CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-285

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:	September 12, 2008
To:	Russell Katz, M.D. Director, Division of Neurology Products
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From:	Diane C. Smith, PharmD, Safety Evaluator Division of Medication Error Prevention and Analysis
Subject:	Proprietary Name Review
Drug Name(s):	Keppra XR (Levetiracetam Extended-release) Tablets 500 mg
Application Type/Number:	NDA 22-285
Applicant:	UCB, Inc.
OSE RCM #:	2008-1158

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EXECUTIVE SUMMARY

Our analysis of the proposed proprietary name Keppra XR indicates that confusion can occur between Keppra and Keppra XR. Although this finding would lead to DMEPA objecting to the proposed name our FMEA determined the use of an alternate proprietary name can lead to concomitant therapy with Keppra and the alternate name. The Applicant's proposal to add a modifier to the Keppra root name is a recognized naming convention commonly used when an extended release dosage form is added to a product line with an existing immediate-release product. Therefore, we will not object to the use of the name, Keppra XR, for this product. However, we recommend at the time of product launch the Applicant inform healthcare practitioners about the differences between Keppra XR and other currently marketed Keppra products. Further enhancements to the labels and labeling will also minimize the confusion between Keppra and Keppra XR. Comments pertaining to the label and labeling are identified in OSE review# 2008-1060.

1 BACKGROUND

1.1 INTRODUCTION

This review was written in response to a request from the Division of Neurology Products, for assessment of the proposed proprietary name, Keppra XR, regarding potential name confusion with other proprietary or established drug names.

The Applicant submitted container labels, carton and insert labeling for review and comments. DMEPA's assessment of the labels and labeling will be forwarded in OSE Review #2008-1060.

1.2 PRODUCT INFORMATION

Keppra XR (levetiracetam) is an antiepileptic drug indicated for adjunct therapy in the treatment of partial onset seizures in patients [redacted] years of age or older with epilepsy. Treatment should be initiated with a dose of 1000 mg once daily. The daily dosage may be adjusted in increments of 1000 mg every 2 weeks to a maximum recommended daily dose of 3000 mg. Keppra XR will be supplied in bottles of 60 tablets. b(4)

The root name Keppra, of the proposed name Keppra XR is a proprietary name associated with 3 NDA's.

NDA#	Tradename	Strength	Dosage form	Approval Date
21-035	Keppra	250 mg, 500 mg, 750 mg and 1000 mg	Tablet	November 30, 1999
21-505	Keppra	100 mg/mL	Oral Solution	July 15, 2003
21-872	Keppra	500 mg/5 mL	Injectable for IV infusion	July 31, 2006

All of the Keppra products are currently marketed. Keppra 500 mg (immediate-release tablets) and Keppra XR 500 mg (extended-release tablets) will share overlapping characteristic such as dosage forms, strength, dosage and route, but will not share frequency.

2 METHODS AND MATERIALS

This section describes the methods and materials used by the Division of Medication Error Prevention and Analysis staff conducting a proprietary name risk assessment (see 2.1 Proprietary Name Risk Assessment). The primary focus for the assessment is to identify and remedy potential sources of medication error prior to drug approval. The Division of Medication Error Prevention and Analysis

defines a medication error as any preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of the health care professional, patient, or consumer. [1]

2.1 PROPRIETARY NAME RISK ASSESSMENT

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

For the proprietary name, Keppra XR, the Medication Error Prevention staff search a standard set of databases and information sources to identify names with orthographic and phonetic similarity (see Sections 2.1.1.1 for detail) and held an CDER Expert Panel discussion to gather professional opinions on the safety of the proposed proprietary name (see 2.1.2). We also conduct internal CDER prescription analysis studies (see 2.1.3). DMEPA also evaluated the appropriateness of the proposed modifier/suffix, and considered the potential for modifier/suffix's omission or misinterpretation, and verified that the modifier/suffix did not appear on the error-prone abbreviation list maintained by the Institute of Safe Medication Practices (ISMP). Additionally, the suffix/modifier was assessed for resemblance to any numbers, dosing instructions, or medical abbreviations and evaluation for the potential for the suffix/modifier to be confusing or misleading was taken into consideration.

The Safety Evaluator assigned to the Proprietary Name Risk Assessment is responsible for considering the collective findings, and provides an overall risk assessment of the proposed proprietary name (see detail 2.1.4). The overall risk assessment is based on the findings of a Failure Modes and Effects Analysis (FMEA) of the proprietary name, and is focused on the avoidance of medication errors. FMEA is a systematic tool for evaluating a process and identifying where and how it might fail. [2] Additionally, for this review DMEPA conducted a second Failure Mode and Effects Analysis (FMEA) to evaluate whether marketing the proposed product under the name, Keppra XR, or an alternate proprietary name would be less prone to medication errors. FMEA is used to analyze whether the drug names identified with look- or sound-alike similarity to the proposed name could cause confusion that subsequently leads to medication errors in the clinical setting. The Division of Medication Error Prevention and Analysis 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] Our Division uses the clinical expertise of the medication error 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. As such, the Staff considers the product characteristics associated with the proposed drug throughout the risk assessment, since the product characteristics of the proposed may provide a context for communication of the drug name and ultimately determine the use of the product in the *usual* clinical practice setting.

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

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

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

Typical product characteristics considered when identifying drug names that could potentially be confused with the proposed drug name include, but are not limited to established name of the proposed product, the proposed indication, dosage form, route of administration, strength, unit of measure, dosage units, recommended dose, typical quantity or volume, frequency of administration, product packaging, storage conditions, patient population, and prescriber population. Because drug name confusion can occur at any point in the medication use process, we 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.[4]

2.1.1 Search Criteria

The Medication Error Staff consider 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 'K' 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.[5][6] With regard to the modifier, the search criteria also took into consideration that the modifier could be misinterpreted as numbers, dosing instructions or medical abbreviations.

To identify drug names that may look similar to Keppra XR, the Staff also consider the other orthographic appearance of the name on lined and unlined orders. Specific attributes taken into consideration include the length of the name (8 letters), upstrokes (3, capital letters 'K', 'X' and 'R'), downstokes (two, 'p'), cross-strokes (none), and dotted letters (none). Additionally, several letters in Keppra XR may be vulnerable to ambiguity when scripted, including the letter 'K' may appear as 'R'; lower case 'e' appear as a lower case 'a' or 'i'; lower case 'p' may appear as 'x' or 'y'; lower case 'r' may appear as 'n'; lower case 'a' may appear as 'e' or 'o'; capital 'X' may appear as 'Y'; and capital 'R' may appear as 'B' or 'PR'. As such, the Staff also considers these alternate appearances when identifying drug names that may look similar to Keppra XR.

When searching to identify potential names that may sound similar to Keppra XR, the Medication Error Staff search for names with similar number of syllables (4), stresses (KEP-pra xr; ke-PPRA xr and kep-pra XR), and placement of vowel and consonant sounds. In addition, several letters in Keppra XR may be subject to interpretation when spoken, including the letters "Kep" may be interpreted as 'Kip', or 'Kept'; the letter 'e' may be interpreted as 'i'; the letter 'a' may be interpreted as 'e'; and the modifier may be interpreted as 'SR'. As such, the staff also considers there alternate pronunciations when identifying drug names that may sound similar to Keppra XR. We also considered how the inclusion of "XR" may change the sound of the name. The Applicant's intended pronunciation of the proprietary name could not be expressly taken into consideration, as this was not provided with the proposed name submission.

The Staff also consider 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 (Keppra XR), the established name (levetiracetam), proposed indication (seizures),

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[4] Institute of Medicine. Preventing Medication Errors. The National Academies Press: Washington DC. 2006.

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

[6] Kondrack, G and Dorr, B. Automatic Identification of Confusable Drug Names. Artifical Inteligence in Medicine (2005)

strength (500 mg), dose (1000 mg to 3000 mg), frequency of administration (once a day), route (oral) and dosage form the product (extended-release tablet). Appendix A provides a more detailed listing of the product characteristics the medication error staff general take into consideration.

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

2.1.2 Database and Information Sources

The proposed proprietary name, Keppra XR, was provided to the medication error staff of the Division of Medication Error Prevention and Analysis staff to conduct a search of the internet, several standard published drug product reference texts, and FDA databases to identify existing and proposed drug names that may sound-alike or look-alike to Keppra XR using the criteria outlined in 2.1.1. Additionally, the modifier 'XR' was assessed for resemblance to any numbers, dosing instructions, or medical abbreviations. A standard description of the databases used in the searches is provided in Section 6. To complement the process, the Medication Error Staff use a computerized method of identifying phonetic and orthographic similarity between medication names. The program, Phonetic and Orthographic Computer Analysis (POCA), uses complex algorithms to select a list of names from a database that have some similarity (phonetic, orthographic, or both) to the trademark being evaluated. Lastly, the Medication Error Staff review the United States Adopted Names (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.

2.1.3 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, Keppra XR. Potential concerns regarding drug marketing and promotion related to the proposed names are also discussed. This group is composed of Medication Errors Prevention Staff and representatives from the Division of Drug Marketing, Advertising, and Communications (DDMAC).

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

2.1.4 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 Keppra XR 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 Keppra XR 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 medication error staff.

Figure 1. Keppra XR Study (conducted on August 13, 2008)

HANDWRITTEN PRESCRIPITON AND MEDICATION ORDER	VERBAL PRESCRIPTION
Outpatient Prescription: Keppra XR 500 mg # 60 2 tablets by mouth daily	Keppra XR #60 2 tablets by mouth daily
Inpatient Prescription Order: Keppra XR 500 mg 2 tabs po qd	

2.1.5 FDA Adverse Event Reporting System (AERS) Database

Since the root name Keppra has been marketed since 1999, DMEPA conducted a search of the Adverse Event Reporting System (AERS) database to determine if there are any medication errors associated with the currently marketed Keppra products which may be indicative of potential confusion with Keppra XR. The MedDRA Higher Level Group Term (HLGT) Medication Error, the Preferred Term (PT) Pharmaceutical Product Complaint (PPC), verbatim substance names "Kepp%" and Levetir%, tradename "Keppra", and active ingredient "Levetiracetam" were used as search criteria.

The cases were manually reviewed to determine if medication errors occurred. Those cases that did not describe a medication error were excluded from further analysis. The cases that did describe a medication error were categorized by type of error. We reviewed the cases within each category to identify factors that contributed to the medication errors, and to ascertain if these risks might apply to the proposed Keppra XR.

2.1.6 Safety Evaluator Risk Assessment of the Proposed Proprietary Name

Based on the criteria set forth in Section 2.1.1, the Safety Evaluator Risk Assessment applies their individual expertise gained from evaluating medication errors reported to FDA to conduct a Failure Modes and Effects Analysis and provide an overall risk of name confusion. Failure Mode and Effects Analysis (FMEA) is a systematic tool for evaluating a process and identifying where and how it might fail.[7] 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 then remedies available in the post-approval phase.

In order to perform a 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 Keppra XR convincing 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 Keppra XR 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 posses 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 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

[7] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston, IHI:2004.

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. We identify 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. Medication Error Staff identify 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 another drug product.

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

If none of these conditions are met, then we will not object to the use of the proprietary name. If any of these conditions are met, then we will object to the use of the proprietary name. The threshold set for objection to the proposed proprietary name may seem low to the Applicant; however, the safety concerns set forth in criteria 1 through 5 are supported either by FDA Regulation or by external healthcare authorities, including The Institute of Medicine, The World Health Organization, The Joint Commission, and The Institute For Safe Medication Practices, which have examined medication errors resulting from look- or sound-alike drug names and called for Regulatory Authorities to address the issue prior to approval.

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

Additionally, post-marketing experience has demonstrated that medication errors resulting from drug name confusion are notoriously difficult to remedy post-approval. Educational efforts and so on are low-leverage strategies that have proven to have limited effectiveness at alleviating the medication errors involving drug name confusion. Higher-leverage strategies, such as drug name changes, have been undertaken in the past; but at great financial cost to the Applicant, and at the expense of the public welfare, not to mention the Agency's credibility as the authority responsible for the approving the error-prone proprietary name. Moreover, even after Applicant's have changed a product's proprietary name in the post-approval phase, it is difficult to eradicate the original proprietary name from practitioner's vocabulary, and as such, the Agency has continued to receive reports of drug name confusion long after a name change in some instances. Therefore, we believe 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 we object to a proposed proprietary name on the basis that drug name confusion could lead to medication errors, the FMEA process is used to identify strategies to reduce the risk of medication errors.

Our Division is likely to recommend that the Applicant select an alternative proprietary name and submit the alternate name to the Agency for review by our Division. However, in rare instances FMEA may identify plausible strategies that could reduce the risk of medication error of the currently proposed name, and so we may be able to provide the Applicant with recommendations that reduce or eliminate the potential for error would render the proposed name acceptable.

3 RESULTS

3.1 PROPRIETARY NAME RISK ASSESSMENT

3.1.1 Data base and Information Sources

In total, 12 names were identified as having some similarity to the name Keppra XR. Nine of twelve names were thought to look like Keppra XR, which include: Hepsera, Kefurox, Hepron, Hepralin, Heprinar, Repronex, Septra, Inspra and Heparin. One name (Clopra) was thought to sound similar to Keppra XR. The remaining two names (Keppra and Kaletra) were thought to look and sound similar to Keppra XR.

In analysis of the potential for the "XR" modifier to resemble any numbers, dosing instructions or medical abbreviation, post-marketing reporting has found that "XR" has been misinterpreted as "x 2." This confusion occurred when the XR suffix was first approved. However, we have not seen recent confusion and this abbreviation does not appear on the ISMP "List of Error Prone Abbreviations, Symbols, and Dose Designations." Additionally, the modifier "XR" is identified by standard references[8] as extended-release X-linked, recessive, X-ray, and Xeroradiography. These interpretations should not result in confusion. We noted, the "X" of XR is associated with the Roman numeral "ten" and "R" could be misinterpreted as the Roman numeral "L", thus "XL" or "40". However, we have not had such reports of confusion with the use of the XR suffix/modifier.

When evaluating the appropriateness of the modifier we noted fifteen products (Adderall XR, Augmentin XR, Cipro XR, Dilacor XR, Effexor XR, Focalin XR, Glucophage XR, Lodrane XR, Proquin XR, Sanctura XR, Seroquel XR, Tegretol XR, Voltaren XR, Xanax XR and Zerit XR) listed in the Orange Book and/or Drugs@FDA contained the modifier 'XR' in their proprietary names. These fifteen proprietary names represent product line extensions in which the "XR" modifier describes the "extended release" dosage form.

Twelve of fifteen identified proprietary names (n=12) are dosed once daily, while the remaining three (n=3) are dosed twice daily to three times daily. Of the three drugs not dosed once daily, one was a monograph drug product (Lodrane XR), and (Tegretol XR) was approved by the Agency in 1996 and thus not reviewed by DMEPA. The third name Augmentin XR was reviewed by DMEPA, however, this was prior to the release of the Institute of Medicine report "Preventing Medication Errors" (2006)[9] or the National Coordinating Council for Medication Error Reporting and Prevention (NCC MERP) meeting on "Drug Name Suffixes and Medication Errors" (2005)[10] which identified safety concerns with modifiers that have no standard meaning.

As of August 11 2008, the proposed name, Keppra XR, did not contain a United State Adopted Name (USAN) stem.

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[8] http://www.pharma-lexicon.com/, 02May2007.

[9] July 20, 2006, Institute of Medicine (IOM) Report "Preventing Medication Errors" recommendation number four

[10] NCC MERP meeting "Drug Name Suffixes and Medication Errors: Exploring the Relationship and Minimizing the Risk". October 2005.

3.1.2 CDER Expert Panel Discussion

The Expert Panel reviewed the pool of names identified by medication error staff (see section 3.1.1. above), and noted no additional proprietary names thought to have orthographic or phonetic similarity to the proprietary Keppra XR and have the potential for confusion.

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

3.1.3 FDA Prescription Analysis Studies

A total of 31 practitioners responded. One respondent in the inpatient written study misinterpreted the name as "Keppra", a prescription product currently marketed in the U.S. About 84% of the participants (n=26) interpreted the name correctly as "Keppra XR", with correct interpretation occurring more frequently in the outpatient written study. The remainder of the responses misinterpreted the drug name. See Appendix B for the complete listing of interpretations from the verbal and written prescription studies.

3.1.4 FDA Adverse Event Reporting System (AERS) Database

For this review, an updated search of the FDA Adverse Event Reporting System (AERS) was conducted on August 1, 2008, for medication errors submitted for Keppra since the previous review dated January 26, 2005 (OSE review # 2005-0013). A total of 129 cases involving Keppra were retrieved. One hundred sixteen of these cases were either duplicates, determined not to involve a medication error or were discussed in previous OSE Reviews (# 03-0290, 02-0167 or 05-0013).

The remaining 13 cases involved errors of wrong technique (1), wrong route (1), and incorrect dose (1). The wrong route and technique cases were associated with the Keppra intravenous formulation, whereas, the incorrect dose case was associated with the oral solultion formulation. Therefore, DMEPA will not discuss these three cases further as they are not applicable to this review.

Five of the 10 cases involved Keppra confusion with proprietary names Zyprexa (n=1), Trileptal (n=1), and Keflex (n=3). The remaining five cases involved confusion with the established names Levofloxacin (n=3) and Levocarnitine (n=2). The confusion between the established names Levetiracetam and Levofloxacin or Levocarnitine will not be discussed further because the addition of Keppra XR to the product line will not exacerbate this confusion (see Appendix E).

3.1.5 Safety Evaluator Risk Assessment

Independent searches by the primary Safety Evaluator did not identify any additional names, thought to look similar to Keppra XR and represent a potential source of drug name confusion. However, the AERS search identified five additional names that look like the root name "Keppra" and resulted in confusion and medication errors. As such, a total of seventeen names were analyzed to determine if the drug names could be confused with Keppra XR and if the drug name confusion would likely result in a medication error.

All of the identified names were determined to have some orthographic and/or phonetic similarity to Keppra XR, and thus determined to present some risk of confusion. Failure mode and effect analysis was then applied to determine if the proposed name, Keppra XR, could potentially be confused with any of the sixteen names and lead to medication errors.

This analysis determined that the name similarity between Keppra XR and the identified names was unlikely to result in medication errors for 16 of the 17 products for the reasons described in Appendix C through F.

The remaining name, Keppra, was determined to be vulnerable to confusion due to orthographic and phonetic similarities with the proposed name Keppra XR as discussed in section 4.

The results of DMEPA's second FMEA indicated that using Keppra XR or an alternative proprietary name would result in similar error-prone scenarios including underdose, or overdose of Levetiracetam.

4 DISCUSSION

Keppra XR will be added to an existing product line that already has two oral dosage formulations (tablets and oral solution) and a formulation for intravenous administration. The Applicant proposes to use the root name Keppra and the modifier XR to differentiate the extended-release formulation from the currently marketed products. This naming convention is commonly used when an extended release dosage form is added to a product line with an existing immediate-release formulation.

Post-marketing experience has shown that the introduction of product line extensions result in medication errors if the modifier is omitted and product characteristics are similar or overlap. In this instance both solid oral dosage forms of Keppra and Keppra XR have overlapping product characteristics [i.e., established name (levetiracetam), indication of use (seizures), route of administration (oral), dosage form (tablet), strength (500 mg) and total daily dose (3000 mg)]. By choosing to develop an extended-release formulation of levetiracetam tablets with product characteristics that overlap with those of the currently marketed Levetiracetam immediate-release tablets, the Applicant has eliminated a potentially valuable error-reduction strategy that has been employed in other product line extensions. For this product, the Applicant should have chosen a product strength with a small deviation from the 500 mg immediate-release Keppra strength. Thus, if the modifier were omitted or overlooked, the differences in strength offer an opportunity for an error to be caught before it reaches the patient, provided it is a dose that could not be achieved with the current formulation. However, since the Applicant has completed their clinical trials and submitted their new drug application, DMEPA acknowledges it is unlikely that the product strength will be changed at this time.

In conducting the FMEA, we identified failure modes including omission of the modifier between the solid oral dosage forms of Keppra and Keppra XR. These failures were not identified with the intravenous or oral solution formulations because a prescription for these formulations would require a route of administration (IV) or a teaspoonful/mL amount and/or a dispensing volume respectively. The aforementioned components of a prescription would alert the practitioner that there is a difference between these formulations and Keppra XR. Conversely, if the XR modifier is omitted with the solid oral dosage form it is almost certain that Keppra (immediate-release tablets) will be dispensed for Keppra XR because of the overlapping product characteristics. In order to determine the clinical significance of the inadvertent administration of Keppra immediate release in place of Keppra XR, DMEPA contacted the Division of Neurology Products (DNP). DNP indicated they were uncertain of the clinical significance if such an error were to occur.

DMEPA also analyzed the approach of using an alternative proprietary name for the Levetiracetam extended-release product while maintaining the Keppra name for the immediate release product. This FMEA identified the additional failure mode of concomitant therapy which was not identified in the FMEA for Keppra XR. To assess the potential clinical significance of concomitant therapy with Keppra and Keppra XR, DMEPA contacted DNP. DNP indicated that these products have a labeled maximum dose of 3000 mg and they were uncertain of the clinical significance of concomitant therapy with Keppra and Keppra XR.

These findings indicate there may be risk of confusion in either direction and the clinical consequences of each risk are not well defined.

5 CONCLUSIONS AND RECOMMENDATIONS

Our analysis of the proposed proprietary name Keppra XR indicates that confusion can occur between Keppra and Keppra XR and with Keppra and an alternative name. The Applicant's proposal to add a modifier to the Keppra root name is a recognized naming convention commonly used when an extended release dosage form is added to a product line with an existing immediate-release product and the modifier XR is appropriate to describe this product's characteristics. Therefore, we will not object to the use of the name, Keppra XR, for this product. However, to minimize product line confusion we recommend at the time of product launch the Applicant inform healthcare practitioners about the differences between Keppra XR and other currently marketed Keppra products. Additionally, further enhancements to the label and labeling will also minimize the confusion between Keppra and Keppra XR. Comments pertaining to the label and labeling are identified in OSE review# 2008-1060.

5.1 COMMENTS TO THE DIVISION

If the product approval is delayed beyond 90 days form the date of this review, the proposed name must be resubmitted for evaluation.

Container labels, carton and insert labeling will be included in a separate review OSE Review (# 2008-1060).

The Division of Medication Error Prevention and Analysis would appreciate feedback on the final outcome of this review. We would be willing to meet with the Division for further discussion, if needed. Please copy the Division of Medication Error Prevention and Analysis on any communication to the Applicant with regard to this review. If you have further questions or need clarifications, please contact Daniel Brounstein, OSE Project Manager, at 301-796-0674.

6 REFERENCES

1. Adverse Events Reporting System (AERS)

AERS is a database application in CDER FDA that contains adverse event reports for approved drugs and therapeutic biologics. These reports are submitted to the FDA mostly from the manufacturers that have approved products in the U.S. The main utility of a spontaneous reporting system that captures reports from health care professionals and consumers, such as AERS, is to identify potential post marketing safety issues. There are inherent limitations to the voluntary or spontaneous reporting system, such as underreporting and duplicate reporting; for any given report, there is no certainty that the reported suspect product(s) caused the reported adverse event(s); and raw counts from AERS cannot be used to calculate incidence rates or estimates of drug risk for a particular product or used for comparing risk between products.

2. Micromedex Integrated Index (http://csi.micromedex.com)

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

3. Phonetic and Orthographic Computer Analysis (POCA)

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

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

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

5. AMF Decision Support System [DSS]

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

6. Division of Medication 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.

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

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

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

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

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

Provides information regarding patent and trademarks.

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

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

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

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

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

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

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

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

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

List contains all the recognized USAN stems.

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

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

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

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

17. ***Medical Abbreviations Book***

Contains commonly used medical abbreviations and their definitions.

APPENDICES

Appendix A:

The Medication Error Staff consider the spelling of the name, pronunciation of the name when spoken, and appearance of the name when scripted. We also compare the spelling of the proposed proprietary name with the proprietary and established name of existing and proposed drug products because similarly spelled names may have greater likelihood to sound similar to one another when spoken or look similar to one another when scripted. The Medication Error Staff 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* dissimilarly spelled drug name pairs to appear very similar to one another and the similar appearance of drug names when scripted has lead to medication errors. The Medication Error Staff apply their expertise gained from root-cause analysis of such medication errors to identify sources of ambiguity within the name that could be introduced when scripting (i.e. "T" may look like "F," lower case 'a' looks like a lower case 'u,' etc), along with other orthographic attributes that determine the overall appearance of the drug name when scripted (see detail in Table 1 below). Additionally, since verbal communication of medication names is common in clinical settings, the Medication Error Staff compare the pronunciation of the proposed proprietary name with the pronunciation of other drug names. If provided, the Division of Medication Error Prevention and Analysis will consider the Applicant's intended pronunciation of the proprietary name. However, because the Applicant has little control over how the name will be spoken in practice, we 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	• 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 Upstokes Downstrokes Cross-stokes	• 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	• Names may sound similar when pronounced and lead to drug name confusion in verbal communication

Appendix B:

CDER Prescription Study Responses

Outpatient Prescription	Inpatient Prescription	Phonetic Prescription
Keppra XR	Keppra XR	Kepra-Pexar
Keppra XR	Keppra XR	Keppra XR
Keppra XR	Keppra XR	Kepra XR
Keppra XR	Keppra XR	Kepra XR
Keppra XR	Keppra XR	Kappra XR
Keppra XR	Keppra XR	Keppra XR
Keppra Xr	Keppra XR	Keppra XR
Keppra XR	Keppra XR	Keppra XR
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	Keppra XR	
	keppra XR	
	Keppra XR	
	Keppra XR	

Appendix C: Names lacking convincing look-alike and/or sound-alike similarities with Keppra XR

Proprietary Name	Similarity to Keppra XR
Hepsera	Look
Kefurox	Look
Hepron	Look
Hepralin	Look
Heprinar	Look
Septra	Look
Heparin	Look
Inspra	Look
Repronex	Look
Clopra	Sound

Appendix D: Names found to have some risk of error through Postmarketing surveillance

Keppra XR (Levetiracetam Extended-Release) Tablets	**500 mg**	**Usual dose: 2 tablets daily**
Failure Mode: Name confusion or look alike products	**Causes (could be multiple)**	**Effects**
Keflex (cephalexin) capsules	Orthographic and phonetic similarity (Both names begin with the same first 2 letters "Ke"). Downstroke in the same position (f vs. p). Both have overlap in strength 500 mg, route of administration (oral) and storage location in the pharmacy. AERS cases identified 3 cases of name confusion between this pair. All 3 cases resulted from poor handwriting.	Wrong Drug *Rationale:* DMEPA believes the risk of confusion between Keflex and the proposed product is minimized since Keppra XR will contain a modifier "XR". The modifier lengthens the name which further differentiates the two names.
Zyprexa (olanzapine)	AERS case showed confusion between Zyprexa 15 mg and Keppra 750 mg.	The confusion was not related to name similarity but similarity between the appearance of the actual tablets. The risk of confusion is minimized because of the differences in the name. Additionally, Zyprexa is a round tablet where as Keppa XR is a white oblong tablet.
Trileptal (oxcarbazepine)	AERS case showed confusion between Trileptal 600 mg and Keppra 750 mg	The confusion was not related to the name similarity but similarity between the appearance of the actual tablets. The risk of confusion is minimized because of the differences in the name. Additionally, Trileptal tablets are yellow whereas, Keppra XR is a white oblong tablet.

Appendix E: Established names found to have some risk of error through Postmarketing surveillance

Keppra XR (Levetiracetam Extended-Release) Tablets	**500 mg**	**Usual dose: 2 tablets daily**
Failure Mode: Name confusion	**Causes** **(could be multiple)**	**Effects**
Levofloxacin	Orthographic and phonetic similarity with the established name Levetiracetam. (Both names begin with the same first three letters "Lev", both appear similar in length 13 vs. 12 letters. Both share overlapping strengths (500 mg and), same route of administration (oral), and same dosage form (tablet). AERS identified 3 cases of established name confusion between this pair.	Wrong Drug ARES identified 3 cases of name confusion *Rationale:* Since Keppra XR is an extended-release product, the addition of this term to the established name (Levetiracetam extended-release) may help minimize name confusion between Levofloxacin and Levetiracetam extended-release. However confusion may occur with the immediate release products. DMEPA will continue to monitor this name pair to determine if interventions need to be implemented.
Levocarnitine	Orthographic and phonetic similarity with the established name Levetiracetam. (Both names begin with the same first three letters "Lev", both have the same number of letters (13). Both share overlapping strengths (100 mg/mL), same rout of administration (oral), and same dosage form (oral solution). AERS identified 2 cases of name confusion between this pair. DMEPA believes the close proximity in approval of the "oral solution" dosage form, contributed to the confusion. (Levocarnitine AP 8/10/04 vs. Levetiracetam AP 7/15/03).	Wrong Drug AERS identified two cases of name confusion *Rationale:* Since Keppra XR is an extended-release product, the addition of this term to the established name (Levetiracetam extended-release) may help minimize name confusion between Levocarnitine and Levetiracetam extended-release. However, confusion may occur with immediate release products. DMEPA will continue to monitor this name pair to determine if interventions need to be implemented.

Appendix F: Failure Mode and Effects Analysis of problematic names

Keppra XR (Levetiracetam Extended-Release) Tablets	500 mg	Usual dose: 2 tablets daily
Failure Mode: **Name confusion**	**Causes**	**Effects**
Kaletra (lopinavir and ritonavir)	The first two letters in both names look similar when scripted ("Ka vs. Ke") and both names end the letters "ra". Additionally, both names sound similar. Both names are also similar in length when scripted. AERS identified 5 cases of name confusion in OSE Reviews (03-0290 and 05-0013).	Wrong Drug *Rationale:* The risk of medication error is minimized since Keppra XR will contain a modifier "XR" which will lengthen the name and help differentiate the pair. DMEPA previously recommended the Applicant consider emphasizing the letters in the middle of name that differ from Keppra. At this time the recommendations have not been forwarded to the Applicant and since there have not been any recent cases. We will continue to monitor this name pair and determine if interventions need to be implemented.

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