CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-251

PROPRIETARY NAME REVIEW(S)

Department of Health and Human Services

Public Health Service

Food and Drug Administration

Center for Drug Evaluation and Research

Office of Surveillance and Epidemiology

Date:	February 06, 2009
To:	Russell Katz, MD Director, Division of Neurology Products
Through:	Denise Toyer, PharmD, Deputy Director Carol Holquist, RPh, Director Division of Medication Error Prevention and Analysis
From:	Zachary Oleszczuk, PharmD, Safety Evaluator Division of Medication Error Prevention and Analysis
Subject:	Proprietary Name Review
Drug Name(s):	Lamictal ODT (Lamotrigine Orally Disintegrating Tablets)
Application Type/Number:	NDA 22-251
Applicant:	GlaxoSmithKline
OSE RCM #:	2008-2053

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

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EXECUTIVE SUMMARY

The findings of the Proprietary Name Risk Assessment indicate that the proposed name, Lamictal ODT is not vulnerable to confusion that could lead to medication errors. Thus, the Division of Medication Error Prevention and Analysis has no objections to the use of the proposed name, Lamictal ODT, for this product at this time.

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 the name must be resubmitted for review. Additionally, if the product approval is delayed beyond 90 days from the signature date of this review, the proposed name must be resubmitted for evaluation.

1 BACKGROUND

1.1 INTRODUCTION

This re-review for the proposed name, Lamictal ODT, was written in order to rule out any objections to the proposed proprietary name based upon approval of other proprietary or established names from the signature date of the previous Division of Medication Error Prevention and Analysis name review.

1.2 REGULATORY HISTORY

The Applicant submitted the proprietary name, "Lamictal ODT" on November 28, 2007, which was found acceptable on September 26, 2008 in OSE Review #2008-1010 and 2008-1149. Additionally, the same review evaluated the modifier 'ODT', the result of a product line extension and whether or not marketing the proposed product under the name, Lamictal ODT or an alternate proprietary name would be less prone to medication errors. As such, DMEPA will not reevaluate the modifier independent of the entire proposed proprietary name, the product line extension, or the use of an alternate name in this evaluation of the proposed name.

The labels and labeling for this product were also evaluated in OSE Review #2008-1010 and 2008-1149 dated September 23, 2008.

1.3 PRODUCT INFORMATION

Lamictal ODT is the proposed name for lamotrigine orally disintegrating tablets. Lamictal ODT is an antiepileptic drug used in the treatment of epilepsy and bipolar disorder.

Lamictal ODT requires that a patient be titrated over several weeks. The dose and speed at which a patient is titrated is dependent upon which other medication(s) the patient is taking and which indication is being treated. Once a patient has been titrated a usual adult dose can range from 100 mg orally once per day to 500 mg daily orally in two divided doses.

Lamictal ODT is manufactured by GlaxoSmithKline. Lamictal ODT will be supplied as 25 mg, 50 mg, 100 mg, and 200 mg tablets. Lamictal ODT will differ in some of the available strengths from the other Lamictal products currently on the market. See Table page 5.

Table 1: Currently Marketed Lamictal Products

Currently Market Lamictal Product							
Drug Name	**Rx or OTC**	**Strength**	**Frequency**	**Dosage Form**	**Route**	**Indication**	**Usual Maintenance Dose After Initial Titration**
Lamictal ODT (lamotrigine hydrochloride orally disintegrating) tablets	Rx	25 mg, 50 mg 100 mg, and 200 mg	Once to twice daily	Orally Disintegrating Tablets	Oral	Epilepsy and Bipolar disorder	100 mg orally once per day to 500 mg orally daily in two divided doses
Lamictal (lamotrigine hydrochloride) tablets	Rx	25 mg, 100 mg, 150 mg, and 200 mg	Once to twice daily	Tablets	Oral	Epilepsy and Bipolar disorder	100 mg orally once per day to 500 mg orally daily in two divided doses
Lamictal CD (lamotrigine hydrochloride chewable dispersible) Tablets	Rx	2 mg, 5 mg, 25 mg	Once to twice daily	Chewable Dispersible Tablets	Oral	Epilepsy and Bipolar disorder	Adult: 100 mg orally once per day to 500 mg orally daily in two divided doses Pediatric: 1 mg/kg to 15 mg/kg orally daily in one or two divided doses
Differences between the products are highlighted in yellow							

2 METHODS AND MATERIALS

This section describes the methods and materials used by the Division of Medication Error Prevention and Analysis (DMEPA) conducting a proprietary name risk assessment (see 2.1 Proprietary Name Risk Assessment). The primary focus of the 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]

2.1 PROPRIETARY NAME RISK ASSESSMENT

FDA's Proprietary Name Risk Assessment considers the potential for confusion between the proposed proprietary name, Lamictal ODT, 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 CDER.

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

For the proprietary name, Lamictal ODT, DMEPA searched a standard set of databases and information sources to identify names with orthographic and phonetic similarity (see section 2.1.1 for detail) and held a CDER Expert Panel discussion to gather professional opinions on the safety of the proposed proprietary name (see section 2.1.3). Additionally, since this name was previously evaluated, the Safety Evaluator assigned to the Proprietary Name Risk Assessment evaluated the previous review of the proprietary name. DMEPA also conducts internal FDA prescription analysis studies (see 2.1.2), and, when provided, external prescription analysis studies results are considered and incorporated into the overall risk assessment. However, since this name was previously evaluated, FDA prescription analysis studies were not conducted upon re-review of the proprietary name Lamictal ODT.

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. [2] 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 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] DMEPA 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, DMEPA 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, 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]

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[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.

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

2.1.1 Search Criteria

DMEPA 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 'L' 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] Additionally, since omission of a modifier is cited in the literature as a common cause of medication errors[7], DMEPA considers 'Lamictal ODT' as a complete name as well as 'Lamictal,' the root term, omitting the modifying term 'ODT'.

To identify drug names that may look similar to Lamictal ODT, DMEPA also considers the orthographic appearance of the name on lined and unlined orders. Specific attributes taken into consideration include the length of the name (11 letters), upstrokes (six; capital letter 'L', lower case letters 't', and 'l', capital letters 'O', 'D' and 'T'), downstrokes (none), cross-strokes (two; lower case 't', and capital 'T'), and dotted letters (one; lower case 'i'). Additionally, several letters in Lamictal ODT may be vulnerable to ambiguity when scripted, including the letter 'L' may appear as capital 'Z'; lower case 'a' may appear as a lower case 'e', 's', 'u', 'x', 'o', and letter combinations lower case 'ci' or 'ce'; lower case 'm' may appear as a lower case 'n', 'z', and letter combination 'ss' or 'onc'; lower case 'i' may appear as a lower case 'e'; lower case c may appear as a lower case 'a'; lower case 't' may appear as lower case 'f', 'r' or 'x'; lower case l appears a lower case 'b', 'e', 'k' or 'p'; and upper case 'T' may appear as upper case 'J', 'F' or 'Z'. As such, the staff also considers these alternate appearances when identifying drug names that may look similar to Lamictal ODT.

When searching to identify potential names that may sound similar to Lamictal ODT, DEMPA searches for names with similar number of syllables in the name (6 syllables), stresses (Lah-mic-tal Oh-Dee-Tee, lah-Mic-tal Oh-Dee-Tee, or lah-mic-Tal Oh-Dee-Tee), and placement of vowel and consonant sounds. In addition, several letters in Lamictal ODT may be subject to interpretation when spoken, including the letter 'm' may be interpreted as 'n'; the letter 'c' may be interpreted as 'z', the letter 't' may be interpreted as 'd' or 'n'; and the letter 'a' may be interpreted as 'o'. We also considered how the inclusion of "ODT" 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.

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, DMEPA was provided with the following information about the proposed product: the proposed proprietary name (Lamictal ODT), the established name (lamotrigine), proposed indication (Epilepsy and Bipolar Disorder), strength (25 mg, 50 mg, 100 mg, and 200 mg), dose (titrated over several weeks, then a maintenance dose between 100 mg to 500 mg per day), frequency of administration (once or two divided doses), route (oral) and dosage form of the product (oral disintegrating tablet). Appendix A provides a more detailed listing of the product characteristics DMEPA generally takes into consideration.

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[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. Artificial Intelligence in Medicine (2005)

[7] Lesar TS. Prescribing Errors Involving Medication Dosage Forms. *J Gen Intern Med.* 2002; 17(8): 579-587.

Lastly, DMEPA 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.

2.1.2 Database and information sources

The proposed proprietary name, Lamictal ODT, was provided to the DMEPA 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 Lamictal ODT using the criteria outlined in 2.1.1. A standard description of the databases used in the searches is provided in Section 6.2. To complement the process, DMEPA staff use a computerized method of identifying phonetic and orthographic similarity between medication names. The program, Phonetic and Orthographic Computer Analysis (POCA), uses complex algorithms to select a list of names from a database that have some similarity (phonetic, orthographic, or both) to the trademark being evaluated. Lastly, the DMEPA staff review the USAN stem list to determine if any USAN stems are present within the proprietary name. The 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 DMEPA to gather CDER professional opinions on the safety of the product and the proprietary name, Lamictal ODT. Potential concerns regarding drug marketing and promotion related to the proposed names are also discussed. This group is composed of DMEPA 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 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.[8] When applying FMEA to assess the risk of a proposed proprietary name, DMEPA 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.

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

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 Lamictal ODT 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 Lamictal ODT 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.

DMEPA 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. DMEPA identifies that the proposed proprietary name is misleading because of similarity in spelling or pronunciation to another proprietary or established name of a different drug or ingredient [CFR 201.10.(C)(5)].
3. FMEA identifies 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 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, 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 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 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, World Health Organization, Joint Commission, and 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, 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, postmarketing 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 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. We are likely to recommend that the Applicant select an alternative proprietary name and submit the alternate name to the Agency for 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 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 Database and Information Sources

In total, 19 names were identified as having some similarity to the name Lamictal ODT. Nine of the 19 names were thought to look like Lamictal ODT; these names include: Lomotil, Fazaclo ODT, Tamiflu, Tamifen, Lunesta, Simulect, Surmontil, Zamicet, and Zamadol. One name (Lambkill) was thought to sound like Lamictal ODT. Nine of the 19 names were thought to look and sound similar to Lamictal ODT; these names include: Lamital, Lamictal, Lamictal CD, Lamisil (Product Line - See Appendix I for currently marketed Lamisil products), Lamidus, Lamictal (b) (4), Lamictin, and Lamictal XR***.

The proposed proprietary name, Lamictal ODT, does not contain a USAN stem as of the last date searched, January 23, 2008.

3.1.2 CDER Expert Panel Discussion

The Expert Panel reviewed the pool of names identified by the DMEPA staff (see section 3.1.1 above), and did not provide any additional names orthographically or phonetically similar to Lamictal ODT.

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

3.1.3 Safety evaluator risk assessment

Independent searches by the primary safety evaluator resulted in ten additional names thought to look or sound similar to Lamictal ODT and represent a potential source of drug name confusion. Nine names were thought to look like Lamictal ODT, which include: Vivactil, (b) (4) Surital, Lamicel, (b) (4), Lamzuid, (b) (4), and Ludiomil. The last name, (b) (4) was thought to look and sound similar to Lamictal ODT. As such, a total of twenty nine names were analyzed to determine if the drug names could be confused with Lamictal ODT and if the drug name confusion would likely result in a medication error.

Fifteen names of the names identified for this review were evaluated in DMEPA's previous review for the name Lamictal ODT (OSE Review #2008-1010 and 2008-1149), and there have been no changes in the product characteristics for Lamictal ODT or any of the names that would change or impact that analysis.

The remaining fourteen names were determined to have some orthographic and/or phonetic similarity to Lamictal ODT, and thus determined to present some risk for confusion. Failure mode and effects analysis (FMEA) was then applied to determine if the proposed name, Lamictal ODT, could potentially be confused with any of the 14 names and lead to medication error. This analysis determined that the name similarity between Lamictal ODT and the identified names was unlikely to result in medication errors for all 14 of the products. See Appendices B through H for our evaluation of the 14 products identified.

4 DISCUSSION

Fourteen names were evaluated for their potential similarity to the proposed name, Lamictal ODT. The FMEA indicates that the proposed name is not likely to result in name confusion that could lead to medication errors for the reasons outlined in Appendices B through H.

5 CONCLUSIONS AND RECOMMENDATIONS

The Proprietary Name Risk Assessment findings indicate that the proposed name, Lamictal ODT, is not vulnerable to name confusion that could lead to medication errors. As such, we do not object to the use of the proprietary name, Lamictal ODT, for this product at this time. Additionally, DDMAC does not object to the proposed name, Lamictal ODT, from a promotional perspective. However, if **any** of the proposed product characteristics as stated in this review are altered prior to approval of the product, we rescind this Risk Assessment finding, and the name must be resubmitted for review. If the approval of this application is delayed beyond 90 days from the signature date of this review, the proposed name must be resubmitted for evaluation.

5.1 COMMENTS TO THE DIVISION

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

5.2 COMMENTS TO THE APPLICANT

We have completed our review of the proposed proprietary name, Lamictal ODT, and have concluded that it is acceptable. Lamictal ODT will be re-reviewed 90 days prior to the approval of the NDA.

If we find the name unacceptable following the re-review, we will notify you.

If **any** of the proposed product characteristics are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

6 REFERENCES

6.1 REVIEWS

1. *OSE Review #2007-388 Medication Error Postmarketing Safety Review for Lamictal (Lamotrigine Tablets), Oleszczuk, Z; August 26, 2008.*
2. *OSE Review #2008-101 and 2008-1149 Proprietary Name, Label and Labeling Review for Lamictal ODT (Lamotrigine Orally Disintegrating Tablets), Oleszczuk, Z: September 26, 2008.*

6.2 DATABASES

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 manufactures 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 postmarketing 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://weblern/)

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 DMEDP, FDA.

4. 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.

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 Error Prevention and Analysis proprietary name consultation requests

This is a list of proposed and pending names that is generated by our Division 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 and generic drugs and therapeutic biological products; prescription and over-the-counter human drugs and therapeutic biologicals, 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. USPTO (http://www.uspto.gov)

Provides information regarding patent and trademarks.

10. 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.

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

12. 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.

13. 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.

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.pharmacist.com)

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

17. Medical Abbreviations Book

Contains commonly used medical abbreviations and their definitions.

*18. MedMarx (https://www.medmarx.com/)****

MEDMARX® is a national, Internet-accessible database that hospitals and health care systems use to track and trend adverse drug events and medication errors. Hospitals and health care systems participate in MEDMARX voluntarily and subscribe to it on an annual basis. MEDMARX is a quality improvement tool, which facilitates productive and efficient documentation, reporting, analysis, tracking, trending, and prevention of adverse drug events.

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. The Division of Medication Error Prevention 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 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, we 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 consider 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 Dotted letters Ambiguity introduced by scripting letters Overlapping product characteristics	• Names may look similar when scripted, and lead to drug name confusion in written communication
Sound-alike	Phonetic similarity	Identical prefix Identical infix Identical suffix Number of syllables Stresses Placement of vowel sounds Placement of consonant sounds Overlapping product characteristics	• Names may sound similar when pronounced and lead to drug name confusion in verbal communication

Appendix B: Names identified in the previous DMEPA review as having some similarity to Lamictal ODT and that have no had changes to their product characteristics.

Product name with potential for confusion	**Similarity to Lamictal ODT**
Lamzuid	Look
Ludiomil	Look
(b) (4)	Look and Sound
	Look
	Look and Sound
	Look
Surital	Look
Vivactil	Look
Lamicel	Look
Lomotil	Look
Limbitrol DS	Look
Lamisil*	Look and Sound
Lamictal	Look and Sound
Lamictal CD	Look and Sound
Lamictal XR***	Look and Sound

* For a Complete listing of all currently marketed Lamisil products see Appendix I

Appendix C: Products that lack orthographic and phonetic similarity to Lamictal ODT.

Product name with potential for confusion	Similarity to Lamictal ODT
Surmontil	Look
Fazaclo ODT	Look

Appendix D: Proprietary names of foreign drugs and are not found in common references such as the RedBook, Clinical Pharmacology, Drugs@FDA, Drug Facts and Comparisons, Lexi-Comp, or the Orange Book.

Proprietary Name	Similarity to Lamictal ODT	Strength	Usual Dose	Country
Tamifen (Tamoxifen)	Look	Tablets: Unknown. Formulation no longer actively marketed per Micromedex	20 mg orally, once daily or in 2 divided doses	Russia, Hong Kong, and Czech Republic
Zamadol (Tramadol)	Look	Unknown	Unknown	United Kingdom, Brazil, and Ireland
Lamidus (Lamotrigine)	Look	Unknown	Unknown	Australia
Lamictal (b) (4). (Lamotrigine)	Look and Sound	Unknown	Unknown	Iceland
Lamicosil (Terbinafine)	Look and sound	Unknown	Unknown	Spain
Lamictin (Lamotrigine)	Look and Sound	Unknown	Unknown	South Africa

Appendix E: Proposed Proprietary names not found in common references such as the RedBook, Clinical Pharmacology, Drugs@FDA, Drug Facts and Comparisons, Lexi-Comp, or the Orange Book.

Proprietary Name	Similarity to Lamictal ODT	Source
Lambkill	Sound	Natural Medicines Comprehensive Database

Appendix F: Name that has been discontinued in the United States, does not have any available generics and not found in common references such as the RedBook, and Clinical Pharmacology.

Proprietary Name	Similarity to Lamictal ODT	Source
Surital	Look	Discontinued by Drugs@FDA

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

Product name with potential for confusion	Similarity to Proposed Proprietary Name	Dosage Form and Strength	Usual Dose (if applicable)
Lamictal ODT (lamotrigine orally disintegrating tablets)		**Dosage From: Tablets** **Strength: 25 mg, 50 mg, 100 mg, and 200 mg**	**100 mg orally once per day to 500 mg orally daily in two divided doses**
Lunesta (eszopiclone)	Look	Dosage From: Tablets Strength: 1 mg, 2 mg and 3 mg	2 mg orally immediately before bedtime
Zamicet (Acetaminophen and Hydrocodone Bitartrate)	Look	Dosage From: Oral Solution Strength: 325 mg of Acetaminophen and 10 mg of Hydrocodone Bitartrate per 15 mls	15 mls orally every 4 to 6 hours as needed

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

Failure Mode: **Name confusion**	**Causes** **(could be multiple)**	**Effects**
Lamictal ODT **(lamotrigine orally disintegrating tablets)**	**Dosage From: Tablets** **Strength:** **25 mg, 50 mg, 100 mg, and 200 mg**	**Usual dose:** **100 mg orally once per day to 500 mg orally daily in two divided doses**
Tamiflu (Oseltamivir) Dosage From: Powder for Oral Suspension and Capsules Strength: Powder for Oral Suspension: 12 mg/ml Capsules: 30 mg, 45 mg and 75 mg Usual Dose: 75 mg orally, once daily for at least 10 days following close contact with an infected individual	Orthographic similarity (the beginning of each name may appear similar when scripted ('Tami-' vs. 'Lami-'), both names contain the same number of upstrokes, 3 (capital 'T', lower case 'f' and 'l' vs. capital 'L', lower case 't', and 'l'), in similar positions (1st letter, 5th letter, and 6th letter vs. 1st letter, 6th letter and 8th letter), if the modifier ODT is omitted from Lamictal ODT, both names contain the same number of dotted letters, 1 (lower case 'i') in the same position (4th letter), both names contain the same number of cross strokes, 1, if the modifier ODT is omitted from Lamictal ODT, and the 7th letter in each name ('u' vs. 'a') may appear similar when scripted. Overlapping dose (75 mg), route of administration (oral), and frequency of administration (once daily).	Orthographic differences in the names in addition to the duration of treatment minimize the likelihood of medication error in the usual practice setting. *Rationale:* The risk for medication error is minimized by the orthographic differences in the names as Tamiflu has a downstroke (lower case 'f') in the 5th position that is not present in Lamictal ODT. Additionally, DMEPA is not aware of any confusion that exists between Tamiflu and the route name "Lamictal" that is currently in the US market place. The addition of the modifier 'ODT' should help to further differentiate the two names since it will provide more letters in the name. Further more, while the Tamiflu and Lamictal ODT share an overlapping strength (75 mg), route of administration (oral) and frequency of administration (once daily), the duration of treatment is different for each product (10 days vs. Chronic therapy). Since the a quantity of length of duration would have to be included on a prescription, the duration of treatment will also help to differentiate the two products and minimize the possibility of a medication error. Despite a overlapping strength; the orthographic differences in addition to the duration of treatment minimizes the potential for confusion between Tamiflu and Lamictal ODT.

Appendix I: Currently marketed Lamisil products

Currently Marketed Lamisil Products					
Drug Name	**Rx or OTC**	**Approval Date**	**Strength**	**Dosage Form**	**Usual Dose**
Lamisil (Terbinafine Hydrochloride)	Rx	March 10, 1996	250 mg	Oral Tablet	Nail fungus: One tablet orally once daily
Lamisil (Terbinafine Hydrochloride)	Rx	September 28,2007	125 mg/ packet 187.5 mg/ packet	Oral granules	Tinea capitus in patients 4 years of age and older: 125 mg, 187.5 mg, or 250 mg once a day for 6 weeks; dose is based upon body weight.
Lamisil (Terbinafine Hydrochloride)	Rx	October 17,1997	1%	Topical Solution	Tinea (pityriasis) versicolor due to Malassezia furfu (formerly Pityrosporum ovale). Apply twice daily to affected area for 7 days.
Lamisil (Terbinafine Hydrochloride)	RX	April 29, 1998	1%	Topical Gel	Tinea (pityriasis) versicolor due to Malassezia furfu (formerly Pityrosporum ovale), tinea pedis (athlete's, foot), tinea corporis (ringworm) or tinea cruris (jock itch). Apply once daily to affected area for 7 days.
Lamisil AT Spray Pump (Terbinafine Hydrochloride) (*Athlete's Foot*)	OTC	March 17, 2000	1%	Topical Spray	Athlete's foot: Spray twice daily Ringworm/Jock itch: Spray once daily
Lamisil AT Spray Pump (Terbinafine Hydrochloride) (*Jock Itch*)	OTC	March 17, 2000	1%	Topical Spray	Jock itch: Spray once daily (morning or night)
Lamisil AT (Terbinafine Hydrochloride) (*Athlete's Foot*)	OTC	March 09, 1999	1%	Topical Cream	Athlete's foot: Apply twice daily Ringworm/Jock itch: Apply once daily
Lamisil AT (Terbinafine Hydrochloride) (*Jock Itch*)	OTC	March 09, 1999	1%	Topical Cream	Jock itch: Apply once daily (morning or night)
Lamisil AT (Terbinafine Hydrochloride) (*Athlete's Foot*) Targeted for Women	OTC	March 09, 1999	1%	Topical Cream	Athlete's foot: Apply twice daily
Lamisil AT Gel Advanced (Terbinafine Hydrochloride) (*Athlete's Foot*)	OTC	July 24, 2006	1%	Topical Gel	Athlete's foot: Apply once daily at bedtime Ringworm and jock itch: Apply once daily (morning or night)

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/s/

Zachary A Oleszczuk
2/6/2009 12:11:07 PM
DRUG SAFETY OFFICE REVIEWER

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DRUG SAFETY OFFICE REVIEWER

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 26, 2008
To:	Russell Katz, MD Director, Division of Neurology Products
Through:	Todd Bridges, RPh, Team Leader Denise Toyer, PharmD, Deputy Director Carol Holquist, RPh, Director Division of Medication Error Prevention and Analysis
From:	Zachary Oleszczuk, PharmD, Safety Evaluator Division of Medication Error Prevention and Analysis
Subject:	Proprietary Name, Label, and Labeling Review
Drug Name(s):	Lamictal ODT (Lamotrigine Orally Disintegrating Tablets)
Application Type/Number:	NDA 22-251
Applicant:	GlaxoSmithKline
OSE RCM #:	2008-1010 and 2008-1149

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

CONTENTS

EXECUTIVE SUMMARY

The introduction of Lamictal ODT into the Lamictal product line may result in name confusion with Lamictal oral tablets and Lamictal CD (chewable dispersible oral tablets). 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 Lamictal or Lamictal CD and the alternate name. Therefore, we will not object to the use of the name, Lamictal ODT, for this product. However, we recommend at the time of product launch the Applicant inform healthcare practitioners about the differences between Lamictal ODT and other currently marketed Lamictal products.

The results of the Label and Labeling Risk Assessment found that the proposed labels submitted on September 17, 2008, do not appear to be vulnerable to confusion that could lead to medication errors.

1 BACKGROUND

1.1 INTRODUCTION

This consult was written in response to a request from the Division of Neurology Products (DNP) to evaluate the product for its potential to contribute to medication errors. The proposed name, Lamictal ODT, is evaluated to determine if the name could potentially be confused with other proprietary or established drug names. Container labels, carton and insert labeling were provided for review and comment.

1.2 REGULATORY HISTORY

Lamictal (lamotrigine) tablets were originally approved on December 27, 1994, for NDA 20-241. A second NDA was approved for Lamictal CD (lamotrigine chewable dispersible) tablets, NDA 20-764, on August 24, 1998. Since this NDA provided for pediatric dosing, Lamictal was granted Pediatric Exclusivity on February 14, 2007. Review OSE #2007-388 was completed in preparation for the November 17, 2008 Advisory Committee scheduled under the Best Pharmaceuticals for Children Act.

For this product the Applicant submitted labels and labeling for review on November 28, 2007 (see Appendices J through S). During the analysis of the labels and labeling DMEPA determined that two packaging configurations, (b) (4) and the Maintenance Packs (see Appendix K), were vulnerable to confusion that could lead to medication error.

(b) (4)

Additionally, DMEPA was concerned with the color scheme used for the Maintenance packs, specifically the (b) (4), used to differentiate the various strengths of the maintenance packs because the color scheme was similar to that of titrations kits (blue, green and orange).

DMEPA's concern regarding the color scheme used for the Maintenance Packs was communicated to the Applicant by teleconference on September 15, 2008. The Applicant agreed to submit revised carton labeling for the Maintenance Packs based on the comments provided by DMEPA. The Applicant submitted revised carton labeling for the Maintenance Packs (see Appendix V) on September 17, 2008. Additionally, the Applicant voluntarily revised the color scheme of the carton labeling of the Institutional Packs (see Appendix W), the carton labeling for the Conversion Packs (see Appendix X) , and the container label for the Unit of Use Bottles (see Appendix Y) to maintain consistency throughout the NDA.

1.3 PRODUCT INFORMATION

Lamictal ODT is the proposed name for lamotrigine orally disintegrating tablets. Lamictal ODT is an antiepileptic drug used in the treatment of epilepsy and bipolar disorder.

Lamictal ODT requires that a patient be titrated over several weeks. The dose and speed at which a patient is titrated is dependent upon which other medication(s) the patient is taking and which indication is being treated. Once a patient has been titrated a usual adult dose can range from 100 mg orally once per day to 500 mg daily orally in two divided doses.

Lamictal ODT is manufactured by GlaxoSmithKline. Lamictal ODT will be supplied as 25 mg, 50 mg, 100 mg, and 200 mg tablets. Lamictal ODT will differ in some of the available strengths from the other Lamictal products currently on the market. See Table page 5.

Table 1: Currently Marketed Lamictal Products

Currently Market Lamictal Product							
Drug Name	**Rx or OTC**	**Strength**	**Frequency**	**Dosage Form**	**Route**	**Indication**	**Usual Maintenance Dose After Initial Titration**
Lamictal ODT (lamotrigine hydrochloride orally disintegrating) tablets	Rx	25 mg, 50 mg 100 mg, and 200 mg	Once to twice daily	Orally Disintegrating Tablets	Oral	Epilepsy and Bipolar disorder	100 mg orally once per day to 500 mg orally daily in two divided doses
Lamictal (lamotrigine hydrochloride) tablets	Rx	25 mg, 100 mg, 150 mg, and 200 mg	Once to twice daily	Tablets	Oral	Epilepsy and Bipolar disorder	100 mg orally once per day to 500 mg orally daily in two divided doses
Lamictal CD (lamotrigine hydrochloride chewable dispersible) Tablets	Rx	2 mg, 5 mg, 25 mg	Once to twice daily	Chewable Dispersible Tablets	Oral	Epilepsy and Bipolar disorder	Adult: 100 mg orally once per day to 500 mg orally daily in two divided doses Pediatric: 1 mg/kg to 15 mg/kg orally daily in one or two divided doses
Differences between the products are highlighted in yellow							

Additionally, Lamictal ODT will be available in several new packaging configurations that were not previously available in other Lamictal Products. See Table 2 for a complete list of packaging configurations of Lamictal products.

Table 2: Packaging Configurations of Lamictal Products

Packaging Configurations of Currently Marketed Lamictal Products						
Drug Name	**Bottles**	**Starter Kit (Lamictal) or Titration Kit (Lamictal ODT)**	**Maintenance Pack**	**Institutional Unit Dose Pack**	**Conversion Pack**	**Samples**
Lamictal ODT (lamotrigine hydrochloride orally disintegrating) tablets	X	X	X	X	X	Sample Titration Kits
Lamictal (lamotrigine hydrochloride) tablets	X	X				Sample Starter Kits
Lamictal CD (lamotrigine hydrochloride chewable dispersible) Tablets	X					Sample Bottles (2 mg, 5 mg, and 25 mg°)

2 METHODS AND MATERIALS

This section consists of two sections which describe 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) and label, labeling, and/or packaging risk assessment (see 2.2 Container Label, Carton Labeling, and Insert Labeling Risk Assessment). The primary focus for both of the assessments 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, Lamictal ODT, 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. Additionally, the modifier/suffix, 'ODT', was assessed for resemblance to any numbers, dosing instructions, or medical abbreviations. Furthermore, the Division of Medication Error Prevention and Analysis evaluated the appropriateness of the proposed modifier/suffix and the potential for it to be confusing or misleading, considered the potential for modifier's omission or misinterpretation, and verified that the modifier does not appear on the error-prone abbreviation list maintained by the Institute of Safe Medication Practices (ISMP).

° The 5 mg and 25 mg sample bottles will be discontinued in November 2008.

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

For the proprietary name, Lamictal ODT, the Medication Error Staff search a standard set of databases and information sources to identify names with orthographic and phonetic similarity (see section 2.1.1 for detail) and held a CDER Expert Panel discussion to gather professional opinions on the safety of the proposed proprietary name (see section 2.1.3). The Division of Medication Error Prevention and Analysis 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.

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, Lamictal ODT, 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 consider 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, 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.

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[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.

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

For this review, particular consideration was given to drug names beginning with the letter 'L' 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] Additionally, since omission of a modifier is cited in the literature as a common cause of medication errors[7], the Medication Error Prevention Staff consider 'Lamictal ODT' as a complete name as well as 'Lamictal,' the root term, omitting the modifying term 'ODT'. Furthermore, 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 Lamictal ODT, 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 (11 letters), upstrokes (six; capital letter 'L', lower case letters 't', and 'l', capital letters 'O', 'D' and 'T'), downstrokes (none), cross-strokes (two; lower case 't', and capital 'T'), and dotted letters (one; lower case 'i'). Additionally, several letters in Lamictal ODT may be vulnerable to ambiguity when scripted, including the letter 'L' may appear as capital 'Z'; lower case 'a' may appear as a lower case 'e', 's', 'u', 'x', 'o', and letter combinations lower case 'ci' or 'ce'; lower case 'm' may appear as a lower case 'n', 'z', and letter combination 'ss' or 'onc'; lower case 'i' may appear as a lower case 'e'; lower case c may appear as a lower case 'a'; lower case 't' may appear as lower case 'f', 'r' or 'x'; lower case l appears a lower case 'b', 'e', 'k' or 'p'; and upper case 'T' may appear as upper case 'J', 'F' or 'Z'. As such, the Staff also considers these alternate appearances when identifying drug names that may look similar to Lamictal ODT.

When searching to identify potential names that may sound similar to Lamictal ODT, the Medication Error Staff search for names with similar number of syllables in the name (6 syllables), stresses (Lah-mic-tal Oh-Dee-Tee, lah-Mic-tal Oh-Dee-Tee, or lah-mic-Tal Oh-Dee-Tee), and placement of vowel and consonant sounds. In addition, several letters in Lamictal ODT may be subject to interpretation when spoken, including the letter 'm' may be interpreted as 'n'; the letter 'c' may be interpreted as 'z', the letter 't' may be interpreted as 'd' or 'n'; and the letter 'a' may be interpreted as 'o'. We also considered how the inclusion of "ODT" 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 were provided with the following information about the proposed product: the proposed proprietary name (Lamictal ODT), the established name (lamotrigine), proposed indication (Epilepsy and Bipolar Disorder), strength (25 mg, 50 mg, 100 mg, and 200 mg), dose (titrated over several weeks, then a maintenance dose between 100 mg to 500 mg per day), frequency of administration (once or two divided doses), route (oral) and dosage form of the product (oral disintegrating tablet). Appendix A provides a more detailed listing of the product characteristics the Medication Error Staff general take into consideration.

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[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. Artificial Intelligence in Medicine (2005)

[7] Lesar TS. Prescribing Errors Involving Medication Dosage Forms. *J Gen Intern Med.* 2002; 17(8): 579-587.

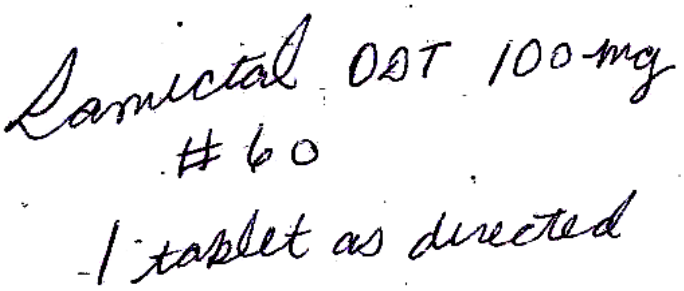
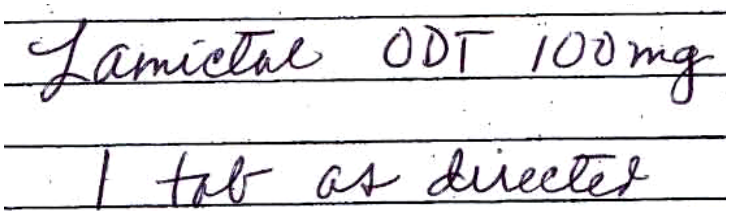
Lastly, the Medication Error Staff also consider the potential for the proposed name to inadvertently function as a source of error for reasons other than name confusion. Postmarketing experience has demonstrated that proprietary names (or components of the proprietary name) can be a source of error in a variety of ways. As such, these broader safety implications of the name are considered and evaluated throughout this assessment and 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 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 Lamictal ODT 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 Lamictal ODT 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. Lamictal ODT Study (conducted on August 13, 2008)

HANDWRITTEN PRESCRIPITON AND MEDICATION ORDER	VERBAL PRESCRIPTION
Outpatient Prescription:  	Lamictal ODT 100 mg #60 1 Tablet as directed
Inpatient Medication Order :  	

2.1.3 Database and information sources

The proposed proprietary name, Lamictal ODT, was provided to the Division of Medication Error Prevention and Analysis 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 Lamictal ODT using the criteria outlined in 2.1.1. Additionally, the modifier 'ODT' was assessed for resemblance to any numbers, dosing instructions, or medical abbreviations. We also evaluated the appropriateness of the modifier for this proposed formulation. A standard description of the databases used in the searches is provided in Section 6.2. To complement the process, DMEPA 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 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.

2.1.4 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, Lamictal ODT. Potential concerns regarding drug marketing and promotion related to the proposed names are also discussed. This group is composed of DMEPA 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.

2.1.5 Medication Error Risk Assessment

Since the root name of this product, "Lamictal" is currently marketed, we normally would conduct a search of the Adverse Event Reporting System (AERS) database to identify any additional names that may potentially be confused with the proposed proprietary name (see section 2.2). However, OSE Review #2007-388 evaluated medication errors related to confusion with the proprietary name Lamictal that included an AERS search, a search of the MedMarx Database****, and a search of the Institute For Safe Medication Practices Databases***. Since these searches and the review were completed during the review process of the proprietary name Lamictal ODT, the Division of Medication Error Prevention and Analysis will not repeat these searches. DMEPA refers to OSE# 2007-388 for the detailed search criteria used.

During this previous review we also learned of a medication error with the Lamictal Starter Kits used for titration. Since the Applicant purposes similar packaging for the ODT formulation we conducted a refined search of the AERS database and the USP MEDMARX*** database, to identify post-marketing cases associated specifically with the "Starter Kits".

2.1.5.1 Adverse Event Reporting System (AERS)

The AERS search on August 1, 2008, used the MedDRA Higher Level Terms (HLT) "Maladministration", and "Medication Errors NEC"; Preferred Terms "Overdose", "Accidental overdose", "Accidental exposure", and "Pharmaceutical complaint"; and tradename "Lamictal", active ingredient "Lamotrigine", and verbatim "Lam%" as search criteria. In addition the search was limited from January 1, 1998 to August 1, 2008 since Starter Kits were not marketed prior to this time.

The narratives of these cases identified in the above search were computationally searched to identify key words. The following letter strings were included as search criteria: Titrat%, Starter, Pack, Pak, Blue, Green, Orang (truncated), Kit, and Mixup. The cases identified by the software program that included at least one of these strings where then manually reviewed to determine if a medication error existed. Those cases that did not describe a medication error were excluded from further analysis. The cases that described a medication error were categorized by type of error. Our Division 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 Lamictal ODT.

2.1.5.2 MedMarx Database***

The Division of Medication Error Prevention requested a search of the USP MEDMARX*** database to identify reports of medication errors involving the "Starter Kits" of Lamictal.

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.[8] 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 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 Lamictal ODT 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 Lamictal ODT 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.

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

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 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. 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 and another drug product.

In the event that our Division objects 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, World Health Organization, Joint Commission, and 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, we contend 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, postmarketing 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 our Division 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. We are likely to recommend that the Applicant select an alternative proprietary name and submit the alternate name to the Agency for 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 we may be able to provide the Applicant with recommendations that reduce or eliminate the potential for error would render the proposed name acceptable.

2.2 LABEL AND LABELING RISK ASSESSMENT

The label and labeling of a drug product are the primary means by which practitioners and patients (depending on configuration) interact with the pharmaceutical product. The container label and carton labeling communicate critical information including proprietary and established name, strength, form, container quantity, expiration, and so on. The insert labeling is intended to communicate to practitioners all information relevant to the approved uses of the drug, including the correct dosing and administration.

Given the critical role that the label and labeling has in the safe use of drug products, it is not surprising that 33 percent of medication errors reported to the USP-ISMP Medication Error Reporting Program may be attributed to the packaging and labeling of drug products, including 30 percent of fatal errors.[9]

Because the Medication Error Prevention and Analysis staff analyzes reported misuse of drugs, the staff are able to use this experience to identify potential errors with all medication similarly packaged, labeled or prescribed. We use FMEA and the principles of human factors to identify potential sources of error with the proposed product labels and insert labeling, and provided recommendations that aim at reducing the risk of medication errors.

For this product, the Applicant submitted the following labeling for our review on November 28, 2007:

- Insert Labeling (no image)

[9] Institute of Medicine. Preventing Medication Errors. The National Academies Press: Washington DC. 2006. p275.

On April 29, 2008, the Applicant submitted the following labels and labeling for our review (see Appendices O through S):

- Container Labels for Maintenance Packs: 25 mg, 50 mg, 100 mg, and 200 mg
- Container Labeling for Institutional Unit Dose Packs: 25 mg, 50 mg, 100 mg, and 200 mg
- Container Labels for Titration Kit: Blue Kit, Green Kit, and Orange Kit
- Carton Labeling for Titration Kit: Blue Kit, Green Kit, and Orange Kit
- Container Labels for Conversion Kit: 100 mg

On June 23, 2008, the Applicant submitted the following comparison of labels and labeling for our review (see Appendices T and Appendix U):

- Container Labels for Lamictal Tablets 25 mg, 100 mg, 150 mg, and 200 mg; and Lamictal CD 2 mg, 5 mg, and 25 mg.
- Carton Labeling for Lamictal Tablets Starter Kits (Blue Kit, Green Kit, and Orange Kit) and Lamictal ODT Titration Kits (Blue Kit, Green Kit, and Orange Kit).

On September 17, 2008, the Applicant submitted the following Labels and Labeling for review (see Appendix V through Y):

- Carton Labeling for Maintenance Packs: 25 mg, 50 mg, 100 mg, and 200 mg
- Carton Labeling for Institutional Unit Dose Packs: 25 mg, 50 mg, 100 mg, and 200 mg
- Container Labels for Unit of Use Bottles: 25 mg, 50 mg, 100 mg and 200 mg
- Carton Labeling for Conversion Kit: 100 mg

3 RESULTS

3.1 PROPRIETARY NAME RISK ASSESSMENT

3.1.1 Database and Information Sources

In total, 15 names were identified as having some similarity to the name Lamictal ODT. Ten of the 15 names were thought to look like Lamictal ODT; these names include: Vivactil, Lomotil, (b) (4) Surital, Lamicel, (b) (4), Lamzuid, (b) (4), and Ludiomil. Five of the 15 names were thought to look and sound similar to Lamictal ODT; these names include: Lamictal, Lamictal CD, Lamisil (Product Line - See Appendix I for currently marketed Lamisil products), (b) (4), and Lamictal XR***.

The proposed modifier 'ODT' did not resemble any numbers, or dosing instructions. However, the proposed modifier 'ODT' has been used as a medical abbreviation for O-Desmethyltramadol, Occlusive Dressing Technique, Octadecanethiol, Octadecyltitania Stationary Phase, Oculodynamic Methodology, Oculodynamic Test, Oculodynamic Text, Oculodynamic Tract, Odor Detection Test, Odor Detection Threshold, Of Lower Extremity Discomfort, Olympic Distance Triathlon Performance, On Direct Testing, Once-Daily Tobramycin, Optical Doppler Tomography, Orally Dispersible Tablets, Order-Disorder Transition, Organ Donation And Transplant, Oscillatory Displacement Threshold, Osteochondrosis Dissecans Of The Talus, or Right Occipitotransverse[10]. These interpretations should not result in confusion when Lamictal ODT is prescribed or dispensed.

[10] Medilexicom, http://www medilexicon.com/medicalabbreviations.php. May 28, 2008

The proposed modifier 'ODT' does not appear on the ISMP "List of Error Prone Abbreviations, Symbols, and Dose Designations." When assessing the appropriateness of the modifier for this formulation, we noted six products (Aricept ODT, Fazaclo ODT, Orapred ODT, Reglan ODT, Tovalt ODT, and Zofran ODT) listed in the Orange Book contained the Modifier 'ODT' in their proprietary names. The six proprietary names found in the Orange Book use the "ODT" modifier to describe the "orally disintegrating tablets" dosage form. Additionally, DMEPA is not aware of any postmarketing evidence of misinterpretation of the modifier 'ODT'.

The proposed proprietary name, Lamictal ODT, does not contain a USAN stem as of the last date searched, August 13, 2008.

3.1.2 CDER Expert Panel Discussion

The Expert Panel reviewed the pool of names identified by the Medication Error Prevention and Analysis Staff (see section 3.1.1 above), and did not provide any additional names orthographically or phonetically similar to Lamictal ODT.

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

3.1.3 CDER Prescription Analysis Studies

A total of 31 practitioners responded, five of which omitted the modifier 'ODT' resulting in an overlap with the existing product Lamictal. Three participants (n=3) in the voice prescription study misspelled the root name, one spelling it with an extra 'a' (Lamicatal ODT) and two spelling the root name replacing the second 'a' with the letter 'i' (Lamictil ODT). Twenty three (n=23) out of the thirty one participants interpreted the name correctly as "Lamictal ODT". The majority of misinterpretations occurred due to omission of the modifier 'ODT' and occurred in each of the three studies. However, when the modifier was reported there were no misinterpretations of the modifier.

3.1.4 Medication Error Risk Assessment

3.1.4.1 Adverse Event Reporting System (AERS)

The AERS search preformed on August 1, 2008, yielded 76 reports. These reports were manually reviewed for medication errors related to labeling and specifically the starter packs. After removing duplicate reports and reports that did not have medication errors related to labeling, six cases remained (see Appendix I). Of the 6 cases, three cases involved a patient receiving the wrong pack based on their current concomitant medications. The outcomes of those 3 cases were 1 hospitalization, one minor adverse event and no outcome reported. One case reported causality as a knowledge deficit and a computer selection error. Causality was not reported in the other 2 cases.

The remaining 3 cases involved patients taking the starter pack incorrectly. The outcomes for these three cases were 2 hospitalizations and 1 minor adverse event ("fuzziness and buzzing" in her head). Causality was not reported in the 3 cases.

3.1.4.2 MedMarx Database***

A search of the USP MEDMARX*** database did not identify any cases of medication errors involving the "Starter Kits" of Lamictal Tablets.

3.1.5 Safety evaluator risk assessment

Independent searches by the primary safety evaluator did not result in any additional names thought to look or sound similar to Lamictal ODT and represent a potential source of drug name confusion. As such, a total of 15 names were analyzed to determine if the drug names could be confused with Lamictal ODT 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 Lamictal ODT, and thus determined to present some risk for confusion. Failure modes and effects analysis (FMEA) was then applied to determine if the proposed name, Lamictal ODT, could potentially be confused with any of the 15 names and lead to medication error. This analysis determined that the name similarity between Lamictal ODT and the identified names was unlikely to result in medication errors for 13 of the products. See Appendices B through H for our evaluation of the 13 products identified.

For the remaining two names, Lamictal and Lamictal CD, FMEA determined that confusion may occur due to the orthographic and phonetic similarities with the proposed name Lamictal ODT if the modifier 'ODT' is omitted or misinterpreted. These two names are discussed in section 4.

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

3.2 LABEL AND LABELING RISK ASSESSMENT

Review of the labels, and labeling of Lamictal ODT and comparison of these with the labels and labeling of currently marketed Lamictal products identified that the three packaging configurations; the Maintenance Pack, the Conversion Pack and the Institutional unit dose packaging that are not currently marketed for other Lamictal products introduce opportunities for confusion and error that did not previously exist with the other Lamictal products.

3.2.1 Container Label for Maintenance Pack

No comments at this time.

3.2.2 Container Labeling for Hospital Unit Dose Packs

No comment at this time.

3.2.3 Container Labels for Titration Kits

No comment at this time.

3.2.4 Carton Labeling for Titration Kits

No comment at this time.

3.2.5 Container Labels for Conversion Kit

No comment at this time.

3.2.6 Carton Labeling for Maintenance Pack

No comment at this time.

3.2.7 Carton Labeling for Hospital Unit Dose Packs

No comment at this time.

3.2.8 Container Labels for Unit of Use Bottles

No comments at this time.

3.2.9 Carton Labeling for Conversion Pack

No comments at this time.

3.2.10 Insert Labeling

No comments at this time.

4 DISCUSSION

4.1 PROPRIETARY NAME RISK ASSESSMENT

The Applicant is proposing the introduction of a new dosage form, "orally disintegrating tablets", which will result in a product line extension of Lamictal. The proposed name for this product is Lamictal ODT. The modifier "ODT" is meant to represent "Orally Disintegrating Tablets". This naming convention is commonly used when an orally disintegrating tablet dosage form is added to a product line with an oral formulation.Lamictal is currently marketed as 25 mg, 100 mg, 150 mg, and 200 mg tablets. Additionally, Lamictal CD is currently available as 2 mg, 5 mg, and 25 mg chewable dispersible tablets.

We anticipate errors between the existing Lamictal products and the proposed orally disintegrating tablets because they share the root name "Lamictal" and only differ with regards to dosage form. Regardless of the modifier used, if it is omitted in prescribing Lamictal ODT, the currently marketed Lamictal products may be inadvertently dispensed. Although the patient will receive the correct active ingredient in this case the dosage form is incorrect.

Errors introduced by product line extension are a well known occurrence at all points in the medication use process (i.e., prescribing, computer selection, dispensing, administering, and monitoring). These errors are multi-factorial in nature, and can stem from the timing of the product launch, the similarity of product names, overlapping product characteristics coupled with the low level of awareness of knowledge with respect to the introduction of new formulations of existing products by healthcare professionals and patients. Thus, there will be a need for making practitioners aware of this new dosage form and in communicating the differences between Lamictal tablets, Lamictal chewable dispersible tablets, and Lamictal orally disintegrating tablets.

DMEPA also analyzed the approach of using an alternative proprietary name for the Lamotrigine orally disintegrating tablets product while maintaining the Lamictal and Lamictal CD name for the other Lamotrigine products. This FMEA identified the additional failure mode of concomitant therapy which was not identified in the FMEA for Lamictal ODT. These findings indicate there may be risk of confusion in either direction and the clinical consequences of each risk are not well defined.

4.2 LABEL AND LABELING RISK ASSESSMENT

DMEPA has evidence that the currently marketed Starter Kits have been confused for one another and that patients have not followed the directions even if the correct kit was dispensed. For the Lamictal ODT product the Applicant is proposing a Titration Kit that mimics the Starter Kits currently marketed. Although these kits contain different dosage forms they are both used to titrate patients. DMEPA anticipates that there will be similar errors identified with the Titration Kits once the product is marketed, but acknowledges the necessity for the Titration Kits and Starter Kits because of the complexity of initiating Lamictal therapy.

Additionally, DMEPA anticipates that confusion may occur between the Titration Kits and the currently marketed Starter Kits. To avoid this confusion the Applicant has attempted to differentiate the Kits by using different size cartons and by the way the information is presented on the carton labeling. Additionally, the Applicant has named the kits differently (i.e., Starter Kit vs. Titration Kit) for further differentiation. Although the Starter Kits and Titration Kits are not ideal, these packaging configurations are necessary to address the complexity of initiation of Lamictal.

Lamictal ODT has three packaging configurations; the Maintenance Pack, Conversion Pack and Institutional unit dose packaging that are not currently marketed for other Lamictal products. These packaging configurations, specifically the Maintenance Pack, introduce opportunities for confusion and error that did not previously exist with the other Lamictal products. Although opportunity for error is introduced by the three new packaging configurations, the packaging configurations are well differentiated which should help minimize errors.

5 CONCLUSIONS AND RECOMMENDATIONS

The Proprietary Name Risk Assessment findings indicate that the proposed name, Lamictal ODT, appears to be vulnerable to name confusion and could lead to medication errors. Specifically, the findings indicate that the proposed name Lamictal ODT will be confused with currently market products Lamictal and Lamictal CD. However, our analysis of an alternative name concluded that there is the additional risk of concomitant therapy, while confusion between Lamictal ODT and Lamictal or Lamictal ODT and Lamictal CD would result in a patient receiving the intended drug, at the intended dose, at the intended frequency, by the intended route of administration but by an unintended dosage form. As such, the Division of Medication Prevention and Analysis does not object to the use of the proprietary name, Lamictal ODT, for this product.

However, at the time of product launch, DMEPA recommends that the applicant inform healthcare practitioners about the differences between the proposed Lamictal ODT product versus the other Lamictal products, Lamictal and Lamictal CD (e.g., Dear Healthcare Professional letter). Educating practitioners and communicating the differences between Lamictal tablets, Lamictal chewable dispersible tablets, and Lamictal orally disintegrating tablets should help to minimize the risk for errors.

Additionally, DDMAC has no objections to the proposed name, Lamictal ODT, from a promotional perspective.

The results of the Label and Labeling Risk Assessment found that the various packaging configurations for Lamictal and Lamictal ODT appear to be vulnerable to confusion that could lead to medication errors. However, the packaging configurations are well differentiated which should minimize the risks of error. Additionally, the packaging configurations are necessary to address the complexity of initiation of Lamictal.

5.1 COMMENTS TO THE DIVISION

The results of the Proposed Proprietary Name Risk Assessment found that the proprietary name Lamictal ODT is vulnerable to confusion that could lead to medication errors. However, the Division of Medication Error Prevention and Analysis believes that the risks of medication errors can be minimized by education of healthcare practitioners. Thus, the Division of Medication Error Prevention and analysis does not object to the use of the proprietary name, Lamictal ODT for this product.

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. Furthermore, this name must be re-evaluated approximately 90 days prior to the expected approval of the NDA. A re-review of the name prior to NDA approval will rule out any objections based upon approval of other proprietary or established names from the signature date of this document.

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

6 REFERENCES

6.1 REVIEWS

1. *OSE Review #2007-388 Medication Error Postmarketing Safety Review for Lamictal (Lamotrigine Tablets), Oleszczuk, Z; August 26, 2008.*

6.2 DATABASES

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 manufactures 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 postmarketing 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://weblern/)

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 DMEDP, FDA.

4. 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.

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 Error Prevention and Analysis proprietary name consultation requests

This is a list of proposed and pending names that is generated by our Division 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 and generic drugs and therapeutic biological products; prescription and over-the-counter human drugs and therapeutic biologicals, 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. USPTO (http://www.uspto.gov)

Provides information regarding patent and trademarks.

10. 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.

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

12. 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.

13. 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.

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.pharmacist.com)

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

17. Medical Abbreviations Book

Contains commonly used medical abbreviations and their definitions.

*18. MedMarx (https://www.medmarx.com/)****

MEDMARX® is a national, Internet-accessible database that hospitals and health care systems use to track and trend adverse drug events and medication errors. Hospitals and health care systems participate in MEDMARX voluntarily and subscribe to it on an annual basis. MEDMARX is a quality improvement tool, which facilitates productive and efficient documentation, reporting, analysis, tracking, trending, and prevention of adverse drug events.

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. The Division of Medication Error Prevention 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 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, we 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 consider 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 Dotted letters Ambiguity introduced by scripting letters Overlapping product characteristics	• Names may look similar when scripted, and lead to drug name confusion in written communication
Sound-alike	Phonetic similarity	Identical prefix Identical infix Identical suffix Number of syllables Stresses Placement of vowel sounds Placement of consonant sounds Overlapping product characteristics	• Names may sound similar when pronounced and lead to drug name confusion in verbal communication

Appendix B: CDER Prescription Study Responses for Lamictal ODT

Outpatient Prescription	Voice Prescription	Inpatient Medication Order
Lamictal	Lamicatal ODT	Lamictal
Lamictal ODT	Lamictal	Lamictal
Lamictal ODT	Lamictal ODT	Lamictal
lamictal ODT	Lamictal ODT	Lamictal ODT
Lamictal ODT	Lamictal ODT	Lamictal ODT
Lamictal ODT	Lamictal ODT	Lamictal ODT
Lamictal ODT	Lamictil ODT	Lamictal ODT
Lamictal ODT	Lamictil ODT	Lamictal ODT
		Lamictal ODT
		Lamictal ODT
		Lamictal ODT
		Lamictal ODT
		Lamictal ODT
		Lamictal ODT
		Lamictal ODT

Appendix C: Products that lack orthographic and phonetic similarity to Lamictal ODT.

Product name with potential for confusion	Similarity to Lamictal ODT
(b) (4)	Look
Ludiomil	Look

Appendix D: Proprietary names of foreign drugs.

Proprietary Name	Similarity to Lamictal ODT	Strength	Usual Dose	Country
(b) (4)	Look and Sound	(b) (4)		

Appendix E: Proposed Proprietary names never marketed in the United States and not found in common references such as the RedBook, Clinical Pharmacology, Drugs@FDA, Drug Facts and Comparisons, Lexi-Comp, or the Orange Book.

Proprietary Name	Similarity to Lamictal ODT	Source
(b) (4)	Look	(b) (4)
	Look	
	Look	
Lamictal XR*** (Lamotrigine extended Release)	Look and Sound	Division of Medication Error Prevention and Analysis proprietary name consultation requests. This product has not yet been approved and is not currently being reviewed.

Appendix F: Name that have been discontinued in the United States, does not have any available generics and not found in common references such as the RedBook, Clinical Pharmacology, and Drug Facts and Comparisons.

Proprietary Name	Similarity to Lamictal ODT	Source
Surital	Look	Discontinued by Drugs@FDA

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

Failure Mode: **Name confusion**	**Causes** **(could be multiple)**	**Effects**
Lamictal ODT **(lamotrigine orally disintegrating tablets)**	**Dosage From:** **Tablets** **Strength:** **25 mg, 50 mg, 100 mg, and 200 mg**	**Usual dose:** **100 mg orally once per day to 500 mg orally daily in two divided doses**
Vivactil (Protriptyline Hydrochloride) Dosage From: Tablets Strength: 5 mg and 10 mg Usual Dose: 15 mg to 40 mg orally per day in 3 to 4 divided doses	Orthographic similarity (both names contain the same number of letters, 8, if the modifier ODT is omitted from Lamictal ODT, both names contain the same number of upstrokes, 3 (capital 'V', lower case 't' and 'l' vs. capital 'L', lower case 't' and 'l', if the modifier ODT is omitted from Lamictal ODT, both names contain the same numbers of downstrokes (0), and both names contain similar letters ('ctil' vs. 'ctal' located in the same position (fifth letter through eighth letter)) Similar numerical strength (5 mg and 10 mg vs. 50 mg and 100 mg if a trailing zero is included. For Vivactil example 5.0 mg) Overlapping dosage form (tablet), and route of administration (oral) Achievable dose (25mg)	The unlikelihood of the inclusion of a trailing zero and the differing dosing frequency minimize the likelihood of medication error in the usual practice setting. *Rationale:* Although Vivactil and Lamictal ODT do have a numerical overlapping strengths (5 mg and 10 mg vs. 50 mg and 100 mg if a trailing zero is included. For Vivactil example 5.0 mg) usual practice would not typically involve the inclusion of a trailing zero, though medication errors have been linked to this dangerous habit. Numerous campaigns (Joint Commission, Institute of Safe Medication Practices, and Food and Drug Administration) to eliminate use of trailing zeros when communicating drug information should help to further reduce risk of medication error. Additionally, while the route of administration (oral) is the same for both products the frequency (3 to 4 times daily vs. once to twice daily) of each product is different. Since the frequency will most likely be included on a prescription the possibility of a medication error is minimized. Despite a numerical overlap in strength; the unlikelihood of the inclusion of a trailing zero, and the difference in frequency minimizes the potential for confusion between Vivactil and Lamictal ODT.

Lamicel (Laminaria) <u>Dosage From:</u> Tent <u>Strength:</u> 2 mm – 10 mm in diameter and 60 mm to 70 mm in length <u>Usual Dose:</u> Place one tent in the cervix for up to 24 hours	Orthographic similarity (both names contain the same numbers of downstrokes (0), and both names begin with the same letters 'Lamic-', both names contain an 'l' in a similar position (7^{th} letter vs. 8^{th} letter))	The differing context of use, dose, dosing frequency, and route of administration minimize the likelihood of medication error in the usual practice setting. *Rationale:* Although Lamicel and Lamictal ODT contain the same first five letters, the context of use would be different. Lamicel would only be ordered as a once time dose to ripen the cervix. Lamictal would not be ordered in this setting. Additionally, the route of administration (intrauterine vs. oral), size/dose (2 mm – 10 mm in diameter and 60 mm to 70 mm in length vs. 100 mg to 500 mg) and frequency (once for up to 24 hours vs. once or twice per day for chronic therapy) are different. Since the frequency and size/dose will most likely be included on a prescription the possibility of a medication error is minimized. Despite the orthographic similarities; the difference in context of use, frequency, dose and route of administration minimizes the potential for confusion between Lamicel and Lamictal ODT.

Lomotil (Diphenoxylate Hydrochloride with Atropine Sulfate) <u>Dosage From:</u> Tablets and Oral Solution <u>Strength:</u> Tablets: 0.025 mg/2.5 mg Oral Solution: 0.025 mg/2.5 mg per 5 ml <u>Usual Dose:</u> Initially: 5 mg by mouth 3 to 4 times per day then reduce to 2.5 mg by mouth 3 to 4 times per day as needed	Orthographic similarity (both names contain the same number of upstrokes, 3 (capital 'L', lower case 't' and 'l' vs. capital 'L', lower case 't' and 'l', if the modifier ODT is omitted from Lamictal ODT) in similar positions (1st letters, 5th letter vs. 6th letter and 7th letter vs. 8th letter) , both names contain the same numbers of downstrokes (0), and both names begin with the letter 'L', the second letter of each name may appear similar when scripted ('o' vs. 'a'), and both names contain the same letter 'm' located in the same position (third letter)) Similar numerical strength (2.5 mg vs. 25 mg if the decimal point is omitted or overlooked. For example Lomotil 25 mg) Overlapping dosage form (tablet), and route of administration (oral)	Orthographic differences in the names in addition to differentiating product characteristics minimize the likelihood of medication error in the usual practice setting. *Rationale:* While the Division of Medication Error Prevention and Analysis acknowledges that there has been confusion with Lomotil and the root name Lamictal, the modifier 'ODT' should add another differentiating characteristic to minimize the errors between Lomotil and Lamictal ODT. Additionally, while the route of administration (oral) is the same for both products the frequency (3 to 4 times daily vs. once to twice daily) of each product is different. Since the frequency will most likely be included on a prescription the possibility of a medication error is minimized. Furthermore, Lomotil is usually scheduled on an as needed basis where as Lamictal is scheduled around the clock. This difference in prescribing should help minimize the possibility of a medication error. Despite a numerical overlap in strength; the orthographic differences and the difference in frequency and scheduling minimizes the potential for confusion between Lomotil and Lamictal ODT.

Limbitrol DS (chlordiazepoxide and amitriptyline) <u>Dosage From:</u> Tablets <u>Strength:</u> 10 mg chlordiazepoxide and 25 mg amitriptyline <u>Usual Dose:</u> 10 mg chlordiazepoxide with 25 mg amitriptyline 3 or 4 times daily in divided doses; increase to 6 times daily, as required	Orthographic similarity (both names contain the same number of letters (11), both names contain the same numbers of downstrokes (0), both names contain the same number of upstrokes (6, Capital letter 'L', lower case 'b', 't', 'l', capitals letter 'D' and 'S' vs. Capital letter 'L', lower case 't', 'l', capitals letter 'O', 'D' and 'T') and both names begin with the letter 'L', and both names contain the same letter 'm' located in the same position (third letter)) Similar numerical strength (25 mg of the amitriptyline component vs. 25 mg) Overlapping dosage form (tablet), and route of administration (oral)	Orthographic differences in the names in addition to differentiating product characteristics minimize the likelihood of medication error in the usual practice setting. *Rationale:* The risk for medication error is minimized by the orthographic differences in the names as Limbitrol DS has an upstroke at the 4th position ('b') that is not present in Lamictal ODT. Additionally, while the route of administration (oral) is the same for both products the frequency of administration (3 to 4 times daily vs. once to twice daily) of each product is different. Since the frequency will most likely be included on a prescription the possibility of a medication error is minimized. Despite a numerical overlap in strength; the orthographic differences in addition to the difference in frequency of administration minimizes the potential for confusion between Limbitrol DS and Lamictal ODT.

Lamisil (Terbinafine Hydrochloride Tablets) <u>Dosage From:</u> Tablets* <u>Strength:</u> 250 mg <u>Usual Dose:</u> 250 mg once daily	Phonetic similarity (both names contain the same number of syllables, 3, if the modifier ODT is omitted from Lamictal ODT, both names have the same beginning 'Lami-', the endings of each name ('-il' vs. 'al' if the modifier ODT is omitted from Lamictal ODT) may sound similar when spoken) Orthographic similarity (both names contain the same numbers of downstrokes (0), both names begin with the same letters 'Lami-', and both names contain an 'l' in a similar position (7th letter vs. 8th letter)) Similar numerical strength (250 mg vs. 25 mg if a trailing zero is included. For Lamictal example 25.0 mg) Overlapping dosage form (tablet), route of administration (oral), dose (250 mg), and frequency (once daily)	Phonetic and Orthographic differences in the names in addition to efforts made by GlaxoSmithKline and the FDA minimize the likelihood of medication error in the usual practice setting. *Rationale:* While the Division of Medication Error Prevention and Analysis acknowledges that there has been confusion with Lamisil and the root name Lamictal, the modifier 'ODT' should add another differentiating characteristic to minimize the errors between Lamisil and Lamictal ODT. Additionally, Lamisil and Lamictal confusion is a well documented medication error. GlaxoSmithKline and the FDA have developed an extensive communication program to communicate this error to patients and healthcare providers. The efforts of communication continue as of today and are planned for the foreseeable future. The FDA is also monitoring these errors and working with all parties to minimize errors between Lamisil and Lamictal.

* For a Complete listing of all currently marketed Lamisil products see Appendix I

Appendix H: Currently marketed Lamisil products

Currently Marketed Lamisil Products					
Drug Name	**Rx or OTC**	**Approval Date**	**Strength**	**Dosage Form**	**Usual Dose**
Lamisil (Terbinafine Hydrochloride)	Rx	March 10, 1996	250 mg	Oral Tablet	Nail fungus: One tablet orally once daily
Lamisil (Terbinafine Hydrochloride)	Rx	September 28,2007	125 mg/ packet 187.5 mg/ packet	Oral granules	Tinea capitus in patients 4 years of age and older: 125 mg, 187.5 mg, or 250 mg once a day for 6 weeks; dose is based upon body weight.
Lamisil (Terbinafine Hydrochloride)	Rx	October 17,1997	1%	Topical Solution	Tinea (pityriasis) versicolor due to Malassezia furfu (formerly Pityrosporum ovale). Apply twice daily to affected area for 7 days.
Lamisil (Terbinafine Hydrochloride)	RX	April 29, 1998	1%	Topical Gel	Tinea (pityriasis) versicolor due to Malassezia furfu (formerly Pityrosporum ovale), tinea pedis (athlete's, foot), tinea corporis (ringworm) or tinea cruris (jock itch). Apply once daily to affected area for 7 days.
Lamisil AT Spray Pump (Terbinafine Hydrochloride) (*Athlete's Foot*)	OTC	March 17, 2000	1%	Topical Spray	Athlete's foot: Spray twice daily Ringworm/Jock itch: Spray once daily
Lamisil AT Spray Pump (Terbinafine Hydrochloride) (*Jock Itch*)	OTC	March 17, 2000	1%	Topical Spray	Jock itch: Spray once daily (morning or night)
Lamisil AT (Terbinafine Hydrochloride) (*Athlete's Foot*)	OTC	March 09, 1999	1%	Topical Cream	Athlete's foot: Apply twice daily Ringworm/Jock itch: Apply once daily
Lamisil AT (Terbinafine Hydrochloride) (*Jock Itch*)	OTC	March 09, 1999	1%	Topical Cream	Jock itch: Apply once daily (morning or night)
Lamisil AT (Terbinafine Hydrochloride) (*Athlete's Foot*) Targeted for Women	OTC	March 09, 1999	1%	Topical Cream	Athlete's foot: Apply twice daily
Lamisil AT Gel Advanced (Terbinafine Hydrochloride) (*Athlete's Foot*)	OTC	July 24, 2006	1%	Topical Gel	Athlete's foot: Apply once daily at bedtime Ringworm and jock itch: Apply once daily (morning or night)

Appendix I: Adverse Event Reporting System (AERS) Summary

ISR # FDA Receipt Date	Age	Error	Causality	Outcome	Narrative
4925811 11/11/03	28 years	Patient received wrong Starter Pack	None reported	Minor adverse events (nausea, headache, tremor)	This case was reported by a consumer and described the occurrence of nausea in a 28-year-old female patient who received Lamotrigine (Lamictal) tablet for epilepsy. A physician or other health care professional has not verified this report. Concurrent medical conditions included benign neoplasm of brain, epilepsy and chronic neck and back pain. Concurrent medications included Chlorazapate,Valium and Loratab. On 11 November 2003 the patient took lamotrigine (oral) at 200 mg three times per day and experienced nausea, tremor and bad headache. Treatment with Lamotrigine was continued. The outcome of the events is unknown. Patient ran out of Lamictal and was given samples by her physician to tide her over. The nurse gave her the wrong escalation pack, for patients not taking enzyme inducing drugs or valproate.

ISR # FDA Receipt Date	Age	Error	Causality	Outcome	Narrative
4727247 06/30/05	26 years	Patient took the wrong dose	None reported	Hospitalization	This case was reported by a physician, via a sales representative, and described the occurrence of prolonged erection in a male patient who received Lamotrigine (Lamictal) tablet over a period of 4 Weeks for bipolar disorder. Concurrent medical conditions included bipolar disorder. Concurrent medications included Seroquel. In June 2005 the patient started Lamotrigine (oral) at an unknown dosage. Weeks later, in June 2005, while taking a lamotrigine dose of 50 mg twice per day, the patient experienced a prolonged, painful erection. The physician considered the events to be disabling. Treatment with Lamotrigine was discontinued. The events resolved. The reporting physician considered the events were probably related to treatment with Lamotrigine. The patient experienced erection for approximately two weeks while taking Lamictal. The patient started taking Lamictal with a Bipolar Disorder Starter Kit sometime in June of 2005. The patient referred to his physician sometime during the week preceding (b) (4) and his penis was black and blue; the event resulted in tissue damage. The patient's erection was painful. Upon follow-up, the physician reported that the patient started Lamictal titration on 04 May 2005. The patient was to take 25 mg at bedtime for two weeks, then 50 mg at bedtime for two weeks, then 100 mg at bedtime. The patient reported to the physician on 20 June 2005 that he had been experiencing a continuous erection for the preceding two weeks. The patient was supposed to be taking Lamictal at 100 mg at bedtime, but he took the dose twice daily. The patient was found to have priapism by the urologist. Concurrent medication was corrected to by Symbyax, rather than Seroquel. The patient was hospitalized and the physician indicated that the event was clinically significant or required intervention. As of 19 July 2005, the event was improved, but still present. (The event had not resolved as was previously reported.) Lamotrigine was not reintroduced.

ISR # FDA Receipt Date	Age	Error	Causality	Outcome	Narrative
4926507 06/15/05	51 years	Patient took the wrong dose	None reported	Minor adverse event (“fuzziness and buzzing” in her head)	This case was reported by a consumer and described the occurrence of fuzzy head in a 51-year-old female patient who received Lamotrigine (Lamictal) tablet over a period of 40 Days for bipolar disorder. A physician or other health care professional has not verified this report. The patient's past medical history included hormone replacement. Concurrent medical conditions included depression, gastric ulcer and thyroid disorder. Concurrent medications included Celexa, Lipitor, Synthroid, Protonix, Ortho prefest and Xanax. On 12 March 2005 the patient started Lamotrigine (oral) at 12.5 mg daily. Approximately 1 days later, on 13 March 2005, the patient experienced fuzzy head, head buzzing and product complaint. The events resolved. The patient explained that she has experienced fuzziness in her head and buzzing in her head after beginning the Orange Lamictal Starter kit for Bipolar Disorder. The patient explained that she had taken one half tablets of the 25 mg for two weeks followed by 25 mg daily for one week, and 50 mg daily for two weeks. The patient had taken five tablets of the fifth week which contained peach colored tablets. On 17 April 2005, the patient stopped feeling the symptoms in her head. Quality Assurance reports that no sample was returned for testing. Without a lot number or sample, a conclusive investigation cannot be performed. This complaint is found to be inconclusive.

ISR # FDA Receipt Date	Age	Error	Causality	Outcome	Narrative
5250295 04/03/06	16 years	Patient took the wrong dose	None reported	Hospitalization	This case was reported by a physician and described the occurrence of Stevens Johnson syndrome in a 16-year-old male patient who received Lamotrigine (Lamictal) tablet over a period of 2 weeks for unknown drug indication. Concurrent medical conditions included bipolar disorder. On an unknown date, the patient started Lamotrigine (oral) at 50 mg daily. Approximately 2 weeks later, (b) (6) the patient experienced stevens johnson syndrome and overdose. The patient was hospitalised and the physician considered the events to be disabling, life threatening and clinically significant (or requiring intervention). Treatment with Lamotrigine was discontinued. At the time of reporting, the events were unresolved. Patient took five weeks of medication in a two week period. It is not clear if the patient intentionally overdosed or not. Patient is hospitalized at this point and it is unclear whether the patient will survive. Follow-up was received from the physician on 03 April 2006. A 16 year-old male patient had a flu-like illness prior to initiation of treatment with lomotrigine (Lamictal). On 22 February 2006, the patient began the orange colored starter pack, containing a five week supply of lamotrigine, 25 mg tablets. Concurrent medications included risperidone (Risperdal), sertraline (Zoloft) and an unspecified medication. Approximately (b) (6), the patient experienced onset of Stevens Johnson syndrome. The patient had taken the entire five week supply in a (b) (6) period. Lamotrigine was permanently discontinued. At time of reporting, the events had slightly improved but were still present. The physician considered the events to be almost certainly related to the use of lamotrigine.

ISR # FDA Receipt Date	Age	Error	Causality	Outcome	Narrative
5251489 05/17/06	UNK	Patient received the wrong starter kit	None reported	Hospitalization	This case was reported by a physician, via a sales representative, and described the occurrence of rash in a female patient in her 20's, who received lamotrigine (Lamictal) tablet for bipolar disorder. Concurrent medical conditions included bipolar disorder. Concurrent medications included semisodium valproate (Depakote). In April 2006 the patient started Lamotrigine (oral) at 50 mg daily in error. She should have received the starter pack with the dosage of 25 mg every other day. In April 2006, the patient experienced rash (not considered a serious rash) and was hospitalised as a precautionary measure due to receiving the incorrect starter dose pack. Treatment with Lamotrigine and semisodium valproate was discontinued. The patient was still in the hospital (b) (6). Two weeks later the rash had resolved. Duration of hospitalization was not known. The reporting physician considered the events were not related to treatment with Lamotrigine. It is not known whether the patient will be rechallenged with lamotrigine.

ISR # FDA Receipt Date	Age	Error	Causality	Outcome	Narrative
5427228 0720/07	UNK	Patient received the wrong starter kit	Knowledge deficit Computer error	No adverse event reported	Starter Kits for Lamictal therapy are specifically designed to provide the recommended initial dose and dose escalation regimen for the first 5 weeks of treatment. There are 3 kits designed to take into account various drug interactions of medications (e.g., phenytoin, carbamazepine). Another pharmacy called the reporter to request to transfer a script for a Lamictal sample kit to the reporter's store because their inventory was depleted. Unfortunately, the pharmacist was not familiar with the design of the kits and generically entered in the green kit for the patient, which incidentally is designed for patients who are on NO other interacting medications and therefore has a higher escalating dose. The pharmacy computer system contributed to this error. The selection screen is configured to display eight medications on one screen. The enter key can be pressed to move to a second or third screen that displays any additional formulations of the medication. For Lamictal, the starter pack happened to be the eighth medication on the list of the first screen and feature the text, "Lamictal tab start pack (GREGSK)". "GREGSK" signified that it was the green pack, "GRE" for green and "GSK" signified the manufacturer, Glaxo-Smith Kline. Incidentally the green pack was the only pack the pharmacy had in stock at the time. The pharmacist thought there was only one formulation, the green pack, which happened to be what populated the screen. The other two packs would have displayed on the selection screen by hitting the enter key to move to the next screen of product formulations. The reporting Pharmacist was alerted to the error by the patient's physician. No harm resulted from this error. The physician also stated that the patient was on other neurologically active meds and the interactions had the potential to be significant. Interestingly enough, the pharmacist noted that the store had no record of the interacting medications in the patient's profile and assumes that they have prescriptions filled at more than one pharmacy.

ISR # FDA Receipt Date	Age	Error	Causality	Outcome	Narrative
5427228 0720/07 (cont)	UNK	Patient received the wrong starter kit	Knowledge deficit Computer error	No adverse event reported	Submitted via ISMP The reporting Pharmacist was alerted to the error by the patient's physician. No harm resulted from this error. The physician also stated that the patient was on other neurologically active meds and the interactions had the potential to be significant. The pharmacy computer system contributed to this error. The selection screen is configured to display eight medications on one screen. The enter key can be pressed to move to a second or third screen that displays any additional formulations of the medication. For Lamictal, the starter pack happened to be the eighth medication on the list of the first screen and feature the text, "Lamictal tab start pack (GREGSK)". "GREGSK" signified that it was the green pack, "GRE" for green and "GSK" signified the manufacturer, Glaxo-Smith Kline. Incidentally the green pack was the only pack the pharmacy had in stock at the time. The pharmacist thought there was only one formulation, the green pack, which happened to be what populated the screen. The other two packs would have displayed on the selection screen by hitting the enter key to move to the next screen of product formulations. medication error

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