the most common adverse reaction seen with intravenous amiodarone. In clinical trials, treatment-emergent, drug-related hypotension was reported as an adverse

effect in 288 (16%) of 1836 patients treated with intravenous amiodarone. Clinically significant hypotension during infusions was seen most often in the first several hours of treatment and was not dose related, but appeared to be related to the rate of infusion. Hypotension necessitating alterations in intravenous amiodarone therapy was reported in 3% of patients, with permanent discontinuation required in less than 2% of patients.

Treat hypotension initially by slowing the infusion; additional standard therapy may be needed, including the following: vasopressor drugs, positive inotropic agents, and volume expansion. *Monitor the initial rate of infusion closely and do not exceed the recommended rate [see Dosage and Administration (2)].*

In some cases, hypotension may be refractory and result in a fatal outcome [*see Adverse Reactions (6.2)*].

5.2 Bradycardia and Atrio-ventricular Block

In 90 (4.9%) of 1836 patients in clinical trials, drug-related bradycardia that was not dose-related occurred while they were receiving intravenous amiodarone for life-threatening VT/VF. Treat bradycardia by slowing the infusion rate or discontinuing NEXTERONE. In some patients, inserting a pacemaker is required. Despite such measures, bradycardia was progressive and terminal in 1 patient during the controlled trials. Treat patients with a known predisposition to bradycardia or AV block with NEXTERONE in a setting where a temporary pacemaker is available.

5.3 Liver Enzyme Elevations

Elevations of blood hepatic enzyme values [alanine aminotransferase (ALT), aspartate aminotransferase (AST), and gamma-glutamyl transferase (GGT)] are commonly seen in patients with immediately life-threatening VT/VF. Interpreting elevated AST activity can be difficult because the values may be elevated in patients who have had recent myocardial infarction, congestive heart failure, or multiple electrical defibrillations. Approximately 54% of patients receiving intravenous amiodarone in clinical studies had baseline liver enzyme elevations, and 13% had clinically significant elevations. In 81% of patients with both baseline and on-therapy data available, the liver enzyme elevations either improved during therapy or remained at baseline levels. Baseline abnormalities in hepatic enzymes are not a contraindication to treatment.

Acute, centrilobular confluent hepatocellular necrosis leading to hepatic coma, acute renal failure, and death has been associated with the administration of intravenous amiodarone at a much higher loading dose concentration and much faster rate of infusion than recommended (*see Dosage and Administration (2)*).

In patients with life-threatening arrhythmias, the potential risk of hepatic injury should be weighed against the potential benefit of NEXTERONE therapy. Carefully monitor patients receiving NEXTERONE for evidence of progressive hepatic injury. In such cases, consider reducing the rate of administration or withdrawing NEXTERONE.

5.4 Proarrhythmia

Like all antiarrhythmic agents, NEXTERONE may cause a worsening of existing arrhythmias or precipitate a new arrhythmia. Proarrhythmia, primarily torsade de pointes (TdP), has been associated with prolongation, by intravenous amiodarone, of the QTc interval to 500 ms or greater. Although QTc prolongation occurred frequently in patients receiving intravenous amiodarone, TdP or new-onset VF occurred infrequently (less than 2%). Monitor patients for QTc prolongation during infusion with NEXTERONE. Reserve the combination of amiodarone with other antiarrhythmic therapies that prolong the QTc to patients with life-threatening ventricular arrhythmias who are incompletely responsive to a single agent.

Fluoroquinolones, macrolide antibiotics, and azoles are known to cause QTc prolongation. There have been reports of QTc prolongation, with or without TdP, in patients taking amiodarone when fluoroquinolones, macrolide antibiotics, or azoles were administered concomitantly [*see Drug Interactions (7)*].

Amiodarone causes thyroid dysfunction in some patients, which may lead to potentially fatal breakthrough or exacerbated arrhythmias.

5.5 Pulmonary Disorders

Early-onset Pulmonary Toxicity

There have been postmarketing reports of acute-onset (days to weeks) pulmonary injury in patients treated with intravenous amiodarone. Findings have included pulmonary infiltrates and masses on X-ray, bronchospasm, wheezing, fever, dyspnea, cough, hemoptysis, and hypoxia. Some cases have progressed to respiratory failure or death.

ARDS

Two percent (2%) of patients were reported to have adult respiratory distress syndrome (ARDS) during clinical studies involving 48 hours of therapy.

Pulmonary Fibrosis

Only 1 of more than 1000 patients treated with intravenous amiodarone in clinical studies developed pulmonary fibrosis. In that patient, the condition was diagnosed 3 months after treatment with intravenous amiodarone, during which time the patient received oral amiodarone. Pulmonary toxicity is a well-recognized complication of long-term amiodarone use (see package insert for oral amiodarone).

5.6 Loss of Vision

Cases of optic neuropathy and optic neuritis, usually resulting in visual impairment, have been reported in patients treated with oral amiodarone. In some cases, visual impairment has progressed to permanent blindness. Optic neuropathy and neuritis may occur at any time following initiation of therapy. A causal relationship to the drug has not been clearly established. Perform an ophthalmic examination if symptoms of visual impairment appear, such as changes in visual acuity and decreases in peripheral vision. Re-evaluate the necessity of amiodarone therapy if optic neuropathy or neuritis is suspected. Perform regular ophthalmic examination, including fundoscopy and slit-lamp examination, during administration of NEXTERONE.

5.7 Long-Term Use

There has been limited experience in patients receiving intravenous amiodarone for longer than 3 weeks. See package insert for oral amiodarone.

5.8 Thyroid Abnormalities

Amiodarone inhibits peripheral conversion of thyroxine (T4) to triiodothyronine (T3) and may cause increased T4 levels, decreased T3 levels, and increased levels of inactive reverse T3 (rT3) in clinically euthyroid patients. Amiodarone is also a potential source of large amounts of inorganic iodine and can cause either hypothyroidism or hyperthyroidism. Evaluate thyroid function prior to treatment and periodically thereafter, particularly in elderly patients, and in any patient with a history of thyroid nodules, goiter, or other thyroid dysfunction. Because of the slow elimination of amiodarone and its metabolites, high plasma iodide levels, altered thyroid function, and abnormal thyroid-function tests may persist for several weeks or even months following NEXTERONE withdrawal.

There have been postmarketing reports of thyroid nodules/thyroid cancer in patients treated with amiodarone. In some instances hyperthyroidism was also present [*see Adverse Reactions 6.2*].

Hyperthyroidism and Thyrotoxicosis

Hyperthyroidism occurs in about 2% of patients receiving amiodarone, but the incidence may be higher among patients with prior inadequate dietary iodine intake. Amiodarone-induced hyperthyroidism usually poses a greater hazard to the patient than hypothyroidism because of the possibility of thyrotoxicosis and arrhythmia breakthrough or aggravation, all of which may result in death. There have been reports of death associated with amiodarone-induced thyrotoxicosis. Consider the possibility of hyperthyroidism if any new signs of arrhythmia appear.

Identify hyperthyroidism by relevant clinical signs and symptoms, subnormal serum levels of thyroid stimulating hormone (TSH), abnormally elevated serum free T4, and elevated or normal serum T3. Since arrhythmia breakthroughs may accompany amiodarone-induced hyperthyroidism, aggressive medical treatment is indicated, including, if possible, dose reduction or withdrawal of amiodarone. Amiodarone hyperthyroidism may be followed by a transient period of hypothyroidism.

The institution of antithyroid drugs, β -adrenergic blockers or temporary corticosteroid therapy may be necessary. The action of antithyroid drugs may be especially delayed in amiodarone-induced thyrotoxicosis because of substantial quantities of preformed thyroid hormones stored in the gland. Radioactive iodine therapy is contraindicated because of the low radioiodine uptake associated with amiodarone-induced hyperthyroidism.

When aggressive treatment of amiodarone-induced thyrotoxicosis has failed or amiodarone cannot be discontinued because it is the only drug effective against the resistant arrhythmia, surgical management may be an option. Experience with thyroidectomy as a treatment for amiodarone-induced thyrotoxicosis is limited, and this form of therapy could induce thyroid storm. Therefore, surgical and anesthetic management require careful planning.

Neonatal Hypo- or Hyperthyroidism

Amiodarone can cause fetal harm when administered to a pregnant woman. Although amiodarone use during pregnancy is uncommon, there have been a small number of published reports of congenital goiter/hypothyroidism and hyperthyroidism associated with oral administration. Inform the patient of the potential hazard to the fetus if NEXTERONE is administered during pregnancy or if the patient becomes pregnant while taking NEXTERONE.

Hypothyroidism

Hypothyroidism has been reported in 2 to 4% of patients in most series, but in 8 to 10% in some series. This condition may be identified by relevant clinical symptoms and particularly by elevated serum TSH levels. In some clinically hypothyroid amiodarone-treated patients, free thyroxine index values may be normal. Manage hypothyroidism by reducing the NEXTERONE dose and considering the need for thyroid hormone supplement. However, therapy must be individualized, and it may be necessary to discontinue oral amiodarone in some patients.

5.9 Surgery

Perform close perioperative monitoring in patients undergoing general anesthesia who are on amiodarone therapy as they may be more sensitive to the myocardial depressant and conduction defects of halogenated inhalational anesthetics.

5.10 Corneal Refractive Laser Surgery

Advise patients that most manufacturers of corneal refractive laser surgery devices contraindicate corneal refractive laser surgery in patients taking amiodarone.

5.11 Electrolyte Disturbances

Correct hypokalemia or hypomagnesemia whenever possible before initiating treatment with NEXTERONE, as these disorders can exaggerate the degree of QTc prolongation and increase the potential for TdP. Give special attention to electrolyte and acid-base balance in patients experiencing severe or prolonged diarrhea or in patients receiving concomitant diuretics.

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

In a total of 1836 patients in controlled and uncontrolled clinical trials, 14% of patients received intravenous amiodarone for at least one week, 5% received it for at least 2

weeks, 2% received it for at least 3 weeks, and 1% received it for more than 3 weeks, without an increased incidence of severe adverse reactions. The mean duration of therapy in these studies was 5.6 days; median exposure was 3.7 days.

The most important adverse reactions were hypotension, asystole/cardiac arrest/pulseless electrical activity (PEA), cardiogenic shock, congestive heart failure, bradycardia, liver function test abnormalities, VT, and AV block. Overall, treatment was discontinued for about 9% of the patients because of adverse reactions. The most common adverse reactions leading to discontinuation of intravenous amiodarone therapy were hypotension (1.6%), asystole/cardiac arrest/PEA (1.2%), VT (1.1%), and cardiogenic shock (1%).

Table 4 lists the most common (incidence $\geq 2\%$) adverse reactions during intravenous amiodarone therapy considered at least possibly drug-related. These data were collected in clinical trials involving 1836 patients with life-threatening VT/VF. Data from all assigned treatment groups are pooled because none of the adverse reactions appeared to be dose-related.

Table 4: ADVERSE REACTIONS IN PATIENTS RECEIVING INTRAVENOUS AMIODARONE IN CONTROLLED AND OPEN-LABEL STUDIES (≥ 2% INCIDENCE)

Study Event	Controlled Studies (n = 814)	Open-Label Studies (n = 1022)	Total (n = 1836)
Body as a whole			
Fever	24 (2.9%)	13 (1.2%)	37 (2.0%)
Cardiovascular System			
Bradycardia	49 (6.0%)	41 (4.0%)	90 (4.9%)
Congestive heart failure	18 (2.2%)	21 (2.0%)	39 (2.1%)
Heart arrest	29 (3.5%)	26 (2.5%)	55 (2.9%)
Hypotension	165 (20.2%)	123 (12.0%)	288 (15.6%)
Ventricular tachycardia	15 (1.8%)	30 (2.9%)	45 (2.4%)
Digestive System			
Liver function tests abnormal	35 (4.2%)	29 (2.8%)	64 (3.4%)
Nausea	29 (3.5%)	43 (4.2%)	72 (3.9%)

Other adverse reactions reported in less than 2% of patients receiving intravenous amiodarone in controlled and uncontrolled studies included the following: abnormal kidney function, atrial fibrillation, diarrhea, increased ALT, increased AST, lung edema, nodal arrhythmia, prolonged QT interval, respiratory disorder, shock, sinus bradycardia, Stevens-Johnson syndrome, thrombocytopenia, VF, and vomiting.

6.2 Post-Marketing Experience

The following adverse reactions have been identified during post-approval use of amiodarone. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Body as a Whole: anaphylactic/anaphylactoid reaction (including shock), fever

Cardiovascular: hypotension (sometimes fatal), sinus arrest

Dermatologic: toxic epidermal necrolysis (sometimes fatal), exfoliative dermatitis, erythema multiforme, Stevens-Johnson syndrome, skin cancer, pruritus, angioedema

Endocrine: syndrome of inappropriate antidiuretic hormone secretion (SIADH)

Hematologic: pancytopenia, neutropenia, hemolytic anemia, aplastic anemia, thrombocytopenia, agranulocytosis, granuloma

Hepatic: hepatitis, cholestatic hepatitis, cirrhosis

Injection Site Reactions: pain, erythema, edema, pigment changes, venous thrombosis, phlebitis, thrombophlebitis, cellulitis, necrosis, and skin sloughing

Musculoskeletal: myopathy, muscle weakness, rhabdomyolysis

Nervous System: hallucination, confusional state, disorientation, and delirium, pseudotumor cerebri

Pancreatic: pancreatitis

Renal: renal impairment, renal insufficiency, acute renal failure,

Respiratory: bronchospasm, possibly fatal respiratory disorders (including distress, failure, arrest and ARDS), bronchiolitis obliterans organizing pneumonia (possibly fatal), dyspnea, cough, hemoptysis, wheezing, hypoxia, pulmonary infiltrates, and /or mass, pleuritis

Thyroid: thyroid nodules/thyroid cancer

Vascular: vasculitis

7 DRUG INTERACTIONS

Amiodarone is metabolized to the active metabolite desethylamiodarone by the cytochrome P450 (CYP450) enzyme group, specifically cytochromes P4503A4 (CYP3A) and CYP2C8. The CYP3A isoenzyme is present in both the liver and intestines.

Amiodarone is an inhibitor of CYP3A. Therefore, amiodarone has the potential for interactions with drugs or substances that may be substrates, inhibitors or inducers of CYP3A. While only a limited number of in vivo drug-drug interactions with amiodarone have been reported, chiefly with the oral formulation, the potential for other interactions should be anticipated. This is especially important for drugs associated with serious toxicity, such as other antiarrhythmics. If such drugs are needed, reassess their dose and, where appropriate, measure plasma concentrations. In view of the long and variable half-life of amiodarone, potential for drug interactions exists not only with concomitant medication but also with drugs administered after discontinuation of amiodarone.

Since amiodarone is a substrate for CYP3A and CYP2C8, drugs/substances that inhibit these isoenzymes may decrease the metabolism and increase serum concentration of amiodarone. Reported examples include the following:

Protease inhibitors:

Protease inhibitors are known to inhibit CYP3A to varying degrees. A case report of one patient taking amiodarone 200 mg and indinavir 800 mg three times a day resulted in increases in amiodarone concentrations from 0.9 mg/L to 1.3 mg/L. DEA concentrations were not affected. There was no evidence of toxicity. Consider monitoring for amiodarone toxicity and serial measurement of amiodarone serum concentration during concomitant protease inhibitor therapy.

Histamine H₁ antagonists:

Loratadine, a non-sedating antihistaminic, is metabolized primarily by CYP3A. QT interval prolongation and TdP have been reported with the co-administration of loratadine and amiodarone.

Histamine H₂ antagonists:

Cimetidine inhibits CYP3A and can increase serum amiodarone levels.

Antidepressants:

Trazodone, an antidepressant, is metabolized primarily by CYP3A. QT interval prolongation and TdP have been reported with the co-administration of trazodone and amiodarone.

Other substances:

Grapefruit juice given to healthy volunteers increased amiodarone AUC by 50% and C_{max} by 84%, resulting in increased plasma levels of amiodarone. Do not take grapefruit juice during treatment with amiodarone.

Amiodarone inhibits p-glycoprotein and certain CYP450 enzymes, including CYP1A2, CYP2C9, CYP2D6, and CYP3A. This inhibition can result in unexpectedly high plasma levels of other drugs which are metabolized by those CYP450 enzymes or are substrates for p-glycoprotein. Reported examples of this interaction include the following:

Immunosuppressives:

Cyclosporine (CYP3A substrate) administered in combination with oral amiodarone has been reported to produce persistently elevated plasma concentrations of cyclosporine resulting in elevated creatinine, despite reduction in dose of cyclosporine.

HMG-CoA Reductase Inhibitors:

Simvastatin (CYP3A substrate) in combination with amiodarone has been associated with reports of myopathy/rhabdomyolysis.

Cardiovasculars:

Cardiac glycosides: In patients receiving *digoxin* therapy, administration of oral amiodarone regularly results in an increase in serum digoxin concentration that may reach toxic levels with resultant clinical toxicity. Amiodarone taken concomitantly with digoxin increases the serum digoxin concentration by 70% after one day. On administration of oral amiodarone, review the need for digitalis therapy and reduce the dose of digitalis by approximately 50% or discontinue digitalis. If digitalis treatment is continued, monitor serum levels closely and observe patients for clinical evidence of toxicity.

Antiarrhythmics:

Other antiarrhythmic drugs, such as *quinidine*, *procainamide*, *disopyramide*, and *phenytoin*, have been used concurrently with amiodarone. There have been case reports of increased steady-state levels of quinidine, procainamide, and phenytoin during concomitant therapy with amiodarone. Phenytoin decreases serum amiodarone levels. Amiodarone taken concomitantly with quinidine increases quinidine serum concentration by 33% after two days. Amiodarone taken concomitantly with procainamide for less than seven days increases plasma concentrations of procainamide and n-acetyl procainamide by 55% and 33%, respectively. Reduce quinidine and procainamide doses by one-third when either is administered with amiodarone.

Plasma levels of *flecainide* have been reported to increase in the presence of oral amiodarone; adjust the dose of flecainide when these drugs are administered concomitantly. In general, initiate any added antiarrhythmic drug at a lower than usual dose and monitor the patient carefully.

Reserve the combination of amiodarone with other antiarrhythmic therapy to patients with life-threatening ventricular arrhythmias who are incompletely responsive to a single agent or incompletely responsive to amiodarone. During transfer to oral amiodarone, reduce the dose levels of previously administered agents by 30 to 50% several days after the addition of oral amiodarone. Review the continued need for the other antiarrhythmic agent after the effects of amiodarone have been established, and attempt discontinuation. If the treatment is continued, carefully monitor these patients for adverse effects, especially for conduction disturbances and exacerbation of tachyarrhythmias. In amiodarone-treated patients who require additional antiarrhythmic therapy, the initial dose of such agents should be approximately half of the usual recommended dose.

Antihypertensives:

Use amiodarone with caution in patients receiving β -receptor blocking agents (e.g., *propranolol*, a CYP3A inhibitor) or calcium channel antagonists (e.g., *verapamil*, a CYP3A substrate, and *diltiazem*, a CYP3A inhibitor) because of the possible potentiation of bradycardia, sinus arrest, and AV block; if necessary, amiodarone can continue to be used after insertion of a pacemaker in patients with severe bradycardia or sinus arrest.

Anticoagulants:

Potentiation of *warfarin*-type (CYP2C9 and CYP3A substrate) anticoagulant response is almost always seen in patients receiving amiodarone and can result in serious or fatal bleeding. Since the concomitant administration of warfarin with amiodarone increases the prothrombin time by 100% after 3 to 4 days, reduce the dose of the anticoagulant by one-third to one-half, and monitor prothrombin times closely.

Clopidogrel, an inactive thienopyridine prodrug, is metabolized in the liver by CYP3A to an active metabolite. A potential interaction between clopidogrel and amiodarone resulting in ineffective inhibition of platelet aggregation has been reported.

Some drugs/substances are known to accelerate the metabolism of amiodarone by stimulating the synthesis of CYP3A (enzyme induction). This may lead to low amiodarone serum levels and potential decrease in efficacy. Reported examples of this interaction include the following:

Antibiotics:

Rifampin is a potent inducer of CYP3A. Administration of rifampin concomitantly with oral amiodarone has been shown to result in decreases in serum concentrations of amiodarone and desethylamiodarone.

Other substances, including herbal preparations:

St. John's Wort (Hypericum perforatum) induces CYP3A. Since amiodarone is a substrate for CYP3A, *St. John's Wort* likely reduces amiodarone levels.

Other reported interactions with amiodarone:

Fentanyl (CYP3A substrate) in combination with amiodarone may cause hypotension, bradycardia, and decreased cardiac output.

Sinus bradycardia has been reported with oral amiodarone in combination with *lidocaine* (CYP3A substrate) given for local anesthesia. Seizure, associated with increased lidocaine concentrations, has been reported with concomitant administration of intravenous amiodarone.

Dextromethorphan is a substrate for both CYP2D6 and CYP3A. Amiodarone inhibits CYP2D6.

Cholestyramine increases enterohepatic elimination of amiodarone and may reduce its serum levels and $t_{1/2}$.

Disopyramide causes QT prolongation which could induce arrhythmia.

Fluoroquinolones, macrolide antibiotics, and azoles are known to cause QTc prolongation. There have been reports of QTc prolongation, with or without TdP, in patients taking amiodarone when fluoroquinolones, macrolide antibiotics, or azoles were administered concomitantly [see *Warnings and Precautions (5.4)*].

Hemodynamic and electrophysiologic interactions have also been observed after concomitant administration with *propranolol, diltiazem, and verapamil*.

Volatile Anesthetic Agents: Patients who are on amiodarone therapy may be more sensitive to the myocardial depressant and conduction defects of halogenated inhalational anesthetics [see *Warnings and Precautions (5.9)*].

In addition to the interactions noted above, chronic (> 2 weeks) *oral* amiodarone administration impairs metabolism of phenytoin, dextromethorphan, and methotrexate.

8 Use in Specific Populations

8.1 Pregnancy

Pregnancy Category D [see *Warnings and Precautions (5.8)*].

In addition to causing infrequent congenital goiter/hypothyroidism and hyperthyroidism, amiodarone has caused a variety of adverse effects in animals.

In a reproductive study in which amiodarone was given intravenously to rabbits at dosages of 5, 10, or 25 mg/kg per day (about 0.1, 0.3, and 0.7 times the maximum recommended human dose [MRHD] on a body surface area basis), maternal deaths occurred in all groups, including controls. Embryotoxicity (as manifested by fewer full-

term fetuses and increased resorptions with concomitantly lower litter weights) occurred at dosages of 10 mg/kg and above. No evidence of embryotoxicity was observed at 5 mg/kg and no teratogenicity was observed at any dosages.

In a teratology study in which amiodarone was administered by continuous IV infusion to rats at dosages of 25, 50, or 100 mg/kg per day (about 0.4, 0.7, and 1.4 times the MRHD when compared on a body surface area basis), maternal toxicity (as evidenced by reduced weight gain and food consumption) and embryotoxicity (as evidenced by increased resorptions, decreased live litter size, reduced body weights, and retarded sternum and metacarpal ossification) were observed in the 100 mg/kg group.

Use NEXTERONE during pregnancy only if the potential benefit to the mother justifies the risk to the fetus.

8.2 Labor and Delivery

It is not known whether the use of amiodarone during labor or delivery has any immediate or delayed adverse effects. Preclinical studies in rodents have not shown any effect on the duration of gestation or on parturition.

8.3 Nursing Mothers

Amiodarone and one of its major metabolites, desethylamiodarone (DEA), are excreted in human milk, suggesting that breast-feeding could expose the nursing infant to a significant dose of the drug. Nursing offspring of lactating rats administered amiodarone have demonstrated reduced viability and reduced body weight gains. The risk of exposing the infant to amiodarone must be weighed against the potential benefit of arrhythmia suppression in the mother. Advise the mother to discontinue nursing.

8.4 Pediatric Use

The safety and effectiveness of amiodarone in pediatric patients have not been established; therefore, the use of amiodarone in pediatric patients is not recommended. In a pediatric trial of 61 patients, aged 30 days to 15 years, hypotension (36%), bradycardia (20%), and AV block (15%) were common dose-related adverse reactions and were severe or life-threatening in some cases. Injection site reactions were seen in 5 (25%) of the 20 patients receiving intravenous amiodarone through a peripheral vein irrespective of dose regimen.

8.5 Geriatric Use

Clinical studies of amiodarone did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. Carefully consider dose selection in an elderly patient. In general, start at the low end of the dosing range in the elderly to reflect the greater frequency of decreased hepatic, renal, or cardiac function, and concomitant disease or other drug therapy.

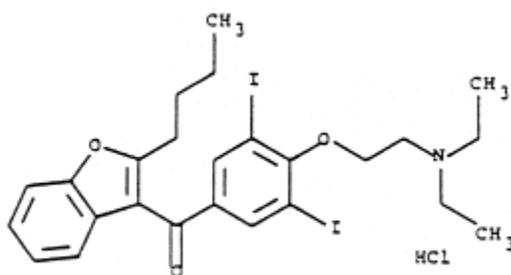
10 OVERDOSAGE

There have been cases, some fatal, of amiodarone overdose. Effects of an inadvertent overdose of intravenous amiodarone include hypotension, cardiogenic shock, bradycardia, AV block, and hepatotoxicity. Treat hypotension and cardiogenic shock by slowing the infusion rate or with standard therapy: vasopressor drugs, positive inotropic agents, and volume expansion. Bradycardia and AV block may require temporary pacing. Monitor hepatic enzyme concentrations closely. Amiodarone is not dialyzable.

11 DESCRIPTION

NEXTERONE contains amiodarone HCl ($C_{25}H_{29}I_2NO_3 \cdot HCl$), a class III antiarrhythmic drug. Amiodarone HCl is (2-butyl-3-benzo-furanyl)[4-[2-(diethylamino)ethoxy]-3,5-diiodophenyl]methanone hydrochloride.

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. NEXTERONE Premixed Injection is a sterile clear, colorless to slightly yellow solution visually free from particulates. NEXTERONE Premixed Injection is available as a ready-to-use, nonpyrogenic, iso-osmotic solution for intravenous administration in 100mL GALAXY containers with 150 mg of amiodarone HCl (1.5mg/mL) in dextrose, and 200mL GALAXY containers with 360 mg of amiodarone HCl (1.8 mg/mL) in dextrose.

NEXTERONE Premixed Injection (150 mg/100 mL, 1.5 mg/mL):

Each mL contains 1.5 mg of amiodarone HCl, 15 mg sulfobutylether beta-cyclodextrin sodium, 0.362 mg citric acid anhydrous, 0.183 mg sodium citrate dihydrate and 42.1 mg dextrose anhydrous in water for injection. Sodium hydroxide or hydrochloric acid may have been added to adjust pH.

NEXTERONE Premixed Injection (360 mg/200 mL, 1.8 mg/mL):

Each mL contains 1.8 mg of amiodarone HCl, 18 mg sulfobutylether beta-cyclodextrin sodium, 0.362 mg citric acid anhydrous, 0.183 mg sodium citrate dihydrate and 41.4 mg dextrose anhydrous in water for injection. Sodium hydroxide or hydrochloric acid may have been added to adjust pH.

NEXTERONE does not contain polysorbate 80 or benzyl alcohol.

The GALAXY container is fabricated from a specially designed multilayered plastic (PL 2501). Solutions are in contact with the polyethylene layer of the container and can leach out certain chemical components of the plastic in very small amounts within the expiration period. The suitability and safety of the plastic have been confirmed in tests in animals according to the USP biological tests for plastic containers, as well as by tissue culture toxicity studies.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Amiodarone is generally considered a class III antiarrhythmic drug, but it possesses electrophysiologic characteristics of all four Vaughan Williams classes. Like class I drugs, amiodarone blocks sodium channels at rapid pacing frequencies, and like class II drugs, amiodarone exerts a noncompetitive antisymphathetic 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 antisymphathetic action and the block of 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.

Intravenous amiodarone administration prolongs intranodal conduction (Atrial-His, AH) and refractoriness of the atrioventricular node (ERP AVN), but has little or no effect on sinus cycle length (SCL), refractoriness of the right atrium and right ventricle (ERP RA and ERP RV), repolarization (QTc), intraventricular conduction (QRS), and infra-nodal conduction (His-ventricular, HV). A comparison of the electrophysiologic effects of intravenous amiodarone and oral amiodarone is shown in the table below.

Table 5: EFFECTS OF INTRAVENOUS AND ORAL AMIODARONE ON ELECTROPHYSIOLOGIC PARAMETERS

Formulation	SCL	QRS	QTc	AH	HV	ERP RA	ERP RV	ERP AVN
Intravenous	↔	↔	↔	↑	↔	↔	↔	↑
Oral	↑	↔	↑	↑	↔	↑	↑	↑

↔ No change

At higher doses (>10 mg/kg) of intravenous amiodarone, prolongation of the ERP RV and modest prolongation of the QRS have been seen. These differences between oral and IV administration suggest that the initial acute effects of intravenous amiodarone may be predominately focused on the AV node, causing an intranodal conduction delay and increased nodal refractoriness due to slow channel blockade (class IV activity) and noncompetitive adrenergic antagonism (class II activity).

12.2 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.

No data are available on the activity of DEA in humans, but in animals, it has significant electrophysiologic and antiarrhythmic effects generally similar to amiodarone itself. DEA's precise role and contribution to the antiarrhythmic activity of oral amiodarone are not certain. The development of maximal ventricular class III effects after oral amiodarone administration in humans correlates more closely with DEA accumulation over time than with amiodarone accumulation. On the other hand, after intravenous amiodarone administration, there is evidence of activity well before significant concentrations of DEA are attained [see *Clinical Trials (14)*].

12.3 Pharmacokinetics

Disposition:

Amiodarone exhibits complex disposition characteristics after intravenous administration. Peak serum concentrations after single 5 mg/kg 15-minute intravenous infusions in healthy subjects range between 5 and 41 mg/L. Peak concentrations after 10-minute infusions of 150 mg intravenous amiodarone in patients with ventricular fibrillation (VF) or hemodynamically unstable ventricular tachycardia (VT) range between 7 and 26 mg/L. Due to rapid distribution, serum concentrations decline to 10% of peak values within 30 to 45 minutes after the end of the infusion. In clinical trials, after 48 hours of continued infusions (125, 500 or 1000 mg/day) plus supplemental (150 mg) infusions (for recurrent arrhythmias), amiodarone mean serum concentrations between 0.7 to 1.4 mg/L were observed (n=260).

Metabolism:

N-desethylamiodarone (DEA) is the major active metabolite of amiodarone in humans. DEA serum concentrations above 0.05 mg/L are not usually seen until after several days of continuous infusion but with prolonged therapy reach approximately the same concentration as amiodarone. Amiodarone is metabolized to DEA by the cytochrome P450 (CYP450) enzyme group, specifically cytochrome P4503A (CYP3A) and CYP2C8. The CYP3A isoenzyme is present in both the liver and intestines. The highly variable systemic

availability of oral amiodarone may be attributed potentially to large interindividual variability in CYP3A activity

Distribution/Elimination:

From in vitro studies, the protein binding of amiodarone is >96%. Amiodarone and DEA cross the placenta and both appear in breast milk. Neither amiodarone nor DEA is dialyzable.

Amiodarone is eliminated primarily by hepatic metabolism and biliary excretion and there is negligible excretion of amiodarone or DEA in urine. In studies in healthy subjects following single intravenous administration (5 mg/kg of amiodarone over 15 min), the plasma concentration vs. time profile could be characterized by linear sum of four exponential terms with terminal elimination half-lives ($t_{1/2}$) of 9 - 36 days for amiodarone and 9 - 30 days for DEA. The clearance of amiodarone and DEA ranged between 63 - 231 mL/hr/kg and 140 -400 ml/h/kg, respectively. In clinical studies of 2 to 7 days, clearance of amiodarone after intravenous administration in patients with VT and VF ranged between 220 and 440 mL/hr/kg.

Special Populations:

Effect of Age: The pharmacokinetics of amiodarone and DEA are affected by age. Normal subjects over 65 years of age show lower clearances (about 100 mL/hr/kg) than younger subjects (about 150 mL/hr/kg) and an increase in $t_{1/2}$ from about 20 to 47 days.

Effect of Gender: Pharmacokinetics of amiodarone and DEA are similar in males and females.

Renal Impairment: Renal disease does not influence the pharmacokinetics of amiodarone or DEA.

Hepatic Impairment: After a single dose of intravenous amiodarone to cirrhotic patients, significantly lower C_{max} and average concentration values are seen for DEA, but mean amiodarone levels are unchanged.

Cardiac Disease: In patients with severe left ventricular dysfunction, the pharmacokinetics of amiodarone are not significantly altered but the terminal elimination $t_{1/2}$ of DEA is prolonged.

Although no dosage adjustment for patients with renal, hepatic, or cardiac abnormalities has been defined during chronic treatment with oral amiodarone, close clinical monitoring is prudent for elderly patients and those with severe left ventricular dysfunction.

Exposure-Response: There is no established relationship between drug concentration and therapeutic response for short-term intravenous use.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

No carcinogenicity studies were conducted with intravenous administration of amiodarone. However, oral amiodarone caused a statistically significant, dose-related increase in the incidence of thyroid tumors (follicular adenoma and carcinoma) in rats. The incidence of thyroid tumors in rats was greater than the incidence in controls even at the lowest dose level tested, i.e., 5 mg/kg/day (much less, on a body surface area basis, than the maximum recommended human maintenance dose of 600 mg/day).

Mutagenicity studies conducted with amiodarone HCl (Ames, micronucleus, and lysogenic induction tests) were negative.

No fertility studies were conducted with intravenous administration of amiodarone. However, in a study in which amiodarone HCl was orally administered to male and female rats, beginning 9 weeks prior to mating, reduced fertility was observed at a dose level of 90 mg/kg/day (approximately 1.4 times the maximum recommended human maintenance dose of 600 mg/day).

14 CLINICAL STUDIES

Apart from studies in patients with VT or VF, described below, there are two other studies of amiodarone showing an antiarrhythmic effect before significant levels of DEA

could have accumulated. A placebo-controlled study of intravenous amiodarone (300 mg over 2 hours followed by 1200 mg/day) in post-coronary artery bypass graft patients with supraventricular and 2- to 3-consecutive-beat ventricular arrhythmias showed a reduction in arrhythmias from 12 hours on. A baseline-controlled study using a similar IV regimen in patients with recurrent, refractory VT/VF also showed rapid onset of antiarrhythmic activity; amiodarone therapy reduced episodes of VT by 85% compared to baseline.

The acute effectiveness of intravenous amiodarone in suppressing recurrent VF or hemodynamically unstable VT is supported by two randomized, parallel, dose-response studies of approximately 300 patients each. In these studies, patients with at least two episodes of VF or hemodynamically unstable VT in the preceding 24 hours were randomly assigned to receive doses of approximately 125 or 1000 mg over the first 24 hours, an 8-fold difference. In one study, a middle dose of approximately 500 mg was evaluated. The dose regimen consisted of an initial rapid loading infusion, followed by a slower 6-hour loading infusion, and then an 18-hour maintenance infusion. The maintenance infusion was continued up to hour 48. Additional 10-minute infusions of 150 mg intravenous amiodarone were given for "breakthrough" VT/VF more frequently to the 125 mg dose group, thereby considerably reducing the planned 8-fold differences in total dose to 1.8- and 2.6-fold, respectively, in the two studies.

The prospectively defined primary efficacy end point was the rate of VT/VF episodes per hour. For both studies, the median rate was 0.02 episodes per hour in patients receiving the high dose and 0.07 episodes per hour in patients receiving the low dose, or approximately 0.5 versus 1.7 episodes per day ($p=0.07$, 2-sided, in both studies). In one study, the time to first episode of VT/VF was significantly prolonged (approximately 10 hours in patients receiving the low dose and 14 hours in patients receiving the high dose). In both studies, significantly fewer supplemental infusions were given to patients in the high-dose group. At the end of double-blind therapy or after 48 hours, all patients were given open access to whatever treatment (including intravenous amiodarone) was deemed necessary. Mortality was not affected in these studies.

16 HOW SUPPLIED/ STORAGE AND HANDLING

NEXTERONE (amiodarone HCl) Premixed Injection is supplied as a ready-to-use, sterile, nonpyrogenic, iso-osmotic solution in 100 mL and 200 mL single-dose GALAXY containers (PL 2501 plastic) packaged in individual cartons as follows:

150 mg/100 mL NDC 43066 – 150 – 10 2G3451
360 mg/200 mL NDC 43066 – 360 – 20 2G3450

Store at 20° - 25°C (68° - 77°F); excursions permitted to 15° - 30°C (59° - 86°F). See USP Controlled Room Temperature.

Protect from light and excessive heat. Protect from freezing.

Use carton to protect contents from light until used.

17 PATIENT COUNSELING INFORMATION

Amiodarone has the potential to cause serious side effects that limit its use to life-threatening and hemodynamically unstable cardiac arrhythmias. Advise female patients to discontinue nursing while being treated with amiodarone, as breast-feeding could expose the nursing infant to a significant dose of the drug. Recommend that patients avoid grapefruit juice, over-the-counter cough medicine (that commonly contain dextromethorphan), and *St. John's Wort*. Inform patients that most manufacturers of corneal refractive laser surgery devices contraindicate corneal refractive laser surgery in patients taking amiodarone. Discuss the symptoms of hypo- and hyper-thyroidism, particularly if patients will be transitioned to oral amiodarone.

Baxter and Galaxy are registered trademarks of Baxter International Inc.
NEXTERONE is a registered trademark of Prism Pharmaceuticals, Inc.

Manufactured by:
Baxter Healthcare Corporation
Deerfield, IL 60015

For:



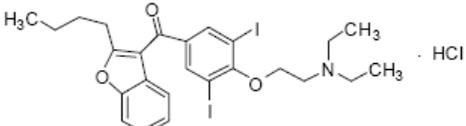
Prism Pharmaceuticals, Inc.
King of Prussia, PA 19406

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

022325Orig1s001

CHEMISTRY REVIEW(S)

CHEMIST'S REVIEW		1. ORGANIZATION ONDQA		2. NDA NUMBER 22-325	
3. NAME AND ADDRESS OF APPLICANT (City and State) Prism Pharmaceuticals, Inc. 1150 First Avenue, Suite 1050, King of Prussia, PA 19406				4. AF NUMBER	
				5. SUPPLEMENT (S) NUMBER(S) DATES(S)	
6. NAME OF DRUG NEXTERONE		7. NONPROPRIETARY NAME Amiodarone HCl		SCS-01	5-5-2010
8. SUPPLEMENT PROVIDES FOR: manufacturing both 1.5 mg/mL and 1.8 mg/mL solutions of Nexterone (amiodarone HCL) in premixed bag containers for bioequivalence studies.				9. AMENDMENTS DATES	
10. PHARMACOLOGICAL CATEGORY ventricular fibrillation		11. HOW DISPENSED RX OTC X		12. RELATED IND/NDA/DMF	
13. DOSAGE FORM(S) Injection		14. POTENCY 50 mg/ml			
15. CHEMICAL NAME AND STRUCTURE  Molecular formula: C ₂₅ H ₂₉ I ₂ N ₃ •HCl Molecular weight: 681.78 Chemical Abstracts Service (CAS) registry number: 19774-82-4 Chemical Name: 2-butyl-3-benzofuranyl 4-(2-diethylaminoethoxy)-3,5-diiodophenyl ketone HCl United States Adopted Name (USAN), free base: Amiodarone				16. RECORDS AND REPORTS CURRENT YES <input checked="" type="checkbox"/> NO REVIEWED YES <input checked="" type="checkbox"/> NO	
17. COMMENTS See review notes					
18. CONCLUSIONS AND RECOMMENDATIONS Approval is recommended from CMC standpoint pending DMEPA consult.					
19. REVIEWER					
NAME Chengyi Liang, Ph.D.		SIGNATURE		DATE COMPLETED 9-1-2010	
<u>DISTRIBUTION</u>	ORIGINAL NDA	DIVISION FILE	Reviewer: C.Y. Liang		Branch Chief H. Patelh

REVIEW NOTES

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Table 3.2.P.8.3-2: Stability Data for Lot NC055814A^a (49160) at 40°C/20%RH

(b) (4)

The photostability study was conducted per ICH Guideline Q1B (option 2). Results indicated that the single unit cardboard carton provides adequate light protection for the 150 mg/100 ml and 360 mg/200 ml premixed DP injection products. No significant change in assay and impurity, pH, visual inspection, visual appearance, and particle counts were observed between test samples and negative controls.

Based on the acceptable data available through 6 months accelerated (40°C) storage and 6 months long-term (25°C) storage, a 12 month shelf-life is proposed for premixed DP Injection in PL 2501 plastic container. The proposed storage statement is: “Store at 20° to 25°C (68° to 77°F); excursions permitted to 15° to 30°C (59° to 86°F). See USP Controlled Room Temperature”.

The DP carton and bag labels are provided indicating the DP formulation as premixed injection. The PI for premixed DP formulation is established based on the current PI for pre-filled syringe DP formulation. The minor revisions in sections of Dosage and Administration, Dosage Form and Strengths, Description and How Supplied/Storage and Handling are related to concentrations of premixed DP (150 mg/100 ml and 360 mg/200 ml) and found to be acceptable.

The drug product will be infused at the starting dose about 1000 mg over the first 24 hours of therapy:

- Initial Load: 150 mg per 100 ml infused over 10 minutes
- Followed by: 1 mg/min for 6 hours
- Followed by: 0.5 mg/min thereafter

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

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22325	SUPPL-1	PRISM PHARMACEUTICA LS INC	NEXTERONE IV (AMIODARONE HCL) 50MG/ML

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/s/

CHENG YI LIANG
09/03/2010

HASMUKH B PATEL
09/03/2010

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

022325Orig1s001

MICROBIOLOGY/VIROLOGY REVIEW(S)

Product Quality Microbiology Review

30 August 2010

NDA: 22-325/S-001

Drug Product Name
Proprietary:

Nexterone Injection; Nexterone
Premixed Injection.

Non-proprietary:

Amlodarone hydrochloride.

Review Number:

1.

Dates of Submission(s) Covered by this Review

Submit	Received	Review Request	Assigned to Reviewer
05 MAY 2010	05 MAY 2010	19 AUG 2010	19 AUG 2010
30 AUG 2010	30 AUG 2010	N/A	N/A

Applicant/Sponsor

Name:

Prism Pharmaceuticals, Inc.

Address:

1016 West Ninth Ave.

Suite 130

King of Prussia, PA 19406

Representative:

Daniel Cushing

Telephone:

610-986-1024

Name of Reviewer:

John W. Metcalfe, Ph.D.

Conclusion:

Recommend approval.

Product Quality Microbiology Data Sheet

- A. 1. TYPE OF SUBMISSION:** Prior Approval CMC Supplement.
- 2. SUBMISSION PROVIDES FOR:** The introduction of the following new presentations of the subject drug product:
- 1.5 mg/mL of the subject drug product in 5% dextrose in premixed bags (Baxter Galaxy[®] System).
 - 1.8 mg/mL of the subject drug product in 5% dextrose in premixed bags (Baxter Galaxy[®] System).
- 3. MANUFACTURING SITE:**
Baxter Healthcare Corporation
Round Lake Drug Delivery
25212 W. Illinois Route 120
Round Lake, IL 60073.
- 4. DOSAGE FORM, ROUTE OF ADMINISTRATION AND STRENGTH/POTENCY:**
- Solution.
 - Intravenous injection.
 - 1.5 mg/mL and 1.8 mg/mL of the subject drug product in 5% dextrose in premixed bags (Baxter Galaxy[®] System).
- 5. METHOD(S) OF STERILIZATION:** (b) (4)
(b) (4)
- 6. PHARMACOLOGICAL CATEGORY:** The subject drug product is indicated for the treatment of ventricular tachycardia and ventricular fibrillation.

B. SUPPORTING/RELATED DOCUMENTS:

- Microbiology Review of DMF 6344; Dated 18 DEC 2007.
- Microbiology Review of DMF 6344; Dated 26 FEB 2008.
- Microbiology Review of DMF 6344; Dated 11 DEC 2009.

C. REMARKS:

The "Request for Consultation" was submitted to the New Drug Microbiology Staff by the Office of New Drug Quality Assessment on 19 August 2010 with a requested completion date of 01 September 2010 (allowing 8 business days to review a supplemental application with a 4 month review clock).

The subject supplement is submitted electronically in the CTD format.

A Microbiology Information Request was forwarded to Dr. Daniel Cushing (applicant representative) electronically by this reviewer on 27 August 2010. Following is the IR:

A microbiology review of NDA 22-325/S-001 is in progress. Please provide the following information or reference to its location in the subject submission:

1. Whether the [REDACTED] (b) (4)
[REDACTED] If so, provide the [REDACTED] (b) (4) test method and acceptance criterion.
2. Whether [REDACTED] (b) (4)
[REDACTED] If so, provide the [REDACTED] (b) (4) test method and acceptance criterion.

Reviewer's Comment

It is noted that the drug product total maximum holding time [REDACTED] (b) (4)

Further, it is noted that the proposed new formulation contains 5% dextrose.

3. Identify the maximum holding time between the [REDACTED] (b) (4)
[REDACTED] (b) (4)
4. Provide microbiological data in support of this holding period or a rationale describing why data are not necessary.

An amendment to the subject NDA was submitted on 30 August 2010. The responses are summarized and reviewed in appropriate sections of this review.

Executive Summary

I. Recommendations

- A. **Recommendation on Approvability** – NDA 22-325/S-001 is recommended for approval on the basis of product quality microbiology.
- B. **Recommendations on Phase 4 Commitments and/or Agreements, if Approvable** – Not applicable.

II. Summary of Microbiology Assessments

- A. **Brief Description of the Manufacturing Processes that relate to Product Quality Microbiology** – The subject drug product is sterilized by (b) (4)
- B. **Brief Description of Microbiology Deficiencies** – There are no microbiology deficiencies identified.
- C. **Assessment of Risk Due to Microbiology Deficiencies** – Not applicable.

III. Administrative

- A. **Reviewer's Signature** _____
John W. Metcalfe, Ph.D.
- B. **Endorsement Block** _____
Bryan S. Riley, Ph.D.
- C. **CC Block**
N/A

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Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22325	SUPPL-1	PRISM PHARMACEUTICA LS INC	NEXTERONE IV (AMIODARONE HCL) 50MG/ML

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/s/

JOHN W METCALFE
08/31/2010

BRYAN S RILEY
08/31/2010
I concur.

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

022325Orig1s001

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

BIOPHARMACEUTICS REVIEW

Office of New Drugs Quality Assessment

Application No.:	NDA 22-325/PAS-030	Reviewer: Angelica Dorantes, Ph.D
Submission Date:	May 5, 2010	Supervisor: Patrick J. Marroum, Ph.D
Division:	DCRP	Date Assigned: May 19, 2010
Sponsor:	Prism Pharmaceuticals	Date of Review: August 24, 2010
Trade Name:	NEXTERONE® (amiodarone HCl) Premixed Injection	Type of Submission: Prior Approval Supplement PAS-030
Generic Name:	Amiodarone HCL Injection	
Indication:	NEXTERONE is an antiarrhythmic agent indicated for initiation of treatment and prophylaxis of frequently recurring ventricular fibrillation (VF) and hemodynamically unstable ventricular tachycardia (VT) in patients refractory to other therapy.	
Formulation/strengths	<ul style="list-style-type: none"> ○ Injection 1.5 mg/mL (150 mg/100 mL) Premixed in Dextrose ○ Injection, 1.8 mg/mL (360 mg/200 mL) Premixed in Dextrose 	
Route of Administration	Injection for intravenous use	
Type of Review:	BIOEQUIVALENCE STUDY	

SUBMISSION:

Prism Pharmaceuticals received approval for NDA 22-325 in December 2008 for NEXTERONE® (amiodarone HCl) Injection, 50 mg/ml, in 3 mL, 9 mL, and 18 mL sterile, single-use vials, as well as a 3mL sterile, single-use, pre-filled syringe. Prior Approval Supplement PAS-030 provides information for NEXTERONE® (amiodarone HCl) Premixed Injection 1.5 mg/mL in 100mL dextrose and NEXTERONE® (amiodarone HCl) Premixed Injection 1.8 mg/mL in 200mL dextrose, each in premixed bag containers (Baxter GALAXY System). The dosing regimen for NEXTERONE®, and the Amiodarone HCl Injection Reference Listed Drug, includes admixture of the 50 mg/mL solution in 5% Dextrose to achieve either a 1.5 mg/mL or 1.8 mg/mL concentration for administration. Prism has developed both a 1.5 mg/mL and 1.8 mg/mL solution of NEXTERONE® in 5% dextrose in premixed bag containers (Baxter GALAXY System).

The clinical development program for NEXTERONE® Premixed Injection includes one bioequivalence study (Study No. 106) entitled, “*A randomized, single-blind, 2-period crossover trial to determine the relative bioavailability of NEXTERONE® (amiodarone HCl) Premixed Injection and Amiodarone Hydrochloride (amiodarone HCl) Injection in healthy adult volunteers*”, whose objective was to compare NEXTERONE® Premixed Injection to Amiodarone HCl Injection Reference Listed Drug. Establishment of bioequivalence provides the basis for approval of NEXTERONE® Premixed Injection.

BIOPHARMACEUTICS:

Pharmaceutical Development:

Two NEXTERONE® Premixed Injection products were developed based on the Dosage and Administration

instructions for NEXTERONE® (amiodarone HCl) Injection (50mg/mL) to deliver either a 1.5mg/mL or a 1.8mg/mL amiodarone infusion. One is a NEXTERONE® (amiodarone HCl) Premixed Injection [150 mg/100 mL (1.5 mg/mL)] and the other is a NEXTERONE® (amiodarone HCl) Premixed Injection [360 mg/200 mL (1.8 mg/mL)], each formulated in an iso-osmotic dextrose solution containing (b) (4). Both products are (b) (4) and packaged in a flexible plastic container closure configuration, GALAXY (PL 2501) and in a single unit cardboard carton for light protection. The products are ready-to-use and do not require further dilution prior to administration.

Comparison of NEXTERONE® (amiodarone HCl) Injection Formulations

Formulation	100 mL (Premixed)	200 mL (Premixed)	Syringe/Vial (Admix)1	Syringe/Vial (Admix)2
Amiodarone HCl	1.5 mg/mL	1.8 mg/mL		(b) (4)
Captisol®	15.0 mg/mL (b) (4)	18.0 mg/m (b) (4)		
Citric Acid Anhydrous (b) (4)	0.362 mg/mL	0.362 mg/mL		
Sodium Citrate Dihydrate (b) (4)	0.183 mg/mL	0.183 mg/mL		
Dextrose Anhydrous (b) (4)	42.1 mg/mL	41.4 mg/mL		
Hydrochloric Acid (b) (4) Sodium Hydroxide (b) (4)	As required to achieve pH	As required to achieve pH		

Product Composition:

NEXTERONE ® Premixed Injection is a sterile, clear, colorless to slightly yellow iso-osmotic solution of Captisol-enabled ® amiodarone HCl in dextrose, intended for intravenous use. The proposed premixed drug products are packaged in ready-to-use, 100 mL and 200 mL single port GALAXY PL 2501 plastic containers. Each plastic container is placed within a single unit cardboard carton for light protection. There are two presentations: 150 mg/100 mL (1.5 mg/mL amiodarone HCl in a 100 mL container) and 360 mg/200 mL (1.8 mg/mL amiodarone HCl in 200 mL container). NEXTERONE ® Premixed Injection does not contain polysorbate 80 or benzyl alcohol. A list of all components of the dosage forms of NEXTERONE ® Premixed Injection and their amounts on a per unit basis are provided in the next Table.

Composition of the Drug Product - NEXTERONE® Premixed Injection

Component	Function	150 mg/100 mL (1.5 mg/mL)		360 mg/200 mL (1.8 mg/mL)	
		Component Quantity		Component Quantity	
		Per mL	Per 100 mL ¹	Per mL	Per 200 mL ²
Amiodarone HCl	Active Drug Substance	1.5 mg	150 mg	1.8 mg	360 mg
Captisol® (sulfobutylether-β-cyclodextrin sodium salt)	Solubilizing/Complexing Agent for Active Drug Substance	15.0 mg (b) (4)	1,500 mg (b) (4)	18.0 mg (b) (4)	3,600 mg (b) (4)
Citric Acid Anhydrous	(b) (4)	0.362 mg	36.2 mg	0.362 mg	72.4 mg
Sodium Citrate Dihydrate		0.183 mg	18.3 mg	0.183 mg	36.6 mg
Dextrose Anhydrous		42.1 mg	4,210 mg	41.4 mg	8,280 mg
Hydrochloric Acid	pH Adjuster	As needed	As needed	As needed	As needed
Sodium Hydroxide	pH Adjuster	As needed	As needed	As needed	As needed
Water for Injection					(b) (4)

SUMMARY - BIOEQUIVALENCE Study No. 106:

Study Title: A randomized, single-blind, 2-period crossover trial to determine the relative bioavailability of NEXTERONE® (amiodarone HCl) Premixed Injection and Amiodarone Hydrochloride (amiodarone HCl) Injection in healthy adult volunteers.

Investigator/Study Center: Scott Rasmussen, MD/ MDS Pharma Services, Lincoln, NE 68502

Study Period: 21 October 2009 to 20 January 2010

Objectives: The primary objective of this study was to compare the relative bioavailability of the test (NEXTERONE Premix Injection, amiodarone HCl) and reference (amiodarone HCl Injection) products following intravenous administration.

Study Subjects: Approximately 88 subjects meeting the inclusion/exclusion criteria were included in the study. The safety population included all 88 subjects who were enrolled and were administered study drug. The PK population included 84 evaluable subjects who completed both pharmacokinetic sampling periods and who had sufficient concentrations above the limit of quantification to obtain reliable estimates of the key PK variables.

Study Products, Dose and Mode of Administration, Batch Number:

- ***Test:*** NEXTERONE (amiodarone hydrochloride) Premix Injection, 150 mg in 100 mL D5W infused over 10 minutes. Lot Number: NC055814
- ***Reference:*** Amiodarone HCl (amiodarone hydrochloride) Injection, 150 mg in 100 mL D5W infused over 10 minutes. Lot Number: 31306838B

Study Design: This study compared a 10-minute infusion of NEXTERONE® Premixed Injection with a 10-minute infusion of Amiodarone HCl Injection (Reference Listed Drug); the comparison of these two regimens was discussed and previously agreed.

Group	Treatment
A	NEXTERONE (amiodarone HCl) Premix Injection, 150 mg in 100 mL D5W infused over 10 minutes
B	Amiodarone HCl (amiodarone HCl) Injection, 150 mg in 100 mL D5W infused over 10 minutes

A 2- period crossover design was chosen to obtain the maximum pharmacokinetic and safety data with a minimum number of subjects. A washout period of at least 42 days between doses was chosen based on prior experience from Study 101 indicating that 42 days should be sufficient to allow amiodarone concentrations to decrease to below the lower limit of detection by the start of the second treatment period.

Methodology: Subjects attended a screening visit within 21 days prior to Period 1, and eligible subjects returned to the clinic on the evening of Day -1. On Day 1, prior to dosing, subjects were randomized to receive either the test product (NEXTERONE Premix Injection) or the reference product (Amiodarone HCl Injection) during the first treatment period and the alternate product during the second treatment period. Each dose of intravenous amiodarone was separated by a minimum of a 42-day washout period. Administration of concomitant medications was prohibited during the study period, beginning two (2) weeks prior to the first dose of any study-related treatment and continuing until the subjects were discharged from the study. Subjects

received a standard diet while in the clinical research facility, with the exception that no xanthine-containing foods or beverages (e.g., coffee, tea, cola, chocolate), or grapefruit juice were permitted while in the clinical research facility. This exclusion extended to four (4) weeks for any medication (prescription or OTC) or nutritional supplement which may induce or inhibit hepatic drug metabolism, including grapefruit and grapefruit juice or any CYP2C8 or CYP3A4 inducer or inhibitor. Medications that are substrates for p-glycoprotein or are metabolized by CYP1A2, CYP2C9, CYP2D6, or CYP3A4 were prohibited during the study.

Blood Sampling: Samples of venous blood for PK analysis of amiodarone and its metabolite desethylamiodarone were obtained within 30 minutes prior to dose administration (0, pre-dose), 1, 5, 10 (end of infusion), 20 and 30 minutes, and 1, 2, 3, 4, 6, 8, 12, 24, 36, 48, 60, and 72 hours after infusion start. The PK blood samples for amiodarone and desethylamiodarone were obtained from the opposite arm (arm #2; blood draw site) than that used for dosing (arm #1; infusion site). PK blood samples were obtained by direct venipuncture.

Duration of Treatment: Screening occurred within 21 days of Day -1. For each study period, subjects reported to the clinic on the day prior to study medication administration (Day -1). On Day 1 subjects were administered study medication and remained at the clinic until Day 4, and were released by the investigator after the 72-hour blood sample was drawn. Each treatment period was separated by a washout period of at least 42 days (from the first dose of amiodarone HCl to the second dose).

Determination of Sample Size

Assuming a within-subject coefficient of variation (CV) of 0.4 and expected test/reference ratio between 0.95 and 1.052, a sample size of 88 subjects would provide 90% power to show that the 90% CI of the geometric mean ratio (test/reference) falls in the range of 0.80 and 1.25 for the AUC and C_{max}, using nQuery 4.0. A total of 88 subjects were randomized in the trial. Randomized subjects that dropped out or terminated early were not replaced.

Assessments:

- ***Pharmacokinetics:*** Samples of venous blood for PK analysis were obtained within 30 minutes prior to dose administration (0, pre-dose), 1, 5, 10 (end of infusion), 20 and 30 minutes, and 1, 2, 3, 4, 6, 8, 12, 24, 36, 48, 60, and 72 hours after infusion start. PK variables for amiodarone and its metabolite desethylamiodarone included the following: C_{max}, T_{max}, C_{last}, I_z, T_{1/2}, AUCT, AUC.
- ***Safety:*** Safety was evaluated through the assessment of adverse events (AEs), clinical laboratory tests, vital signs, concomitant medication use, electrocardiogram results, and physical examination findings.

Statistical Methods:

- ***Pharmacokinetics:*** Pharmacokinetic variables for amiodarone and its metabolite were calculated from the plasma concentration data using standard, non-compartmental methods using WinNonlin Enterprise 5.2. All pharmacokinetic results were summarized using appropriate descriptive statistics. Following log-transformation (natural log), AUC, AUCT, and C_{max} results for amiodarone were analyzed for the pharmacokinetic evaluable population using an analysis of variance (ANOVA) model with effects for sequence, subject within a sequence, treatment, and period. The carry-over effect was assessed. The 90% CIs of ratios of the least square geometric means were calculated for AUC, AUCT, and C_{max} based on results from the ANOVA. If the 90% CIs for the amiodarone AUCT and C_{max} fell in the limit of 0.80 and 1.25, the test (NEXTERONE Premix Injection) and reference (Amiodarone HCl Injection)

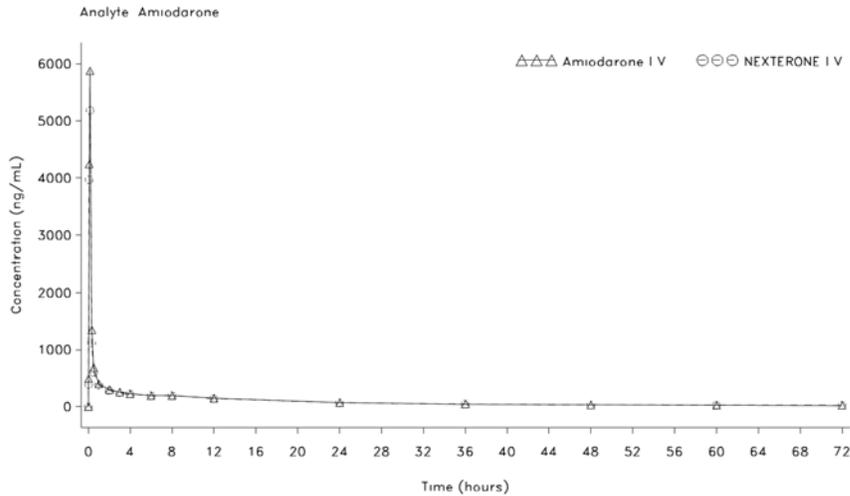
formulations were considered bioequivalent.

- **Safety:** All safety variables (including adverse events, vital signs measurements, clinical laboratory results, electrocardiogram results, and other safety variables) were listed by subject and domain. The incidence of all treatment-emergent adverse events (AEs), and treatment-related treatment-emergent adverse events was tabulated by MedDRA™ system organ class preferred term, treatment group, and severity. All laboratory results, vital sign measurements, and other safety variables were summarized using appropriate descriptive statistics. No hypothesis testing was performed.

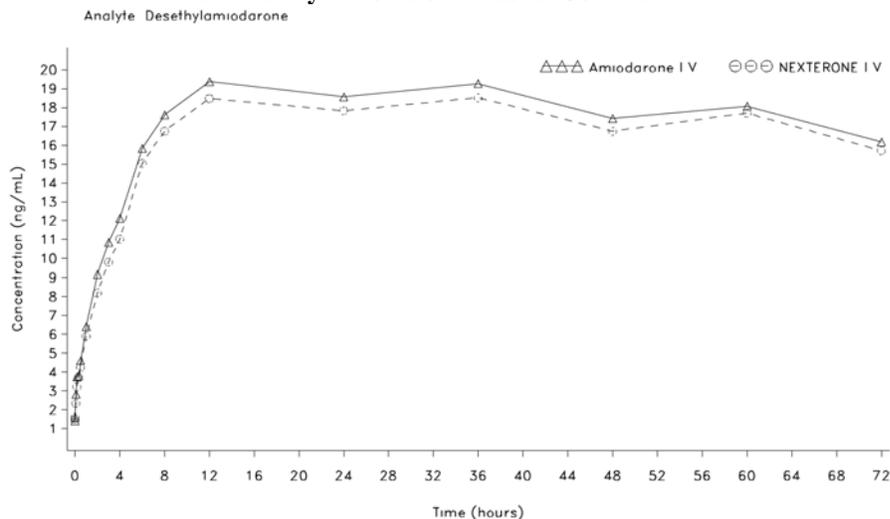
RESULTS:

Pharmacokinetics: Mean amiodarone plasma concentrations following either NEXTERONE Premix Injection or Amiodarone HCl Injection were comparable. The plasma concentration of the primary metabolite, desethyamidarone, peaked after 12 hours after both NEXTERONE Premix Injection and Amiodarone HCl Injection. Plasma concentrations leveled then declined slowly after this point. Mean plasma concentrations of amiodarone and desethylamidarone for NEXTERONE Premix Injection and Amiodarone HCl Injection are shown below.

Mean Amiodarone Plasma Conc vs. Time



Mean Desethylamidarone Plasma Conc vs. Time



PK Analysis: Mean Cmax, Tmax, AUCt, AUC, Clast, z, and T½ were comparable for NEXTERONE Premix Injection and Amiodarone HCl Injection, indicating that the rate and extent of exposure to amiodarone and desethylamiodarone following a single intravenous administration of 150 mg of the two amiodarone formulations was similar.

Amiodarone: A summary of mean amiodarone PK parameters following NEXTERONE Premix Injection and Amiodarone HCl Injection are presented in the next Table.

Summary of PK Parameters for Amiodarone following NEXTERONE Premix Injection							
	AUC0-inf	AUC0-t	Cmax	Tmax	Clast	lz	T½
Parameter	ng*hr/mL	ng*hr/mL	ng/mL	hr	ng/mL	1/hr	hr
N	83	84	84	84	84	83	83
Mean	7956.65	6848.87	5296.37	0.159	21.14	0.0199	36.77
SD	2274.01	1884.33	1663.76	0.028	7.42	0.0043	10.02
CV%	28.58	27.51	31.41	17.674	35.11	21.6841	27.24
Geo. Mean	7666.75	6614.32	5063.26	0.156	20.01	0.0194	35.70
Summary of PK Parameters for Amiodarone following Amiodarone HCl Injection							
	AUC0-inf	AUC0-t	Cmax	Tmax	Clast	lz	T½
Parameter	ng*hr/mL	ng*hr/mL	ng/mL	hr	ng/mL	1/hr	hr
N	83	84	84	84	84	83	83
Mean	8197.92	7078.17	6014.30	0.161	20.92	0.0206	35.34
SD	2180.09	1810.43	1722.72	0.025	7.34	0.0043	8.58
CV%	26.59	25.58	28.64	15.267	35.10	21.1240	24.27
Geo. Mean	7935.89	6865.94	5795.77	0.158	19.84	0.0201	34.46

Comparison of the PK results for NEXTERONE Premix Injection and the marketed amiodarone formulation, Amiodarone HCl Injection, show a similar extent (AUCt) and rate (Cmax) of exposure to amiodarone.

Desethylamiodarone: A summary of mean Desethylamiodarone PK parameters following NEXTERONE Premix Injection and Amiodarone HCl Injection are presented in the Table below.

Summary of PK Parameters for Desethylamiodarone following NEXTERONE Premix Injection							
	AUC0-inf	AUC0-t	Cmax	Tmax	Clast	lz	T½
Parameter	ng*hr/mL	ng*hr/mL	ng/mL	hr	ng/mL	1/hr	hr
N	23	84	84	84	84	23	23
Mean	4052.49	1213.91	20.36	30.862	15.72	0.0061	128.05
SD	1720.44	318.08	5.45	19.624	4.05	0.0020	45.38
CV%	42.45	26.20	26.79	63.585	25.75	33.1495	35.44
Geo. Mean	3662.66	1173.54	19.67	24.092	15.17	0.0057	120.93

Summary of PK Parameters for for Desethylamiodarone following Amiodarone HCl Injection

	AUC0-inf	AUC0-t	Cmax	Tmax	Clast	lz	T_{1/2}
Parameter	ng*hr/mL	ng*hr/mL	ng/mL	hr	ng/mL	1/hr	hr
N	32	84	84	84	84	32	32
Mean	3897.47	1262.52	20.96	29.390	16.17	0.0071	116.17
SD	2309.19	325.73	5.40	19.063	4.23	0.0025	69.96
CV%	59.25	25.80	25.77	64.861	26.17	34.7498	60.22
Geo. Mean	3496.27	1222.92	20.31	23.073	15.63	0.0066	105.06

Mean (\pm SD) AUC of desethylamiodarone was calculable for only 23 and 32 subjects in each treatment arm due to the prolonged half-life of this metabolite. Mean AUCT for the desethylamiodarone metabolite was comparable between treatments, and was 1213.91 ± 318.08 and 1262.52 ± 325.73 ng*hr/mL following NEXTERONE Premix Injection and Amiodarone HCl Injection, respectively.

Bioequivalence Analysis:

Results for the primary analysis of bioequivalence are shown in the Table below.

ANALYSIS OF BIOEQUIVALENCE: NEXTERONE Premix Injection and Amiodarone HCl Injection					
	Geometric LS Means				
Parameter	Test NEXTERONE Premix	Reference Amiodarone Injection	Geometric Mean Ratio^a	90% CI	Intrasubject %CV^b
AUCT (ng*hr/mL)	6619.43	6863.57	0.96	94.4 - 98.6	8.48
Cmax (ng/mL)	5065.44	5791.31	0.87	84.0 - 91.1	15.81
AUC (ng*hr/mL)	7699.94	7907.40	0.97	95.1 - 99.7	8.95

MODEL: Parameter = treatment + sequence + period + subject(sequence)
a. Test/Reference
b. Intrasubject %CV = derived from residual error – $100*\sqrt{\text{exp}(\text{mse}) - 1}$

The 90% CIs around the geometric mean ratio for amiodarone AUCT and Cmax fell completely within the bioequivalence limits of 80 and 125%, indicating that NEXTERONE Premix Injection and the reference (Amiodarone HCl Injection) formulation were bioequivalent. Because both formulations were administered intravenously and the PK plasma sampling was completed at 72 hours (which was anticipated to be less than or equal to one elimination half-life), the analysis of bioequivalence used AUCT instead of AUC.

Safety Results

NEXTERONE Premix Injection was well tolerated. There were no treatment-related SAEs nor were there discontinuations from the study due to AEs. Adverse events occurred in 42 (49.4%) and 42 (47.7%) subjects overall in the NEXTERONE Premix Injection and Amiodarone HCl Injection groups, respectively. The AE most commonly reported overall was headache. Nausea and vomiting were most often reported as treatment-related AEs. Two SAEs, appendicitis and spider bite, were not related to treatment. Additional safety measures, including clinical laboratory evaluations, physical examinations, vital signs, concomitant medications, and ECG results showed no remarkable changes over the test period.

Reviewer Comments:

- 1. The results from BE study No. 106 show that NEXTERONE Premix Injection was well tolerated.*
- 2. Following administration of NEXTERONE Premix Injection and Amiodarone HCl Injection, AUCT and Cmax of amiodarone plasma concentrations are comparable. The geometric least squares means ratio for both AUCT and Cmax were 0.96 (CI: .94.4-98.6) and 0.87 (CI: 84.0- 91.1), respectively. The 90% CIs for both AUCT and Cmax fell within FDA's established bioequivalence criteria of 80 to125%.*
- 3. From the ONDQA-Biopharmaceutics perspective, BE study No. 106 is acceptable.*
- 4. Regarding the labeling, the proposed revisions throughout the labeling for the dosage form, strengths, dosage and administration (i.e., Injection, 50 mg/mL 1.5 mg/mL (150 mg/100 mL) Premixed in Dextrose (3) **and** Injection, 1.8 mg/mL (360 mg/200 mL) Premixed in Dextrose (3), **are acceptable from the Biopharmaceutics viewpoint.***

RECOMMENDATION:

The ONDQA-Biopharmaceutics has reviewed the information included in NDA 22-325 for Nexterone Injection. Based on the results from BE study No. 106 demonstrating that NEXTERONE® Premixed Injection is bioequivalent to Amiodarone HCl Injection Reference Listed Drug, Prior Approval Supplement 030 supporting the approval of NEXTERONE® (amiodarone HCl) Premixed Injection 1.5 mg/mL in 100mL dextrose and NEXTERONE® (amiodarone HCl) Premixed Injection 1.8 mg/mL in 200 mL dextrose, each in premixed bag containers (Baxter GALAXY System) is acceptable.

Please convey the Recommendation as appropriate to the sponsor.

Angelica Dorantes, Ph. D.

Biopharmaceutics Team Leader
Office of New Drugs Quality Assessment

Patrick J. Marroum, Ph. D.

Biopharmaceutics Supervisor
Office of New Drugs Quality Assessment

cc: NDA 22-325, Don Henry, Russell Fortney

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22325	SUPPL-1	PRISM PHARMACEUTICA LS INC	NEXTERONE IV (AMIODARONE HCL) 50MG/ML

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/s/

ANGELICA DORANTES
08/25/2010

PATRICK J MARROUM
08/26/2010

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

022325Orig1s001

OTHER REVIEW(S)

RHPM Review of Labeling

Application: NDA 22325/S-001
Nexterone (amiodarone HCl) Injection

Applicant: Prism Pharmaceuticals, Inc.

Document Date: May 5, 2010

Receipt Date: May 5, 2010

Submission Type: Prior Approval

Background:

With this supplement Prism is proposing two new premixed bag formulations of Nexterone. Nexterone was approved in December 2008 as vials and syringes which required dilution prior to administration. The premixed bag formulations are 150 mg/100 ml, which is meant to be used for ten-minute bolus infusions, and 360 mg/200 ml, which is meant for the continuous maintenance infusions.

The sponsor has submitted a separate package insert for the premixed formulations, as their syringe and vial formulations are not currently marketed. The new labeling is identical to the approved labeling except for those sections affected by the change in formulation

Review:

In a line-by-line review of the labeling, the following changes were noted:

1. The HIGHLIGHTS page has been revised as follows:
 - A. The product is described as Nexterone (amiodarone HCl) Premixed Injection.
 - B. Under Dosage and Administration, "(in D₅W or Normal Saline)" has been deleted, as the new product is only available as a dextrose-containing solution.
 - C. The Dosage Forms and Strengths section has been revised to describe the available formulations.
2. Throughout the labeling Nexterone has been replaced with Nexterone Premixed Injection.
3. The DOSAGE AND ADMINISTRATION section has been revised describe the use of the new premixed formulations. The highlighted changes are shown below:

2 DOSAGE AND ADMINISTRATION

Amiodarone shows considerable interindividual variation in response. Although a starting dose adequate to suppress life-threatening arrhythmias is needed, close monitoring with adjustment of dose is essential. The recommended starting dose of NEXTERONE is about 1000 mg over the first 24 hours of therapy, delivered by the following infusion regimen:

Table 1: NEXTERONE PREMIXED INJECTION DOSE RECOMMENDATIONS: FIRST 24 HOURS

Loading infusions	First Rapid: 150 mg over the FIRST 10 minutes (15 mg/min).
	<u>Directly infuse NEXTERONE Premixed Injection (150 mg/100 mL; 1.5mg/mL) at a rate of 10mL/min.</u>
	Add 3 mL of NEXTERONE (150 mg) to 100 mL D ₅ W 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).
	<u>Directly infuse NEXTERONE Premixed Injection (360 mg/200 mL; 1.8 mg/mL) at a rate of 0.556 mL/min.</u>
	Add 18 mL of NEXTERONE (900 mg) to 500 mL D ₅ W 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. <u>Directly infuse NEXTERONE Premixed Injection (360 mg/200 mL; 1.8 mg/mL) at a rate of 0.278 mL/min.</u>

After the first 24 hours, continue the maintenance infusion rate of 0.5 mg/min (720 mg per 24 hours) by directly infusing NEXTERONE Premixed Injection (360 mg/200 mL; 1.8 mg/mL) at a rate of 0.278 mL/min utilizing a concentration of 1 to 6 mg/mL (Use a central venous catheter for NEXTERONE concentrations greater than 2 mg/mL). The rate of the maintenance infusion may be increased to achieve effective arrhythmia suppression.

In the event of breakthrough episodes of VF or hemodynamically unstable VT, use 150 mg supplemental infusions of NEXTERONE (~~mixed in 100 mL of D₅W or normal saline and~~ infused over 10 minutes to minimize the potential for hypotension).

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. Do not exceed an initial infusion rate of 30 mg/min.

Based on the experience from clinical studies of intravenous amiodarone, a maintenance infusion of up to 0.5 mg/min can be 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.

Administer NEXTERONE, whenever possible, through a central venous catheter dedicated to that purpose. Use an in-line filter during administration.

Intravenous amiodarone loading infusions at much higher concentrations and rates of infusion much faster than recommended have resulted in hepatocellular necrosis and acute renal failure, leading to death [*see Warnings and Precautions (5.3)*].

Intravenous amiodarone concentrations greater than 3 mg/mL have been associated with a high incidence of peripheral vein phlebitis; however, concentrations of 2.5 mg/mL or less appear to be less irritating. Therefore, for infusions longer than 1 hour, do not exceed NEXTERONE concentrations of 2 mg/mL, unless a central venous catheter is used [*see Adverse Reactions (6.2)*].

~~NEXTERONE may be diluted in D₅W or saline and administered in polyvinyl chloride (PVC), polyolefin, or glass containers.~~

~~Do not use evacuated glass containers for admixing, as incompatibility with a buffer in the container may cause precipitation.~~

NEXTERONE Premixed Injection is available in GALAXY® containers as a single-use, ready-to-use, iso-osmotic solution in dextrose for intravenous administration. No further dilution is required. NEXTERONE Premixed Injection should not be combined with any product in the same intravenous line or premixed container. Protect from light until ready to use.

NEXTERONE does not need to be protected from light during administration.

Since the premixed container is for single-use only, any unused portion should be discarded.

NOTE: Inspect parenteral drug products for particulate matter and discoloration prior to administration, whenever solution and container permit. Check for minute leaks prior to use by squeezing the bag firmly. If leaks are detected, discard solution as sterility may be impaired.

CAUTION: Do not use plastic containers in series connections. Such use could result in air embolism due to residual air being drawn from the primary container before the administration of the fluid from the secondary container is complete.

Preparation of NEXTERONE Premixed Injection for administration:

1. Suspend container from eyelet support.
2. Remove protector from outlet port at bottom of container.
3. Attach administration set. Refer to complete directions accompanying set.

Admixture Incompatibility

NEXTERONE in D₅W is incompatible with the drugs shown in Table 2.

Table 2: Y-SITE INJECTION INCOMPATIBILITY

Drug	Vehicle	Amiodarone Concentration	Comments
Aminophylline	D ₅ W	4 mg/mL	Precipitate
Cefamandole Nafate	D ₅ W	4 mg/mL	Precipitate
Cefazolin Sodium	D ₅ W	4 mg/mL	Precipitate
Mezlocillin Sodium	D ₅ W	4 mg/mL	Precipitate
Heparin Sodium	D ₅ W	--	Precipitate
Sodium Bicarbonate	D ₅ W	3 mg/mL	Precipitate

Intravenous to Oral Transition

Patients whose arrhythmias have been suppressed by NEXTERONE may be switched to oral amiodarone. The optimal dose for changing from intravenous to oral administration of amiodarone will depend on the dose of NEXTERONE already administered, as well as the bioavailability of oral amiodarone. When changing to oral amiodarone therapy, clinical monitoring is recommended, particularly for elderly patients. See package insert for oral amiodarone.

Since grapefruit juice is known to inhibit CYP3A-mediated metabolism of oral amiodarone in the intestinal mucosa, resulting in increased plasma levels of amiodarone, do not drink grapefruit juice during treatment with oral amiodarone [see *Drug Interactions (7)*].

Table 3 provides suggested doses of oral amiodarone to be initiated after varying durations of NEXTERONE administration. These recommendations are made on the basis of a similar total body amount of amiodarone delivered by the intravenous and oral routes, based on 50% bioavailability of oral amiodarone.

Table 3: RECOMMENDATIONS FOR ORAL DOSAGE AFTER INTRAVENOUS INFUSION

Duration of NEXTERONE Infusion [#]	Initial Daily Dose of Oral Amiodarone
< 1 week	800-1600 mg
1-3 weeks	600-800 mg
> 3 weeks*	400 mg

[#] Assuming a 720 mg/day infusion (0.5 mg/min).

* NEXTERONE is not intended for maintenance treatment.

4. The DOSAGE FORMS AND STRENGTHS section has been revised as follows:

3 DOSAGE FORMS AND STRENGTHS

~~Injection, 50 mg/mL~~

Injection, 1.5 mg/mL (150 mg/100 mL) Premixed in Dextrose

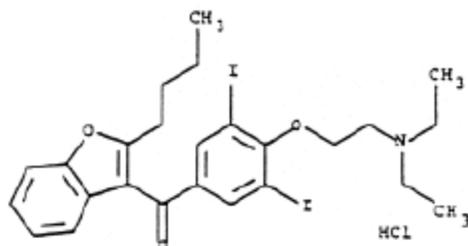
Injection, 1.8 mg/mL (360 mg/200 mL) Premixed in Dextrose

5. The DESCRIPTION section has been revised as follows:

11 DESCRIPTION

NEXTERONE contains amiodarone HCl ($C_{25}H_{29}I_2NO_3 \cdot HCl$), a class III antiarrhythmic drug. Amiodarone HCl is (2-butyl-3-benzo-furanyl)[4-[2-(diethylamino)ethoxy]-3,5-diiodophenyl]methanone hydrochloride.

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. NEXTERONE Premixed Injection is a sterile clear, colorless to slightly yellow solution visually free from particulates. Each mL of NEXTERONE contains 50 mg of amiodarone HCl, 225 mg sulfobutylether beta-cyclodextrin sodium, 3.8 mg citric acid monohydrate, 2.1 mg sodium citrate dihydrate and water for injection. Sodium hydroxide or citric acid monohydrate may be added to adjust pH. NEXTERONE Premixed Injection is available as a ready-to-use, nonpyrogenic, iso-osmotic solution for intravenous administration in 100mL GALAXY containers with 150 mg of amiodarone HCl (1.5mg/mL) in dextrose, and 200mL GALAXY containers with 360 mg of amiodarone HCl (1.8 mg/mL) in dextrose.

NEXTERONE Premixed Injection (150 mg/100 mL, 1.5 mg/mL):

Each mL contains 1.5 mg of amiodarone HCl, 15 mg sulfobutylether beta-cyclodextrin sodium, 0.362 mg citric acid anhydrous, 0.183 mg sodium citrate dihydrate and 42.1 mg dextrose anhydrous in water for injection. Sodium hydroxide or hydrochloric acid may have been added to adjust pH.

NEXTERONE Premixed Injection (360 mg/200 mL, 1.8 mg/mL):

Each mL contains 1.8 mg of amiodarone HCl, 18 mg sulfobutylether beta-cyclodextrin sodium, 0.362 mg citric acid anhydrous, 0.183 mg sodium citrate dihydrate and 41.4 mg dextrose anhydrous in water for injection. Sodium hydroxide or hydrochloric acid may have been added to adjust pH.

NEXTERONE does not contain polysorbate 80 or benzyl alcohol.

The GALAXY container is fabricated from a specially designed multilayered plastic (PL 2501). Solutions are in contact with the polyethylene layer of the container and can leach out certain chemical components of the plastic in very small amounts within the expiration period. The suitability and safety of the plastic have been confirmed in tests in animals according to the USP biological tests for plastic containers, as well as by tissue culture toxicity studies.

6. The HOW SUPPLIED/STORAGE AND HANDLING section has been revised as follows:

16 **HOW SUPPLIED/ STORAGE AND HANDLING**
NEXTERONE (amiodarone HCl) is available in single use glass vials packaged in individual cartons as follows:

150 mg/3 mL in a 5 mL vial NDC 43066 - 101 - 02
450 mg/9 mL in a 10 mL vial NDC 43066 - 101 - 03
900 mg/18 mL in a 20 mL vial NDC 43066 - 101 - 04

NEXTERONE (amiodarone HCl) is available in single-use glass prefilled syringes packaged in blister packs as follows:

150 mg/3 mL in a 5 mL prefilled syringe NDC 43066 - 101 - 01

NEXTERONE (amiodarone HCl) Premixed Injection is supplied as a ready-to-use, sterile, nonpyrogenic, iso-osmotic solution in 100 mL and 200 mL single-dose GALAXY containers (PL 2501 plastic) packaged in individual cartons as follows:

150 mg/100 mL NDC 43066 - 150 - 10 2G3451
360 mg/200 mL NDC 43066 - 360 - 20 2G3450

Store at 20° - 25°C (68° - 77°F); excursions permitted to 15° - 30°C (59° - 86°F). See USP Controlled Room Temperature.

Protect from light and excessive heat. Protect from freezing.

Use carton or blister pack to protect contents from light until used.

~~Stoppers and tip caps do not contain natural rubber latex~~

7. The manufacturer information has been revised.

Comments/Recommendations

Microbiology: Dr. Metcalfe's review recommends approval.

CMC: Dr. Liang's review recommends approval pending completion of a DMEPA review of the container labels.

ONDQA Biopharmaceutics: Dr. Dorantes's review recommends approval.

DMEPA: DMEPA provided comments regarding the labels on 11/3/10. These comments were conveyed to the sponsor. The sponsor provided revised labels via email on 11/4/10. The revised labels corrected all of the deficiencies noted in the DMEPA comments.

An approval letter will be drafted for Dr. Stockbridge's signature.

Russell Fortney
Regulatory Health Project Manager
11/9/10

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

/s/

RUSSELL FORTNEY
11/18/2010

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Date: November 3, 2010

To: Norman Stockbridge, MD, Director
Division of Cardiovascular and Renal Products (DCRP)

Application Type/Number: NDA 022325

Through: Carlos Mena-Grillasca, RPh, Team Leader
Carol Holquist, RPh, Director
Division of Medication Error Prevention and Analysis (DMEPA)

From: Chi-Ming Tu, PharmD, Safety Evaluator
Division of Medication Error Prevention and Analysis (DMEPA)

Subject: Label and Labeling Review

Drug Name(s): Nexterone
(Amiodarone HCl)
Premixed Injection: 150 mg/100 mL, 360 mg/ 200 mL
Injection: 150 mg/3 mL, 450 mg/9 mL, 900 mg/18 mL

Applicant/sponsor: Prism Pharmaceuticals

OSE RCM #: RCM 2010-1907

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1 INTRODUCTION

This review responds to a request from the Division of Cardiovascular and Renal Products (DCRP) for DMEPA assessment of Nexterone Premixed Injection container labels and carton labeling, submitted on May 5, 2010 (NDA 022325/S-01), for potential areas that could lead to medication errors.

2 PRODUCT INFORMATION

Nexterone (Amiodarone HCl) Injection is an antiarrhythmic agent indicated for initiation of treatment and prophylaxis of frequent recurring ventricular fibrillations (VF) and hemodynamically unstable ventricular tachycardia (VT) in patients refractory to other therapies. The recommended starting dose is about 1,000 mg intravenously over the first 24 hours of therapy, delivered by the following infusion regimen:

- Initial load: 150 mg per 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 thereafter

Nexterone received approval for the following packaging presentations:

- Single-use vials: 150 mg/3 mL, 450 mg/9 mL, 900 mg/18 mL
- Single-use prefilled syringes: 150 mg/3 mL

However, according to DCRP Nexterone has never been marketed in these packaging presentations (vials and syringes). The premixed bags currently under review will be the first product to be marketed and depending on market uptake of the bags, the syringes and vials may be marketed later.

3 REGULATORY HISTORY

Nexterone Injection, single-use vials and pre-filled syringes, were approved on December 24, 2008. DMEPA previously reviewed the proposed container labels and carton labeling in OSE RCM# 2007-2582, dated November 6, 2008. The approval letter stated that the Applicant should “submit final printed carton and container labels that are identical to the submitted carton and immediate container labels as soon as they are available, but no more than 30 days after they are printed.” The Applicant was also given the direction to designate this submission as “Final Printed Carton and Container Labels for approved NDA 22-325.”

The Applicant submitted the final container label and carton labelings for Nexterone Injection under the directed designation on July 30, 2009. In January 29, 2010, the Applicant submitted Annual Report-1 stating that container label and carton labelings submitted on July 30, 2009 are “the final intended artwork for the product.”

In reviewing the materials submitted for this review, DMEPA noted that the final container label and carton labelings submitted by the Applicant for Nexterone Injection on July 30, 2009 differ significantly from the previously reviewed labels and labeling in OSE RCM# 2007-2582.

4 METHODS AND MATERIALS

DMEPA searched the FDA Adverse Event Reporting System (AERS) database for reported medication errors associated with the use of Amiodarone injectable products, and reviewed all of the most recently submitted container labels and carton labelings for both Nexterone Injection and Premixed Injection.

4.1 ADVERSE EVENT REPORTING SYSTEM (AERS)

DMEPA searched AERS on September 3, 2010 using the following search terms: active ingredients “amioda%” and verbatim “amioda%,” and reactions “Medication Errors” (HLGT) and “Product Quality Issues” (HLGT). The date was limited from June 30, 2008, the last date searched for OSE RCM# 2007-2582, to the search date September 3, 2010.

All the cases retrieved were manually reviewed to determine if a medication error occurred. If an error occurred, we categorized the errors by type then reviewed the case to determine if the root cause could be associated with the labels or labeling of the intravenously administered amiodarone hydrochloride product, and thus pertinent to this review. Those cases that did not describe a medication error or did not describe an error applicable to this review (such as errors not related to amiodarone or errors with the oral amiodarone) were excluded from further analysis.

The results from the previous AERS search were also reviewed for any additional information that would contribute to this container label and carton labelings review.

4.2 LABELS AND LABELING

On May 5, 2010, the Applicant submitted a request for approval of Nexterone (amiodarone HCl) Premixed Injection and submitted draft container label and carton labeling for review (NDA 022325/S-01). The following container labels and carton labelings for Nexterone Injection and Nexterone Premixed Injection were reviewed:

- Nexterone Injection, sterile single-use vial
 - Container labels: 150 mg/3 mL, 450 mg/9 mL, 900 mg/18 mL
 - Carton labeling: 150 mg/3 mL, 450 mg/9 mL, 900 mg/18 mL
- Nexterone Injection, sterile single-use syringe
 - Container label: 150 mg/3 mL
 - Carton labeling: 150 mg/3 mL
- Nexterone Premixed Injection
 - Container labels: 150 mg/100 mL, 360 mg/200 mL
 - Carton labeling: 150 mg/100 mL, 360 mg/200 mL

5 RESULTS

Our AERS search identified a total of eight cases (n=8) since our last review. A summary of the eight medication errors associated with the use of intravenous amiodarone hydrochloride is described below:

5.1 WRONG TIME (N=1)

One domestic case (ISR# 5847736) received on August 14, 2008 reported that “the drug strength is very small- 150 mg/3 mL” on an amiodarone vial and difficult to read, causing a delay in drug administration in a code situation. The outcome of this event was not reported.

The proposed container label and carton labeling emphasize the total drug content (e.g. 150 mg/3 mL) when compared to the concentration (e.g. 50 mg/mL) and adequately display the total drug content and strength on the label and labeling so the display of this information will not contribute to other type of error.

5.2 WRONG DRUG (N=1)

One foreign case (ISR# 6498188) received on November 13, 2009 reported that a female patient experienced a fatal outcome as a result of being given amiodarone instead of atropine during cardiac arrest. Both amiodarone and atropine were supplied in prefilled syringes in identical yellow boxes. The reporter stated that “there have been twelve similar incidents in the past three years, and believed that the packaging must be changed to make each drug easier to distinguish.” Although the case was forwarded from Bausch & Lomb, Inc., the case narrative did not provide the manufacturer’s name for each product thus we were unable to further evaluate the packaging of these prefilled syringes. Nexterone is approved as a prefilled syringe; however, it is not currently marketed.

5.3 WRONG TECHNIQUE (N=1)

One domestic case (ISR# 6500024) received on November 29, 2009 reported possible extravasation of either intravenous amiodarone or technetium given in the same line, resulting in phlebitis of the mid-forearm.

5.4 WRONG RATE (N=2)

Two domestic cases (ISR# 5847383 received on May 30, 2008 and ISR# 6375104 received on September 17, 2009) reported wrong rate medication errors due to failure to program infusion pump accurately. Non-serious outcome was reported for one case (ISR#5847383) while the other case (ISR# 6375104) did not report an outcome.

5.5 OVERDOSE (N=3)

All three cases were foreign. The first case (ISR# 6417004) received on October 23, 2009 reported a life-threatening overdose that resulted from administration of 10 times the recommended intravenous dose in a (b) (6). The life-threatening overdose caused profound hypotension, requiring cardiopulmonary resuscitation for 20 minutes and other treatments. The neonate was eventually discharged with normal cardiac and neurological function. The second case (ISR# 5879881) received on September 12, 2008 described an overdose medication error resulting in cardiovascular collapse in a neonate patient. The error was caused by a calculation error leading to 3 times the prescribed dose to be administered. The patient was (b) (6) after extracorporeal membrane oxygenation (ECMO) decannulation. The third case (ISR# 6795787) received on June 15, 2010 reported an overdose after administration of “amiodarone 450 mg per infusion (given in 2 hours) for 8 days and oral amiodarone 600 mg/day.” The outcomes reported for this event include increased blood pressure, lack of appetite, bradycardia, and ongoing atrial fibrillation. Causality of the event was not reported for this case.

6 DISCUSSION

Our review of the container labels and carton labeling found that the presentation of information and design of the proposed carton and container labels is vulnerable to confusion that could lead to medication errors.

The new artwork proposed for the container labels and carton labeling submitted on July 30, 2009 presents the proprietary name Nexterone (b) (4) DMEPA notes that the new artwork includes an (b) (4) and uses a form of (b) (4). In addition, with the new artwork the established name does not have a prominence commensurate with the prominence of the proprietary name.

Additionally, “premixed injection” is not an official dosage form recognized by USP.¹

We also noted the use of the

(b) (4)

(b) (4)

(b) (4) Therefore, our preference is to use the term “intravenous”

(b) (4)

(b) (4)

Lastly, the container labels and carton labeling of all three strengths of single-use vials utilize the same color scheme, making all three strengths of the product appear similar. The uniform color scheme presents a risk of medication error as the wrong strength may be retrieved from the shelf, where these products are likely to be stored side-by-side. Better differentiation is needed to highlight the three strengths.

DMEPA provides our recommendations that aim to reduce the potential for medication errors in Section 7.

7 CONCLUSIONS AND RECOMMENDATIONS

Our evaluation noted areas where information on the container labels and carton labeling submitted on January 29, 2010 and May 5, 2010 can be improved to minimize the potential for medication errors. We request the Applicant revise the labels and labeling as described below prior to approval.

Please copy DMEPA on any communication to the Applicant with regards to this review. If you have any questions or need clarification, please contact the OSE Safety Regulatory Project Manager Phoung (Nina) Ton at 301-796-1648.

7.1 COMMENTS TO THE DIVISION

We note that “Premixed Injection” is not a recognized USP dosage form. DMEPA recommends the Review Division consult CDER Labeling and Nomenclature Committee (LNC) and ONDQA regarding the appropriate dosage form designation for Nexterone products packaged in premixed bags. We prefer the following presentation be considered to clearly convey the type of solution in the premixed bag:

“Nexterone (Amiodarone HCl) in XX% Dextrose Injection”.

7.2 COMMENTS TO THE APPLICANT

A. General Comments

1. Revise the presentation of the proprietary name to use a (b) (4) As currently presented the use of the (b) (4) (b) (4) In addition, the use of (b) (4) in the presentation of the proprietary name is a form of (b) (4). We reserve the use of (b) (4) (b) (4).

¹ USP/NF, General Chapter 1, Injections; viewed at <http://www.uspnf.com/uspnf/pub/index?usp=32&nf=27&s=2&officialOn=December%201.%202009> on September 13, 2010.

² Institute for Safe Medication Practices (ISMP), ISMP Medication Safety Alert, 7 (13), June 26, 2002.

³ Institute for Safe Medication Practices (ISMP), ISMP’s List of Error-Prone Abbreviations, Symbols, and Dose Designations; viewed at <http://www.ismp.org/Tools/errorproneabbreviations.pdf> on September 13, 2010.

2. Delete the [REDACTED] (b) (4) [REDACTED] (such as differentiating between multiple strengths).
3. Revise the established name so it has a prominence commensurate with the prominence of the proprietary name, including typography, layout, contrast, and other printing features per 21 CFR 201.10(g)(2).
4. Revise the statement “Must Be Diluted” to read “Must be Diluted before Intravenous Use”.

B. Single-use vials

1. Container Labels

- i. Relocate the NDC number to the top third of the principal display panel of the container label per 21 CFR 207.35(b)(3)(i). To achieve this change, consider decreasing the size or relocating the company name and logo as well as the manufacturer information to the side panel.
- ii. Revise the route of administration statement to read “For Intravenous Use Only” for the 150 mg/3 mL and 450 mg/9 mL vials. As currently presented, the [REDACTED] (b) (4) [REDACTED]
- iii. Delete the word [REDACTED] (b) (4) as it crowds the label and does not provide relevant information.
- iv. Increase the size of the concentration statement and relocate it to appear below the total drug content. To achieve this change, consider decreasing the size or relocating the company name and logo as well as the manufacturer information to the side panel.
- v. Revise the color scheme to distinguish the three different strengths from each other. Current use of the same color scheme for all three different strengths presents a risk for medication error.
- vi. Add the statement “Discard unused portion” immediately following or under the “Single Use Vial” statement.

2. Carton Labeling

- i. Increase the size of the concentration statement and relocate below the total drug content.
- ii. Revise the color scheme to distinguish the three different strengths from each other. Current use of the same color scheme for all three different strengths presents a risk for medication error.
- iii. Add the statement “Discard unused portion” immediately following or under the “Single Use Vial” statement.

C. Single-use syringe

1. Container labels

- i. Relocate the NDC number to the top third of the principal display panel of the container label per 21 CFR 207.35(b)(3)(i).

- ii. Revise the route of administration statement to read “For Intravenous Use Only.”
[REDACTED] (b) (4)
- iii. Delete the word [REDACTED] (b) (4) as it crowds the label and does not provide relevant information.
- iv. Increase the size of the concentration statement and relocate below the total drug content. To achieve this change, consider decreasing the size or relocating the company name and logo as well as the manufacturer information to the side panel.
- v. Add the statement “Discard unused portion” immediately following or under the “Single Use Syringe” statement.

2. Blister Labeling

- i. Relocate the NDC number to the top third of the principal display panel of the container label per 21 CFR 207.35(b)(3)(i).
- ii. Delete the word [REDACTED] (b) (4) from the [REDACTED] (b) (4)” statement, as it is duplicative. The statement [REDACTED] (b) (4) appears elsewhere on the blister labeling.
- iii. Increase the size of the concentration statement and relocate below the total drug content.
- iv. Add the statement “Discard unused portion” immediately following or under the “Single Use Syringe” statement.

3. Carton Labeling

- i. Increase the size of the concentration statement.
- ii. Add the statement “Discard unused portion” immediately following or under the “Single Use Vial” statement.

D. Premixed Bags

1. Container labels

- i. Relocate the NDC number to the top third of the principal display panel of the container label per 21 CFR 207.35(b)(3)(i).
- ii. Relocate the net quantity statement away from the total drug content and concentration statements.
- iii. Revise the presentation of the total drug content to use the same size font for the volume (e.g. 150 mg/100 mL instead of the currently proposed **150** mg/100 mL).
- iv. Delete the statement [REDACTED] (b) (4)
- v. Add the statement “Discard unused portion” immediately following or under the “Single Dose Container” statement.
- vi. Delete all non relevant or duplicative information to increase the amount of white space and improve readability. For example: [REDACTED] (b) (4) [REDACTED] (b) (4) “Iso-osmotic solution in Dextrose”.

2. Carton Labeling

- i. Revise the presentation of the total drug content to use the same size font for the volume (e.g. 150 mg/100 mL instead of the currently proposed **150** mg/100 mL).
- ii. Delete the statement ^{(b) (4)}.
- iii. Add the statement “Discard unused portion” immediately following or under the “Single Dose Container” statement.

3. Box Labeling

- i. Revise the presentation of the total drug content to use the same size font for the volume (e.g. 150 mg/100 mL instead of the currently proposed **150** mg/100 mL).

8 REFERENCES

1. Adverse Events Reporting System (AERS)

AERS is a database application in CDER FDA that contains adverse event reports for approved drugs and therapeutic biologics. These reports are submitted to the FDA mostly from the manufactures that have approved products in the U.S. The main utility of a spontaneous reporting system that captures reports from health care professionals and consumers, such as AERS, is to identify potential post-marketing safety issues. There are inherent limitations to the voluntary or spontaneous reporting system, such as underreporting and duplicate reporting; for any given report, there is no certainty that the reported suspect product(s) caused the reported adverse event(s); and raw counts from AERS cannot be used to calculate incidence rates or estimates of drug risk for a particular product or used for comparing risk between products.

2. OSE RCM 2007-2582; Nexterone IV (Amiodarone HCl) Injection 150 mg/3 mL, 450 mg/9 mL, and 900 mg/18 mL Proprietary Name, Label and Labeling Review; Abate, R; November 6, 2008.

8 Pages of Draft Labeling have been Withheld in Full immediately following this page.

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/s/

CARLOS M MENA-GRILLASCA
11/03/2010

CAROL A HOLQUIST
11/03/2010

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

022325Orig1s001

ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION		REQUEST FOR CONSULTATION			
TO (Division/Office): Mail: OSE			FROM: Russell Fortney DCRP, 6-1068		
DATE 9/1/10	IND NO.	NDA NO. 22325/S-001	TYPE OF DOCUMENT supplement	DATE OF DOCUMENT 5/5/10	
NAME OF DRUG Nexterone (amiodarone HCl) Injection		PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE 9/15/10	
NAME OF FIRM: Prism Pharmaceuticals					
REASON FOR REQUEST					
I. GENERAL					
<input type="checkbox"/> NEW PROTOCOL <input type="checkbox"/> PROGRESS REPORT <input type="checkbox"/> NEW CORRESPONDENCE <input type="checkbox"/> DRUG ADVERTISING <input type="checkbox"/> ADVERSE REACTION REPORT <input type="checkbox"/> MANUFACTURING CHANGE/ADDITION <input type="checkbox"/> MEETING PLANNED BY		<input type="checkbox"/> PRE--NDA MEETING <input type="checkbox"/> END OF PHASE II MEETING <input type="checkbox"/> RESUBMISSION <input type="checkbox"/> SAFETY/EFFICACY <input type="checkbox"/> PAPER NDA <input type="checkbox"/> CONTROL SUPPLEMENT		<input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER <input type="checkbox"/> FINAL PRINTED LABELING <input type="checkbox"/> LABELING REVISION <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE <input type="checkbox"/> FORMULATIVE REVIEW <input checked="" type="checkbox"/> OTHER (SPECIFY BELOW):	
II. BIOMETRICS					
STATISTICAL EVALUATION BRANCH			STATISTICAL APPLICATION BRANCH		
<input type="checkbox"/> TYPE A OR B NDA REVIEW <input type="checkbox"/> END OF PHASE II MEETING <input type="checkbox"/> CONTROLLED STUDIES <input type="checkbox"/> PROTOCOL REVIEW <input type="checkbox"/> OTHER (SPECIFY BELOW):			<input type="checkbox"/> CHEMISTRY REVIEW <input type="checkbox"/> PHARMACOLOGY <input type="checkbox"/> BIOPHARMACEUTICS <input type="checkbox"/> OTHER (SPECIFY BELOW):		
III. BIOPHARMACEUTICS					
<input type="checkbox"/> DISSOLUTION <input type="checkbox"/> BIOAVAILABILITY STUDIES <input type="checkbox"/> PHASE IV STUDIES			<input type="checkbox"/> DEFICIENCY LETTER RESPONSE <input type="checkbox"/> PROTOCOL-BIOPHARMACEUTICS <input type="checkbox"/> IN-VIVO WAIVER REQUEST		
IV. DRUG EXPERIENCE					
<input type="checkbox"/> PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL <input type="checkbox"/> DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below) <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP			<input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE <input type="checkbox"/> POISON RISK ANALYSIS		
V. SCIENTIFIC INVESTIGATIONS					
<input type="checkbox"/> CLINICAL			<input type="checkbox"/> PRECLINICAL		
COMMENTS/SPECIAL INSTRUCTIONS: Please review the carton and container labels for this supplement. Nexterone injection (vials and syringes, for dilution prior to administration) was approved in December 2008. That product has not yet been marketed. The sponsor submitted this supplement for pre-mixed bags (one bag is for the 150mg bolus dose, the other is for the maintenance infusion). EDR link to submission: \\CDSESUB1\EVSPROD\NDA022325\022325.enx					
SIGNATURE OF REQUESTER Russell Fortney			METHOD OF DELIVERY (Check one) <input checked="" type="checkbox"/> MAIL/DARTS <input type="checkbox"/> HAND		
SIGNATURE OF RECEIVER			SIGNATURE OF DELIVERER		

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22325	SUPPL-1	PRISM PHARMACEUTICA LS INC	NEXTERONE IV (AMIODARONE HCL) 50MG/ML

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/s/

RUSSELL FORTNEY
09/01/2010

REQUEST FOR CONSULTATION

TO (Office/Division): Sylvia Gantt New Drug Microbiology
Staff OC/OO/CDER/OPS/NDMS

FROM (Name, Office/Division, and Phone Number of Requestor): Don Henry
Project Manager, ONDQA, 301-796-4227

DATE
August 19, 2010

IND NO.

NDA NO.
22-325 s001

TYPE OF DOCUMENT
NDA supplement

DATE OF DOCUMENT
May 5, 2010

NAME OF DRUG
Nexterone Injection

PRIORITY CONSIDERATION
prior approval

CLASSIFICATION OF DRUG
cardio-renal

DESIRED COMPLETION DATE
September 1, 2010

NAME OF FIRM: Prism Pharmaceuticals

REASON FOR REQUEST

I. GENERAL

- | | | |
|--|--|--|
| <input type="checkbox"/> NEW PROTOCOL | <input type="checkbox"/> PRE-NDA MEETING | <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER |
| <input type="checkbox"/> PROGRESS REPORT | <input type="checkbox"/> END-OF-PHASE 2a MEETING | <input type="checkbox"/> FINAL PRINTED LABELING |
| <input type="checkbox"/> NEW CORRESPONDENCE | <input type="checkbox"/> END-OF-PHASE 2 MEETING | <input type="checkbox"/> LABELING REVISION |
| <input type="checkbox"/> DRUG ADVERTISING | <input type="checkbox"/> RESUBMISSION | <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE |
| <input type="checkbox"/> ADVERSE REACTION REPORT | <input type="checkbox"/> SAFETY / EFFICACY | <input type="checkbox"/> FORMULATIVE REVIEW |
| <input type="checkbox"/> MANUFACTURING CHANGE / ADDITION | <input type="checkbox"/> PAPER NDA | <input checked="" type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> MEETING PLANNED BY | <input type="checkbox"/> CONTROL SUPPLEMENT | |

II. BIOMETRICS

- | | |
|---|---|
| <input type="checkbox"/> PRIORITY P NDA REVIEW | <input type="checkbox"/> CHEMISTRY REVIEW |
| <input type="checkbox"/> END-OF-PHASE 2 MEETING | <input type="checkbox"/> PHARMACOLOGY |
| <input type="checkbox"/> CONTROLLED STUDIES | <input type="checkbox"/> BIOPHARMACEUTICS |
| <input type="checkbox"/> PROTOCOL REVIEW | <input type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> OTHER (SPECIFY BELOW): | |

III. BIOPHARMACEUTICS

- | | |
|--|--|
| <input type="checkbox"/> DISSOLUTION | <input type="checkbox"/> DEFICIENCY LETTER RESPONSE |
| <input type="checkbox"/> BIOAVAILABILITY STUDIES | <input type="checkbox"/> PROTOCOL - BIOPHARMACEUTICS |
| <input type="checkbox"/> PHASE 4 STUDIES | <input type="checkbox"/> IN-VIVO WAIVER REQUEST |

IV. DRUG SAFETY

- | | |
|--|--|
| <input type="checkbox"/> PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL | <input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY |
| <input type="checkbox"/> DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES | <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE |
| <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below) | <input type="checkbox"/> POISON RISK ANALYSIS |
| <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP | |

V. SCIENTIFIC INVESTIGATIONS

- | | |
|-----------------------------------|--------------------------------------|
| <input type="checkbox"/> CLINICAL | <input type="checkbox"/> NONCLINICAL |
|-----------------------------------|--------------------------------------|

COMMENTS / SPECIAL INSTRUCTIONS: The supplement provides for a new drug substance supplier for an addition of a pre-mixed bag of Nexterone (amiodarone HCl) which was originally approved as pre-filled syringes. A review of the manufacturing/filling process and specifications are requested. This is an electronic submission

SIGNATURE OF REQUESTOR
{See appended electronic signature page}

METHOD OF DELIVERY (Check one)
 DFS EMAIL MAIL HAND

PRINTED NAME AND SIGNATURE OF RECEIVER

PRINTED NAME AND SIGNATURE OF DELIVERER

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22325	SUPPL-1	PRISM PHARMACEUTICA LS INC	NEXTERONE IV (AMIODARONE HCL) 50MG/ML

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/s/

DON L HENRY
08/19/2010

Prior Approval Supplement

APPEARS THIS
WAY ON
ORIGINAL

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22325	SUPPL-1	PRISM PHARMACEUTICA LS INC	NEXTERONE IV (AMIODARONE HCL) 50MG/ML

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/s/

SANDRA P MATTHEWS
05/11/2010



NDA 22-325/S-001

PRIOR APPROVAL SUPPLEMENT

Prism Pharmaceuticals, Inc.
Attention: Daniel J. Cushing, Ph.D.
VP, Drug Development & Regulatory Affairs
Chief, Scientific Officer
1016 West Ninth Avenue, Suite 130
King of Prussia, PA 19406

Dear Dr. Cushing:

We have received your May 5, 2010 Supplemental New Drug Application (sNDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: Nexterone (amiodarone HCl) 50 mg/mL, 1.5 mg/mL and 1.8 mg/mL
Injection

NDA Number: 22-325

Supplement number: 001

Date of supplement: May 5, 2010

Date of receipt: May 5, 2010

This supplemental application, submitted as a Chemistry, Manufacturing and Control Supplement, provides for both 1.5 mg/mL and 1.8 mg/mL solution of Nexterone (amiodarone HCL) in 5% dextrose in premixed bag containers.

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on July 4, 2010 in accordance with 21 CFR 314.101(a). If the application is filed, the user fee goal date will be September 5, 2010.

Please cite the application number listed above at the top of the first page of all submissions to this application.

Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Cardiovascular and Renal Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

If you have questions, please contact:

Russell Fortney, R.Ph.
Regulatory Health Project Manager
(301) 796-1068

Sincerely,

{See appended electronic signature page}

Edward Fromm, R.Ph., RAC
Chief, Project Management Staff
Division of Cardiovascular and Renal Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22325	SUPPL-1	PRISM PHARMACEUTICA LS INC	NEXTERONE IV (AMIODARONE HCL) 50MG/ML

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/s/

EDWARD J FROMM
05/11/2010