

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**125288Orig1s000**

**PROPRIETARY NAME REVIEW(S)**

**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:	February 28, 2011
Application Type/Number:	BLA 125288
Through:	Irene Z. Chan, PharmD, BCPS, Acting Team Leader <i>[Signature]</i> 2/28/11 Carol Holquist, RPh, Director <i>Carol Holquist 2/28/11</i> Division of Medication Error Prevention and Analysis (DMEPA)
From:	L. Sheneé Toombs, Pharm.D., Safety Evaluator <i>L. Sheneé Toombs 2/28/2011</i> Division of Medication Error Prevention and Analysis
Subject:	Proprietary Name Review
Drug Name(s):	Nulojix (Belatacept) for Injection 250 mg per vial
Applicant/sponsor:	Bristol-Myers Squibb
OSE RCM #:	2010-2582

\*\*\* This document contains proprietary and confidential information that should not be released to the public.\*\*\*

## CONTENTS

EXECUTIVE SUMMARY .....	3
1 BACKGROUND .....	3
1.1 Introduction .....	3
1.2 Regulatory History .....	3
1.3 Product Information.....	3
2 METHODS AND MATERIALS .....	3
2.1 Search Criteria .....	3
2.2 FDA Prescription Analysis Studies .....	4
2.3 External Proprietary Name Risk Assessment.....	5
2.4 Name Similarity Risk Assessment Poll .....	5
3 RESULTS .....	5
3.1 Database and Information Sources .....	5
3.2 CDER Expert Panel Discussion .....	6
3.3 FDA Prescription Analysis Studies .....	6
3.4 External Study .....	6
3.5 Name Similarity Risk Assessment .....	6
3.6 Safety Evaluator Searches .....	7
3.7 Comments from the Division of Special Pathogens and Transplant Products (DSPTP) .....	7
4 DISCUSSION .....	7
4.1 Promotional Assessment.....	7
4.2 Safety Assessment .....	7
5 CONCLUSIONS AND RECOMMENDATIONS .....	8
5.1 Comments to the Applicant .....	8
6 REFERENCES .....	9
APPENDICES .....	11

## **EXECUTIVE SUMMARY**

This review summarizes DMEPA's evaluation of the proposed proprietary name, Nulojix (Belatacept) for Injection. Our evaluation did not identify concerns that would render the name unacceptable based on the product characteristics and safety profile known at the time of this review. Thus, DMEPA finds the proposed proprietary name, Nulojix, acceptable for this product. The proposed proprietary name must be re-reviewed 90 days before the approval of the NDA.

Additionally, if any of the proposed product characteristics as stated in this review are altered, DMEPA rescinds this finding and the name must be resubmitted for review. The conclusions upon re-review are subject to change. DMEPA will notify the applicant of these findings via letter.

## **1 BACKGROUND**

### **1.1 INTRODUCTION**

This review responds to a request from Bristol-Myers Squibb, dated December 3, 2010, for an assessment of the proposed proprietary name, Nulojix, from a promotional and safety perspective.

### **1.2 REGULATORY HISTORY**

DMEPA previously reviewed this proposed proprietary name, Nulojix, under IND 9418/BLA 125288 (OSE Review #2008-849/2009-1301 dated October 6, 2009). We found the name conditionally acceptable at that time.

### **1.3 PRODUCT INFORMATION**

Nulojix (Belatacept for Injection) is an immunosuppressant indicated for the prophylaxis of organ rejection in renal allograft recipients. The recommended dose is 10 mg/kg as a 30 minute intravenous infusion on day of transplant (Day 1), then Days 5, Day 14 and Day 28, at the end of week 8 and week 12; then 5 mg/kg intravenously as a 30 minute intravenous infusion every 4 weeks starting at the end of week 16. Nulojix will be available as a single-use vial that provides 250 mg of active ingredient. Nulojix is stored at 2°-8°C (36 °-46 °F).

## **2 METHODS AND MATERIALS**

Appendix A describes the general methods and materials used by the Division of Medication Error Prevention and Analysis (DMEPA) when conducting a proprietary name risk assessment for all proprietary names. Sections 2.1., 2.2., 2.3. and 2.4 identify specific information associated with the methodology for the proposed proprietary name Nulojix.

### **2.1 SEARCH CRITERIA**

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.<sup>1,2</sup>

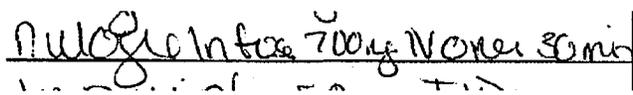
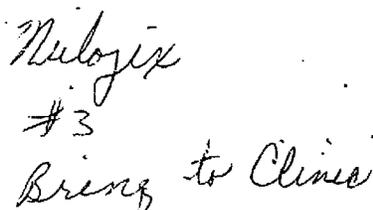
To identify drug names that may look similar to Nulojix, the DMEPA staff also considers the orthographic appearance of the name on lined and unlined orders. Specific attributes taken into consideration include the length of the name (seven letters), upstrokes (two, capital letter ‘N’ and lower case ‘l’), downstrokes (one, lower case ‘j’), cross-strokes (one, lower case ‘x’) and dotted letters (one, lower case ‘i’). Additionally, several letters in Nulojix may be vulnerable to ambiguity when scripted (see Appendix B). As a result, the DMEPA staff also considers these alternate appearances when identifying drug names that may look similar to Nulojix.

When searching to identify potential names that may sound similar to Nulojix, the DMEPA staff searches for names with similar number of syllables (3), stresses (NU-lo-jix or nu-LO-jix or nu-lo-JIX), and placement of vowel and consonant sounds. The Applicant’s intended pronunciation (NU-LO-JIX) was also taken into consideration, as it was included in the Proprietary Name Review Request. However, names are often mispronounced and/or spoken with regional accents and dialects, so other potential pronunciations of the name are considered. Additionally, the DMEPA staff considers that pronunciation of parts of the name can vary (see Appendix B).

## 2.2 FDA PRESCRIPTION ANALYSIS STUDIES

In order to evaluate the potential for misinterpretation of the proposed proprietary name in handwriting and verbal communication of the name, the following inpatient medication order, outpatient and verbal prescriptions were communicated during the FDA prescription studies.

**Figure 1. Nulojix Rx Study (conducted on January 10, 2011)**

HANDWRITTEN REQUISITION MEDICATION ORDER	VERBAL PRESCRIPTION
<p><u>Inpatient Medication Order :</u>  </p>	<p>Nulojix  Dispense #3  Bring to clinic</p>
<p><u>Outpatient Prescription:</u>  </p>	

<sup>1</sup> Institute for Safe Medication Practices. Confused Drug name List (1996-2006). Available at <http://www.ismp.org/Tools/confuseddrugnames.pdf>

<sup>2</sup> Kondrack, G and Dorr, B. Automatic Identification of Confusable Drug Names. Artificial Intelligence in Medicine (2005)

### **2.3 EXTERNAL PROPRIETARY NAME RISK ASSESSMENT**

For this product, the Applicant submitted an external evaluation of the proposed proprietary name. The Division of Medication Error Prevention and Analysis 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 DMEPA'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 associated with 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 Division's risk assessment concurs or differs with the findings. When the proprietary name risk assessment differs, the Division of Medication Error Prevention and Analysis provides a detailed explanation of these differences.

### **2.4 NAME SIMILARITY RISK ASSESSMENT POLL**

To further assist in determining the overall risk of confusion between Nulojix and a specific name, the reviewing safety evaluator conducted a poll of the DMEPA staff to determine if they had concerns with the orthographic and/or phonetic similarity of these two names. The poll questions are listed in Appendix D.

## **3 RESULTS**

The following sections represent the results from DMEPA's database searches, Expert Panel Discussion (EPD), Prescription studies, SE Poll, and the Safety Evaluator Risk Assessment. We also sought input from the Division of Special Pathogens and Transplant Products (DSPTP) regarding the proprietary name.

### **3.1 DATABASE AND INFORMATION SOURCES**

The DMEPA database searches yielded a total of 26 names as having some similarity to the proposed proprietary name, Nulojix.

Twenty of the names were thought to look like Nulojix by the DMEPA Safety Evaluators (Calcijex, Methampex, Mifeprex, Nalfon, Nalfrx, Nallpen in plastic container, Naloxone, Natacyn, Natazia, Niferex, Norflex, Norlutin, Nubain, (b) (4) Nulytely, Nuromax, NutrilYTE, Nutrivit, Nutropin, Provigil, Wolfina)

Two of the names (Novolog Mix, Nullo) were thought to sound like Nulojix

The three remaining names were thought to look and sound similar to Nulojix by the DMEPA Safety Evaluators (Neupogen, Nolvadex, Nuvigil)

---

\*\*\* This document contains proprietary and confidential information that should not be released to the public.

Additionally, DMEPA did not identify any United States Adopted Names (USAN) stems in the proposed proprietary name as of January 27, 2011.

### **3.2 CDER EXPERT PANEL DISCUSSION**

The Expert Panel reviewed the pool of names identified by DMEPA Safety Evaluators (See Section 3.1 above) and did not note any additional names thought to have orthographic or phonetic similarity to Nulojix.

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

### **3.3 FDA PRESCRIPTION ANALYSIS STUDIES**

A total of 28 practitioners responded to the prescription analysis studies. However, one of the responses from the verbal prescription studies was not included in the analysis due to data integrity concerns. Therefore, 27 practitioner responses were evaluated.

Five practitioners in the written studies interpreted the name correctly as Nulojix. The remainder of the respondents (n=22) misinterpreted the drug name, primarily because the lower case letter 'j' was misinterpreted as 'g' or 'y', or lower case letter 'o' was misinterpreted as 'a', or lower case letter 'i' was misinterpreted as 'e' or 'l', or lower case letter 'x' was misinterpreted as 'n', 'c', or 'e' in the written studies. In the verbal study responses were misspelled phonetic variations of the proposed name, Nulojix, with the most common variations occurring in the first syllable ('New', 'Nel', 'Neu' or 'Nu') and the third syllable of the name ('gix', 'gex' or 'ject' vs 'jix'). See Appendix C for the complete listing of interpretations from the verbal and written prescription studies.

### **3.4 EXTERNAL STUDY**

The Sponsor's external name study, conducted by the (b) (4), identified a total of 35 names. All 35 names were identified by (b) (4) as having orthographic and/or phonetic similarity to Nulojix. These include Chronulac, Dolgic, Dolgic LQ, Dolorex, Enulose, Naloxone, Nebupent, Neoloid, Nexium, Nizoral, Norcet, Norco, Norcuron, Norditropin, Norel EX, Norflex, Norgesic, Nullo, Numobid, Nutraloric, Namenda, Neulasta, Nuvaring, Aciphex, Calcijex, Maalox, Neupogen, Nolvadex, Novolog, Nulev, Nulytely, Nuromax, Nutropin, Nuvigil and Rulox.

Of the 35 names, 10 names (Calcijex, Naloxone, Neupogen, Nolvadex, Norflex, Nullo, Nulytely, Nuromax, Nutropin, and Nuvigil) were also identified by DMEPA staff and in the Expert Panel Discussion. The remaining 25 names will be reviewed in Section 4.2.

### **3.5 NAME SIMILARITY RISK ASSESSMENT POLL**

Eleven DMEPA staff members responded to the poll conducted on February 17, 2010, which asked, "Are the names Nulojix and Neupogen convincingly similar (phonetically), which may cause practitioners to become confused at any point in the usual practice setting? (Yes or No) (Why or Why not). All participants responded "No". The comments provided by the participants are included in Appendix D. The eleven participants believed that the phonetic differences of the second syllable ('lo' vs 'po') and the third syllable ('jix' vs 'gen') minimize the risk of error.

### **3.6 SAFETY EVALUATOR SEARCHES**

Independent searches by the primary Safety Evaluator resulted in the identification of six additional names (Melanex, (b) (4) Zelapar, Zolinza, Nallpen and Milprosa) which were thought to look similar to Nulojix and represent a potential source of drug name confusion.

Thus, a total of 57 names were identified for their similarity to Nulojix from the combined searches: 6 identified by the primary safety evaluator, 26 identified in section 3.1 and 25 identified in section 3.4.

### **3.7 COMMENTS FROM THE DIVISION OF SPECIAL PATHOGENS AND TRANSPLANT PRODUCTS (DSPTP)**

On February 23, 2011 DMEPA notified the Division of Special Pathogens and Transplant Products (DSPTP) via e-mail that we have no objections to the proposed proprietary name Nulojix. Per e-mail correspondence from DSPTP on February 28, 2011 they indicated they had no issues with our assessment of the proposed proprietary name, Nulojix.

## **4 DISCUSSION**

Nulojix is the proposed proprietary name for Belatacept for Injection. This proposed name was evaluated from a safety and promotional perspective based on the product characteristics provided by the Applicant. We sought input from pertinent disciplines involved with the review of this application and considered their comments accordingly.

### **4.1 PROMOTIONAL ASSESSMENT**

DDMAC had no concerns regarding the proposed name from a promotional perspective, and did not offer any additional comments relating to the proposed name. DMEPA concurred with the findings of DDMAC's promotional assessment of the proposed name.

### **4.2 SAFETY ASSESSMENT**

We identified a total of 57 names as having some similarity to Nulojix. No other aspects of the name were determined to represent a potential source of confusion.

Forty-nine of the 57 names were eliminated for the following reasons (see Appendices E, F, G, H, and I): thirty-eight names were previously reviewed in OSE review 2008-849/2009-1301 dated October 6, 2009. Since the product characteristics of Nulojix have not changed since our previous review, these names were not re-reviewed. Eight of the names lacked convincing orthographic and/or phonetic similarity to the proposed proprietary name, Nulojix, one name was not approved by the Agency, one name was a discontinued product with no available generics and one name was not found in commonly used references.

One name, Neupogen, was previously identified as having orthographic similarity to Nulojix and reviewed in OSE review 2008-849/2009-1301. In our current review of Nulojix, Neupogen was again identified in the database searches as having orthographic in addition to phonetic similarities to the proposed proprietary name Nulojix. Furthermore, a direct hit was identified in

---

\*\*\* Note: This review contains proprietary and confidential information that should not be released to the public.\*\*\*

the verbal studies conducted on January 10, 2011. Therefore, we reassessed the name Neupogen considering the phonetic similarities between the names Nulojix and Neupogen. However, upon further analysis it was determined that the direct hit response in the verbal study would be eliminated due to data integrity concerns. We also further analyzed the name pair for confusion due to phonetic similarity. We conducted a risk assessment poll to further assist in determining the overall risk of confusion between Nulojix and Neupogen. All respondents ultimately determined the name similarity between Nulojix and Neupogen would not cause practitioners to become confused at any point in the usual practice setting, and our analysis concurred with this opinion. Our analysis determined the risk for confusion due to phonetic similarity is minimized due to phonetic differences of the second ('lo' vs 'po') and third syllables ('jix' vs 'gen'). See Appendix K for our complete analysis of Neupogen.

Failure Mode and Effects Analysis (FMEA) was then applied to determine if the proposed proprietary name, Nulojix, could potentially be confused with the remaining seven names and lead to medication errors. This analysis determined that the name similarity to Nulojix was unlikely to result in medication errors with any of the seven products for the reasons presented in Appendices J through K.

## **5 CONCLUSIONS AND RECOMMENDATIONS**

The Proprietary Name Risk Assessment findings indicate that the proposed name, Nulojix, is not vulnerable to name confusion that could lead to medication errors, nor is it considered promotional. Thus, the Division of Medication Error Prevention and Analysis (DMEPA) has no objections to the proprietary name, Nulojix, for this product at this time. The proposed proprietary name must be re-reviewed 90 days before the approval of the NDA. The Applicant will be notified via letter from DMEPA.

If any of the proposed product characteristics as stated in this review are altered, DMEPA rescinds this finding and the name must be resubmitted for review. The conclusions upon re-review are subject to change.

If you have further questions or need clarifications on this review, please contact the OSE Regulatory Project Manager, Karen Townsend, at 301-796-5413.

### **5.1 COMMENTS TO THE APPLICANT**

We have completed our review of the proposed proprietary name, Nulojix, and have concluded that the name is acceptable.

Nulojix will be re-reviewed 90 days prior to the approval of the NDA. If we find the name unacceptable following the re-review, we will notify you.

## 6 REFERENCES

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

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

2. ***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 Division of Medication Error Prevention and Analysis, FDA.

3. ***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.

4. ***FDA Document Archiving, Reporting & Regulatory Tracking System [DARRTS]***

DARRTS is a government database used to organize Applicant and Sponsor submissions as well as to store and organize assignments, reviews, and communications from the review divisions.

5. ***Division of Medication Errors Prevention and Analysis proprietary name consultation requests***

This is a list of proposed and pending names that is generated by the Division of Medication Error Prevention and Analysis from the Access database/tracking system.

6. ***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, generic drugs, therapeutic biological products, prescription and over-the-counter human drugs and discontinued drugs and “Chemical Type 6” approvals.

7. ***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.

8. ***U.S. Patent and Trademark Office*** (<http://www.uspto.gov>)

Provides information regarding patent and trademarks.

9. ***Clinical Pharmacology Online*** ([www.clinicalpharmacology-ip.com](http://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.

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

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

11. ***Natural Medicines Comprehensive Databases*** ([www.naturaldatabase.com](http://www.naturaldatabase.com))

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

12. ***Stat!Ref*** ([www.statref.com](http://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.

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

List contains all the recognized USAN stems.

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

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

15. ***Lexi-Comp*** ([www.lexi.com](http://www.lexi.com))

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

16. ***Medical Abbreviations Book***

Contains commonly used medical abbreviations and their definitions.

17. OSE Review #2008-849/2009-1301, Proprietary Name Review for Nulojix (Belatacept for Injection) 250 mg per vial, Jones-Smith, T; October 6, 2009.

## APPENDICES

### Appendix A:

FDA's Proprietary Name Risk Assessment considers the potential for confusion between the proposed proprietary name 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 the Center. DMEPA 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.<sup>5</sup>

For the proposed proprietary name, DMEPA staff search a standard set of databases and information sources to identify names with orthographic and phonetic similarity and hold a Center for Drug Evaluation and Research (CDER) Expert Panel discussion to gather professional opinions on the safety of the proposed proprietary name. DMEPA staff also conducts internal CDER prescription analysis studies. When provided, DMEPA considers external prescription analysis study results and incorporate into the overall risk assessment.

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. DMEPA bases the overall risk assessment on the findings of a Failure Mode and Effects Analysis (FMEA) of the proprietary name, and focuses on the avoidance of medication errors.

FMEA is a systematic tool for evaluating a process and identifying where and how it might fail.<sup>6</sup> DMEPA uses FMEA to analyze whether the drug names identified with orthographic or phonetic similarity to the proposed proprietary name could cause confusion that subsequently leads to medication errors in the clinical setting. DMEPA uses the clinical expertise of its staff to anticipate the conditions of the clinical setting where the product is likely to be used 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. Accordingly, the DMEPA staff considers the product characteristics associated with the proposed drug throughout the risk assessment because the product characteristics of the proposed may provide a context for 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 proprietary name include, but are not limited to; established name of the proposed product, proposed indication of use, 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, DMEPA staff considers the

---

<sup>5</sup> National Coordinating Council for Medication Error Reporting and Prevention.  
<http://www.nccmerp.org/aboutMedErrors.html>. Last accessed 10/11/2007.

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

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.<sup>7</sup> DMEPA provides the product characteristics considered for this review in section one.

The Division of Medication Error Prevention and Analysis considers the spelling of the name, pronunciation of the name when spoken, and appearance of the name when scripted. DMEPA 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. DMEPA 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 even dissimilarly spelled drug name pairs to appear very similar to one another. The similar appearance of drug names when scripted has led to medication errors. The DMEPA staff applies expertise gained from root-cause analysis of such medication errors to identify sources of ambiguity within the name that could be introduced when scripting (e.g., “T” may look like “F,” lower case ‘a’ looks like a lower case ‘u,’ etc). Additionally, other orthographic attributes that determine the overall appearance of the drug name when scripted (see Table 1 below for details). In addition, the DMEPA staff compares the pronunciation of the proposed proprietary name with the pronunciation of other drug names because verbal communication of medication names is common in clinical settings. If provided, DMEPA will consider the Applicant’s intended pronunciation of the proprietary name. However, DMEPA also considers a variety of pronunciations that could occur in the English language because the Applicant has little control over how the name will be spoken in clinical practice.

**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"> <li>Names may appear similar in print or electronic media and lead to drug name confusion in printed or electronic communication</li> <li>Names may look similar when scripted and lead to drug name confusion in written communication</li> </ul>
	Orthographic similarity	Similar spelling Length of the name Upstrokes Down strokes Cross-strokes Dotted letters Ambiguity introduced by scripting	<ul style="list-style-type: none"> <li>Names may look similar when scripted, and lead to drug name confusion in written communication</li> </ul>

<sup>7</sup> Institute of Medicine. Preventing Medication Errors. The National Academies Press: Washington DC. 2006.

		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"> <li>Names may sound similar when pronounced and lead to drug name confusion in verbal communication</li> </ul>

Lastly, the DMEPA staff also considers the potential for the proposed proprietary 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. Consequently, DMEPA considers and evaluates these broader safety implications of the name throughout this assessment and the medication error staff provides additional comments related to the safety of the proposed proprietary name or product based on professional experience with medication errors.

### 1. Database and Information Sources

DMEPA staff conducts searches 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 the proposed proprietary name using the criteria outlined in Section 2.1. Section 6 provides a standard description of the databases used in the searches. To complement the process, the DMEPA staff use 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 DMEPA staff review the USAN stem list to determine if any USAN stems are present within the proprietary name. The individual findings of multiple safety evaluators are pooled and presented to the CDER Expert Panel.

### 2. CDER Expert Panel Discussion

DMEPA conducts an Expert Panel Discussion to gather CDER professional opinions on the safety of the proposed product and the proposed proprietary name. The Expert Panel is composed of Division of Medication Errors Prevention (DMEPA) staff and representatives from the Division of Drug Marketing, Advertising, and Communications (DDMAC). The Expert Panel also discusses potential concerns regarding drug marketing and promotion related to the proposed names.

The primary Safety Evaluator presents the pooled results of the DMEPA staff 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 primary Safety Evaluator to supplement the pooled results, or general advice to consider when reviewing the proposed proprietary name.

### **3. 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 the proposed proprietary name 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 healthcare professionals (pharmacists, physicians, and nurses), and attempts to simulate the prescription ordering process. The primary Safety Evaluator uses the results to identify orthographic or phonetic vulnerability of the proposed name to be misinterpreted by healthcare practitioners.

In order to evaluate the potential for misinterpretation of the proposed proprietary name in handwriting and verbal communication of the name, inpatient medication orders and outpatient prescriptions are written, each consisting of a combination of marketed and unapproved drug products, including the proposed name. These orders are optically scanned and one prescription is delivered to a random sample of the 123 participating health professionals via e-mail. In addition, a verbal prescription 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 DMEPA.

### **4. Comments from the OND review Division or Generic drugs**

DMEPA requests the Office of New Drugs (OND) or Office of Generic Drugs (OGD) Regulatory Division responsible for the application for their comments or concerns with the proposed proprietary name and any clinical issues that may impact the DMEPA review during the initial phase of the name review. Additionally, when applicable, at the same time DMEPA requests concurrence/non-concurrence with DDMAC's decision on the name. The primary Safety Evaluator addresses any comments or concerns in the safety evaluator's assessment.

The OND or OGD Regulatory Division is contacted a second time following our analysis of the proposed proprietary name. At this point, DMEPA conveys their decision to accept or reject the name. The OND or OGD Regulatory Division is requested to concur/not concur with DMEPA's final decision.

### **5. Safety Evaluator Risk Assessment of the Proposed Proprietary Name**

The primary Safety Evaluator applies his/her individual expertise gained from evaluating medication errors reported to FDA, conducts a Failure Mode and Effects Analysis, and provides an overall risk assessment 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.<sup>8</sup> When applying FMEA to assess the risk of a proposed proprietary name, DMEPA seeks to evaluate the potential for a proposed proprietary name to be confused with another drug name because of name confusion and, thereby, 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 orthographically or phonetically similar

---

<sup>8</sup> Institute for Healthcare Improvement (IHI). Failure Mode and Effects Analysis. Boston. IHI:2004.

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 primary Safety Evaluator must analyze the use of the product at all points in the medication use system. Because the proposed product is has not been marketed, the primary Safety Evaluator anticipates the use of the product in the usual practice settings by considering the clinical and product characteristics listed in Section one. 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 Discussion, and prescription studies, external studies, and identifies potential failure modes by asking:

***“Is the proposed proprietary name 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 the proposed proprietary name 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, thus the name is eliminated from further review.

In the second stage of the Risk Assessment, the primary Safety Evaluator evaluates all potential failure modes 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 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 not ultimately be a source of medication errors in the usual practice setting, the primary Safety Evaluator eliminates the name 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 the use of an alternate proprietary name.

DMEPA will object to the use of proposed proprietary name when the primary Safety Evaluator identifies one or more of the following conditions in the 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 PROPRIETARY name or otherwise [21 U.S.C 321(n); See also 21 U.S.C. 352(a) & (n)].
2. DMEPA 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 the potential for confusion between the proposed proprietary name and other proprietary or established drug name(s), 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 (United States Adopted Names) stem.
5. DMEPA identifies a potential source of medication error within the proposed proprietary name. For example, 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.

If DMEPA objects to a proposed proprietary name on the basis that drug name confusion could lead to medication errors, the primary Safety Evaluator uses the FMEA process to identify strategies to reduce the risk of medication errors. DMEPA is likely to recommend that the Applicant select an alternative proprietary name and submit the alternate name to the Agency for DMEPA to review. However, in rare instances FMEA may identify plausible strategies that could reduce the risk of medication error of the currently proposed name. In that instance, DMEPA may be able to provide the Applicant with recommendations that reduce or eliminate the potential for error and, thereby, would render the proposed name acceptable.

In the event that DMEPA objects to the use of the proposed proprietary name, based upon the potential for confusion with another proposed (but not yet approved) proprietary name, DMEPA will provide a contingency objection based on the date of approval. Whichever product, the Agency approves first has the right to use the proprietary name, while DMEPA will recommend that the second product to reach approval seek an alternative 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 a through e are supported either by FDA regulation or by external healthcare authorities, including the Institute of Medicine (IOM), World Health Organization (WHO), Joint Commission on Accreditation of Hospitals (JCOAH), and the Institute for Safe Medication Practices (ISMP). These organizations have examined medication errors resulting from look- or sound-alike drug names and called for regulatory authorities to address the issue prior to approval. Additionally, DMEPA contends that the threshold set for the Proprietary Name Risk Assessment is reasonable because proprietary drug name confusion is a predictable and a preventable source of medication error that, in many instances, the Agency and/or Applicant can identify and rectify prior to approval to avoid patient harm.

Furthermore, post-marketing experience has demonstrated that medication errors resulting from drug name confusion are notoriously difficult to rectify post-approval. Educational and other post-approval efforts are low-leverage strategies that have had limited effectiveness at alleviating medication errors involving drug name confusion. Applicants have undertaken higher-leverage strategies, such as drug name changes, 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 approving the error-prone proprietary name. Moreover, even after Applicants' have changed a product's proprietary name in the post-approval phase, it is difficult to eradicate the original proprietary name from practitioners' vocabulary, and as a result, the Agency has continued to receive reports of drug name confusion long after a name change in some instances. Therefore, DMEPA 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 Section 4 for limitations of the process).

**Appendix B:** Letters with possible orthographic or phonetic misinterpretation

Letters in Name, Nulojix	Scripted may appear as	Spoken may be interpreted as
Capital 'N'	M, U, Z, V, W	Kn, M
lower case 'u'	i, o, e, eu, a	any vowel
lower case 'l'	d, e, r, b, i	-----
lower case 'o'	any vowel	any, vowel
lower case 'j'	g, f, y, q, p, z	g, dg,
lower case 'i'	c, e, l	any vowel
lower case 'x'	c, n, t, s, f, v, y	ks, kz, s, x,

**Appendix C:** FDA Prescription Study Responses (conducted January 10, 2010).

Written Outpatient	Written Inpatient	Verbal Prescription
Nulojix	Nulagen	Newlogix
Nulojix	Nulogic	Nuligix
Nulogix	Nulogix	Nuloject
Nuloyix	Nulogie	Nelagex
Nulojix	Nuloju	Neuogen
Nulojix	Nulogle	Neulogix
Nulojix	Nulogic	Nulagen
	Nulogie	Neulogex
	Nulogle	Neulogex
	Nulogie	Newlogen

**Appendix D: Safety Evaluator Poll Responses**

Poll Questions	Are the names Nulojix and Neupogen convincingly similar (phonetically), which may cause practitioners to become confused at any point in the usual practice setting? (Yes or No)	Why or Why not?
Staff Responses	No.	Although both names begin with 'N' and the prefixes are pronounced the same ('Nu' vs 'Neu'), logix does not sound like pogen
	No.	The second syllable starts with differing consonants ('ll' vs 'pp') in addition, the names end with differing consonant sounds ('cks' vs 'nn')
	No.	'lo' is a distinct sound compared to 'po'. The 'x' sound is distinct from 'n'
	No.	New-Lo-Gixx vs New-po-Gin
	No.	Nu-lo-jix vs Neu-po-gen
	No.	The 'l' in the middle of the Nulojix causes this phonetic dissimilarity
	No.	I think the letter 'l' in Nulojix sounds very different from the corresponding letter 'p' in Neupogen
	No.	The letter string '-jix' is not phonetically similar to '-gen' due to the presence of the crossstroke 'x'
	No.	Both names when pronounced several different ways sound very different
	No	They don't appear to be pronounced in a similar fashion to me
	No	The two names sound different to my ears

**Appendix E: Names previously reviewed in OSE Review # 2008-849/2009-1301**

Name	Similarity to Nulojix
Aciphex	(b) (4)
Calcijex	Look
Chronulac	(b) (4)
Dolgic	
Dolgic LQ	
Dolorex	
Enulose	

Maalox	(b) (4)
Mifeprex	Look
Naloxone	Look
Namenda	(b) (4)
Nebupent	(b) (4)
Neoloid	(b) (4)
Neulasta	(b) (4)
Nexium	(b) (4)
Niferex	Look
Nizoral	(b) (4)
Nolvadex	Look and Sound
Norcet	(b) (4)
Norco	(b) (4)
Norcuron	(b) (4)
Norditropin	(b) (4)
Norel EX	(b) (4)
Norflex	Look
Norgesic	(b) (4)
Novolog	(b) (4)
(b) (4)	Look
Nulev	(b) (4)
Nulllo	Sound
Nulytely	Look
Numobid	(b) (4)

\*\*\* This document contains proprietary and confidential information that should not be released to the public

Nuromax	Look
Nutraloric	(b) (4)
Nutropin	Look
Nuvaring	(b) (4)
Nuvigil	Look and Sound
Rulox	(b) (4)
Zolinza	Look

**Appendix F: Names Lacking Orthographic and/or Phonetic Similarity.**

Name	Similarity to Nulojix
Methampex	Look
Norlutin	Look
Novolog Mix	Sound
Nubain	Look
Nutrilite	Look
Nutrivit	Look
Provigil	Look
Nallpen in plastic container	Look

**Appendix G: Proprietary names not approved by the Agency**

Proprietary Name	Similarity to Nulojix	Reason for Discard
(b) (4)		

**Appendix H: Discontinued products with no available generics**

Proprietary Name	Active Ingredient	Similarity to Nulojix
Wolfina	Rauwolfia Serpentina Root	Look

**Appendix I: Names not found in commonly used references**

Proprietary Name	Similarity to Nulojix	Reason
Nalfrx	Look	Name identified in Clinical Pharmacology and Facts and Comparisons without full product characteristics. Name could not be found in commonly used references (RedBook, Drugs@FDA, Lexi-comp, Orange-Book, MicroMedex,

\*\*\* This document contains proprietary and confidential information that should not be released to the public

**Appendix J: Products with multiple differentiating characteristics**

Product name with potential for confusion	Similarity to Nulojix	Strength/Dosage Form	Usual Dose (if applicable)	Differentiating Product Characteristics and Orthographic Differences
<p>Nulojix (Belatacept lyophilized powder for injection)</p>		<p>250 mg</p>	<p><u>Initial Phase:</u> 10 mg/kg intravenously over 30 minutes</p> <p>Day of transplant (Day 1), then Days 5, Day 14 and Day 28 (1 month after transplant), then end of week 8 and week 12</p> <p><u>Maintenance Phase:</u> 5 mg/kg intravenously over 30 minutes every 4 weeks starting at the end of week 16</p>	
<p>Melanex (hydroquinone)</p>	<p>Look</p>	<p>Topical Solution: 3%</p>	<p>Apply sufficient amount to affected area twice daily</p>	<p>-Dosage form (injectable vs. topical solution)</p> <p>-Route of administration (Intravenous vs topical)</p> <p>-Dose: (10 mg/kg or 5 mg/kg) vs “sufficient amount”)</p> <p>-Frequency of administration: (Days 1, 5, 14, 28, week 8, 12, then every 4 weeks vs twice</p>

				daily)
(b) (4)				
Nalfon (fenoprofen)	Look	Capsules: 200 mg, 400 mg	200 mg to 600 mg every three, four or six hours as needed  Not to exceed 3200 mg per day	-Dosage form (injectable vs. capsule)  -Route of administration (Intravenous vs. Oral)  -Frequency of administration: (Days 1, 5, 14, 28, week 8, 12, then every 4 weeks vs every three, four or six hours)
Natacyn (natamycin)	Look	Ophthalmic suspension: 5%	Initial: One drop in conjunctival sac every one to two hours. Frequency reduction after Day 3: One drop in conjunctival sac six to eight times daily	-Dosage form (injectable vs. ophthalmic solution)  -Route of administration (oral vs. intraocular) -Dose: (10 mg/kg or 5 mg/kg) vs “one drop”)  -Frequency of administration: (Days 1, 5, 14, 28, week 8, 12, then every 4 weeks vs every one to two hours or six to eight times daily)

\*\*\* This document contains proprietary and confidential information that should not be released to the public

**Appendix J(cont'd): Products with multiple differentiating characteristics**

<p>Natazia  (estradiol valerate and estradiol valerate/dienogest)</p>	<p>Look</p>	<p>Tablets: (Dose pack) 2 tablets: 3 mg estradiol valerate 5 tablets: 2 mg estradiol valerate/2 mg dienogest 17 tablets: 2 mg estradiol valerate/ 3 mg dienogest 2 tablets: 1 mg estradiol valerate 2 tablets: inert</p>	<p>One tablet daily</p>	<p>-Dosage form (injectable vs. tablets)  -Route of administration (oral vs. oral)  -Dose: (10 mg/kg or 5 mg/kg vs one tablet)  -Frequency of administration: (Days 1, 5, 14, 28, week 8, 12, then every 4 weeks vs once daily)</p>
<p>Zelapar  (Selegiline)</p>	<p>Look</p>	<p>Orally Disintegrating Tablet: 1.25 mg</p>	<p>1.25 mg or 2.5 mg once daily in the morning</p>	<p>Dosage form (injectable vs. tablet) -Route of administration (Intravenous vs. oral) -Frequency of administration (Days 1, 5, 14, 28, week 8, 12, then every 4 weeks vs once daily) -Dose (no overlap): (5 mg/kg to 10 mg/kg vs 1.25 mg or 2.5 mg</p>

**Appendix K (cont'd): Potential confusing names with orthographic differences which minimize potential for confusion**

<p><b>Proposed Name:</b> Nulojix (Belatacept lyophilized powder for injection)</p>	<p><b>Strength:</b> Injectable 250 mg</p>	<p><b>Usual Dose:</b> <u>Initial Phase:</u> 10 mg/kg intravenously over 30 minutes  Day of transplant (Day 1), then Days 5, Day 14 and Day 28 (1 month after transplant), then end of week 8 and week 12  <u>Maintenance Phase:</u> 5 mg/kg intravenously over 30 minutes every 4 weeks starting at the end of week 16</p>
<p><b>Failure Mode: Name confusion</b></p>	<p><b>Causes (could be multiple)</b></p>	<p><b>Effects</b></p>
<p>Neupogen (Filgrastim)  Prefilled syringe/Vial: 300 mcg, 480 mcg  5 to 10 mcg/kg/day subcutaneous of intravenous once or twice daily  For treatment of neutropenia</p>	<p>Orthographic similarities: -similar length of letters (7 letters vs 8 letters)  -same beginning letter string ('Nu-' vs 'Ne-').  -The ending letters ('jix-' and '-gen' can look similar when scripted.  Phonetic: -same sounding first syllable ('Neu-' vs 'Nu') -rhyming second syllable ('-lo-' vs '-po-') -similar sounding beginning letter of third syllable ('-gen' vs '-jix')  Product Characteristic Similarities: Numeric similarity in Dose: (10 mg/kg or 5 mg/kg vs 5 mcg/kg or 10 mcg/kg)  Overlapping route of administration (intravenous)  Dosage forms: (Injectable)</p>	<p>The orthographic differences and differing product characteristics will minimize the likelihood of medication errors in usual practice settings.  Rationale:  Although both names have orthographic, phonetic and product similarities, orthographic differences including: -Nulojix contains one upstroke ('l') and one downstroke ('j') while the name Neupogen contains two downstrokes ('p' and 'g') which help to differentiate the names when scripted. -Although both names are similar length of letters, Neupogen appears longer due to the middle letterstring ('-pog-')  While both products are given one time per day, Nulojix is given as a one time dose on Days 1, 5, 14, 28, week 8, 12, then every 4 weeks vs, whereas Neupogen is given once daily or twice daily over successive days.  The name "Nulojix" is likely sufficiently phonemically distinct from "Neupogen". The most compelling argument for this difference comes from comparing the syllabic stress patterns of the two names. In "Nulojix," the second syllable has primary stress; in "Neupogen" the first syllable has primary stress. If the stress patterns are maintained by speakers, then the "u" (/ə/) would be sufficiently distinct from the "ew" (/u/) not to be pronounced as the same vowel sound. The pair /l/ and /p/ which occur in congruent</p>

**Appendix K: Potential confusing names with orthographic differences which minimize potential for confusion**

<p><b>Proposed Name:</b> Nulojix (Belatacept lyophilized powder for injection)</p>	<p><b>Strength:</b> <b>Injectable:</b> 250 mg</p>	<p><b>Usual Dose:</b> <u>Initial Phase:</u> 10 mg/kg intravenously over 30 minutes  Day of transplant (Day 1), then Days 5, Day 14 and Day 28 (1 month after transplant), then end of week 8 and week 12  <u>Maintenance Phase:</u> 5 mg/kg intravenously over 30 minutes every 4 weeks starting at the end of week 16</p>
<p><b>Failure Mode: Name confusion</b></p>	<p><b>Causes (could be multiple)</b></p>	<p><b>Mitigation of failure</b></p>
<p>Nallpen (Nafcillin) The proprietary name, Nallpen, is discontinued with available generics  Injectable: 500 gram, 1 gram, 2 gram, 10 gram  Treatment of infections caused by susceptible penicillinase-producing staphylococci.  Adult: 0.5 gram to 2 grams every 4 hours Pediatric: 50 mg/kg/day to 100 mg/kg/day in equal divided doses every 6 hours</p>	<p>Orthographic similarities: -same length of letters (7 letters) -same beginning letter 'N.' -similar letter string ('Nul-' vs 'Nal-'  Ability for dose overlap with pediatric dosing.</p>	<p>The orthographic differences and differing product characteristics will minimize the likelihood of medication errors in usual practice settings.  Rationale: Although both names have orthographic and product similarities, orthographic differences including: -placement of the upstroke (lowercase 'l' in the fourth letter position in Nallpen versus the lowercase letter 'o' in Nulojix visually differentiates the two names.)  Although, there is a possibility for a pediatric dose of Nallpen to overlap with an adult dose of Nulojix, the differing frequency of administration will differentiate the two products. (Days 1, 5, 14, 28, week 8, 12, then every 4 weeks vs every 4 to 6 hours)</p>

		<p>places in the two words are highly distinct consonants, differing in sonorance, place of articulation, and manner of airflow. Further, the /ks/ pronunciation of the “x” is highly differentiated from the /n/, also in place, manner, and sonorance. In the event that “Nulojix” is pronounced with the same stress pattern as “Neupogen” (NEW-Luh-jiks, rather than the company’s preferred “Nuh-LOW-jiks” which was produced in the verbal RX study), then the first vowel could experience centralization and become less differentiated from Neupogen. However, even in such an instance, the /l/-/p/ and /ks/-/n/ distinctions would provide sufficient basis for differentiation between these proprietary names.</p>
--	--	---