

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-217s000

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: October 15, 2009

To: Bob Rappaport, M.D., Director
Division of Anesthesia, Analgesia, and Rheumatology Products

Through: Melina Griffis, R.Ph., Acting Team Leader
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Division of Medication Error Prevention and Analysis (DMEPA)

From: Anne Crandall, PharmD, Safety Evaluator
Division of Medication Error Prevention and Analysis (DMEPA)

Subject: Proprietary Name Review

Drug Name(s): Exalgo (Hydromorphone Hydrochloride) Extended-release Tablets,
8 mg, 12 mg, 16 mg, 32 mg,

Application Type/Number: NDA 021217

Applicant: Neuromed Pharmaceuticals

OSE RCM #: 2009-1105

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1 INTRODUCTION

This re-assessment of the proprietary name is written in response to a notification that NDA 021217 may be approved within 90 days. The Division of Medication Error Prevention and Analysis (DMEPA) found the proposed proprietary name, Exalgo, acceptable in OSE Review #2009-84, dated June 1, 2009. The Division of Anesthesia, Analgesia, and Rheumatology Products did not have any concerns with the proposed name, Exalgo, and the Division of Drug Marketing, Advertising and Communications (DDMAC) found the name acceptable from a promotional perspective on January 22, 2009.

2 METHODS AND RESULTS

For the proposed proprietary name, DMEPA staff search a standard set of databases and information sources (see section 4) to identify names with orthographic and/or phonetic similarity to the proposed name that have been approved since the previous (OSE Review #2009-84) proprietary name review. We used the same search criteria previously used and we re-analyzed the names from OSE Review #2009-84 because of the applicant's decision to not produce or market the 64 mg strength. Additionally, DMEPA searched the USAN stem list to determine if the name contains any USAN stems as of the last USAN updates. DMEPA bases the overall risk assessment on the findings of a Failure Mode and Effects Analysis¹ (FMEA) of the proposed proprietary name, and focuses on the avoidance of medication errors

The searches of the databases referenced in Section 4 yielded no additional new names which were thought to have look-alike or sound-alike similarity to the name, Exalgo. A re-analysis of the names identified in OSE Review #2009-84, due to the exclusion of the 64 mg strength, did not introduce any new vulnerabilities with these names.

DMEPA staff did not identify any United States Adopted Names (USAN) stems in the proposed proprietary name, Exalgo, as of October 6, 2009.

3 CONCLUSIONS AND RECOMMENDATIONS

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

DMEPA considers this a final review; however, if approval of the NDA is delayed beyond 90 days from the date of this review, the Division of Anesthesia, Analgesia, and Rheumatology Products should notify DMEPA because the proprietary name must be re-reviewed prior to the new approval date.

¹ Institute for Healthcare Improvement (IHI). Failure Mode and Effects Analysis. Boston. IHI:2004.

4 REFERENCES

1. OSE review # 2009-84 Proprietary Name Review of Exalgo; Crandall, Anne K.

2. *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.

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

USAN Stems List contains all the recognized USAN stems.

4. *CDER Proposed Name List*

Compiled list of proposed proprietary names submitted to the Division of Medication Error Prevention and Analysis (DMEPA) for review. The list is updated weekly and maintained by DMEPA.

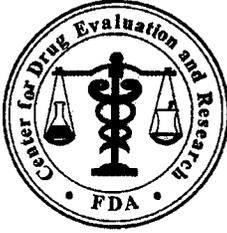
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**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology**

Date: June 1, 2009

To: Bob Rappaport, MD, Director
Division of Analgesics, Anesthetics, and Rheumatology Products

Thru: Melina Griffis, RPh, Acting Team Leader
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Division of Medication Error Prevention and Analysis

From: Anne Crandall, PharmD, Safety Evaluator
Division of Medication Error Prevention and Analysis

Subject: Proprietary Name Review

Drug Name(s): Exalgo (Hydromorphone Hydrochloride) Extended-release Tablets,
8 mg, 12 mg, 16 mg, 32 mg, 64 mg

Application Type/Number: IND # 78,223

Applicant/sponsor: Neuromed Pharmaceuticals, Inc.

OSE RCM #: 2009-84

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

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EXECUTIVE SUMMARY

The results of the Proprietary Name Risk Assessment found that the proposed name, Exalgo, is not vulnerable to name confusion that could lead to medication errors. Thus the Division of Medication Error Prevention and Analysis has no objection to the proprietary name, Exalgo, for this product.

However, if any of the proposed product characteristics as stated in this review are altered prior to approval of the product, DMEPA rescinds this Risk Assessment finding and recommends that the name 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.

In addition, the proposed name must be reevaluated 90 days before approval of the NDA, even if the proposed product characteristics as stated in this review are not altered.

1 BACKGROUND

1.1 INTRODUCTION

This review is in response to a request from Neuromed Pharmaceuticals, dated January 13, 2009 for an assessment of the proposed proprietary name, Exalgo, for Hydromorphone hydrochloride Extended-release tablets. An external name study conducted by the (b) (4) was submitted by Neuromed Pharmaceuticals along with this request.

1.2 REGULATORY HISTORY

The Exalgo IND (#78,223) was submitted by Neuromed Pharmaceuticals, Inc. on July 20, 2007. The IND is active with studies currently ongoing.

1.3 PRODUCT INFORMATION

Exalgo (Hydromorphone Hydrochloride) is a long acting, opioid analgesic for moderate to severe pain for patients needing chronic therapy. The recommended dose is one tablet by mouth once daily with a maximum daily dose of 32 mg to 64 mg. Exalgo will be available as 8 mg, 12 mg, 16 mg, 32 mg and 64 mg extended release oral tablets supplied in bottles containing (b) (4) tablets. Exalgo is the first extended release hydromorphone product under development (Palladone, an extended release hydromorphone product was pulled from the market after less than one year due to adverse outcomes).

2 METHODS AND MATERIALS

This section describes methods and materials used by DMEPA staff conducting a proprietary name risk assessment (see 2.1 Proprietary Name Risk Assessment).

The primary focus for this assessment is to identify and remedy potential sources of medication error prior to drug approval. 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.¹

¹ Institute for Healthcare Improvement (IHI). Failure Mode and Effects Analysis. Boston. IHI:2004.

2.1 PROPRIETARY NAME RISK ASSESSMENT

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

For the proprietary name, Exalgo, DMEPA search a standard set of databases and information sources to identify names with orthographic and phonetic similarity (see Sections 2.1.1 for detail) and held an CDER Expert Panel discussion to gather professional opinions on the safety of the proposed proprietary name (see 2.1.1.2). The Division also conducts internal CDER prescription analysis studies (see 2.1.2), and, when provided, external prescription analysis studies results are considered and incorporated into the overall risk assessment (see detail 2.1.4).

The Safety Evaluator assigned to the Proprietary Name Risk Assessment is responsible for considering the collective findings, and provides an overall risk assessment of the proposed proprietary name (see detail 2.1.4). The overall risk assessment is based on the findings of a Failure Mode and Effects Analysis (FMEA) of the proprietary name, and is focused on the avoidance of medication errors.

FMEA is a systematic tool for evaluating a process and identifying where and how it might fail.¹ FMEA is used to analyze whether the drug names identified with look- or sound-alike similarity to the proposed name could cause confusion that subsequently leads to medication errors in the clinical setting. DMEPA uses the clinical expertise of the DMEPA staff to anticipate the conditions of the clinical setting that the product is likely to be used in based on the characteristics of the proposed product.

In addition, the product characteristics provide the context for the verbal and written communication of the drug names and can interact with the orthographic and phonetic attributes of the names to increase the risk of confusion when there is overlap, or, in some instances, decrease the risk of confusion by helping to differentiate the products through dissimilarity. Accordingly, the DMEPA staff considers the product characteristics associated with the proposed drug throughout the risk assessment, since the product characteristics of the proposed may provide a context for communication of the drug name and ultimately determine the use of the product in the *usual* clinical practice setting.

Typical product characteristics considered when identifying drug names that could potentially be confused with the proposed drug name include, but are not limited to established name of the proposed product, the proposed indication 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, the DMEPA staff considers the potential for confusion throughout the entire U.S. medication use process, including drug procurement, prescribing and ordering, dispensing, administration, and monitoring the impact of the medication.²

² Institute of Medicine. Preventing Medication Errors. The National Academies Press: Washington DC. 2006.

2.1.1 Search Criteria

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

For this review, particular consideration was given to drug names beginning with the letter 'E' 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.^{3,4}

To identify drug names that may look similar to Exalgo, the staff also consider the orthographic appearance of the name on lined and unlined orders. Specific attributes taken into consideration include the length of the name (6 letters), upstrokes (two, capital letter 'E' and 'l'), downstrokes (one, 'g'), cross-strokes (one, 'x'), and dotted letters (none). Additionally, several letters in Exalgo may be vulnerable to ambiguity when scripted, including the letter 'E' may appear as 'L'; lower case 'x' appears as a lower case 'z' or 'v'; lower case 'a' may appear as lower case, 'u', 'o', or 'e'; lower case 'l' may appear as lower case 'f' or 't'; and lower case 'g' may appear as lower case 'j', 'z' or 'p' and lower case 'o' may appear as lower case 'a', 'e' or 'u'. As such, the Staff also considers these alternate appearances when identifying drug names that may look similar to Exalgo.

When searching to identify potential names that may sound similar to Exalgo, the DMEPA staff search for names with similar number of syllables (three), stresses (EX-al-go, ex-AL-go or ex-al-GO), and placement of vowel and consonant sounds. In addition, several letters in Exalgo may be subject to interpretation when spoken, including the letters 'Ex' may be interpreted as 'Es', 'Ect' or 'X'; the letters 'al' may be interpreted as 'all' and the letter 'g' may be interpreted as 'j' or 'k'. The Applicant's intended pronunciation of the proprietary name (eks-al-goh) was provided by the sponsor in the submission.

DMEPA also considers the product characteristics associated with the proposed drug throughout the identification of similar drug names, since the product characteristics of the proposed drug ultimately determine the use of the product in the clinical practice setting. For this review, the medication error staff was provided with the following information about the proposed product: the proposed proprietary name (Exalgo), the established name (Hydromorphone hydrochloride), proposed indication (treatment of moderate to severe pain for patients needing chronic therapy), strength (8 mg, 12 mg, 16 mg, 32 mg and 64 mg), dose (one tablet), frequency of administration (once daily), route of administration (oral) and dosage form of the product (tablet). Appendix A provides a more detailed listing of the product characteristics DMEPA generally takes into consideration.

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

³ Institute for Safe Medication Practices. Confused Drug name List (1996-2006). Available at <http://www.ismp.org/Tools/confuseddrugnames.pdf>

⁴ Kondrack, G and Dorr, B. Automatic Identification of Confusable Drug Names. Artificial Intelligence in Medicine (2005)

2.1.1.1 Database and Information Sources

The proposed proprietary name, Exalgo, was provided to DMEPA to conduct a search of the internet, several standard published drug product reference texts, and FDA databases to identify existing and proposed drug names that were not identified in the previous reviews that may sound-alike or look-alike to Exalgo using the criteria outlined in 2.1.1. A standard description of the databases used in the searches is provided in Section 7. To complement the process, DMEPA uses a computerized method of identifying phonetic and orthographic similarity between medication names. The program, Phonetic and Orthographic Computer Analysis (POCA), uses complex algorithms to select a list of names from a database that have some similarity (phonetic, orthographic, or both) to the trademark being evaluated. Lastly, the DMEPA staff reviews the USAN stem list to determine if any USAN stems are present within the proprietary name. The findings of the individual Safety Evaluators were then pooled and presented to the Expert Panel.

2.1.1.2 CDER Expert Panel Discussion

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

The pooled results of the DMEPA staff were presented to the Expert Panel for consideration. Based on the clinical and professional experiences of the Expert Panel members, the Panel may recommend the addition of names, additional searches by the Safety Evaluator to supplement the pooled results, or general advice to consider when reviewing the proposed proprietary name.

2.1.2 FDA Prescription Analysis Studies

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

In order to evaluate the potential for misinterpretation of Exalgo 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 prescriptions are optically scanned and one prescription is delivered to a random sample of 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 the DMEPA staff.

Figure 1. CDER Rx Study 0130 (January 30, 2009)

| HANDWRITTEN PRESCRIPITON AND MEDICATION ORDER | VERBAL PRESCRIPTION |
|---|--|
| <p><u>Inpatient Medication Order #1:</u></p> <p>Exalgo 32 mg 1 tablet by mouth daily</p> | <p>Exalgo 32 mg Dispense # 30 One tablet by mouth once daily</p> |
| <p><u>Outpatient Medication Orders</u></p> <p>Exalgo 32 mg # 30 1 tab p.o q day</p> | |

2.1.3 External Proprietary Name Risk Assessment

For this product, the Sponsor submitted a name validation study conducted by (b) (4) (b) to evaluate the proposed proprietary name Exalgo. 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 assessment of the proposed name, the Safety Evaluator compares the findings of their overall risk assessment with the findings of the proprietary name risk assessment submitted by the Sponsor. The Safety Evaluator then determines whether the Division’s risk assessment concurs or differs with the findings. When the proprietary name risk assessments differ, the Division of Medication Error Prevention and Analysis provides a detailed explanation of these differences.

2.1.4 Comments from the OND review Division or Generic drugs

DMEPA requests the regulatory division in the Office of New Drugs 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. Any comments or concerns are addressed in the safety evaluator’s assessment.

The 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 regulatory division is requested to concur/not concur with DMEPA's final decision.

2.1.5 Safety Evaluator Risk Assessment of the Proposed Proprietary Name

Based on the criteria set forth in Section 2.1.1, the Safety Evaluator Risk Assessment applies their individual expertise gained from evaluating medication errors reported to FDA to conduct a Failure Mode and Effects Analysis and provide an overall risk of name confusion. Failure Mode and Effects Analysis (FMEA) is a systematic tool for evaluating a process and identifying where and how it might fail.⁵ When applying FMEA to assess the risk of a proposed proprietary name, the Division of Medication Error Prevention and Analysis seeks to evaluate the potential for a proposed name to be confused with another drug name as a result of the name confusion and cause errors to occur in the medication use system. FMEA capitalizes on the predictable and preventable nature of medication errors associated with drug name confusion. FMEA allows the Agency to identify the potential for medication errors due to look- or sound-alike drug names prior to approval, where actions to overcome these issues are easier and more effective than remedies available in the post-approval phase.

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

In the initial stage of the Risk Assessment, the Safety Evaluator compares the proposed proprietary name to all of the names gathered from the above searches, expert panel evaluation, and studies, and identifies potential failure modes by asking:

“Is the name Exalgo 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 Exalgo to be confused with another proprietary or established drug name because of look- or sound-alike similarity. If the answer to the question is no, the Safety Evaluator is not convinced that the names possess similarity that would cause confusion at any point in the medication use system and the name is eliminated from further review.

In the second stage of the Risk Assessment, all potential failure modes are evaluated to determine the likely *effect* of the drug name confusion, by asking:

“Could the confusion of the drug names conceivably result in medication errors in the usual practice setting?”

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

⁵ Institute for Healthcare Improvement (IHI). Failure Mode and Effects Analysis. Boston. IHI:2004.

reformulation to avoid an overlap in strength or an alternate modifier designation may be recommended as a means of reducing the risk of medication errors resulting from drug name confusion.

The Division of Medication Error Prevention and Analysis will object to the use of proposed proprietary name when the one or more of the following conditions are identified in the Safety Evaluator's Risk Assessment:

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

In the event that 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 is awarded approval first has the right to the use the name, while DMEPA will recommend that the second product to reach approval seek an alternative name.

If none of these conditions are met, then DMEPA will not object to the use of the proprietary name. If any of these conditions are met, then DMEPA will object to the use of the proprietary name. The threshold set for objection to the proposed proprietary name may seem low to the Sponsor; however, the safety concerns set forth in criteria 1 through 5 are supported either by FDA Regulation or by external healthcare authorities, including the IOM, WHO, JCAHO, and ISMP, have examined medication errors resulting from look- or sound-alike drug names and called for Regulatory Authorities to address the issue prior to approval.

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

Additionally, post-marketing experience has demonstrated that medication errors resulting from drug name confusion are notoriously difficult to remedy post-approval. Educational efforts and so on are low-leverage strategies that have proven to have limited effectiveness at alleviating the medication errors involving drug name confusion. Higher-leverage strategies, such as drug name changes, have been undertaken in the past; but at great financial cost to the Sponsor, and at the expense of the public welfare, not to mention the Agency's credibility as the authority responsible

for the approving the error-prone proprietary name. Moreover, even after Sponsor's have changed a product's proprietary name in the post-approval phase, it is difficult to eradicate the original proprietary name from practitioner's vocabulary, and as such, the Agency has continued to receive reports of drug name confusion long after a name change in some instances. Therefore, 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 limitations of the process).

If DMEPA objects to a proposed proprietary name on the basis that drug name confusion could lead to medication errors, the FMEA process is used to identify strategies to reduce the risk of medication errors. DMEPA is likely to recommend that the Sponsor 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, and so DMEPA may be able to provide the Sponsor with recommendations that reduce or eliminate the potential for error would render the proposed name acceptable.

3 RESULTS

3.1 DATABASE AND INFORMATION SOURCES

For this review, DMEPA identified 14 names as having some similarity to the name Exalgo. The names Exelon, Exforge, (b) (4), Exaltone, Exalver, Exjade, Exolpen (b) (4), Ertazco, Lexapro, and Exacta were thought to look like Exalgo. Synaglos-DC was thought to sound like Exalgo. The names Exalgon and Exalgin were thought to look and sound like Exalgo.

A search of the United States Adopted Name stem list on May 18, 2009 identified no USAN stem names in the proposed name, Exalgo.

3.2 CDER EXPERT PANEL DISCUSSION

The Expert Panel reviewed the pool of names identified by the Division of Medication Error Prevention staff (see section 3.1.1. above), but did not identify any additional names with similarity to Exalgo. A safety issue regarding dose overlap of immediate release hydromorphone 8 mg and Exalgo 8 mg was discussed and potential problems that may ensue.

The sporadic use of the modifier, OROS, throughout the IND, was discussed in EPD and whether this was acceptable in the established name.

DDMAC had no concerns regarding the proposed name from a promotional perspective.

3.3 FDA PRESCRIPTION ANALYSIS STUDIES

A total of 26 practitioners responded, but none of the responses overlapped with any existing or proposed drug names. About 46 % of the participants (n=112) interpreted the name correctly as 'Exalgo', with correct interpretation occurring more frequently in the written studies. The remainder of the responses misinterpreted the drug name. The predominant misinterpretation that occurred in the phonetic prescription study was the misinterpretation of the 'g' as a 'j', one respondent misinterpreted 'al' for 'tel'. In the written studies the most common misinterpretation occurred with the letter 'g' and was misinterpreted for other downstroke letters including; 'y', 'j' and 'p'. One respondent misinterpreted 'x' for 's', however no other respondents misinterpreted this letter. See Appendix B for the complete listing of interpretations from the verbal and written prescription studies.

3.4 COMMENTS FROM THE DIVISION

In response to the OSE e-mail sent January 22, 2009, the Division of Analgesics, Anesthetics, and Rheumatology Products did not forward any comments and or concerns on the proposed proprietary name at the initial phase of the name review.

DMEPA notified the Division of Analgesics, Anesthetics, and Rheumatology Products, via e-mail, that we had no objections to the proposed proprietary name; Exalgo, on March 23, 2009. Per e-mail correspondence from the Division of Analgesics, Anesthetics, and Rheumatology Products on March 23, 2009 they indicated they concur with our assessment of the proposed proprietary name, Exalgo.

3.4 EXTERNAL NAME STUDY

In the submission the applicant provided a proposed name validation study conducted by the (b) (b) (4) which identified 13 names that look or sound similar to the proposed proprietary name, Exalgo. (b) utilized an Internal Expert Panel Discussion, Rx Studies and Computerized Orthographic and Phonologic Analysis to identify names that look or sound like to Exalgo. The following 13 names were identified by (b) Dexalone, Excedrin, Exelon, Exjade, Exsel, Exubera, Flexall, Hexalen, Ixemptra, Lexapro, Lexxel, Maxalt, and Trexall. Three of these names (Exelon, Exjade, and Lexapro) were also found by DMEPA.

3.5 SAFETY EVALUATOR RISK ASSESSMENT

It was noted that the sponsor used the term OROS inconsistently with the established name throughout the labeling. Additionally, there were safety concerns regarding the overlap in strength between the 8 mg Exalgo and the currently marketed Hydromorphone Immediate-release formulation (Dilaudid) and the potential for medication errors.

Independent searches by the primary Safety Evaluator did not identify any additional names which were thought to look or sound similar to Exalgo and represent a potential source of drug name confusion. Twenty four names were analyzed to determine if the drug names could be confused with Exalgo and if the drug name confusion would likely result in a medication error.

Six names lacked significant orthographic similarity to Exalgo, therefore these names did not undergo further analysis for drug name confusion.

Failure mode and effect analysis (FMEA) was then applied to determine if the name could potentially be confused with any of the remaining 18 names and lead to medication errors. This analysis determined that the name similarity between Exalgo and the identified names was unlikely to result in medication errors with any of the 18 products identified for the reasons presented in Appendices D through H.

4 DISCUSSION

Exalgo is the first extended-release hydromorphone product to be approved since Palladone (Palladone was pulled from the market in 2005). Thus our evaluation of the proposed product considered the name and product characteristics and post marketing history of medication errors involving hydromorphone.

4.1 PROPOSED PROPRIETARY NAME

Twenty four names were evaluated for their potential similarity to the proposed name, Exalgo. The FMEA indicates that the proposed name is not likely to result in name confusion that could lead to

medication errors. This finding was consistent with and supported by an independent risk assessment of the proprietary name submitted by the Applicant.

4.2 PROPOSED ESTABLISHED NAME

The Sponsor uses two different established names throughout the IND; OROS Hydromorphone Hydrochloride and Hydromorphone Hydrochloride. OROS is an osmotic drug delivery system. Drug delivery systems are not recognized as a component of the established name, thus the abbreviation, OROS, should not be part of the established name. However, DMEPA will defer final determination of the established name and dosage form to the Labeling and Nomenclature Committee (LNC) for further analysis.

4.2 AVAILABILITY OF TWO 8 MG HYDROMORPHONE PRODUCTS

The introduction of Exalgo to the market place will create the availability of two 8 mg hydromorphone products, Exalgo and Dilaudid. Because the proprietary name has no recognized modifier (e.g. XR) indentifying it as an extended release product coupled with the lack of awareness of the product upon approval, could lead to medication errors when generic substitutions are prescribed or dispensed. Since Exalgo and Dilaudid are dosed differently (once daily vs. every 4 hours to 6 hours as needed) an inadvertent substitution could lead to a significant overdose or under-dose of hydromorphone. This safety issue was conveyed via email to the clinical team from DAARP, on March 20, 2009. The clinical team discussed this issue with DMEPA via conference call on March 23, 2009.

Ideally, DMEPA would prefer that an overlap of strength be avoided, however after discussion with the medical officers in DAARP we acknowledge that the development of Exalgo is near completion and recognize that an 8 mg initial dose of Exalgo is necessary and coincides with the conversion from other opioid doses. Per the discussion, both DMEPA and DAARP agreed that the best way to ensure safe prescribing and dispensing, when Exalgo is introduced in the marketplace, is to educate providers regarding the introduction of a new hydromorphone product that has an overlapping strength (8 mg) with the existing immediate release hydromorphone product on the market. DMEPA will also provide recommendations when the labeling is submitted with the NDA that may help mitigate errors by communicating to practitioners that Exalgo is dosed once daily.

5 CONCLUSIONS AND RECOMMENDATIONS

The Proprietary Name Risk Assessment findings indicate that the proposed name, Exalgo, is not vulnerable to name confusion that could lead to medication errors, nor is the name promotional. This finding was consistent with and supported by an independent risk assessment of the proprietary name submitted by the Sponsor. As such, the Division of Medication Error Prevention and Analysis does not object to the use of the proprietary name, Exalgo, for this product.

However, an overlap in strength between the currently marketed immediate release hydromorphone and the proposed product will require educational, label and labeling strategies to avert potential confusion between the hydromorphone immediate release products and this extended-release formulation.

If any of the proposed product characteristics as stated in this review are altered prior to approval of the product, the Division of Medication Error Prevention and Analysis rescinds this Risk Assessment finding, and recommends that the name be resubmitted for review.

5.1 COMMENTS TO THE DIVISION

We would be willing to meet with the Division for further discussion, if needed. Please copy the Division of Medication Error Prevention on any communication to the Applicant with regard to this review. If you have any questions or need clarification, contact Chris Wheeler, Project Manager, at 301-796-0151.

We note in certain instances throughout the IND the established name of Exalgo is referred to as OROS Hydromorphone Hydrochloride. Delivery systems or dosage forms should not be incorporated into the established name, however we defer to LNC to provide guidance for established names.

Additionally, per discussions with the DAARP clinical team, DMEPA and DAARP concur that the introduction of a second 8 mg hydromorphone product, as well as a new long acting opiate formulation, will introduce a potential for medication errors that will require prescriber education and detailed labeling. We look forward to collaborating in the future, upon submission of the NDA, to ensure that all labeling appropriately conveys and mitigates the concerns regarding the introduction of this opioid product to the market.

5.2 COMMENTS TO THE APPLICANT

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

A request for proprietary name review for Exalgo should be submitted once the NDA is submitted.

If any of the proposed product characteristics are altered as stated in your January 13, 2009 submission the proprietary name should be resubmitted for review.

Additionally, the introduction of Exalgo to the market place will create the availability of two 8 mg hydromorphone products, Exalgo and Dilaudid. Because the proprietary name has no recognized modifier (e.g. XR) indentifying it as an extended release product coupled with the lack of awareness of the product upon approval could lead to medication errors. Since Exalgo and Dilaudid are dosed differently (once daily vs. every 4 hours to 6 hours as needed) an inadvertent substitution could lead to a significant overdose or under-dose of hydromorphone. Theses concerns should be addressed in labeling upon submission of the NDA.

7 REFERENCES

1. ***Micromedex Integrated Index*** (<http://weblern/>)

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, FDA.

3. ***Drug Facts and Comparisons, online version, St. Louis, MO*** (<http://weblern/>)

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

4. ***AMF Decision Support System [DSS]***

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

5. ***Division of Medication Errors and Technical Support proprietary name consultation requests***

This is a list of proposed and pending names that is generated by the Division of Medication Error Prevention 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 and generic drugs and therapeutic biological products; prescription and over-the-counter human drugs and therapeutic biologicals, 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. ***WWW location*** <http://www.uspto.gov>.

Provides information regarding patent and trademarks.

9. ***Clinical Pharmacology Online*** (<http://weblern/>)

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 tradenames that are used in about 50 countries worldwide. The data is provided under license by IMS HEALTH.

11. Natural Medicines Comprehensive Databases (<http://weblern/>)

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

12. Stat!Ref (<http://weblern/>)

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.pharmacist.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:

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. The 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* dissimilarly spelled drug name pairs to appear very similar to one another and the similar appearance of drug names when scripted has led to medication errors. The DMEPA staff applies their expertise gained from root-cause analysis of such medication errors to identify sources of ambiguity within the name that could be introduced when scripting (i.e. "T" may look like "F," lower case 'a' looks like a lower case 'u,' etc), along with other orthographic attributes that determine the overall appearance of the drug name when scripted (see detail in Table 1 below). Additionally, since verbal communication of medication names is common in clinical settings, the DMEPA staff compares the pronunciation of the proposed proprietary name with the pronunciation of other drug names. If provided, DMEPA will consider the Sponsor's intended pronunciation of the proprietary name. However, because the Sponsor has little control over how the name will be spoken in practice, DMEPA also considers a variety of pronunciations that could occur in the English language.

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

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

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

Appendix B: CDER Prescription Study Responses- Exalgo Study 0130

| Inpatient Medication Order | Voice Prescription | Outpatient Medication Order |
|----------------------------|--------------------|-----------------------------|
| Exalgo | Exaljo | Exalyc |
| Esalgo | Exaljo | Exalgo |
| Exalgo | Exaljo | Exalyo |
| Exalso | Exteljo | Exelgo |
| Exalgo | | Exalgo |
| Exalgo | | Exalejo |
| Exalgo | | Exalgo |
| Exalgo | | Exalep |
| | | Exalego |
| | | Exalgo |
| | | Exalapro |
| | | Exalejo |
| | | Exalgo |
| | | Exalgo |

Appendix C: Names lacking significant orthographic or phonetic similarities

| Proprietary Name | Similarity to Exalgo | Source |
|------------------|----------------------|--------|
| Excedrin | Both | (b) |
| Flexall | Both | (b) |
| Lexxel | Sound | (b) |
| Maxalt | Sound | (b) |
| Trexall | Both | (b) |
| Synaglos-DC | Sound | EPD |

Appendix D: Proprietary name approved, drug application withdrawn before product marketed

| Proprietary name/ NDA# | Established name | NDA withdrawn |
|------------------------|------------------|---------------|
| (b) (4) | (b) (4) | |
| (b) (4) | (b) (4) | |

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

Appendix E: Proprietary name internationally registered

| Proprietary Name (Established Name) | Similarity to Exalgo | Countries | Source |
|--|----------------------|-------------|------------|
| Exalgon | Not provided | Germany | Saegis |
| Exalver (Paracetamol/Pseudoephedrine/dextromethorphan) | Look | Mexico | Micromedex |
| Exolpen (Ambroxol) | Look | Philippines | Micromedex |
| Exalgin (Dipyrone) | Both | Mexico | Micromedex |

Appendix F: Name identified is not a drug product

| Name | Source | Website |
|----------------------------------|--------|---|
| Exaltone (Cyclopentadecanone) | EPD | Micromedex-RTECS (Registry of Toxic Effects of Chemical Substances) |

Appendix G: Products with no numerical overlap in strength and dose

| Product name with potential for confusion | Similarity to Exalgo | Strength | Usual Dose (if applicable) |
|---|----------------------|--|--|
| Exalgo (OROS Hydromorphone Hydrochloride) | | 8 mg, 12 mg, 16 mg, 32 mg, 64 mg oral tablet | Usual dose: One tablet orally once daily, max daily dose is 32 mg to 64 mg |
| Dexalone (Dextromethorphan hydrobromide) | Both | 30 mg oral capsules | 1 capsule orally every 6 hours to 8 hours as needed |
| Exjade (Deferasirox) | Both | 125 mg, 250 mg, 500 mg tablets for oral suspension (dispersible tablets) | 20 mg to 30 mg per kg orally once daily |
| Exsel (Selenium sulfide) Discontinued as Exsel, available as generic | Sound | 2.5 % shampoo/lotion | Shampoo twice weekly then one to four times per month as necessary. Lotion apply topically once daily |
| Hexalen (Altretamine) | Both | 50 mg oral capsule | 260 mg/m ² per day for 14 or 21 consecutive days in a 28 day cycle. Total daily dose should be given as 4 divided oral doses after meals and at bedtime |
| Ixempra (Ixabepilone) | Look | 15 mg, 45 mg powder for injection kit (with diluent) | 40 mg per meter squared per dose intravenously every 3 weeks |
| Lexapro (Escitalopram) | Look | 5 mg, 10 mg, 20 mg oral tablets 5 mg/mL oral solution | 10 mg to 20 mg orally once daily |

| Product name with potential for confusion | Similarity to Exalgo | Strength | Usual Dose (if applicable) |
|--|----------------------|---|---|
| Exalgo (OROS Hydromorphone Hydrochloride) | | 8 mg, 12 mg, 16 mg, 32 mg, 64 mg oral tablet | Usual dose: One tablet orally once daily, max daily dose is 32 mg to 64 mg |
| Exforge (Amlodipine besylate/Valsartan) | Look | 5 mg/160 mg, 10 mg/160 mg, 5 mg/320 mg, 10 mg/320 mg oral tablets | One tablet orally once daily |
| Ertazco (Sertaconazole) | Look | 2 % Topical cream | Apply twice daily to feet for 4 weeks |
| Exacta (Barium sulfate) | Look | 1.2 %, 1.5 % oral suspension; 10 % oral tablet; 100 % oral powder | Drink orally, or administer rectally based on type of procedure one to two hours prior to procedure |

Appendix H: Names of products with same dose or achievable dose, but differentiating product characteristics

| Product name with potential for confusion | Similarity to Proposed Proprietary Name | Strength | Usual Dose (if applicable) | Other differentiating product characteristics |
|---|---|--|---|--|
| Exalgo (OROS Hydromorphone Hydrochloride) | | 8 mg, 12 mg, 16 mg, 32 mg, 64 mg oral tablets | One tablet orally once daily, max daily dose is 32 mg to 64 mg | |
| Exubera* (Recombinant insulin, human) * Removed from market as of 2008 | Sound | 1 mg, 3 mg blisters for oral inhalation | Dose varies per patient, inhaled immediately prior to meals | <i>Frequency of administration</i> (once daily vs. three times daily) <i>Dosage form</i> (tablet vs. blister with powder for inhalation) <i>Directions for use</i> (Exubera is a rapidly acting insulin so must be taken 10 minutes before meal, directions would likely include the directions with food or meal) |

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

| Exalgo (OROS Hydromorphone Hydrochloride) | 8 mg, 12 mg, 16 mg, 32 mg, 64 mg oral tablets | Usual dose: One tablet orally once daily, max daily dose is 32 mg to 64 mg |
|---|---|--|
| Failure Mode: Name Confusion | Causes (could be multiple) | Rationale |
| <p>Exelon (Rivastigmine tartrate)</p> <p>Oral capsules; 1.5 mg, 3 mg, 4.5 mg, 6 mg</p> <p>Oral suspension; 2 mg/mL</p> <p>Transdermal patch 4.6 mg/24 hours, 9.5 mg/24 hours</p> <p>1.5 mg to 6 mg orally twice daily</p> <p>4.5 mg or 9.5 mg patch applied topically per day</p> | <p>Orthographic (Both begin with 'Ex', similar length, both have 'l' as fourth letter providing upstroke)</p> <p>Phonetic (3 syllables, begin with "X" sound)</p> <p>Route of administration (oral)</p> <p>Dosage form (capsule vs. tablet, oral solution)</p> <p>Attainable dose (12 mg tablet vs. 2 capsules of 6 mg)</p> | <p>Orthographically Exalgo has a down stroke 'g' vs. no downstrokes in Exelon, ends with 'go' in Exalgo vs. 'on' in Exelon.</p> <p>Phonetically the second syllable for Exalgo consists of the sound AL vs. E in Exelon. The L sound in Exelon is heard in third syllable as LAHN vs. no L sound in the third syllable of Exalgo. The third syllable GO in Exalgo has no similarity in sound to LAHN in Exelon.</p> <p>Dosing is once daily for Exalgo vs. twice daily for Exelon. The maximum milligram per dose for Exelon is 6 mg. Exalgo is not available as a 6 mg dosage form and cannot be broken due to the extended release formulation. In order to obtain the 12 mg dose for Exalgo, the patient would have to ingest two of the 6 mg capsules which exceeds the maximum recommended dosage for Exelon.</p> |

Linked Applications

Sponsor Name

Drug Name / Subject

IND 78223

NEUROMED PHARMA
INC

OROS HYDROMORPHONE TABS

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

/s/

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