

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

22-325

PROPRIETARY NAME REVIEW(S)



**Department of Health and Human Services
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Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology**

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Subject: Proprietary Name, Label and Labeling Review for Nexterone IV

Drug Name(s): Nexterone IV (Amiodarone HCl) Injection 150 mg/3 mL,
450 mg/9 mL, and 900 mg/18 mL

Application Type/Number: NDA 22-325

Applicant: Prism Pharmaceuticals

OSE RCM #: 2007-2582

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EXECUTIVE SUMMARY

The Proprietary Name Risk Assessment found the proposed name, Nexterone IV, is not vulnerable to name confusion that could lead to medication errors. The Division of Medication Error Prevention and Analysis objects to the inclusion of 'IV' as part of the proprietary name because Nexterone IV will be available only as injection for intravenous use and other medical abbreviations are often misinterpreted as 'IV' including the Roman numeral four and 'IU' meaning international units. As such, the medication error prevention staff objects to the use of the proprietary name, Nexterone IV, for this product. However, we have no objection to the use of Nexterone alone.

The Label and Labeling Risk Assessment findings indicate that the presentation of information and design of the proposed carton labeling and container labels introduces vulnerability to confusion that could lead to medication errors. The medication error prevention staff believes the risks we have identified can be addressed and mitigated prior to drug approval, and provides recommendations in Section 5.2 that aim at reducing the risk of medication errors.

1 BACKGROUND

1.1 INTRODUCTION

This review is in response to request from the Division of Cardiovascular and Renal Products for assessment of the proposed proprietary name, Nexterone IV, regarding its potential confusion with other proprietary or established drug names in normal practice settings.

Additionally, container labels, carton and insert labeling were provided for analysis for their potential to contribute to medication errors.

1.2 PRODUCT INFORMATION

Nexterone IV (Amiodarone HCl) injection is an alternative formulation of Amiodarone HCl injection which does not contain polysorbate 80 or benzyl alcohol. Nexterone IV, like existing Amiodarone HCl injection products, is indicated for the treatment or prophylaxis of frequently recurring ventricular fibrillation and unstable ventricular tachycardias in patients not responding to other therapy. A loading dose of 150 mg may be diluted and administered over ten minutes. The Applicant states in the proposed labeling that the _____

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_____ After the loading dose, an Amiodarone HCl infusion is made by diluting 900 mg of Nexterone IV in 500 mL of 5% dextrose _____ The diluted Amiodarone HCl is infused at 1 mg/min for six hours followed by 0.5 mg/min thereafter. The proposed product will be available as 150 mg/3 ml pre-filled syringes as well as 150 mg/3 mL, 450 mg/9 mL, and 900 mg/18 mL vials to be stored at room temperature.

Also, we note the Applicant states in the labeling that _____

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_____ This stability data differs from the currently marketed Amiodarone HCl injection products.

2 METHODS AND MATERIALS

This section consists of two sections which describe the methods and materials used by the medication error prevention staff conducting a proprietary name risk assessment (see 2.1 Proprietary Name Risk Assessment) and label, labeling, and/or packaging risk assessment (see 2.2 Label and Labeling Risk Assessment). The primary focus for both of the assessments is to identify and remedy potential sources of medication error prior to drug approval. The medication error prevention staff defines a medication error as any preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of the health care professional, patient, or consumer.¹

2.1 PROPRIETARY NAME RISK ASSESSMENT

FDA's Proprietary Name Risk Assessment considers the potential for confusion between the proposed proprietary name, Nexterone IV, and the proprietary and established names of drug products existing in the marketplace and those pending IND, NDA, BLA, and ANDA products currently under review by CDER.

For the proprietary name, Nexterone IV, the medication error prevention staff searches a standard set of databases and information sources to identify names with orthographic and phonetic similarity (see Sections 2.1.1 for detail) and held an CDER Expert Panel discussion to gather professional opinions on the safety of the proposed proprietary name (see 2.1.1.2). Our Division also conducts internal CDER prescription analysis studies (see 2.1.2), and, when provided, external prescription analysis studies results are considered and incorporated into the overall risk assessment (see detail 2.1.3).

The Safety Evaluator assigned to the Proprietary Name Risk Assessment is responsible for considering the collective findings, and provides an overall risk assessment of the proposed proprietary name (see detail 2.1.4). The overall risk assessment is based on the findings of a Failure Modes and Effects Analysis (FMEA) of the proprietary name, and is focused on the avoidance of medication errors. FMEA is a systematic tool for evaluating a process and identifying where and how it might fail.² FMEA is used to analyze whether the drug names identified with look- or sound-alike similarity to the proposed name could cause confusion that subsequently leads to medication errors in the clinical setting. The medication error prevention staff uses our clinical expertise to anticipate the conditions of the clinical setting that the product is likely to be used in based on the characteristics of the proposed product.

In addition, the product characteristics provide the context for the verbal and written communication of the drug names and can interact with the orthographic and phonetic attributes of the names to increase the risk of confusion when there is overlap, or, in some instances, decrease the risk of confusion by helping to differentiate the products through dissimilarity. As such, the staff considers the product characteristics associated with the proposed drug throughout the risk assessment, since the product characteristics of the proposed may provide a context for

¹ National Coordinating Council for Medication Error Reporting and Prevention. <http://www.nccmerp.org/aboutMedErrors.html>. Last accessed 10/11/2007.

² Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

communication of the drug name and ultimately determine the use of the product in the *usual* clinical practice setting.

Typical product characteristics considered when identifying drug names that could potentially be confused with the proposed drug name include, but are not limited to established name of the proposed product, the proposed indication, dosage form, route of administration, strength, unit of measure, dosage units, recommended dose, typical quantity or volume, frequency of administration, product packaging, storage conditions, patient population, and prescriber population. Because drug name confusion can occur at any point in the medication use process, the medication error prevention staff considers the potential for confusion throughout the entire U.S. medication use process, including drug procurement, prescribing and ordering, dispensing, administration, and monitoring the impact of the medication.³

2.1.1 Search Criteria

The medication error prevention staff considers the spelling of the name, pronunciation of the name when spoken, and appearance of the name when scripted as outlined in Appendix A.

For this review, particular consideration was given to drug names beginning with the letter 'N' when searching to identify potentially similar drug names, as 75% of the confused drug names reported by the USP-ISMP Medication Error Reporting Program involve pairs beginning with the same letter.^{4,5} With regard to the modifier, 'IV,' the search criteria also took into consideration that the modifier could be misinterpreted as numbers, dosing instructions or medical abbreviations.

To identify drug names that may look similar to Nexterone IV or the root name, Nexterone, the staff also considers the other orthographic appearance of the name on lined and unlined orders. Specific attributes taken into consideration include the length of the name (nine letters), upstrokes (two, capital letter 'N' and the letter 't'), downstrokes (none), cross-strokes (two, the letters 'x' and 't'), and dotted letters (none). Additionally, several letters in Nexterone may be vulnerable to ambiguity when scripted, including the letter 'N' may appear as 'M,' 'U,' or 'V;' lower case 'n' appear as a lower case 'm,' 'r,' 'u,' or 'v;' lower case 'e' may appear as a lower case 'i' or 'l;' lower case 'x' may appear as lower case 'a,' 'f,' 'p,' 'r,' or 't;' lower case 't' may appear as lower case 'f,' 'l' if uncrossed, or 'r;' lower case 'r' may appear as lower case 'n,' 't,' or 'v;' and lower case 'o' may appear as a lower case 'a'. As such, the staff also considers these alternate appearances when identifying drug names that may look similar to Nexterone IV.

When searching to identify potential names that may sound similar to Nexterone IV, the medication error prevention staff searched for names with similar number of syllables (three), stresses (nex-TER-one or NEX-ter-one), and placement of vowel and consonant sounds. Several letters may be prone to misinterpretation when spoken including: 'n' may be misinterpreted as 'm' and 'xt' may be misinterpreted as 'st.' The staff also considers these alternate interpretations when identifying drug names that may sound similar to Nexterone. The Applicant's intended

³ Institute of Medicine. Preventing Medication Errors. The National Academies Press: Washington DC. 2006.

⁴ Institute for Safe Medication Practices. Confused Drug name List (1996-2006). Available at <http://www.ismp.org/Tools/confuseddrugnames.pdf>

⁵ Kondrack, G and Dorr, B. Automatic Identification of Confusable Drug Names. Artificial Intelligence in Medicine (2005)

pronunciation of the proprietary name could not be expressly taken into consideration, as this was not provided with the proposed name submission.

The staff also considers the product characteristics associated with the proposed drug throughout the identification of similar drug names, since the product characteristics of the proposed drug ultimately determine the use of the product in the clinical practice setting. For this review, the medication error prevention staff were provided with the following information about the proposed product: the proposed proprietary name (Nexterone IV), the established name (Amiodarone HCl), proposed indication (treatment or prophylaxis of frequently recurring ventricular fibrillation and unstable ventricular tachycardias in patients not responding to other therapy), strength (150 mg/3 mL, 450 mg/9 mL and 900 mg/18 mL), dose (1 mg/minute, or 0.5 mg/minute), frequency of administration (continuously), route (intravenous) and dosage form of the product (injection as a prefilled syringe and vials). Appendix A provides a more detailed listing of the product characteristics the Staff generally takes into consideration.

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Lastly, the medication error prevention staff also considers the potential for the proposed name to inadvertently function as a source of error for reasons other than name confusion. Post-marketing experience has demonstrated that proprietary names (or components of the proprietary name) can be a source of error in a variety of ways. As such, these broader safety implications of the name are considered and evaluated throughout this assessment and the medication error prevention staff provides additional comments related to the safety of the proposed name or product based on their professional experience with medication errors.

2.1.1.1 Database and Information Sources

The proposed proprietary name, Nexterone IV, was provided to the medication error prevention staff to conduct a search of the internet, several standard published drug product reference texts, and FDA databases to identify existing and proposed drug names that may sound-alike or look-alike to Nexterone IV using the criteria outlined in 2.1.1. A standard description of the databases used in the searches is provided in Section 6. To complement the process, the medication error prevention staff uses a computerized method of identifying phonetic and orthographic similarity between medication names. The program, Phonetic and Orthographic Computer Analysis (POCA), uses complex algorithms to select a list of names from a database that have some similarity (phonetic, orthographic, or both) to the trademark being evaluated. Lastly, the medication error prevention staff reviews the United States Adopted Name stem list to determine if any USAN stems are present within the proprietary name. The findings of the individual safety evaluators were then pooled and presented to the Expert Panel.

2.1.1.2 CDER Expert Panel Discussion

An Expert Panel Discussion is held by the medication error prevention staff to gather CDER professional opinions on the safety of the product and the proprietary name, Nexterone IV. Potential concerns regarding drug marketing and promotion related to the proposed names are also discussed. This group is composed of the medication error prevention staff and representatives from the Division of Drug Marketing, Advertising, and Communications (DDMAC).

The pooled results of the medication error staff were presented to the Expert Panel for consideration. Based on the clinical and professional experiences of the Expert Panel members,

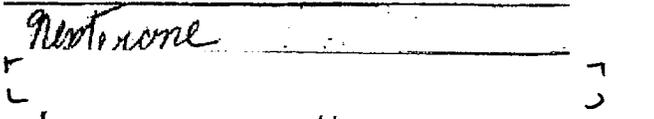
the Panel may recommend the addition of names, additional searches by the Safety Evaluator to supplement the pooled results, or general advice to consider when reviewing the proposed proprietary name.

2.1.2 FDA Prescription Analysis Studies

Three separate studies are conducted within the Centers of the FDA for the proposed proprietary name to determine the degree of confusion of Nexterone with marketed U.S. drug names (proprietary and established) due to similarity in visual appearance with handwritten prescriptions or verbal pronunciation of the drug name. The studies employ a total of 123 healthcare professionals (pharmacists, physicians, and nurses), and attempts to simulate the prescription ordering process. The results are used by the Safety Evaluator to identify any orthographic or phonetic vulnerability of the proposed name to be misinterpreted by healthcare practitioners.

In order to evaluate the potential for misinterpretation of Nexterone in handwriting and verbal communication of the name, two inpatient medication orders are written, each consisting of a combination of marketed and unapproved drug products, including the proposed name. These prescriptions are optically scanned and one medication order is delivered to a random sample of 123 participating health professionals via e-mail. In addition, a verbal inpatient medication order is recorded on voice mail. The voice mail messages are then sent to a random sample of the participating health professionals for their interpretations and review. After receiving either the written or verbal prescription orders, the participants send their interpretations of the orders via e-mail to the medication error staff.

Figure 1. Nexterone IV Study (conducted on March 22, 2008)

HANDWRITTEN MEDICATION ORDERS	VERBAL MEDICATION ORDER
<p><u>Inpatient Medication Order #1 :</u></p> 	<p>Nexterone</p> <hr/>
<p><u>Inpatient Medication Order #2 :</u></p> 	

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2.1.3 External Proprietary Name Risk Assessment

For this product, the Applicant submitted an independent risk assessment of the proposed proprietary name conducted by a consulting firm. The medication error prevention staff conducts an independent analysis and evaluation of the data provided, and responds to the overall findings of the assessment. When the external proprietary name risk assessment identifies potentially confusing names that were not captured in the medication error prevention

staff medication error prevention staff's database searches or in the Expert Panel Discussion, these names are included in the Safety Evaluator's Risk Assessment and analyzed independently by the Safety Evaluator to determine if the potentially confusing name could lead to medication errors in usual practice settings.

After the Safety Evaluator has determined the overall risk assessment of the proposed name, the Safety Evaluator compares the findings of their overall risk assessment with the findings of the proprietary name risk assessment submitted by the Applicant. The Safety Evaluator then determines whether the medication error prevention staff's risk assessment concurs or differs with the findings. When the proprietary name risk assessments differ, the medication error prevention staff provides a detailed explanation of these differences.

2.1.4 Safety Evaluator Risk Assessment of the Proposed Proprietary Name

Based on the criteria set forth in Section 2.1.1, the Safety Evaluator Risk Assessment applies their individual expertise gained from evaluating medication errors reported to FDA to conduct a Failure Modes and Effects Analysis and provide an overall risk of name confusion. Failure Mode and Effects Analysis (FMEA) is a systematic tool for evaluating a process and identifying where and how it might fail.⁶ When applying FMEA to assess the risk of a proposed proprietary name, the medication error prevention staff seeks to evaluate the potential for a proposed name to be confused with another drug name as a result of the name confusion and cause errors to occur in the medication use system. FMEA capitalizes on the predictable and preventable nature of medication errors associated with drug name confusion. FMEA allows the Agency to identify the potential for medication errors due to look- or sound-alike drug names prior to approval, where actions to overcome these issues are easier and more effective than remedies available in the post-approval phase.

In order to perform an FMEA of the proposed name, the Safety Evaluator must analyze the use of the product at all points in the medication use system. Because the proposed product is not yet marketed, the Safety Evaluator anticipates the use of the product in the usual practice settings by considering the clinical and product characteristics listed in Appendix A. The Safety Evaluator then analyzes the proposed proprietary name in the context of the usual practice setting and works to identify potential failure modes and the effects associated with the failure modes.

In the initial stage of the Risk Assessment, the Safety Evaluator compares the proposed proprietary name to all of the names gathered from the above searches, expert panel evaluation, and studies, and identifies potential failure modes by asking: "Is the name Nexterone convincingly similar to another drug name, which may cause practitioners to become confused at any point in the usual practice setting?" An affirmative answer indicates a failure mode and represents a potential for Nexterone to be confused with another proprietary or established drug name because of look- or sound-alike similarity. If the answer to the question is no, the Safety Evaluator is not convinced that the names possess similarity that would cause confusion at any point in the medication use system and the name is eliminated from further review.

In the second stage of the Risk Assessment, all potential failure modes are evaluated to determine the likely *effect* of the drug name confusion, by asking "Could the confusion of the drug names conceivably result in medication errors in the usual practice setting?" The answer to

⁶ Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

this question is a central component of the Safety Evaluator's overall risk assessment of the proprietary name. If the Safety Evaluator determines through FMEA that the name similarity would ultimately not be a source of medication errors in the usual practice setting, the name is eliminated from further analysis. However, if the Safety Evaluator determines through FMEA that the name similarity could ultimately cause medication errors in the usual practice setting, the Safety Evaluator will then recommend that an alternate proprietary name be used. In rare instances, the FMEA findings may provide other risk-reduction strategies, such as product reformulation to avoid an overlap in strength or an alternate modifier designation may be recommended as a means of reducing the risk of medication errors resulting from drug name confusion.

The medication error prevention staff will object to the use of proposed proprietary name when the one or more of the following conditions are identified in the Safety Evaluator's Risk Assessment:

1. DDMAC finds the proposed proprietary name misleading from a promotional perspective, and the review Division concurs with DDMAC's findings. The Federal Food, Drug, and Cosmetic Act provides that labeling or advertising can misbrand a product if misleading representations are made or suggested by statement, word, design, device, or any combination thereof, whether through a trade name or otherwise. [21 U.S.C 321(n); see also 21 U.S.C. 352(a) & (n)].
2. The medication error prevention staff identifies that the proposed proprietary name is misleading because of similarity in spelling or pronunciation to another proprietary or established name of a different drug or ingredient [CFR 201.10.(C)(5)].
3. FMEA identifies potential for confusion between the proposed proprietary name and other proprietary or established drug names, and demonstrates that medication errors are likely to result from the drug name confusion under the conditions of usual clinical practice.
4. The proposed proprietary name contains an USAN stem, particularly in a manner that is contradictory to the USAN Council's definition.
5. The medication error prevention staff identifies a potential source of medication error within the proposed proprietary name. The proprietary name may be misleading, or inadvertently introduce ambiguity and confusion that leads to errors. Such errors may not necessarily involve confusion between the proposed drug and another drug product.

In the event that the medication error prevention staff objects to the use of the proposed proprietary name, based upon the potential for confusion with another proposed (but not yet approved) proprietary name, we will provide a contingency objection based on the date of approval: whichever product is awarded approval first has the right to the use the name, while we will recommend that the second product to reach approval seek an alternative name.

If none of these conditions are met, then the medication error prevention staff will not object to the use of the proprietary name. If any of these conditions are met, then our Division will object to the use of the proprietary name. The threshold set for objection to the proposed proprietary name may seem low to the Applicant; however, the safety concerns set forth in criteria 1 through 5 are supported either by FDA Regulation or by external healthcare authorities, including the Institute of Medicine, the World Health Organization, the Joint Commission, and the Institute for

Safe Medication Practices, that have examined medication errors resulting from look- or sound-alike drug names and called for Regulatory Authorities to address the issue prior to approval.

Furthermore, the medication error prevention staff contends that the threshold set for the Proprietary Name Risk Assessment is reasonable because proprietary drug name confusion is a predictable and preventable source of medication error that, in many instances, can be identified and remedied prior to approval to avoid patient harm.

Additionally, post-marketing experience has demonstrated that medication errors resulting from drug name confusion are notoriously difficult to remedy post-approval. Educational efforts and so on are low-leverage strategies that have proven to have limited effectiveness at alleviating the medication errors involving drug name confusion. Higher-leverage strategies, such as drug name changes, have been undertaken in the past; but at great financial cost to the Applicant, and at the expense of the public welfare, not to mention the Agency's credibility as the authority responsible for the approving the error-prone proprietary name. Moreover, even after Applicant's have changed a product's proprietary name in the post-approval phase, it is difficult to eradicate the original proprietary name from practitioner's vocabulary, and as such, the Agency has continued to receive reports of drug name confusion long after a name change in some instances. Therefore, the medication error prevention staff believes that post-approval efforts at reducing name confusion errors should be reserved for those cases in which the potential for name confusion could not be predicted prior to approval (see limitations of the process).

If the medication error prevention staff objects to a proposed proprietary name on the basis that drug name confusion could lead to medication errors, the FMEA process is used to identify strategies to reduce the risk of medication errors. Our Division is likely to recommend that the Applicant select an alternative proprietary name and submit the alternate name to the Agency for the medication error prevention staff to review. However, in rare instances FMEA may identify plausible strategies that could reduce the risk of medication error of the currently proposed name, and so we may be able to provide the Applicant with recommendations that reduce or eliminate the potential for error would render the proposed name acceptable.

2.2 LABEL AND LABELING RISK ASSESSMENT

The label and labeling of a drug product are the primary means by which practitioners and patients (depending on configuration) interact with the pharmaceutical product. The container labels and carton labeling communicate critical information including proprietary and established name, strength, form, container quantity, expiration, and so on. The insert labeling is intended to communicate to practitioners all information relevant to the approved uses of the drug, including the correct dosing and administration.

Given the critical role that the label and labeling has in the safe use of drug products, it is not surprising that 33 percent of medication errors reported to the USP-ISMP Medication Error Reporting Program may be attributed to the packaging and labeling of drug products, including 30 percent of fatal errors.⁷

⁷ Institute of Medicine. Preventing Medication Errors. The National Academies Press: Washington DC. 2006. p275.

Because the medication error prevention staff analyze reported misuse of drugs, we are able to use this experience to identify potential errors with all medication similarly packaged, labeled or prescribed. Our Division uses FMEA and the principles of human factors to identify potential sources of error with the proposed product labels and insert labeling, and provided recommendations that aim at reducing the risk of medication errors.

2.2.1 Labels, Labeling, and Packaging

For this product the Applicant submitted on February 22, 2008 the following labels and labeling for medication error prevention staff review (see Appendix F, G, and H for images):

- Container Label: _____ b(4)
- Blister Label: 150 mg/3 mL syringe
- Carton Labeling: _____ 150 mg/3 mL, 450 mg/9 mL, and 900 mg/18 mL vials b(4)
- Prescribing Information (no image)
- A sample of an empty _____ syringe without _____ which will be used as the prefilled syringe product was provided by the Applicant upon request of this Division. (no image) b(4)

2.2.2 AERS Database Search

Because Amiodarone HCl injection products are currently marketed, the medication error prevention staff conducted a search of the Adverse Events Reporting System (AERS) database to determine if medication errors related these products have been reported. The safety evaluator searched the database using the following criteria: the High Level Group Term (HLGT) "Medication Errors" and Preferred Term (PT) "Pharmaceutical Product Complaint," and the Active Ingredients "Amiodarone" and "Amiodarone HCl." The search included limiting the Route of Administration to "Intravenous," "Intravenous Drip," "Intravenous Bolus," "Parenteral," "Other" and "Unknown" in an effort to obtain relevant cases. The search was further limited to January 1, 2002 and June 30, 2008 to obtain the most recent cases.

The cases were manually reviewed to determine if a medication error occurred. If an error occurred, the staff reviewed the case to determine if the root cause could be associated with the nomenclature of the 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 (e.g. errors involving a different dosage form) were excluded from further analysis. The cases that did describe a medication error were categorized by type of error. We reviewed the cases within each category to identify factors that contributed to the medication errors.

3 RESULTS

3.1 PROPRIETARY NAME RISK ASSESSMENT

3.1.1 Database and Information Sources

The database search identified 21 names as having some similarity to the name Nexterone.

Ten of the 21 names thought to look like Nexterone include: Dextrose, Malarone, Masterone, Metolazone, Mexiletine, Nectarine, Neutrexin, Nexavar, Nexivir, and Novantrone. Five names (Estrone, Esterone, Listerine, Maxidone, and Progesterone) were thought to sound like Nexterone. Six additional names (Mesterolone, Mestimon, Naloxone, Naltrexone, Nexium and Nicotrol) were thought to look and sound similar to Nexterone.

A search of the United States Adopted Names (USAN) stem list on July 24, 2008 identified no USAN stems included in the root name, Nexterone.

3.1.2 Expert Panel Discussion

The Expert Panel reviewed the pool of names identified by the medication error prevention staff (see section 3.1.1. above), and noted no additional names thought to have orthographic or phonetic similarity to Nexterone. The panel did raise the concern the product may be confused as an anabolic steroid because the USAN stem for these steroids is '-ster-' and this sound similar to the third syllable in the proposed name.

DDMAC had no concerns regarding the proposed name from a promotional perspective, and did not offer any additional comments relating to the proposed name.

3.1.3 FDA Prescription Analysis Studies

A total of 26 practitioners responded, but none of the responses overlapped with any existing or proposed drug names. About half of the participants (n=14) interpreted the name correctly as "Nexterone," with correct interpretation occurring more frequently in the written studies. The remainder of the responses misinterpreted the drug name. The misinterpretations occurring in the phonetic prescription study resulted from one respondent who added the word, "for," as part of the product name, Fornextorin, when the speaker stated, "a prescription for Nexterone," and with the vowels in Nexterone reported as 'o' instead of the second letter 'e' by one respondent, and 'i' instead of 'o' by two respondents. Also, one respondent to the phonetic prescription study ended the name with an 'm' instead of the 'ne.'

In the written prescription studies, four respondents to medication order #1 misinterpreted the lower case 'n' as the letter 'u.' The letter 'x' was misinterpreted as the letter 'p' by four respondents, and as 'so' by one respondent. Other misinterpretations to the written samples involved the final letter 'e' being misinterpreted as 's' by two respondents, as 'l' by one respondent and omitted entirely by one respondent.

We note the CDER Prescription Study omitted the modifier IV. See Appendix A for the complete listing of interpretations from the verbal and written prescription studies.

3.1.4 External Name Studies

In the proposed name risk assessment submitted by the Applicant, Med-E.R.R.S. identified and evaluated a total of two drug names, Nexium and Neptazane. These were thought to have some potential for confusion with the name, Nexterone.

One of the names, Neptazane, was not previously identified in any of the medication error prevention staff searches, the Expert Panel Discussion, or FDA prescription studies. Neptazane was identified as looking similar to Nexterone.

We note Med-E.R.R.S did not include the modifier in the assessment of the proposed name.

3.1.5 Safety Evaluator Risk Assessment

Independent searches by the primary Safety Evaluator identified an additional name, Metaxalone, thought to look similar to Nexterone and represent a potential source of drug name confusion. As such, a total of 23 names were analyzed to determine if the drug names could be confused with Nexterone and if the drug name confusion would likely result in a medication error.

Two of the 23 identified names were determined to lack sufficient orthographic and/or phonetic similarity to Nexterone to present a risk of confusion. These names are Listerine and Nicotrol. Thus, they were not evaluated further.

All of the remaining 21 names were determined to have some orthographic and/or phonetic similarity to Nexterone, and thus determined to present some risk of confusion. Failure mode and effect analysis was then applied to determine if the potential name, Nexterone, could potentially be confused with any of the 21 names and lead to medication errors. However, three names were eliminated from this analysis Nexivir, Nectarine, and Mesterolone. Nexivir could not be located in the databases searched by safety evaluators (See Section 6). Nectarine was identified as a flavoring or fragrance added to products but not as a medication. Mesterolone is an anabolic steroid only available in foreign countries. Thus, 18 names were further evaluated.

The analysis determined that the names similarity between Nexterone and the identified names was unlikely to result in medication errors for the remaining 18 names as described in Appendix C through E.

3.2 LABEL AND LABELING RISK ASSESSMENT

3.2.1 Labels and Labeling

Upon review of the labels and labeling, the Division of Medication Error Prevention and Analysis noted several vulnerabilities that may contribute to medication errors.

The route of administration appears below the established name throughout the labels and labeling. In addition, the labels and labeling lack the dosage form as part of the established name.

The total drug content on the syringe and vials lacks prominence when compared to the 50 mg/mL product concentration on the container label and carton labeling.

The fill volume rather than the net strength/quantity of each vial and syringe appear in Section 16, HOW SUPPLIED/STORAGE AND HANDLING, of the insert labeling. In addition, the fill

size of each vial and the syringe (5 mL, 10 mL, 20 mL, and 5 mL, respectively) appears next to the fill volume in this section.

The abbreviation, IV, is used to describe the intravenous route of administration _____ on the container and blister labels as well as the carton labeling for the _____

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3.2.2 AERS Database

The search yielded a total of 40 cases (n=40) on July 24, 2008. The following cases were excluded as irrelevant: Seven cases (n=7) were adverse events with no medication error identified, six cases (n=6) were medication errors related to oral Amiodarone, and two cases (n=2) listed intravenous Amiodarone as a concurrent medication which was not involved in the medication error.

The remaining twenty-five cases (n=25) involve medication errors related to the use of intravenous Amiodarone HCl. In six of these cases (n=6), a fatal outcome was reported as a result of the medication error.

- Eleven cases (n=11) resulted from mixing the Amiodarone in 0.9% sodium chloride solution. The death of the patient was the reported outcome of the medication error in two cases (n=2). We note all eleven cases occurred in foreign countries. In addition, upon review of the narratives in these cases, the safety evaluator could identify no causes or contributing factors for these errors due to the limited information in the narrative.
- Seven cases (n=7) resulted from a wrong rate of infusion leading to the medication being delivered too fast. All seven cases involved the continuous infusion of Amiodarone rather than the initial ten minute bolus dose. All seven cases resulted in adverse outcomes including death (n=3), hypotension and bradycardia (n=3), and unspecified EKG changes (n=1). A contributing factor identified in one of the death cases was "Confusion on the ward." Wrong rate of administration errors resulted from a prescribing error in one case, and the pharmacy label printed with the wrong rate of infusion in another case. Both of these cases resulted in nonfatal outcomes.
- Three cases (n=3) resulted from improper dosing resulting in an overdose. Two cases (n=2), including the only case involving a pediatric patient, resulted in the patients going into shock, and one case (n=1) resulted in hypotension and bradycardia. However, upon review of the narratives in these cases, the safety evaluator identified no causes or contributing factors for these errors.
- Two cases (n=2) resulted in wrong drug medication errors. The patient in one case (n=1) died after receiving Amiodarone in error, however, the narrative of this case did not identify the medication the patient was intended to receive. The other case resulted from confusion of Cardene IV as Cordarone IV due to the similarities of these proprietary names. The latter error was caught prior to reaching the patient.
- Two cases (n=2) resulted in drug interactions between Amiodarone and other medications. One case involved the concurrent use of fentanyl with intravenous Amiodarone leading to competition for CYP3A4 enzymes reportedly resulting in apnea and bradycardia which responded to medical intervention. One case resulted from the

addition of enoxaparin sodium to an Amiodarone HCl infusion bag resulting in precipitation.

4 DISCUSSION

4.1 PROPRIETARY NAME RISK ASSESSMENT

Our analysis indicates that the proposed name, Nexterone IV, is vulnerable to name confusion because of the inclusion of the modifier IV as part of the proprietary name. The root name, Nexterone, evaluated alone was not vulnerable. This root name finding was consistent with and supported by an independent risk assessment of the proprietary name submitted by the Applicant as Med-E.R.R.S did not include the modifier, 'IV' in their assessment. The Division of Medication Error Prevention and Analysis raises concerns over including the modifier, IV, as part of the proprietary name.

4.1.1 Use of a Modifier

The Applicant proposes to add the modifier 'IV' following the proposed name, Nexterone as part of the proprietary name. Suffixes or modifiers are typically added to distinguish a proposed formulation from something currently marketed. We acknowledge the abbreviation 'IV' is generally understood as standing for intravenous and that intravenous is the intended route of administration for this product. We also acknowledge that other proprietary names utilize this modifier including one of the reference listed drugs, Cordarone I.V. However, Cordarone I.V. has been discontinued, and the application was withdrawn, April 10, 2007, by its sponsor. The proposed proprietary name, Nexterone, is proposed for no other Amiodarone HCl products nor are there any currently marketed Nexterone products. Thus, this product does not require additional differentiation. Additionally, the proposed modifier duplicates the route of administration on the product labels and labeling.

Additionally, post-marketing surveillance demonstrates that other abbreviations are often misinterpreted as 'IV' including the Roman numeral four⁸ and IU meaning international units. FDA launched a campaign on June 14, 2006, warning health care providers and consumers not to use error-prone abbreviations, acronyms, or symbols. Due to the continuing confusion between 'IV' and other abbreviations, the Division of Medication Error Prevention and Analysis raises concern with the inclusion of the abbreviation, 'IV,' as part of a proprietary name or in product labels or labeling.

The findings of the Proprietary Name Risk Assessment are based upon current understanding of factors that contribute to medication errors involving name confusion. Although we believe the findings of the Risk Assessment to be robust, our findings do have limitations. First, because our assessment involves a limited number of practitioners, it is possible that the analysis did not identify a potentially confusing name. Also, there is some possibility that our Risk Assessment

⁸ Institute of Safe Medication Practices, ISMP Medication Safety Alert, 7 (13), June 26, 2002.

failed to consider a circumstance in which confusion could arise. However, the medication error prevention staff believes that these limitations are sufficiently minimized by the use of an Expert Panel, the CDER Prescription Studies that involved 123 CDER practitioners, and, in this case, the data submitted by the Applicant from an independent proprietary name risk assessment firm, which included the responses of frontline practitioners.

However, our risk assessment also faces limitations beyond the control of the Agency. First, our risk assessment is based on current health care practices and drug product characteristics, future changes to either could increase the vulnerability of the proposed name to confusion. Since these changes cannot be predicted for or accounted by the current Proprietary Name Risk Assessment process, such changes limit our findings. To help counterbalance this impact, the medication error prevention staff recommends that the proprietary name be re-submitted for review if approval of the product is delayed beyond 90 days.

4.2 LABELS AND LABELING RISK ASSESSMENT

The results of the Label and Labeling Risk Assessment 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 medication error prevention staff believes the risks we have identified can be addressed and mitigated prior to drug approval, and provides recommendations in Section 5.2 that aim at reducing the risk of medication errors.

4.2.1 Established Name

Upon review of the labels and labeling, we noted the established name lacks the product's dosage form. A complete established name should include the dosage form of the product (e.g., Amiodarone HCl Injection). Additionally, the United States Pharmacopeia lists its drug monographs including standard nomenclature: the drug name, dosage form, and the route of administration unless generally understood from the dosage form.⁹ Although Nexterone is not a monograph product, healthcare providers are accustomed to reading established names in this presentation.

4.2.2 Total Drug Content versus Drug Concentration

The total drug content of the products (150 mg/3 mL, 450 mg/9 mL, and 900 mg/18 mL) appears in the same font size as the product concentration (50 mg/mL). We believe this presentation makes it difficult for healthcare providers to distinguish between these two different but important pieces of information. Post-marketing surveillance of medication errors has demonstrated that the product concentration has been mistaken as a product's total drug content and resulted in overdoses of medication. In fact, the United States Pharmacopeia states "the strength per total volume should be the primary and prominent expression on the principal display panel of the label, followed in close proximity by strength per mL enclosed by parentheses."¹⁰ We acknowledge the total drug content appears in a bolded font compared to the drug concentration. However, it is our opinion that the total drug content could be more prominently presented on the container and blister labels and carton labeling than the drug

⁹ USP/NF, General Chapter 1121, Nomenclature; viewed at www.uspnf.com/uspnf/pub/ on September 26, 2008.

¹⁰ USP/NF, General Chapter 1, Injections; viewed at www.uspnf.com/uspnf/pub/ on September 26, 2008.

concentration to reduce the potential for selecting the wrong strength product when healthcare providers prepare doses of Nexterone for administration.

4.2.3 *Use of the Abbreviation, IV*

The route of administration on the labels and labeling for the Nexterone prefilled syringe includes the abbreviation, _____ As discussed previously in section 4.1.1, this use of this abbreviation contributes to confusion with other abbreviations which lead to medication errors.

b(4)

4.2.4 *Vial Size Presentation*

The insert labeling Section 3, DOSAGE FORMS AND STRENGTHS and Section 16, HOW SUPPLIED/STORAGE AND HANDLING include the volume of solution contained in each vial or syringe as well as the fill volume or capacity of each container. We acknowledge Nexterone injection will only be available in one drug concentration (50 mg/mL). However, the net quantity of Amiodarone HCl in each vial and the syringe is lacking in this section of the insert. The volume of solution may be used by healthcare providers to calculate the net quantity of Amiodarone HCl in each vial, but this section also lacks the drug concentration, 50 mg/mL. It is our opinion that listing the vial and syringe size is confusing and therefore a potential source of medication error. Therefore, we believe the inclusion of the total drug content of Amiodarone of each vial and removal of the fill volume of each vial and the syringe in Section 16 will decrease the potential for healthcare providers to make calculation errors in determining which size product to select.

4.2.5 *Medication Errors Involving Intravenous Amiodarone HCl*

The 25 evaluated medication error cases from the AERS database involving intravenous Amiodarone hydrochloride provide little detail for the safety evaluator to identify root causes or contributing factors. Other than the case of name confusion between Cardene IV and Cordarone IV, the cases that provided details involved systemic problems within the specific patient care settings.

However, the most common identified errors of mixing the infusion with the wrong base solution, sodium chloride, and administering the infusion of Amiodarone too quickly may be impacted by the introduction to the marketplace of Nexterone IV. _____

b(4)

_____. Due to healthcare practitioner familiarity with Amiodarone HCl injection, it is likely that practitioners may intuitively think these existing products and Nexterone are equivalent. Comparing the labels and labeling for Nexterone IV to Amiodarone HCl injection, our analysis identified differences in the use of these products that could lead to medication errors.

4.2.5.1 _____

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4.2.5.2

5 CONCLUSIONS AND RECOMMENDATIONS

The Proprietary Name Risk Assessment findings indicate that the proposed name, Nexterone IV, is not acceptable. The basis of this objection is the inclusion of 'IV' as part of the name. However, we have concerns with the use of the modifier, IV, as part of the proprietary name and recommend it not be included because Nexterone IV will be available only as an injection for intravenous use and other medical abbreviations are often misinterpreted as 'IV' including the Roman numeral four and 'IU' meaning international units. As such, if the IV was removed, the Division of Medication Error Prevention and Analysis would have no objection to the use of Nexterone. This finding was consistent with and supported by an independent risk assessment of the proprietary name submitted by the Applicant.

However, if any of the proposed product characteristics as stated in this review are altered prior to approval of the product, the medication error prevention staff rescinds this Risk Assessment finding, and recommends that the name be resubmitted for review. If the event that our Risk Assessment finding is rescinded, the evaluation of the name on resubmission is independent of the previous Risk Assessment, and as such, the conclusions on re-review of the name are subject to change. Additionally, if the product approval is delayed beyond 90 day from the date of this review, the proposed name must be resubmitted for evaluation.

The Label and Labeling Risk Assessment findings indicate that the presentation of information and design of the proposed carton and container labels introduces vulnerability to confusion that could lead to medication errors. The medication error prevention staff believes the risks we have identified can be addressed and mitigated prior to drug approval, and provides recommendations in Section 5.2 that aim at reducing the risk of medication errors.

5.1 COMMENTS TO THE DIVISION

The Division of Medication Error Prevention and Analysis recommends that the Division consult Richard Lostritto, Chair of the CDER Labeling and Nomenclature Committee (LNC), Deborah Desmer (The Project Manager Assigned to the LNC) and the assigned ONDQA Chemist regarding the lack of the dosage form as part of the established name for Nexterone.

We would appreciate feedback of the final outcome of this review. We would be willing to meet with the Division for further discussion, if needed. Please copy the Division of Medication Error Prevention and Analysis on any communication to the Applicant with regard to this review. If you have further questions or need clarifications, please contact Sean Bradley, project manager, at 301-796-1332.

5.2 COMMENTS TO THE APPLICANT

5.2.1 Proprietary Name

The Division of Medication Error Prevention and Analysis (DMEPA) objects to the inclusion of the modifier, 'IV,' as part of the proposed proprietary name. However, their analysis indicates the root name, Nexterone, is not vulnerable to name confusion leading to medication errors. As such, they do not object to the proposed proprietary name, Nexterone, for this product.

5.2.1.1 Use of a Modifier

DMEPA notes modifiers are utilized to distinguish differing dosage formulations that have the same root proprietary name (e.g., ER for extended-release dosage forms). DMEPA acknowledges the abbreviation 'IV' is generally understood by healthcare practitioners as representing the intravenous route of administration and that intravenous is the intended route of administration for this product. However, because Nexterone IV will be available only as an injection for intravenous use, the modifier simply duplicates route of administration information on the product labels and labeling. Adding further concern is the fact other medical abbreviations are often misinterpreted as 'IV' including the Roman numeral four and 'IU' meaning international units leading to medication errors. DMEPA also acknowledges that other proprietary names utilize the modifier, IV, including one of the reference listed drugs, Cordarone I.V. However, Cordarone I.V. has been discontinued and the application was withdrawn, April 10, 2007, by its sponsor. The proposed proprietary name, Nexterone, is not proposed for other Amiodarone HCl products or currently marketed products and thus does not require additional differentiation.

5.2.2 Labels, Labeling, and Packaging

5.2.2.1 ⌞

1.

2. ⌞

b(4)

5.2.2.2 Blister Label

1. Increase the prominence of the total drug content (e.g. 150 mg/3 mL) of each size compared to the product concentration (50 mg/mL).
2. Remove the abbreviation 'IV' from the route of administration and replace with "intravenous" or "intravenously," as appropriate.

5.2.2.3 Carton Labeling (150 mg/3 mL, 450 mg/9 mL, and 900 mg/18 mL vials and _____)

b(4)

1. Increase the prominence of the total drug content (e.g. 150 mg/3 mL) of each size compared to the product concentration (50 mg/mL).
2. On the prefilled syringe _____ remove the abbreviation 'IV' from the route of administration and replace with "intravenous" or "intravenously," as appropriate.

5.2.2.4 Insert Labeling

1. Replace the solution volume of each vial or syringe in Section 3, DOSAGE FORMS AND STRENGTHS and Section 16, HOW SUPPLIED/STORAGE AND HANDLING, with an expression the total drug content (e.g. change 3 mL to 150 mg/3 mL).
2. Delete the fill volume for each vial and syringe in Section 16.

6 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. *Micromedex Integrated Index (<http://csi.micromedex.com>)*

Contains a variety of databases covering pharmacology, therapeutics, toxicology and diagnostics.

3. *Phonetic and Orthographic Computer Analysis (POCA)*

As part of the name similarity assessment, proposed names are evaluated via a phonetic/orthographic algorithm. The proposed proprietary name is converted into its phonemic representation before it runs through the phonetic algorithm. Likewise, an orthographic algorithm exists which operates in a similar fashion. This is a database which was created for the medication error prevention staff, FDA.

4. Drug Facts and Comparisons, online version, St. Louis, MO
(<http://factsandcomparisons.com>)

Drug Facts and Comparisons is a compendium organized by therapeutic Course; contains monographs on prescription and OTC drugs, with charts comparing similar products.

5. AMF Decision Support System [DSS]

DSS is a government database used to track individual submissions and assignments in review divisions.

6. Division of Medication Error Prevention proprietary name consultation requests

This is a list of proposed and pending names that is generated by the medication error prevention staff from the Access database/tracking system.

7. Drugs@FDA (<http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm>)

Drugs@FDA contains most of the drug products approved since 1939. The majority of labels, approval letters, reviews, and other information are available for drug products approved from 1998 to the present. Drugs@FDA contains official information about FDA approved brand name and generic drugs and therapeutic biological products; prescription and over-the-counter human drugs and therapeutic biologicals, discontinued drugs and "Chemical Type 6" approvals.

8. Electronic online version of the FDA Orange Book
(<http://www.fda.gov/cder/ob/default.htm>)

Provides a compilation of approved drug products with therapeutic equivalence evaluations.

9. US Patent and Trademark Office location <http://www.uspto.gov>.

Provides information regarding patent and trademarks.

10. Clinical Pharmacology Online (www.clinicalpharmacology-ip.com)

Contains full monographs for the most common drugs in clinical use, plus mini monographs covering investigational, less common, combination, nutraceutical and nutritional products. Provides a keyword search engine.

11. Data provided by Thomson & Thomson's SAEGIS™ Online Service, available at
www.thomson-thomson.com

The Pharma In-Use Search database contains over 400,000 unique pharmaceutical trademarks and tradenames that are used in about 50 countries worldwide. The data is provided under license by IMS HEALTH.

12. Natural Medicines Comprehensive Databases (www.naturaldatabase.com)

Contains up-to-date clinical data on the natural medicines, herbal medicines, and dietary supplements used in the western world.

13. Stat!Ref (www.statref.com)

Contains full-text information from approximately 30 texts. Includes tables and references. Among the database titles are: Handbook of Adverse Drug Interactions, Rudolphs Pediatrics, Basic Clinical Pharmacology and Dictionary of Medical Acronyms Abbreviations.

14. **USAN Stems** (<http://www.ama-assn.org/ama/pub/category/4782.html>)

List contains all the recognized USAN stems.

15. **Red Book Pharmacy's Fundamental Reference**

Contains prices and product information for prescription, over-the-counter drugs, medical devices, and accessories.

16. **Lexi-Comp** (www.lexi.com)

A web-based searchable version of the Drug Information Handbook.

17. **Medical Abbreviations Book**

Contains commonly used medical abbreviations and their definitions.

APPENDICES

Appendix A:

The medication error prevention staff considers the spelling of the name, pronunciation of the name when spoken, and appearance of the name when scripted. The medication error prevention staff also compares the spelling of the proposed proprietary name with the proprietary and established name of existing and proposed drug products because similarly spelled names may have greater likelihood to sound similar to one another when spoken or look similar to one another when scripted. The medication error prevention staff also examines the orthographic appearance of the proposed name using a number of different handwriting samples. Handwritten communication of drug names has a long-standing association with drug name confusion. Handwriting can cause similarly *and* dissimilarly spelled drug name pairs to appear very similar to one another and the similar appearance of drug names when scripted has lead to medication errors. The medication error prevention staff applies their expertise gained from root-cause analysis of such medication errors to identify sources of ambiguity within the name that could be introduced when scripting (i.e. "T" may look like "F," lower case 'a' looks like a lower case 'u,' etc), along with other orthographic attributes that determine the overall appearance of the drug name when scripted (see detail in Table 1 below). Additionally, since verbal communication of medication names is common in clinical settings, the medication error prevention staff compares the pronunciation of the proposed proprietary name with the pronunciation of other drug names. If provided, the medication error prevention staff will consider the Applicant's intended pronunciation of the proprietary name. However, because the Applicant has little control over how the name will be spoken in practice, the medication error prevention staff also considers a variety of pronunciations that could occur in the English language.

Table 1. Criteria used to identify drug names that look- or sound-similar to a proposed proprietary name

Type of similarity	Considerations when searching the databases		
	Potential causes of drug name similarity	Attributes examined to identify similar drug names	Potential Effects
Look-alike	Similar spelling	Identical prefix Identical infix Identical suffix Length of the name Overlapping product characteristics	<ul style="list-style-type: none"> Names may appear similar in print or electronic media and lead to drug name confusion in printed or electronic communication Names may look similar when scripted and lead to drug name confusion in written communication
	Orthographic similarity	Similar spelling Length of the name Upstrokes Downstrokes	<ul style="list-style-type: none"> Names may look similar when scripted, and lead to drug name confusion in written communication

		Cross-strokes Dotted letters Ambiguity introduced by scripting letters Overlapping product characteristics	
Sound-alike	Phonetic similarity	Identical prefix Identical infix Identical suffix Number of syllables Stresses Placement of vowel sounds Placement of consonant sounds Overlapping product characteristics	<ul style="list-style-type: none"> Names may sound similar when pronounced and lead to drug name confusion in verbal communication

Appendix B:

CDER Prescription Study Responses

Inpatient Medication Order #1	Voice Prescription	Inpatient Medication Order #2
Nexteroul	Nexterone	formextorin
Nexterous	Nexterone	Nexterone
Nexterone	Nesotrone	Nexterim
Nexterone	NEXTERON	
Nexterone	Nepterone	
Nexterous	Nexterone	
Nexteroue	Nepterone	
Nexterone	Nepterone	
	Nexterone	
	Nexterone	

	Nexterone	
	Nepterone	

Appendix C: Proprietary names of products no longer marketed with no generic equivalents

Proprietary Name	Similarity to Nexterone	Year removed from market
Esterone	Sound	Unknown date of withdrawal
Masterone	Look	Anabolic steroid discontinued in 1995
Neutrexin	Look	2007 (not withdrawn for safety reasons)

Appendix D: Products with no numerical overlap in strength and dose.

Product name with potential for confusion	Similarity to Proposed Proprietary Name	Strength	Usual Dose (if applicable)
Nexterone IV (Amiodarone HCl) injection		Strengths: 150 mg/3 mL, 450 mg/9 mL, and 900 mg/18 mL	Usual dose: 150 mg intravenously once then infuse 1 mg/minute intravenously for 6 hours followed by 0.5 mg/minute thereafter.
Dextrose	Look	5%, 10%, 20%, 50%, 70%	Dose varies based on use and patient needs.
Estrone	Sound	20 mg/10 mL and 50 mg/10 mL	5 to 10 mg IM daily.
Malarone	Look	250 mg/100 mg	Prevention of malaria: one tablet by mouth daily Treatment: three tablets by mouth daily for three days.
Maxidone	Sound	10 mg/750 mg	One tablet by mouth every four to six hours as needed.
Mestinon	Look and Sound	60 mg tablet, 60 mg/5 ml oral liquid, 180 mg extend release tablet, and 10 mg/2 mL injection	Three tablets (180 mg) by mouth three times daily. One to three extended by mouth daily.

Metaxalone	Look	800 mg	One tablet by mouth three to four times daily.
Metolazone	Look	2.5 mg, 5 mg, and 10 mg	One tablet (5 mg) by mouth daily.
Naloxone	Look and Sound	0.4 mg/mL and 1 mg/mL	0.4 mg intravenously one time. Dose may vary based on patient and indication.
Naltrexone	Look and Sound	50 mg tablet and 380 mg for injection kit	380 mg (one kit) intramuscularly every four weeks. One tablet by mouth daily.
Neptazane (discontinued, but generic equivalents available)	Look (Med E.R.R.S.)	25 mg and 50 mg	One to two tablets (50-100 mg) by mouth twice to three times daily.
Nexavar	Look	200 mg	Two tablets (400 mg) by mouth twice daily.
Nexium or Nexium IV	Look and Sound	20 mg and 40 mg capsules 40 mg vials	One capsule by mouth daily. 40 mg intravenously daily.
Novantrone	Look	20 mg/10 mL, 25 mg/ 12.5 mL and 30 mg/15 mL	12 mg/m ² intravenously, frequency based on indication.
Progesterone	Sound	500 mg/10 ml injection in oil and 100 mg vaginal inserts	5-10 mg intramuscularly daily One insert intravaginally twice to three times daily.

Appendix E: Potential confusing name with numerical overlap in strength or dose

Failure Mode: Name confusion	Causes	Effects
Nexterone IV (Amiodarone HCl) injection	Strengths: 150 mg/3 mL, 450 mg/9 mL, and 900 mg/18 mL	Usual dose: 150 mg intravenously once then infuse 1 mg/minute intravenously for 6 hours followed by 0.5 mg/minute thereafter.
Mexiletine HCl (proprietary name Mexitil™) 150 mg, 200 mg, and 250 mg capsules	Orthographic similarity: The beginning three letters appear similar 'Mex' vs. 'Nex;' an upstroke is provided following the 'x' by 'l' vs. 't;' 'et' may appear similar to 'er' when scripted; and both end with the same two letters 'ne'	Orthographic differences in the names and the differing product characteristics reduce the risk of medication errors in the usual practice settings. <i>Rationale:</i> The orthographic differences stem from the Mexiletine contains two upstrokes compared to one in Nexterone. There is an additional letter 'i' falling between the 'x' and the 'l' providing some separation, and the letter 'i' before the final 'ne' differs from the 'o' in Nexterone. Mexiletine is available in three strengths. While these

	<p>Share a numerical strength. (150 mg)</p> <p>Similar indications (ventricular arrhythmias)</p>	<p>products overlap in one strength, the usual dose using the 150 mg strength of Mexiletine is 300 mg or two capsules.</p> <p>The routes of administration differ as well (oral vs. intravenous). Patients should receive Nexterone if they are unable to take Amiodarone orally. (or NPO)</p> <p>Nexterone is an intravenous bolus followed by a continuous infusion, while Mexiletine will have a frequency of every eight or twelve hours.</p>
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Appendix F: Container labels (not to scale)

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Appendix G: Blister label for prefilled syringes (150 mg/3 mL)

b(4)

Connected as set of four.

2 Page(s) Withheld

 Trade Secret / Confidential (b4)

✓ Draft Labeling (b4)

 Draft Labeling (b5)

 Deliberative Process (b5)

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