

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

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PROPRIETARY NAME REVIEW(S)

Department of Health and Human Services
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Office of Surveillance and Epidemiology

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Subject: Proprietary Name Review

Drug Name(s): Nuedexta
(Dextromethorphan Hydrobromide and Quinidine Sulfate) Capsules
20 mg/10 mg

Applicant/sponsor: Avanir Pharmaceuticals, Inc.

OSE RCM #: 2010-1623

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EXECUTIVE SUMMARY

This review summarizes DMEPA's proprietary name risk assessment of Nuedexta (Dextromethorphan Hydrobromide and Quinidine Sulfate) Capsules 20 mg/10 mg. 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, Nuedexta, acceptable for this product. The proposed proprietary name must be re-reviewed 90 days before 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.

1 BACKGROUND

1.1 INTRODUCTION

This review responds to a July 19, 2010 request from for an assessment of the proposed proprietary name, Nuedexta, regarding potential name confusion with other proprietary or established drug names in the usual practice settings.

Additionally, the container labels, carton and insert labeling are being evaluated for their potential contribution to medication errors under separate cover (OSE Review 2010-987).

1.2 REGULATORY HISTORY

The names Neurodex^{***} and Zenvia^{***} were previously proposed for Dextromethorphan Hydrobromide and Quinidine Sulfate capsules. The name Neurodex^{***} was found unacceptable in OSE Review 05-0192-1 dated June 15, 2006 and the name Zenvia^{***} was found unacceptable in OSE Review 2010-986. Thus, the name Nuedexta was submitted on July 19, 2010 for DMEPA evaluation.

This NDA is a 505(b)(2) application. The reference listed drug is Quinidine Sulfate (multiple application holders).

(b) (4)

1.3 PRODUCT INFORMATION

Nuedexta is (b) (4) for Dextromethorphan Hydrobromide and Quinidine Sulfate capsules. Nuedexta is a low-affinity uncompetitive *N*-methyl-D-aspartate receptor antagonist and a sigma-1 receptor agonist indicated for the treatment of pseudobulbar affect. The recommended starting dose is 20 mg/10 mg orally once daily for seven days. Starting on the eighth day and thereafter, the daily dose should be increased by taking a second capsule of Nuedexta 20 mg/10 mg orally every 12 hours. Neudexta will be supplied in 20 mg/10 mg strengths and packaged in 60-count bottles.

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.

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

Sections 2.1 and 2.3 identify specific information associated with the methodology for the proposed proprietary name, Nuedexta.

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.^{1,2}

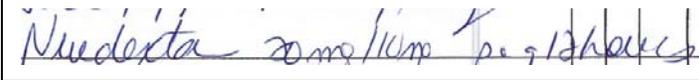
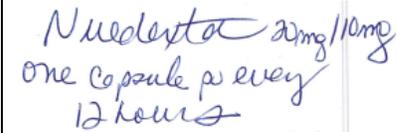
To identify drug names that may look similar to Nuedexta, the DMEPA Safety Evaluators also consider the orthographic appearance of the name on lined and unlined orders. Specific attributes taken into consideration include the length of the name (eight letters), upstrokes (two, lower case “d” and “t”), downstrokes (none), cross strokes (two, lower case “x” and “t”), and dotted letters (none). Additionally, several letters in Nuedexta may be vulnerable to ambiguity when scripted (see Appendix B). As a result, the DMEPA Safety Evaluators also considers these alternate appearances when identifying drug names that may look similar to Nuedexta.

When searching to identify potential names that may sound similar to Nuedexta, the DMEPA Safety Evaluators search for names with similar number of syllables (three), stresses (NUE-dex-ta, nue-DEX-ta, or nue-dex-TA), and placement of vowel and consonant sounds. Additionally, the DMEPA Safety Evaluators consider that pronunciation of parts of the name can vary (see Appendix B). The Applicant’s intended pronunciation of the name is “noo’ dex ta”. However, names are often mispronounced and/or spoken with regional accents and dialects, so other potential pronunciations of the name are considered.

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 prescription was communicated during the FDA prescription studies.

Figure 1. Nuedexta Prescription Studies (conducted on August 13, 2010)

HANDWRITTEN REQUISITION MEDICATION ORDER	VERBAL PRESCRIPTION
<p><u>Inpatient Medication Order:</u></p> 	<p>Nuedexta 20 mg/10 mg po q12hrs</p>
<p><u>Outpatient Prescription:</u></p> 	

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

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

3 RESULTS

3.1 DATABASE AND INFORMATION SOURCES

The DMEPA searches yielded a total of nine names as having some similarity to the name Nuedexta.

Six of the nine names were thought to look like Nuedexta. These names include Neotect, Neo-Delta-Cortef, Herplex, Nutrinat, Neutrexin, and Nordette. One of the names, Mucinex, was thought to sound like Nuedexta. The remaining two names, Neulasta and Nucynta were thought to look and sound similar to Nuedexta.

Additionally, DMEPA Safety Evaluators did not identify any United States Adopted Names (USAN) stems in the proposed proprietary name as of September 29, 2010.

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 noted one additional name, Natroba^{***}, thought to have orthographic or phonetic similarity to Nuedexta.

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 36 practitioners responded. Fifteen of the practitioners interpreted the name correctly as “Nuedexta”. The remainder of the practitioners misinterpreted the drug name. None of the responses overlapped with any existing or proposed drug names. In the verbal studies, all responses were misspelled phonetic variations of the proposed name, Nuedexta. See Appendix C for the complete listing of interpretations from the verbal and written prescription studies.

3.4 COMMENTS FROM THE DIVISION OF NEUROLOGY PRODUCTS (DNP)

3.4.1 Initial Phase of Review

In response to the OSE email dated August 9, 2010, the Division of Neurology Products (DNP) stated “The Medical Team Leader and Reviewer have no objections to the proposed tradename.”

3.4.2 Midpoint of Review

On September 23, 2010, DMEPA notified DNP via e-mail that we had no objections to the proposed proprietary name, Nuedexta. The Division of Neurology Products indicated they did not have any further comment regarding our review of the proposed name during an October 7, 2010 labeling meeting for this application.

3.5 SAFETY EVALUATOR RISK ASSESSMENT

Independent searches by the primary Safety Evaluator identified five additional names which were thought to look or sound similar to Nuedexta and represent a potential source of drug name confusion. The names with look-alike similarities to Nuedexta are Neo-Dex and Neurodex^{***}. The names with look-alike and sound-alike similarities to Nuedexta are Lunesta, Neo-Dexair, and Duexis^{***}.

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

Thus, we evaluated a total of 15 names for their potential similarity to Nuedexta: nine identified in Database and Information Sources (Section 3.1), one identified in the Expert Panel Discussion (Section 3.2), and five identified in this section by the primary Safety Evaluator.

4 DISCUSSION

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 it accordingly.

4.1 PROMOTIONAL ASSESSMENT

DDMAC evaluated the name Nuedexta from a promotional perspective and determined the name was acceptable. The Division of Neurology Products and the Division of Medication Error Prevention and Analysis concurred with this assessment.

4.2 SAFETY ASSESSMENT

In total, 15 names were identified as potential sources of name confusion with the proposed proprietary name, Nuedexta. DMEPA did not identify other aspects of the name that could function as a source of error. Eight of the 15 names were not evaluated further for the following reasons: Three names lack orthographic and/or phonetic similarity, three are discontinued products and there are no generic equivalents currently marketed, one product has a different context of use as compared to Nuedexta, and one is a name that has never been marketed in the U.S. (see Appendices D through G).

Failure mode and effects analysis (FMEA) was then applied to determine if the proposed name could potentially be confused with the remaining seven names and lead to medication errors.

This analysis determined that the name similarity between Nuedexta and these seven products is unlikely to result in medication errors for the reasons presented in Appendices H and I.

5 CONCLUSIONS AND RECOMMENDATIONS

The Proprietary Name Risk Assessment findings indicate that the proposed name, Nuedexta, is not promotional nor is it vulnerable to name confusion that could lead to medication errors. Thus, the Division of Medication Error Prevention and Analysis (DMEPA) has no objection to the proprietary name, Nuedexta, for this product at this time.

However, if any of the proposed product characteristics as stated in this review are altered prior to approval of this product, DMEPA rescinds this Risk Assessment finding and the name must be resubmitted for review. In 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. If the approval of this application is delayed beyond 90 days from the signature date of this review, the proposed name must be re-evaluated. If you have further questions or need clarifications, please contact Laurie Kelley, OSE Project Manager, at 301-796- 5068.

5.1 COMMENTS TO THE APPLICANT

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

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)

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)

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)

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)

Contains full-text information from approximately 30 texts. Includes tables and references. Among the database titles are: Handbook of Adverse Drug Interactions, Rudolph's 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)

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

16. *Medical Abbreviations Book*

Contains commonly used medical abbreviations and their definitions.

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.³

For the proposed proprietary name, DMEPA Safety Evaluators 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 Safety Evaluators also conduct 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.⁴ DMEPA uses FMEA to analyze whether the drug names identified with orthographic or phonetic similarity to the

³ National Coordinating Council for Medication Error Reporting and Prevention. <http://www.nccmerp.org/aboutMedErrors.html>. Last accessed 10/11/2007.

⁴ Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

proposed proprietary name could cause confusion that subsequently leads to medication errors in the clinical setting. DMEPA uses the clinical expertise of its Safety Evaluators 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 Safety Evaluators consider 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 Safety Evaluators consider 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.⁵ 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 Safety Evaluators also examine 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 Safety Evaluators apply 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 Safety Evaluators compare 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.

⁵ Institute of Medicine. Preventing Medication Errors. The National Academies Press: Washington DC. 2006.

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 Down strokes Cross-strokes Dotted letters Ambiguity introduced by scripting letters Overlapping product characteristics	<ul style="list-style-type: none"> Names may look similar when scripted, and lead to drug name confusion in written communication
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

Lastly, the DMEPA Safety Evaluators also consider 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 Safety Evaluators conduct 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 Safety Evaluators 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 Safety Evaluators 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) Safety Evaluators 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.⁶ 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 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:

- a. 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)].
- b. 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)].

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

- c. 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.
- d. The proposed proprietary name contains an USAN (United States Adopted Names) stem.
- e. 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 proposed name “Nuedexta”	When scripted may appear as:	When spoken may be interpreted as:
Capital “N”	h, m, r, v, z	Kn
lower case “u”	a, c, ii, l, m, n, o, v,	any vowel
lower case “e”	a, i, l, o	any vowel
lower case “d”	a, cl, ol,	
lower case “x”	f, k, t, y	
lower case “t”	f, l, x, z	
lower case “a”	ce, ci, e, o, u	any vowel
“Nue”		Knew, Neu, New, Nu
“dex”		decks, decs, deks
“ta”		sa

Appendix C: FDA Prescription Study Responses

Inpatient Medication Order	Outpatient Medication Order	Voice Prescription
Nuedexta	Nuedexta	Nudexa
Neudexta	Nuedexta	Nudexa
Nudextra	Nuedexta	Nudexa
Neudexta	Nuedexta	New Dexa
Nuedexta	Nuedexta	Nudexa
Neudexta	Nuedexta	Nudexa
Nuedexta	Nuedexta	Nudexa
Neudexta	Nuedexta	Newdexa
Nuedexta	Nuedexta?	Nudexa
Nuedexta	Nuedexter	Nudexa
Nudexta	Nuedexter	Newdexa
	Nuedexter	Nudexa
		Nudexa

Appendix D: Names Lacking Orthographic and/or Phonetic Similarity.

Name	Similarity to Nuedexta
Nutrinat	Look
Nordette	Look
Mucinex	Sound

Appendix E: Drug products that are discontinued and no generic equivalent is available

Proprietary Name	Similarity to Nuedexta	Status and Date
Neo-Delta-Cortef (Neomycin Sulfate and Prednisolone Acetate) Ophthalmic suspension Ophthalmic ointment	Look	The ANDAs for these two products were withdrawn in 1992.
Neo-Dex (Dexamethasone Sodium Sulfate and Neomycin Sulfate) Ophthalmic solution	Look	The year of last recorded sales was 1999 ⁷
Neo-Dexair (Neomycin and Dexamethasone) Ophthalmic	Look and Sound	This product has been discontinued, however, we were unable to determine the year it was discontinued. Unable to determine the ophthalmic dosage form of this product.

⁷Data provided by Thomson & Thomson's SAEGIS™ Online Service, available at (www.thomson-thomson.com). Accessed on September 16, 2010.

Appendix F: Name with different context of use

Name	Similarity to Nuedexta	Comments
Neotect (Kit for preparation of technetium Tc99M Depreotide Injection)	Look	This product is a radiopharmaceutical. It is not distributed through the usual pharmacy distribution channels and requires special handling and preparation by pharmacies that are licensed to handle these types of products.

Appendix G: Name that has never been marketed in the U.S.

Name	Similarity to Nuedexta	Comments
Neurodex***	Look	Neurodex*** was a name previously proposed for Dextromethorphan Hydrobromide and Quinidine Sulfate, the product that is the subject of this review. The name Neurodex*** was found unacceptable by DMEPA because the name is used in other countries for products that do not contain Dextromethorphan Hydrobromide and Quinidine Sulfate.

Appendix H: Products with multiple differentiating product characteristics

Product name with potential for confusion	Similarity to Nuedexta	Strength	Signa	Differentiating Product Characteristics (Nuedexta vs. Product)
Nuedexta (Dextromethorphan Hydrobromide and Quinidine Sulfate) Capsules	N/A	20 mg/10 mg	20 mg/10 mg once daily for 7 days then 20 mg/10 mg every 12 hours	N/A
Neutrexin (Trimetrexate Gluconate) for Injection <i>This product was discontinued in 2008.</i>	Look	25 mg and 200 mg	45 mg/m ² (70 kg=79 mg dose) via intravenous infusion over 60 minutes once daily for 21 days	<i>Route of administration:</i> Oral vs. intravenous <i>Dosage form:</i> Capsule vs. injection <i>Dose:</i> 20 mg/10 mg vs. approximately 79 mg for a 70 kg patient
Neulasta (Pegfilgrastim) Injection	Look	6 mg/0.6 mL	6 mg subcutaneously once per chemotherapy cycle	<i>Route of administration:</i> Oral vs. subcutaneous <i>Dosage form:</i> Capsule vs. injection <i>Frequency of administration:</i> Once daily vs. once per chemotherapy cycle
Nucynta (Tapentadol) Tablets <i>Schedule II controlled substance</i>	Look	50 mg, 75 mg, and 100 mg	50 mg to 100 mg orally every 4 to 6 hours as needed for pain	<i>Strength:</i> 20 mg/10 mg vs. 50 mg, 75 mg, and 100 mg <i>Frequency of administration:</i> Once daily vs. every 4 to 6 hours as needed

Product name with potential for confusion	Similarity to Nuedexta	Strength	Signa	Differentiating Product Characteristics (Nuedexta vs. Product)
Nuedexta (Dextromethorphan Hydrobromide and Quinidine Sulfate) Capsules	N/A	20 mg/10 mg	20 mg/10 mg once daily for 7 days then 20 mg/10 mg every 12 hours	N/A
Herplex (Idoxuridine) Ophthalmic solution <i>It appears this product is no longer marketed. The year of last recorded sales was 2000.⁸</i>	Look	0.1%	Unable to find product specific dosage and administration information for this product. However, the dosage for a similar product is as follows: Instill one drop in the affected eye(s) every hour. In acute herpes, dosage may be tapered through every two hours to four times daily prior to discontinuation (treatment should be continued for at least seven days).	<i>Route of administration:</i> Oral vs. ocular <i>Dosage form:</i> Capsule vs. ophthalmic solution <i>Frequency of administration:</i> Once daily vs. every one hour to four times per day
Natroba ^{***} (Spinosad) Suspension	Look and Sound	0.9%	Apply to scalp and hair, leave on for 10 minutes, then rinse	<i>Route of administration:</i> Oral vs. topical <i>Dosage form:</i> Capsule vs. topical suspension <i>Frequency of administration:</i> Once daily vs. once, then repeat in 7 days if necessary

⁸Data provided by Thomson & Thomson's SAEGIS™ Online Service, available at (www.thomson-thomson.com). Accessed on September 16, 2010.

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Appendix I: Names with numerical similarity in strength or dose

Proprietary Name: Nuedexta (Dextromethorphan Hydrobromide and Quinidine Sulfate) Capsules	Strength: 20 mg/10 mg	Signa: 20 mg/10 mg once daily for 7 days then 20 mg/10 mg every 12 hours
Failure Mode: Name confusion	Causes (could be multiple)	Rationale
<p>Lunesta (Eszopiclone) Tablets</p> <p><i>Strength:</i> 1 mg, 2 mg, 3 mg</p> <p><i>Dosage:</i> 2 mg or 3 mg once daily at bedtime</p>	<p>Orthographic similarity: The beginning letters of the names (“N” vs. “L”) may look similar when scripted. The second position letter “u” and the ending letters “ta” are identical to both names.</p> <p>Phonetic similarity: The first two syllables of the names have a rhyming sound (Lu-nes- vs. Nue-dex-). Additionally, the ending syllable (-ta) is identical to both names.</p> <p>There is a potential for numerical overlap between a Nuedexta dose prescribed as 20 mg or 30 mg with a Lunesta dose of 2 mg or 3 mg. The overlap could be exacerbated if a trailing zero (e.g., 2.0 or 3.0) is included with Lunesta 2 mg or 3 mg.</p> <p>Both products have an overlapping “once daily” frequency of administration.</p>	<p>Medication errors unlikely to occur due to orthographic, phonetic, and product characteristic differences between the names.</p> <p><i>Rationale:</i></p> <p>Nuedexta contains the upstroke letter “d” and the cross-stroke letter “x” which helps to differentiate the name from Lunesta.</p> <p>The “ex” sound in Nuedexta give the name a more distinct sound which may help to differentiate it from Lunesta.</p> <p>Lunesta is available in multiple strengths so a verbal prescription would require the prescriber to state the strength. The number twenty does not sound similar to the number two. This may help to differentiate the names verbally.</p> <p>Lunesta is indicated for the treatment of insomnia. Therefore, it is likely that a prescription would state it should be taken at bedtime which may help to differentiate the name from Nuedexta.</p>

Proprietary Name: Nuedexta (Dextromethorphan Hydrobromide and Quinidine Sulfate) Capsules	Strength: 20 mg/10 mg	Signa: 20 mg/10 mg once daily for 7 days then 20 mg/10 mg every 12 hours
Failure Mode: Name confusion	Causes (could be multiple)	Rationale
<p> Duexis^{***} (Ibuprofen and Famotadine) Tablets <i>Strength:</i> 800 mg/26.6 mg <i>Dosage:</i> One tablet orally three times per day <i>Duexis^{***} is a pending name within the Agency. The name was found conditionally acceptable, depending upon whether the application is approved prior to, Daxas^{***}, another pending name within the Agency.</i> </p>	<p> Orthographic similarity: Both names contain the second and third position letters “ue”. Phonetic similarity: Both names contain three syllables. The beginning syllables (Nue- vs. Du-) may sound similar when spoken. Both names contain the letters “ex” which contributes to the similarity in sound of portions of the names. Both products are administered orally and are available in a single strength. </p>	<p> Medication errors unlikely to occur due to orthographic, phonetic, and product characteristic differences. <i>Rationale:</i> Nuedexta contains eight letters and appears longer in length when scripted as compared to Duexis^{***} which contains six letters. Nuedexta contains two upstroke letters (“d” and “t”) whereas Duexis^{***} has none which helps to differentiate the names. The first two syllables in the names (“Due-ex” vs. “Nue-dex”) have a rhyming sound when spoken, however, the strong sound of the letter “d” in Nuedexta may help to differentiate the names phonetically. Additionally, the ending syllables (“ta” vs. “is”) do not sound similar. The frequency of administration differs between Nuedexta (once or twice daily) versus Duexis^{***} (three times per day). </p>

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/s/

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