

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**21-780**

**PROPRIETARY NAME REVIEW(S)**

**CONSULTATION RESPONSE**

**DIVISION OF MEDICATION ERRORS AND TECHNICAL SUPPORT  
OFFICE OF DRUG SAFETY  
(DMETS; HFD-420)**

<b>DATE RECEIVED:</b> August 20, 2004	<b>DESIRED COMPLETION DATE:</b> November 15, 2004 <b>PDUFA DATE:</b> June 4, 2005	<b>ODS CONSULT #:</b> 04-0235
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**TO:** Norman Stockbridge, MD  
Acting Director, Division of Cardio-Renal Drug Products  
HFD-110

**THROUGH:** John David  
Project Manager, Division of Cardio-Renal Drug Products  
HFD-110

<b>PRODUCT NAME:</b> <del>                    </del> Primary Name) Nitro Mist (Secondary Name) (Nitroglycerin Aerosol) 0.4 mg	<b>NDA SPONSOR:</b> NovaDel Pharma, Inc.
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**NDA#:** 21-780

**SAFETY EVALUATOR:** Kristina C. Arnwine, PharmD

**RECOMMENDATIONS:**

1. DMETS has no objections to the use of the proprietary name, Nitro Mist. This is considered a tentative decision and the firm should be notified that this name with its associated labels and labeling must be re-evaluated approximately 90 days prior to the expected approval of the NDA. A re-review of the name prior to NDA approval will rule out any objections based upon approvals of other proprietary or established names from the signature date of this document.
2. DMETS recommends implementation of the label and labeling revisions outlined in section III of this review to minimize potential errors with the use of this product.
3. DDMAC finds the proprietary name, Nitro Mist, acceptable from a promotional perspective.
4. We recommend consulting Guiarag Poochikian, Acting Chair of the USAN council & LNC, for the proper designation of the established name.

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**Division of Medication Errors and Technical Support (DMETS)  
Office of Drug Safety  
HFD-420; PKLN Rm. 6-34  
Center for Drug Evaluation and Research**

**PROPRIETARY NAME REVIEW**

**DATE OF REVIEW:** October 22, 2004

**NDA#:** 21-780

**NAME OF DRUG:** \_\_\_\_\_ Primary Name), Nitro Mist (Secondary Name)  
(Nitroglycerin Aerosol) 0.4 mg

**NDA HOLDER:** NovaDel Pharma, Inc.

**I. INTRODUCTION:**

This consult was written in response to a request from the Division of Cardio-Renal Drug Products (HFD-110), for assessment of the proprietary names, \_\_\_\_\_ and Nitro Mist, regarding potential name confusion with other proprietary or established drug names. Container labels, carton labeling, and insert labeling were provided for review and comment.

Upon the initial steps in the proprietary name review process (EPD), the Division of Drug Marketing, Advertising and Communications (DDMAC) had the following promotional concerns with the proprietary name \_\_\_\_\_

“DDMAC objects to the tradename \_\_\_\_\_ because it is overly fanciful and implies some unique effectiveness. Specifically, the modifier \_\_\_\_\_ implies that this drug is "easy" to take, which may not be the case if the drug is associated with taste aversion or some patients may not find administering an oral spray at the onset of an angina attack an "easy" task. In addition, the tradename, containing "\_\_\_\_\_ in conjunction with "\_\_\_\_\_" implies that the drug "quickly eases" your symptoms. In the absence of substantial evidence to support that ALL patients taking this drug will experience immediate relief from angina attacks, the name is misleading. Furthermore, it is **not** clear that the modifier actually refers to a different formulation i.e., lingual spray. We have consistently objected to drugs with the modifier "\_\_\_\_\_ and there are currently no drugs on the market with this modifier. Please note that 21 CFR 201.10(c)(3) states that a proprietary name that implies that the drug or ingredient has some unique effectiveness or composition would be misleading, if the drug or ingredient is a common substance, the limitations of which are readily recognized when the drug or ingredient is listed by its established name. In addition, the statute also provides that labeling or advertising can misbrand a product if misleading representations are made, whether through a tradename or otherwise; this includes suggestions that a drug is better, more effective, useful in a broader range of conditions or patients, safer, has fewer, or lower incidence of, or less serious side effects or contraindications than has been demonstrated by substantial evidence or substantial clinical experience. [21 U.S.C 321(n); see also 21 U.S.C. 352(a) & (n); 21 CFR 202.1(e)(5)(i);(e)(6)(i)].”

As per discussion with the Division of Cardio-Renal Drug Products Project Manager, John David, on October 26, 2004, the Division concurred with DDMAC's comments. Therefore, DMETS will not proceed with the safety review of the proposed proprietary name, \_\_\_\_\_ since the Division supports DDMAC's objection of the name based on promotional concerns. The alternate name, Nitro Mist will be discussed below.

## PRODUCT INFORMATION

Nitro Mist is a metered-dose spray containing nitroglycerin, a vasodilator which has effects on both arteries and veins. Nitro Mist delivers nitroglycerin in the form of spray droplets into the open mouth. Nitro Mist is indicated for acute relief of an attack or acute prophylaxis of angina pectoris due to coronary artery disease. The usual dose of Nitro Mist is one or two metered sprays at the onset of an attack. A spray may be repeated approximately every five minutes as need. No more than three metered sprays are recommended within a 15-minute period. Nitro Mist may be used prophylactically 5 minutes to 10 minutes prior to engaging in activities which might precipitate an acute attack. Nitro Mist is supplied in bottles containing \_\_\_\_\_ grams of nitroglycerin lingual spray and will deliver \_\_\_\_\_ metered sprays containing 0.4 mg of nitroglycerin per spray.

## **II. RISK ASSESSMENT:**

The medication error staff of DMETS conducted a search of several standard published drug product reference texts<sup>1,2</sup> as well as several FDA databases<sup>3</sup> for existing drug names which sound-alike or look-alike to Nitro Mist to a degree where potential confusion between drug names could occur under the usual clinical practice settings. A search of the electronic online version of the U.S. Patent and Trademark Office's Text and Image Database was also conducted<sup>4</sup>. The Saegis<sup>5</sup> Pharma-In-Use database was searched for drug names with potential for confusion. An expert panel discussion was conducted to review all findings from the searches. In addition, DMETS conducted three prescription analysis studies consisting of two written prescription studies (inpatient and outpatient) and one verbal prescription study, involving health care practitioners within FDA. This exercise was conducted to simulate the prescription ordering process in order to evaluate potential errors in handwriting and verbal communication of the name.

### **A. EXPERT PANEL DISCUSSION (EPD)**

An Expert Panel discussion was held by DMETS to gather professional opinions on the safety of the proprietary name Nitro Mist. Potential concerns regarding drug marketing and promotion related to the proposed name were also discussed. This group is composed of DMETS Medication Errors Prevention Staff and representation from the Division of Drug Marketing, Advertising, and Communications (DDMAC). The group relies on their clinical and other professional experiences and a number of standard references when making a decision on the acceptability of a proprietary name.

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<sup>1</sup> MICROMEDEX Integrated Index, 2004, MICROMEDEX, Inc., 6200 South Syracuse Way, Suite 300, Englewood, Colorado 80111-4740, which includes all products/databases within ChemKnowledge, DrugKnowledge, and RegsKnowledge Systems.

<sup>2</sup> Facts and Comparisons, online version, Facts and Comparisons, St. Louis, MO.

<sup>3</sup> AMF Decision Support System [DSS], the Division of Medication Errors and Technical Support [DMETS] database of Proprietary name consultation requests, New Drug Approvals 98-04, and the electronic online version of the FDA Orange Book.

<sup>4</sup> WWW location <http://www.uspto.gov/tmdb/index.html>.

<sup>5</sup> Data provided by Thomson & Thomson's SAEGIS™ Online Service, available at [www.thomson-thomson.com](http://www.thomson-thomson.com)

1. DDMAC finds the proprietary name, Nitro Mist, acceptable from a promotional perspective.
2. The Expert Panel identified three proprietary names that were thought to have the potential for sound-alike confusion with Nitro Mist. These products are listed in table 1 (see page 4), along with the dosage forms available and usual dosage.

Table 1: Potential Sound-Alike/Look-Alike Names Identified by DMETS Expert Panel

Product Name	Dosage form(s), Established name	Usual adult dose*	Other**
Nitro Mist	Nitroglycerin Aerosol 0.4 mg	1 spray to 2 sprays at onset of attack. One spray may be repeated every 5 minutes as needed. No more than three metered sprays are recommended within a 15 minute period. May be used prophylactically 5 minutes to 10 minutes prior to engaging in activities which might precipitate an acute attack.	
Nitropress	Nitroprusside Sodium for Injection 50 mg	0.3 mcg/kg/min to 10 mcg/kg/min until desired effect is achieved.	SA
Nitrostat	Nitroglycerin Tablets 0.3 mg, 0.4 mg and 0.6 mg	Dissolve 1 tablet under tongue or in buccal pouch (between cheek and gum) at first sign of an acute anginal attack. Repeat approximately every 5 minutes until relief is obtained. Take no more than 3 tablets in 15 minutes. If pain continues, notify physician immediately. May be used prophylactically 5 to 10 minutes prior to activities that might precipitate an acute attack.	SA
Mucomyst	Acetylcysteine Oral Solution 10% and 20%	<b>Nebulization:</b> 1 mL to 10 mL of the 20% solution or 2 mL to 20 mL of the 10% solution every 2 to 6 hours <b>Oral:</b> 140 mg/kg loading dose of acetylcysteine. Administer the first maintenance dose (70 mg/kg) 4 hours after the loading dose. Repeat the maintenance dose at 4 hour intervals for a total of 17 doses unless the acetaminophen assay reveals a nontoxic level.	SA
*Frequently used, not all-inclusive. **L/A (look-alike), S/A (sound-alike)			

#### B. 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. The phonetic search module returns a numeric score to the search engine based on the phonetic similarity to the input text. Likewise, an orthographic algorithm exists which operates in a similar fashion. All names considered to have significant phonetic or orthographic similarities to Nitro Mist were discussed by the Expert Panel (EPD).

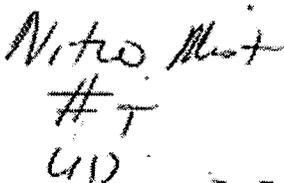
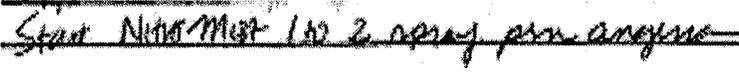
#### C. ADVERSE EVENT REPORTING SYSTEM (AERS)

DMETS searched the FDA Adverse Event Reporting System for cases of medication errors caused by name confusion with any of the products that contain the prefix 'Nitro' that are already marketed in the U.S. (e.g. Nitrobid, Nitrofurantoin, Nitrostat, and Nitro-Dur). The search did not return any evidence of postmarketing confusion between any of the marketed products that contain the prefix 'Nitro.'

D. PRESCRIPTION ANALYSIS STUDIES

1. Methodology:

Three separate studies were conducted within the Centers of the FDA for the proposed proprietary name to determine the degree of confusion of Nitro Mist 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. These studies employed a total of 123 health care professionals (pharmacists, physicians, and nurses). This exercise was conducted in an attempt to simulate the prescription ordering process. An inpatient order and outpatient prescriptions were written, each consisting of a combination of marketed and unapproved drug products and a prescription for Nitro Mist (see below). These prescriptions were optically scanned and one prescription was delivered to a random sample of the participating health professionals via e-mail. In addition, the outpatient orders were recorded on voice mail. The voice mail messages were 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 sent their interpretations of the orders via e-mail to the medication error staff.

HANDWRITTEN PRESCRIPTION	VERBAL PRESCRIPTION
<p>Outpatient RX:</p> 	<p>“Last prescription is Nitro Mist, as directed, #1.”</p>
<p>Inpatient RX:</p> 	

2. Results:

None of the interpretations of the proposed name overlap, sound similar, or look similar to any currently marketed U.S. drug product. See appendix A for the complete listing of interpretations from the verbal and written studies.

E. SAFETY EVALUATOR RISK ASSESSMENT

In reviewing the proprietary name Nitro Mist, the primary concerns related to look-alike and sound-alike confusion with Nitropress, Nitrostat, and Mucomyst. Additionally, DMETS conducted prescription studies to simulate the prescription ordering process. In this case, there was no confirmation that the proposed name could be confused with any of the aforementioned names. However, negative findings are not predicative as to what may occur once the drug is widely prescribed, as these studies have limitations primarily due to a small sample size. The majority of misinterpretations were misspelled/phonetic variations of the proposed name, Nitro Mist.

1. Nitro Mist can sound similar to Nitropress when pronounced. Nitropress is an intravenous antihypertensive agent indicated for hypertensive crises, bleeding reduction during surgery, and acute congestive heart failure. Nitro Mist and Nitropress both begin with 'Nitro,' which is the principal contribution to the sound-alike similarities of each name. Additionally, Nitro Mist and Nitropress both have three syllables. However, the beginning of the third syllable in each name ('Mi' vs. 'pr') helps to distinguish the two names. Furthermore, the endings of Nitro Mist and Nitropress sound different. Moreover, the two products do not overlap in route of administration (oral vs. intravenous), dosage form (lingual spray vs. powder for injection), usual dose (one to two sprays vs. 0.3 mg/kg/min to 10 mcg/kg/min), dosing frequency (as needed vs. once), and product strength (0.4 mg vs. 50 mg). The phonetic differences in the endings of each name along with the differing product characteristics between Nitro Mist and Nitropress decrease the potential for medication errors due to name confusion.
2. Nitro Mist can sound similar to Nitrostat when spoken. Nitrostat is a vasodilator indicated for acute relief of an attack or acute prophylaxis of angina pectoris due to coronary artery disease. Nitro Mist and Nitrostat both begin with 'Nitro,' which is the principal contribution to the sound-alike similarities of each name. Additionally, Nitro Mist and Nitrostat both have three syllables. However, the endings of Nitro Mist and Nitrostat are different ('Mist' vs. 'stat'), which helps to differentiate the two product names. Although, Nitro Mist and Nitrostat overlap in product characteristics such as route of administration (oral), dosing frequency (as needed), product strength (0.4 mg), indication (angina pectoris), and established name (Nitroglycerin), the two products do not overlap in dosage form (lingual spray vs. tablet) or usual dose (one or two sprays vs. one tablet). With the introduction of a new product into the marketplace, there is always potential for confusion leading to medication errors. However, the potential for harm resulting from this error is low since Nitro Mist and Nitrostat are the same product, just in different dosage forms. Furthermore, DMETS has not found any evidence of postmarketing confusion between any of the Nitroglycerin products. It is likely that Nitro Mist and Nitrostat can co-exist safely in the marketplace as long healthcare practitioners are educated about the difference between Nitro Mist and Nitrostat. Hence, upon launching of Nitro Mist, the sponsor should provide educational material (e.g. Dear Healthcare Practitioner Letters) to inform the healthcare professionals of the differences between Nitro Mist and Nitrostat.
3. Nitro Mist can sound similar to Mucomyst when pronounced. Mucomyst is a detoxification agent indicated for use as an antidote for acetaminophen overdose and as adjuvant therapy as a mucolytic agent for the treatment of chronic bronchopulmonary diseases. The greatest contributions to the sound-alike characteristics of each name are the endings of each name which are phonetically identical ('Mist' vs. 'myst'). Additionally, both Nitro Mist and Mucomyst have three syllables. Furthermore, the second syllable of both names end in the letter 'o,' which adds to the sound-alike similarities of each name. However, the first syllable of each name sounds different ('Nigh' vs. 'Mu'). Although Nitro Mist and Mucomyst overlap in route of administration (oral), they do not overlap in product characteristics such as dosage form (lingual spray vs. oral solution), usual dose (one to two sprays vs. 1 mL to 20 mL or 70 mg/kg to 140 mg/kg), dosing frequency (as needed vs. every two to six hours), or product strength (0.4 mg vs. 10% and 20%). Overall, the phonetic differences between the beginnings of each name along with the differing product characteristics decrease the potential for medication errors between Nitro Mist and Mucomyst.

### III. LABELING, PACKAGING, AND SAFETY RELATED ISSUES:

In the review of the container labels, carton labeling and insert labeling of Nitro Mist, DMETS has attempted to focus on safety issues relating to possible medication errors. However, it is not possible to fully assess the safety of the labels and labeling because the information provided did not reflect the label and labeling presentation that will actually be used in the marketplace (i.e. color, placement of name, etc.). Please forward copies of the final container labels, carton labeling and insert labeling of Nitro Mist when they are available for review and comment. DMETS has identified the following areas of possible improvement, which might minimize potential user error.

#### A. GENERAL COMMENTS

DMETS recommends consulting Guiarag Poochikian, Acting Chair of the Labeling and Nomenclature Committee, for the proper designation of the established name.

#### B. CONTAINER LABEL

1. Delete the word \_\_\_\_\_ from the label. \_\_\_\_\_ does not appear anywhere else in the labeling in conjunction with the proprietary name.
2. Relocate the established name so that it appears directly underneath the proprietary name. Additionally, revise the established name so that it is at least half as large as the letters comprising the proprietary name in accordance with 21 CFR 201.10(g)(2).
3. Relocate the net quantity so that it does not appear in close proximity to the product strength.

#### C. INSERT LABELING

##### PRECAUTIONS SECTION, Information for Patients Subsection

In accordance with 21 CFR 201.57(f)(2), reprint the Information for Patients subsection at the end of the labeling. Additionally, in the Information for Patients Subsection, clearly instruct the patients that the device must initially be sprayed \_\_\_\_\_ in order to prime the device and insure they are receiving the appropriate dose of nitroglycerin. Furthermore, instruct the patients that the device must be reprimed with 2 sprays if not used withir \_\_\_\_\_.

**V. RECOMMENDATIONS:**

- A. DMETS has no objections to the use of the proprietary name, Nitro Mist. This is considered a tentative decision and the firm should be notified that this name with its associated labels and labeling must be re-evaluated approximately 90 days prior to the expected approval of the NDA. A re-review of the name prior to NDA approval will rule out any objections based upon approvals of other proprietary and established names from the signature date of this document.
- B. DMETS recommends implementation of the label and labeling revisions outlined in section III of this review that might lead to safer use of the product. We would be willing to revisit these issues if the Division receives another draft of the labeling from the manufacturer.
- C. DDMAC finds the proprietary name, Nitro Mist, acceptable from a promotional perspective
- D. DMETS recommend consulting Guiarag Poochikian, Acting Chair of the USAN council & LNC, for the proper designation of the established name.

DMETS would appreciate feedback of the final outcome of this consult. We would be willing to meet with the Division for further discussion, if needed. If you have further questions or need clarifications, please contact Sammie Beam, project manager, at 301-827-2102.

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Office of Drug Safety

Concur:

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Linda Kim-Jung, PharmD  
Team Leader  
Division of Medication Errors and Technical Support  
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Attachment A

Outpatient Written	Inpatient Written	Verbal
Nitro Mist	Nitro Mist	Nitromint
Nitro Mist	Nitro Mist	Nitromist
Nitro Mist	Nitro Mist	Nitromist
Nitro Mist	Nitro Mist	Nitromist
Nitro Mist	Nitro Mist	Nitromist
Nitro mist	Nitro Mist	Nitromist
Nitro Mist	Nitro Mist	Nitromist
Nitro Mist	Nitro Mist	Nitromist
Nitro Mist	Nitro Mist	Nitromist
Nitro Plegette	Nitro Mist	Nitromist
NitroMist	Nitro MLST	Nitromist
Nitromist	nitromisa	Nitromist
Nitromist	NitroMist	Nitromist
NitroMist	Nitromist	
Nitromist	NitroMist	
	Nitromix	

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/s/

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