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RESEARCH**

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PROPRIETARY NAME REVIEW(S)



**Department of Health and Human Services
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Subject: Proprietary Name Review

Drug Name(s): Lamictal XR (Lamotrigine Extended-Release Tablets)

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Applicant: GlaxoSmithKline

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EXECUTIVE SUMMARY

The findings of Our Proprietary Name Risk Assessment indicate that the proposed name, Lamictal XR is vulnerable to confusion with Seroquel XR that could lead to medication error. However, the Failure Mode and Effects Analysis (FMEA) conducted to evaluate the possibility of using an alternative name for the proposed Lamotrigine Extended-Release product determined that the use of an alternate proprietary name can lead to concomitant therapy with Lamictal or Lamictal CD. Additionally, post marketing evidence suggests that the risk of confusion with Lamictal XR and Seroquel XR occurs infrequently. Therefore, we will not object to the use of the name, Lamictal XR, 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 XR, was written 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

“Lamictal XR” was previously evaluated by DMEPA and found acceptable on December 14, 2006 in OSE Review #2006-891 and the name was reevaluated on August 31, 2007 in OSE Review #2007-1762. Additionally OSE Review #2006-891 evaluated the modifier ‘XR’ and the risks associated with the product line extension. DMEPA noted that confusion may occur between extended-release tablets and Lamictal or Lamictal CD especially during the launch of the extended-release product. However, DMEPA acknowledged that utilizing the modifier XR to denote an extended-release to an existing product line is common for oral dosage forms. Additionally, since the modifier ‘XR’ is well established and well recognized by healthcare practitioners and patients to designate extended-release DMEPA found the modifier ‘XR’ acceptable. As such, DMEPA will not revisit these issues in this review.

The labels and labeling for this product were also evaluated in OSE Review #2006-891 dated December 14, 2006 and in OSE# 2007-1435 dated July 6, 2007.

1.3 PRODUCT INFORMATION

Lamictal XR is the proposed name for lamotrigine extended-release tablets. Lamictal XR is an oral antiepileptic drug used in the treatment of epilepsy.

Lamictal XR requires dose titration over several weeks. Titration schedule is dependent upon which other medication(s) the patient is taking. Once titrated, a usual adult dose can range from 150 mg orally once per day to 600 mg daily orally once per day.

Lamictal XR is manufactured by GlaxoSmithKline. Lamictal XR will be supplied as 25 mg, 50 mg, 100 mg, and 200 mg tablets. Lamictal XR will differ in some of the available strengths from the other Lamictal products currently on the market and proposed Lamictal ODT***. See Table 1 page 5.

Table 1: Lamictal Products

Currently Market Lamictal Product							
Drug Name	Rx or OTC	Strength	Frequency	Dosage Form	Route	Indication	Usual Maintenance Dose After Initial Titration
Lamictal XR (lamotrigine hydrochloride extended release) tablets	Rx	25 mg, 50 mg, 100 mg, and 200 mg	Once daily	Extended Release Tablets	Oral	Epilepsy	150 mg orally once per day to 600 mg orally once per day
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

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

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

2.1 PROPRIETARY NAME RISK ASSESSMENT

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

For the proprietary name, Lamictal XR, 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 XR.

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 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 XR, or an alternate proprietary name would be less prone to medication errors. FMEA is used to analyze whether the drug names identified with look- or sound-alike similarity to the proposed name could cause confusion that subsequently leads to medication errors in the clinical setting. 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.

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

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

Typical product characteristics considered when identifying drug names that could potentially be confused with the proposed drug name include, but are not limited to established name of the proposed product, the proposed indication, dosage form, route of administration, strength, unit of measure, dosage units, recommended dose, typical quantity or volume, frequency of administration, product packaging, storage conditions, patient population, and prescriber population. Because drug name confusion can occur at any point in the medication use process, we consider the potential for confusion throughout the entire U.S. medication use process, including drug procurement, prescribing and ordering, dispensing, administration, and monitoring the impact of the medication.⁴

2.1.1 Search Criteria

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

For this review, particular consideration was given to drug names beginning with the letter ‘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 errors⁷, DMEPA considers ‘Lamictal XR’ as a complete name as well as ‘Lamictal,’ the root term, omitting the modifying term ‘XR’.

To identify drug names that may look similar to Lamictal XR, 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 (10 letters), upstrokes (seven; capital letter ‘L’, lower case letters ‘t’, and ‘l’, capital letters ‘X’ and ‘R’), downstrokes (none), cross-strokes (two; lower case ‘t’, and capital ‘X’), and dotted letters (one; lower case ‘i’). Additionally, several letters in Lamictal XR 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 ‘R’ may appear as upper case ‘B’, ‘K’, ‘R’, or ‘Pr’. As such, the staff also considers these alternate appearances when identifying drug names that may look similar to Lamictal XR.

When searching to identify potential names that may sound similar to Lamictal XR, DMEPA searches for names with similar number of syllables in the name (5 syllables), stresses (Lah-mic-tal-Ecks-Ar, lah-Mic-tal-Ecks-Ar, or lah-mic-Tal-Ecks-Ar), and placement of vowel and consonant sounds. In addition, several letters in Lamictal XR 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’; the letter ‘a’ may be interpreted as ‘o’, the letter ‘x’ may be interpreted as the letter ‘z’ or ‘s’, and the letter ‘r’ may be interpreted as the letter pair ‘wr’. We also considered how the inclusion of “XR” may change the sound of the name. The Applicant’s intended pronunciation of the proprietary name could not be expressly taken into consideration, as this was not provided with the proposed name submission.

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

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

⁶ Kondrack, G and Dorr, B. Automatic Identification of Confusable Drug Names. Artificial Intelligence in Medicine (2005)

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

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 XR), the established name (lamotrigine), proposed indication (Epilepsy), strength (25 mg, 50 mg, 100 mg, and 200 mg), dose (titrated over several weeks, then a maintenance dose between 150 mg to 600 mg per day), frequency of administration (once daily), route (oral) and dosage form of the product (extended-release tablet). Appendix A provides a more detailed listing of the product characteristics DMEPA generally takes into consideration.

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 XR, 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 XR 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 XR. 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 Medication Error Risk Assessment

Since the route name, Lamictal is currently on the US market DMEPA would normally conduct a search of the Adverse Event Reporting System (AERS) database to determine if there are any medication errors associated with name confusion which may be indicative of potential name confusion with Lamictal XR. However, a comprehensive post-market review was completed recently that examined all errors involving Lamictal, OSE Review #2007-338 and 2007-350 dated October 23, 2008. This review will be used as the search of AERS.

2.1.5 Safety Evaluator Risk Assessment of the Proposed Proprietary Name

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

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

In the initial stage of the Risk Assessment, the Safety Evaluator compares the proposed proprietary name to all of the names gathered from the above searches, expert panel evaluation, and studies, and identifies potential failure modes by asking: “Is the name “Lamictal XR” 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 XR to be confused with another proprietary or established drug name because of look- or sound-alike similarity. If the answer to the question is no, the Safety Evaluator is not convinced that the names possess similarity that would cause confusion at any point in the medication use system and the name is eliminated from further review.

In the second stage of the Risk Assessment, all potential failure modes are evaluated to determine the likely *effect* of the drug name confusion, by asking “Could the confusion of the drug names conceivably result in medication errors in the usual practice setting?” The answer to this question is a central component of the Safety Evaluator’s overall risk assessment of the proprietary name. If the Safety Evaluator determines through FMEA that the name similarity would ultimately not be a source of medication errors in the usual practice setting, the name is eliminated from further analysis. However, if the Safety Evaluator determines through FMEA that the name similarity could ultimately cause medication errors in the usual practice setting, the Safety Evaluator will then recommend that an alternate proprietary name be used. In rare instances, the FMEA findings may provide other risk-reduction strategies, such as product 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.

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

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, 20 names were identified as having some similarity to the name Lamictal XR. Ten of the 20 names were thought to look like Lamictal XR; these names include: Lomotil, Tamifen, Lunesta, Simulect, Surmontil, Lescol XL, (b) (4)***, (b) (4).***, Zamicet, and Zamadol. One name (Lambkill) was thought to sound like Lamictal XR. Nine of the 20 names were thought to look and sound similar to Lamictal XR; these names include: Lamital, Lamictal, Lamictal CD, Lamisil (Product Line - See Appendix J for currently marketed Lamisil products), Lamidus, (b) (4), and Lamictal ODT***.

The proposed proprietary name, Lamictal XR, does not contain a USAN stem as of the last date searched, April 29, 2009.

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 XR.

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 twelve additional names thought to look or sound similar to Lamictal XR and represent a potential source of drug name confusion. Eleven names were thought to look like Lamictal XR, which include: Lomefloxacin, (b) (4), labetalol, Campral, Lamivudine, Epivir HBV, Seroquel, Cymbalta, Loxitane, Levetiracetam, and Sanctura XR. The last name, (b) (4) was thought to look and sound similar to Lamictal XR. As such, a total of thirty two names were analyzed to determine if the drug names could be confused with Lamictal XR and if the drug name confusion would likely result in a medication error.

Thirteen of the names identified for this review were evaluated in DMEPA's previous review or memorandum for the name Lamictal XR (OSE Review #2006-891 and in OSE Memorandum #2007-1762.), and there have been no changes in the product characteristics for Lamictal XR or any of the names that would change or impact that analysis (See Appendix B). The remaining 19 names were analyzed to determine if the drug names could be confused with Lamictal XR and if the drug name confusion would likely result in a medication error.

All of the identified names were determined to have some orthographic and/or phonetic similarity to Lamictal XR, 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 XR, could potentially be confused with any of the 19 names and lead to medication error. This analysis determined that the name similarity between Lamictal XR and 16 of the identified names was unlikely to result in medication errors (See Appendices C through I). The remaining three names, Lamictal ODT***, Levetiracetam, and Seroquel will be discussed below in section 4.

The results of DMEPA's second FMEA that evaluated whether using the proprietary name Lamictal XR or an alternate proprietary would be less error prone, indicated that using an alternative proprietary name would result in error-prone scenarios including underdose, or overdose of Lamotrigine.

4 DISCUSSION

Lamictal XR is an extension to the Lamictal product line. DMEPA evaluated Lamictal XR for possible look and sound-alike names including the Lamictal product line, Lamisil and other similar names that could cause confusion and that could lead to medication errors. Our evaluation identified the currently marketed Lamictal products, Levetiracetam, and Seroquel as names of concern to cause confusion and lead to medication errors.

4.1 LAMICTAL PRODUCT LINE AND PENDING ODT***

In addition to the extended-release tablet formulation that is proposed under NDA #22-115, the Applicant proposes a new dosage form, "orally disintegrating tablets" for the Lamictal product line. 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.

We anticipate errors between both of the proposed Lamictal products because they share the root name "Lamictal" and only differ with regards to the modifiers ('XR' vs. 'ODT'). Additionally, if both the extended-release tablets and orally disintegrating tablets are launched in close proximity to one another, this could increase the potential for confusion among patients and healthcare providers. Patients and healthcare providers may not understand that there are two new Lamictal products and instead think that there is one new Lamictal product on the market that is both an extended release product in addition to being an orally disintegrating tablet. Patients and healthcare providers may confuse the dose and frequency of administration of the two products with one another. Although the patient will receive the correct active ingredient in this case the dosage form and frequency would be 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, Lamictal orally disintegrating tablets***, and Lamictal extended release tablets.

4.2 LEVETIRACETAM

The name Levetiracetam was previously evaluated as a possible look-alike name to Lamictal XR in OSE Review #2006-891 and not thought to represent risk for confusion. However, a new formulation of Levetiracetam has been approved since the completion of that review. Levetiracetam extended-release tablets (Keppra XR) was approved on September 12, 2008, under NDA #22-285. Additionally, postmarketing review OSE Review #2007-388 and 2007-350 examined medication errors involving the root name Levetiracetam and the root name Lamictal. These reviews concluded that the confusion between the root name Lamictal and the root name Levetiracetam originated from the similarity of the established names (Lamotrigine vs. Levetiracetam) in addition to the overlapping product characteristics. Since the confusion originates from the similarity of the established name and is not related to the proprietary name Lamictal, DMEPA does not believe the proprietary name, Lamictal XR will exacerbate the cases of ongoing confusion.

4.3 SEROQUEL

The name Seroquel was previously evaluated as a possible look-alike name to Lamictal XR in OSE Review #2006-891 and not thought to present a risk for confusion. However, a new formulation of Seroquel was approved in 2007; Seroquel XR (Quetiapine extended-release tablet) under NDA's #22-047 and #22-172. Seroquel XR is available as 50 mg, 150 mg, 200 mg, 300 mg, and 400 mg extended release-tablets and is given once daily.

DMEPA has postmarketing evidence that the two root names, Seroquel and Lamictal have been confused. Two medication errors were identified in OSE Review #2007-388 and 2007-350. These medication errors involved the root name Seroquel and the root name Lamictal, both reported in 2005 and involved patients of similar age (14 years of age and 16 years of age). Seroquel XR and Lamictal XR overlap in strength (50 mg and 200 mg), usual dose (400 mg to 600 mg), route of administration (oral), dosage form (extended-release tablet), and frequency (once daily). Since the root names of these products have been confused and the extended-release formulations of these products overlap in several product characteristics, DMEPA believes there is a possibility for Seroquel XR and Lamictal XR to be confused and to cause medication error.

Because of this concern, DMEPA analyzed the approach of using an alternate modifier and the root name “Lamictal” or a completely different alternative proprietary name for the Lamotrigine extended-release product while maintaining the Lamictal and Lamictal CD names for the other Lamotrigine products. With respect to the Lamictal line, the modifier ‘XR’ appropriately emphasizes the most notable difference between Lamictal XR and the existing Lamictal product, which is the dosing interval. Choosing an alternate modifier to highlight the difference in dosing intervals of the Lamictal extended-release product and the currently marketed Lamictal products may contribute to confusion of the dosing interval of this product. Although, a different modifier for the extended-release formulation might lessen confusion with Seroquel XR, the opportunity for omission of the modifier would exist and could result in a prescription for “Lamictal XX” to be misinterpreted as Seroquel or as an immediate release formulation of Lamictal. The alternate approach would be to give the Lamictal extended release formulation a completely different proprietary name.

However, the FMEA for the completely different alternate proprietary name identified the additional failure mode of concomitant therapy which was not identified in the FMEA for Lamictal XR. Concomitant therapy with lamotrigine products could result in overdose or supratherapeutic doses.

Since, the modifier ‘XR’ adequately emphasizes the most notable difference between Lamictal XR and the existing Lamictal product, which is the dosing interval, and the modifier XR is a well established and well recognized modifier, DMEPA believes that the modifier ‘XR’ is the most appropriate modifier for this product.

Additionally, DMEPA believes that the risk of concomitant therapy resulting in overdose or supratherapeutic doses with lamotrigine products is greater than the risk of confusion between Seroquel XR and Lamictal XR. As such DMEPA will not object to the use of the proposed proprietary names, Lamictal XR for this product.

5 CONCLUSIONS AND RECOMMENDATIONS

Although our Proprietary Name Risk Assessment indicates that the proposed proprietary name, ‘Lamictal XR’, may be vulnerable to name confusion with ‘Seroquel XR’, we find the proposed proprietary name acceptable. This conclusion is based on concerns that the use of an alternate name which does not use the root name ‘Lamictal’, poses a higher risk of medication errors involving concomitant therapy resulting in overdose and supratherapeutic doses than confusion between Lamictal XR and Seroquel XR. In addition, we cannot identify or recommend an alternate modifier which would fully convey the differences between the proposed product and the other products in the Lamictal product line.

Additionally, DDMAC does not object to the proposed name, Lamictal XR, 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

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 XR, and have concluded that it is acceptable. 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.

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 AND MEMORANDUMS

1. *OSE Review #2006-891 Proprietary Name, Label, and Labeling Review for Lamictal XR (Lamotrigine Extended Release Tablets)*, Pedersen, K; December 14, 2006.
2. *OSE Memorandum #2007-1762 Proprietary Name for Lamictal XR (Lamotrigine Extended Release Tablets)*, Pedersen, K; August 31, 2007.
3. *OSE Review #2007-388 and 2007-350 Medication Error Postmarketing Safety Review for Lamictal (Lamotrigine Tablets)*, Oleszczuk, Z; August 26, 2008.

6.2 DATABASES

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

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

2. *Phonetic and Orthographic Computer Analysis (POCA)*

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

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

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

4. *AMF Decision Support System [DSS]*

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

5. *Division of Medication 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.

6. *Drugs@FDA* (<http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm>)

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

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

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

8. USPTO (<http://www.uspto.gov>)

Provides information regarding patent and trademarks.

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

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

10. Data provided by Thomson & Thomson's SAEGIS™ Online Service, available at www.thomson-thomson.com

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

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

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

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

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

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

List contains all the recognized USAN stems.

14. Red Book Pharmacy's Fundamental Reference

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

15. Lexi-Comp (www.pharmacist.com)

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

16. Medical Abbreviations Book

Contains commonly used medical abbreviations and their definitions.

17. 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	<ul style="list-style-type: none"> Names may appear similar in print or electronic media and lead to drug name confusion in printed or electronic communication Names may look similar when scripted and lead to drug name confusion in written communication
	Orthographic similarity	Similar spelling Length of the name Upstrokes Downstrokes Cross-strokes Dotted letters Ambiguity introduced by scripting letters Overlapping product characteristics	<ul style="list-style-type: none"> Names may look similar when scripted, and lead to drug name confusion in written communication
Sound-alike	Phonetic similarity	Identical prefix Identical infix Identical suffix Number of syllables Stresses Placement of vowel sounds Placement of consonant sounds Overlapping product characteristics	<ul style="list-style-type: none"> Names may sound similar when pronounced and lead to drug name confusion in verbal communication

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

Table 1:

Product name with potential for confusion	Similarity to Lamictal XR
Lescol XL	Look
Lomefloxacin	Look
Campral	Look
Lomotil	Look
Lamivudine	Look
Epivir HBV	Look
Labetalol	Look
Cymbalta	Look
(b) (4)	Look and sound
Loxitane	Look
Sanctura XR	Look
Lamisil*	Look and Sound
Lamictal	Look and Sound

* For a Complete listing of all currently marketed Lamisil products see Appendix B Table 2

Table 2:

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 capitis 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 <i>Malassezia furfu</i> (formerly <i>Pityrosporum ovale</i>). Apply twice daily to affected area for 7 days.
Lamisil (Terbinafine Hydrochloride)	RX	April 29, 1998	1%	Topical Gel	Tinea (pityriasis) versicolor due to <i>Malassezia furfu</i> (formerly <i>Pityrosporum ovale</i>), 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) (<i>Athlete's Foot</i>)	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) (<i>Jock Itch</i>)	OTC	March 17, 2000	1%	Topical Spray	Jock itch: Spray once daily (morning or night)
Lamisil AT (Terbinafine Hydrochloride) (<i>Athlete's Foot</i>)	OTC	March 09, 1999	1%	Topical Cream	Athlete's foot: Apply twice daily Ringworm/Jock itch: Apply once daily
Lamisil AT (Terbinafine Hydrochloride) (<i>Jock Itch</i>)	OTC	March 09, 1999	1%	Topical Cream	Jock itch: Apply once daily (morning or night)
Lamisil AT (Terbinafine Hydrochloride) (<i>Athlete's Foot</i>) Targeted for Women	OTC	March 09, 1999	1%	Topical Cream	Athlete's foot: Apply twice daily
Lamisil AT Gel Advanced (Terbinafine Hydrochloride) (<i>Athlete's Foot</i>)	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 C: Products that lack orthographic and phonetic similarity to Lamictal XR.

Product name with potential for confusion	Similarity to Lamictal XR
Surmontil	Look

Appendix D: Proposed Names that were found unacceptable by DMEPA and have not been Marketed in the United States.

Product name with potential for confusion	Similarity to Lamictal XR	OSE Review Number and Date of Review	Status of Associated Application
(b) (4)	Look and Sound	OSE Review #2007-1156	(b) (4)
(b) (4)	Look and sound	OSE Review #2005-0256	(b) (4)
(b) (4)	Look	OSE Review #2008-376	(b) (4)

Appendix E: 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 XR	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
(b) (4) (Lamotrigine)	Look and Sound	Unknown	Unknown	(b) (4)
Lamicosil (Terbinafine)	Look and sound	Unknown	Unknown	Spain
(b) (4) (Lamotrigine)	Look and Sound	Unknown	Unknown	(b) (4)
Lamitol (labetalol)	Look and Sound	Tablets: 100 mg, 200 mg, and 300 mg Solution for Injection: 5 mg/ml	100 mg orally twice daily 20 mg intravenous push over 2 minutes, may give 40 mg to 80 mg at 10 minute intervals, up to 300 mg total dose	Croatia

Appendix F: 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 XR	Source
Lambkill	Sound	Natural Medicines Comprehensive Database

Appendix G: 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 XR	Source
Surital	Look	Discontinued by Drugs@FDA

Appendix H: Products with no 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 XR (b) (4)		<u>Dosage Form:</u> Extended Release Tablets <u>Strength:</u> 25 mg, 50 mg, 100 mg, and 200 mg	150 mg orally once per day to 600 mg orally once per day
Lunesta (eszopiclone)	Look	<u>Dosage Form:</u> Tablets <u>Strength:</u> 1 mg, 2 mg and 3 mg	2 mg orally immediately before bedtime
Zamicet (Acetaminophen and Hydrocodone Bitartrate)	Look	<u>Dosage Form:</u> Oral Solution <u>Strength:</u> 325 mg of Acetaminophen and 10 mg of Hydrocodone Bitartrate per 15 mls	15 mls orally every 4 to 6 hours as needed

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

Failure Mode: Name confusion	Causes (could be multiple)	Effects
<p>Lamictal XR (lamotrigine orally disintegrating tablets)</p>	<p>Dosage From: Extended Release Tablets</p> <p>Strength: 25 mg, 50 mg, 100 mg, and 200 mg</p>	<p>Usual dose: 150 mg orally once per day to 600 mg orally once per day</p>
<p>Simulect (Basiliximab)</p> <p><u>Dosage From:</u> Lyophilized Powder for Injection</p> <p><u>Strength:</u> 10 mg/vial and 20 mg/vial</p> <p><u>Usual Dose:</u> Two doses of 20 mg each given as a bolus or intravenous infusion over 30 minutes. The first 20 mg dose should be given within 2 hours prior to transplantation surgery. The recommended second 20 mg dose should be given 4 days after transplantation.</p>	<p>Orthographic similarity (both root names contain the same number of letters, 8, both names contain the same number of upstrokes, 3 (capital ‘S’, lower case ‘l’ and ‘t’ vs. capital ‘L’, lower case ‘t’, and ‘l’), in similar positions (1st letter, 6th letter, and 8th letter vs. 1st letter, 6th letter and 8th letter), both names contain the same number of dotted letters, 1 (lower case ‘i’) both names contain the same number of cross strokes, 1, both names contain the same number of downstrokes (none) and the 3rd letter in each name is the letter ‘m’.</p> <p>Numerical Overlapping strengths (10 mg and 20 mg vs. 100 mg and 200 mg), if Simulect is written with a trailing zero (i.e. Simulect 20.0 mg intravenously once 2 hours prior to transplant and then a second dose of 20.0 mg intravenously 4 days after the transplant).</p>	<p>Orthographic differences in the names in addition to the unlikelihood of the inclusion of a trailing zero and differentiating product characteristics minimize the likelihood of medication error in the usual practice setting.</p> <p><i>Rationale:</i></p> <p>The risk for medication error is minimized by the orthographic differences in the names as the first letters in each name (‘S-’ vs. ‘L’) appear different when scripted.</p> <p>Additionally, DMEPA is not aware of any confusion that exists between Simulect and the route name “Lamictal” that is currently in the US market place. The addition of the modifier ‘XR’ should help to further differentiate the two names since it will provide more letters in the name.</p> <p>Although Simulect and Lamictal XR share numerical overlapping strengths (10 mg and 20 mg vs. 100 mg and 200 mg), if Simulect is written with a trailing zero (i.e. Simulect 20.0 mg intravenously once 2 hours prior to transplant and then a second dose of 20.0 mg intravenously 4 days after the transplant), 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.</p> <p>Furthermore, while Simulect and Lamictal XR share numerical overlapping strengths, the route of administration (intravenous vs. oral), and frequency of administration (two doses vs. once daily) are different for each product. Since the route of administration and directions for use would be included on a prescription, the route of administration and direction for use will also help to differentiate the two products and minimize the possibility of a medication error.</p> <p>Despite a overlapping strength; the orthographic differences in addition to the differences in route of administration and directions for use minimize the potential for confusion between Simulect and Lamictal XR.</p>

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/s/

Zachary A Oleszczuk
4/30/2009 03:03:24 PM
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Denise Toyer
5/1/2009 08:13:44 AM
DRUG SAFETY OFFICE REVIEWER

Carol Holquist
5/1/2009 09:53:46 AM
DRUG SAFETY OFFICE REVIEWER

MEMORANDUM

Division of Medication Errors and Technical Support
Office of Surveillance and Epidemiology
HFD-420; WO22, Mail Stop 4447
Center for Drug Evaluation and Research

To: Russell Katz, MD
Director, Division of Neurology Products

Through: Todd Bridges, RPh, Team Leader
Denise Toyer, PharmD, Deputy Director
Carol A. Holquist, RPh, Director
Division of Medication Errors and Technical Support, HFD-420

From: Kimberly Pedersen, RPh, Safety Evaluator
Division of Medication Errors and Technical Support, HFD-420

Date: August 31, 2007

Subject: DMETS Proprietary Name Review
Drug: Lamictal XR (Lamotrigine Extended-release Tablets)
25 mg, 50 mg, 100 mg, and 200 mg
NDA#: 22-115
Sponsor: GlaxoSmithKline

Review #: 2007-1762

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

DMETS evaluated the proposed name, Lamictal XR and associated labels and labeling in OSE Review 2006-891 (dated May 2, 2007) and found the name acceptable at that time. In response to the aforementioned review, the sponsor submitted revised labels and labeling, which DMETS reviewed in OSE Review 2007-1435 (dated August 2, 2007). This memorandum is written in response to a request from the Division of Neurology Products for re-assessment of the proposed proprietary name, Lamictal XR.

Since OSE Review 2006-891, DMETS has identified three additional names (Lescol XL, Lomefloxacin, and (b) (4)***) as having potential look-alike similarities to Lamictal XR. After further analysis of these three names, we determined that two names, Lescol XL and Lomefloxacin, could safely co-exist with Lamictal XR due to differentiating product characteristics (e.g. product strength and indication for use) and a lack of convincing look-alike similarities to Lamictal XR. These characteristics are described in Table 1 (see page 2). The third name of (b) (4)*** is a proprietary name under review at the Agency. We currently have no characteristics for this proposed drug product. Without this information, we cannot fully evaluate the potential confusion between this name pair. There are some orthographic similarities, such as the leading “L”, central “m”, and upstroke letters (“d” of (b) (4) and “t” of Lamictal) in similar positions. Furthermore, depending on scripting characteristics, the concluding (b) (4) in (b) (4) may resemble the upstroke of the concluding letter of “l” in Lamictal. Of note, (b) (4) does not have a modifier as Lamictal XR does, which may help to differentiate this name pair. However,

*** Proprietary and confidential information that should not be released to the public.

without knowledge of all the product characteristics, we cannot fully assess the risk. If for some reason, the approval of this application is delayed, (b) (4)*** and Lamictal XR would need to be further evaluated.

Table 1: Potential Sound-Alike/Look-Alike Names Identified by DMETS Expert Panel

Product Name	Dosage form(s), Established name	Usual adult dose*	Other**	Reason for discard
Lamictal XR	Lamotrigine Extended-release Tablets 25 mg, 50 mg, 100 mg, 200 mg	Daily, variable dose with concomitant therapy and titration		
Lescol XL	Fluvastatin Sodium Extended-release Tablets, 80 mg	One tablet daily.	LA	<ul style="list-style-type: none"> • Indication (Cholesterol lowering agent compared to seizure control) • Strength • Eight letters compared to six letters • Two upstrokes in Lamictal compared to one in Lescol
Lomefloxacin (Maxaquin)	Lomefloxacin Hydrochloride Tablets, 400 mg	One tablet daily for three to fourteen days.	LA	<ul style="list-style-type: none"> • Indication (Infection compared to seizure control) • Strength • Lack of modifier, no reports of error currently with Lamictal • Twelve letters compared to eight letters
*Frequently used, not all-inclusive. **L/A (look-alike)				

In summary, DMETS remains concerned that confusion will likely occur between Lamictal and Lamictal XR because of common prescribing problems noted with drug name suffixes, the overlapping product strengths, and the knowledge deficit that will exist regarding the presence of this product in the marketplace. Thus, DMETS reminds you that the sponsor should institute an educational program to help practitioners be aware of the presence of the new extended-release product in addition to understanding the differences between the products in the Lamictal product line.

The Division of Drug Marketing, Advertising, and Communications (DDMAC) find the name, Lamictal XR, acceptable from a promotional perspective.

We consider this a final review. However, if approval of the NDA is delayed beyond 90 days from the date of this review, the name must be re-evaluated. A re-review of the name before NDA approval will rule out any objections based upon approvals of other proprietary/established names from this date forward. Please copy DMETS on any correspondence to the sponsor pertaining to this review. If you have any questions or need clarification, please contact Daniel Brounstein, OSE Project Manager, at 301-796-0674.

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/s/

Kimberly Culley-Pedersen
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Carol Holquist
9/20/2007 02:42:35 PM
DRUG SAFETY OFFICE REVIEWER

MEMORANDUM**Division of Medication Errors and Technical Support
Office of Surveillance and Epidemiology
WO 22, Mailstop 4447, HFD-420
Center for Drug Evaluation and Research**

To: Russell Katz, MD
Director, Division of Neurology Products, HFD-120

Through: Todd Bridges, RPh, Team Leader
Denise Toyer, PharmD, Deputy Director
Carol Holquist, RPh, Director
Division of Medication Errors and Technical Support, HFD-420

From: Kimberly Pedersen, RPh, Safety Evaluator
Division of Medication Errors and Technical Support, HFD-420

Date: July 6, 2007

Date of Document: June 20, 2007

Subject: OSE Review 2007-1435
Proprietary Name: Lamictal XR
 Lamotrigine Extended-release Tablets
 25 mg, 50 mg, 100 mg, and 200 mg
Sponsor: GlaxoSmithKline
NDA #: 22-115

This memorandum is in response to a June 26, 2007, request from your Division for a review of the revised labels and labeling for Lamictal XR, which were submitted by the sponsor in response to OSE Review #2006-891 (dated May 2, 2007).

In the review of the revised labels and labeling, DMETS has the following comments.

A. General Comments

1. Consider changing the presentation of the tablet imprint so that the XR (as indicated by the arrow below) is adjacent to the root name "Lamictal" (at the top of the tablet). The product strength should remain in its current location at the bottom of the tablet. This is a further means to alleviate potential confusion with immediate-release Lamictal as the name on the tablet will read "Lamictal XR" instead of "Lamictal".



Figure 1. Lamictal XR 100 mg container label.

2. The entire established name should appear in the same font size and style. As currently presented, "lamotrigine" is more prominent than "extended-release tablets". Revise so that "lamotrigine extended-release tablets" is presented in the same font size and style.

B. Container Label

1. The current presentation of the label is crowded. Thus, DMETS recommends moving the statement "Each tablet contains 25 mg of lamotrigine." to the side panel.
2. As the web address is not key information for proper use and prescribing, relocate to the side panel. This should help to limit crowding of the label and increase clarity of the key messages.

C. Patient Titration Kit Labeling

See General Comment A2.

D. GSK Responses (in correspondence dated June 20, 2007) to Agency Comments

1. Reference is made to GSK's response to Agency comment 1. DMETS acknowledges the need to titrate Lamictal for the preferred patient effect. However, early in product development, the sponsor should have considered the potential for misinterpretation and selection errors due to the overlapping product strengths and adjusted the proposed Lamictal XR strengths accordingly. The variances between the Lamictal and Lamictal XR product strengths could have been so low as to not yield any clinical effect, but the result would be non-overlapping product strengths (e.g., 99 mg instead of 100 mg). We encourage consideration of such medication error prevention strategies in future product development.
2. Reference is made to GSK's response to Agency comment 3.

The sponsor states that "For the first months following approval of Lamictal XR, 100% of all Lamictal transactions will be flagged with a pre-edit message". DMETS encourages the sponsor to utilize a pre-edit message which is distinct so that it will not be automatically by-passed by pharmacy staff.

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

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/s/

Todd Bridges
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Also signing for Kimberly Pedersen.

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DRUG SAFETY OFFICE REVIEWER

Carol Holquist
8/2/2007 05:14:42 PM
DRUG SAFETY OFFICE REVIEWER

CONSULTATION RESPONSE
DIVISION OF MEDICATION ERRORS AND TECHNICAL SUPPORT
OFFICE OF SURVEILLANCE AND EPIDEMIOLOGY
(DMETS; WO 22, MAIL STOP 4447)

DATE RECEIVED: November 27, 2006	DESIRED COMPLETION DATE: February 28, 2007	OSE REVIEW #: 2006-891
DATE OF DOCUMENT: November 22, 2006 April 12, 2007	PDUFA DATE: September 22, 2007	

TO: Russell Katz, M.D.
Director, Division of Neurology Products

THROUGH: Denise Toyer, Pharm.D., Deputy Director
Carol Holquist, R.Ph., Director
Division of Medication Errors and Technical Support

FROM: Kimberly Pedersen, R.Ph., Safety Evaluator
Division of Medication Errors and Technical Support

PRODUCT NAME: Lamictal XR Lamotrigine Extended-release Tablets 25 mg, 50 mg, 100 mg, and 200 mg	SPONSOR: GlaxoSmithKline
NDA#: 22-115	

RECOMMENDATIONS:

1. DMETS has no objections to the use of the proprietary name, Lamictal XR. The use of a modifier for product extension is common and in this case, the sponsor chose "XR." However, we anticipate errors between Lamictal and Lamictal XR upon approval of this product because of common prescribing problems noted with drug name suffixes, the product strengths overlap, and the knowledge deficit that will exist upon marketing of this product. Thus, DMETS recommends the sponsor consider revising the strengths of Lamictal XR and institute an educational program to help practitioners be aware of the presence of the new extended-release product in addition to understanding the differences between the Lamictal product line. Moreover, implement the label and labeling revisions outlined in Section III of this review in order to minimize potential selection errors between Lamictal and Lamictal XR. The 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 approvals of other proprietary or established names from the signature date of this document.
2. DDMAC finds the proprietary name of Lamictal XR acceptable from a promotional perspective.

DMETS would appreciate feedback of the final outcome of this consult. We would be willing to meet with the Division for further discussion, if needed. Please copy DMETS on any communication to the sponsor with regard to this review. If you have further questions or need clarifications, please contact Sammie Beam, Project Manager, at 301-796-0080.

**Division of Medication Errors and Technical Support (DMETS)
Office of Surveillance and Epidemiology
WO 22, MAIL STOP 4447
Center for Drug Evaluation and Research**

PROPRIETARY NAME, LABEL, AND LABELING REVIEW

DATE OF REVIEW: December 14, 2006

NDA #: 22-115

NAME OF DRUG: **Lamictal XR**
(Lamotrigine Extended-release Tablets)
25 mg, 50 mg, 100 mg, and 200 mg

NDA SPONSOR: GlaxoSmithKline

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

I. INTRODUCTION

This consult was written in response to a request from the Division of Neurology Drug Products for assessment of the proprietary name "Lamictal XR", regarding potential name confusion with other proprietary or established drug names. Insert labeling, starter kit label and labeling, and container labels were provided for review and comment.

The sponsor is proposing an extension to their Lamictal product line, which currently includes Lamictal tablets and Lamictal Chewable Dispersible Tablets. Lamictal XR contains lamotrigine, which is an antiepileptic medication indicated as adjunctive therapy for partial onset seizures with or without secondary generalization in patients 13 years and older. Lamictal XR will be available in 25 mg, 50 mg, 100 mg, and 200 mg tablets.

Recommended dosing is based on the concomitant medications, but the frequency of dosing of Lamictal XR is once daily, with or without food. Tablets should not be chewed, crushed, or divided. Lamictal XR is associated with rash (ranging from non-serious to Stevens-Johnson syndrome) when the rate of dose escalation or initial dose is exceeded. Lamictal XR should be slowly titrated up or down.

Lamictal XR is not recommended in children below thirteen years of age as safety and effectiveness has not been established. Patients may be converted from immediate-release lamotrigine to the extended-release tablets; thus, the initial dose of the extended-release tablets should match the total daily dose of the immediate-release tablets.

A comparison of the proposed Lamictal line is provided in Table 1 (see page 3).

Table 1: Currently available and proposed Lamictal Products

Lamictal Tablets		Lamictal Chewable Dispersible Tablets		Lamictal XR Tablets	
Strength	Description	Strength	Description	Strength	Description
25 mg	White, shield shaped tablets	2 mg	White to off-white round tablets	25 mg	Yellow with white center
100 mg	Peach, shield shaped tablets	5 mg	White to off-white caplet shaped tablets	50 mg	Green with white center
150 mg	Cream, shield shaped tablets	25 mg	White, super elliptical tablets	100 mg	Orange with white center
200 mg	Blue, shield shaped tablets			200 mg	Blue with white center

Lamictal and Lamictal XR are indicated for the treatment of epilepsy, but therapy is approved for immediate-release Lamictal in patients two years of age and older. Furthermore, Lamictal is also indicated for the treatment of bipolar I disorder.

II. RISK ASSESSMENT:

The medication error staff of DMETS conducted a search of the internet, several standard published drug product reference textsⁱⁱⁱ as well as several FDA databases^{iii,iv} for existing drug names which sound-alike or look-alike to Lamictal XR to a degree where potential confusion between drug names could occur under the usual clinical practice settings. A search of the electronic online version of the U.S. Patent and Trademark Office's Text and Image Database was also conducted^v. The Saegis^{vi} Pharma-In-Use database was searched for drug names with potential for confusion. An expert panel discussion was conducted to review all findings from the searches. In addition, DMETS conducted three prescription analysis studies consisting of two written prescription studies (inpatient and outpatient) and one verbal prescription study, involving health care practitioners within FDA. This exercise was conducted to simulate the prescription ordering process in order to evaluate potential errors in handwriting and verbal communication of the name. Following completion of these initial components, an overall risk assessment is conducted that does not evaluate the name alone. The assessment considers the findings from above and more importantly integrates post-marketing experience in assessing the risk of name confusion, product label/labeling, and product packaging. Because it is the product that is inserted into the complex and unpredictable U.S. healthcare environment, all drug characteristics of a product must be considered in the overall safety evaluator risk assessment.

ⁱ MICROMEDEX Integrated Index, 2006, MICROMEDEX, Inc., 6200 South Syracuse Way, Suite 300, Englewood, Colorado 80111-4740, which includes all products/databases within ChemKnowledge, DrugKnowledge, and RegsKnowledge Systems.

ⁱⁱ Facts and Comparisons, online version, Facts and Comparisons, St. Louis, MO.

ⁱⁱⁱ AMF Decision Support System [DSS], the Division of Medication Errors and Technical Support [DMETS] database of Proprietary name consultation requests, New Drug Approvals 98-06, and the electronic online version of the FDA Orange Book.

^{iv} Phonetic and Orthographic Computer Analysis (POCA)

^v WWW location <http://www.uspto.gov/tmdb/index.html>.

^{vi} Data provided by Thomson & Thomson's SAEGIS™ Online Service, available at www.thomson-thomson.com

A. EXPERT PANEL DISCUSSION

An Expert Panel discussion was held by DMETS to gather professional opinions on the safety of the proprietary name, Lamictal XR. Potential concerns regarding drug marketing and promotion related to the proposed name were also discussed. This group is composed of DMETS Medication Errors Prevention Staff with representation from the Division of Drug Marketing, Advertising, and Communications (DDMAC). The group relies on their clinical and other professional experiences and a number of standard references when making a decision on the acceptability of a proprietary name.

1. DDMAC finds the proprietary names Lamictal XR acceptable from a promotional perspective.
2. The Expert Panel identified five names (Campral, Lamictal/Lamictal CD, Lomotil, Lamisil, and ^{(b) (4)}) as having the potential for confusion with Lamictal XR. Independent investigation identified eight additional names (Lamivudine, Epivir HPV, levetiracetam, Labetolol, Seroquel, Cymbalta, Loxitane, and Sanctura XR^{***}) as having potential for confusion with Lamictal XR. These products along with the available dosage form(s) and usual dosage is listed in Table 5 (see below).

Table 5: Potential Look-Alike and Sound-Alike Names Identified for Lamictal XR

Product Name	Established name, Dosage form(s)	Usual adult dose*	Other**
Lamictal XR	Lamotrigine Extended-release Tablets, 25 mg, 50mg, 100 mg, and 200 mg	Daily, variable dose with concomitant therapy and titration.	
Lamictal	Lamotrigine Tablets 25 mg, 100 mg, 150 mg, and 200 mg Lamotrigine Chewable Dispersible Tablets 2 mg, 5 mg, 25 mg	Daily to twice daily, variable dose with concomitant therapy and titration.	LA/SA
Campral	Acamprosate Calcium Delayed-release Tablets, 333 mg	2 tablets three times daily.	LA
Lomotil	Atropine Sulfate and Diphenoxylate Hydrochloride Tablets: 0.025 mg/2.5 mg Solution: 0.025 mg and 2.5 mg/ 5 mL	Adults: 5 mg four times per day. Children: weight-based, 1.5 mg to 5 mg four times daily.	LA
Lamisil	Terbinafine Tablets: 250 mg Topical Solution: 1% 30 mL bottle Topical Gel: 1% (5 g, 15 g, 30 g)	250 mg once daily for six to twelve weeks Apply twice daily for one week. Apply once daily for seven days.	LA/SA
Lamivudine (Epivir)	Lamivudine Tablets: 150 mg and 300 mg 150 mg: 60 ct bottle 300 mg: 30 ct bottle Solution 10 mg/ mL 240 mL bottle	Adult: 300 mg daily or 150 mg twice daily. Pediatric (3 mos to 16 years): 4 mg/kg twice daily.	LA
Epivir HBV	Lamivudine Tablet: 100 mg Oral Solution: 5 mg/mL	Adults: 100 mg daily. Pediatric: 3 mg/kg daily.	LA

*** Proprietary and confidential information that should not be released to the public.

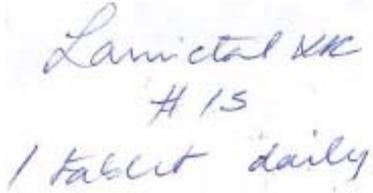
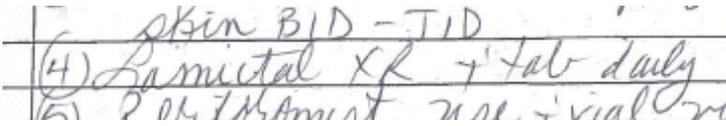
Product Name	Established name, Dosage form(s)	Usual adult dose*	Other**
Lamictal XR	Lamotrigine Extended-release Tablets, 25 mg, 50mg, 100 mg, and 200 mg	Daily, variable dose with concomitant therapy and titration.	
Labetalol	Labetalol Tablets: 100 mg, 200 mg, and 300 mg Injection: 5 mg/mL	Tablets: 100 mg to 400 mg twice daily. Injection: IV- 20 mg for 2 mins, then possible additional injections 40 mg and 80 mg at 10 minute intervals.	LA
Seroquel	Quetiapine Fumarate Tablets, 25 mg, 50 mg, 100 mg, 200 mg, 300 mg, and 400 mg	Bipolar/Depression: taper to 300 mg once daily at bedtime. Mania: 200 mg to 400 mg twice daily. Schizophrenia: 300 to 400 mg in divided doses (twice daily or three times daily).	LA
Cymbalta	Duloxetine Hydrochloride Delayed-release Capsules, 20 mg, 30 mg, and 60 mg	Major Depressive disorder: 20 mg to 30 mg twice daily. Neuropathic Pain: 60 mg daily.	LA
Loxitane Loxitane C (discontinued) Loxitane IM (discontinued)	Loxapine Succinate Capsules, 5 mg, 10 mg, 25 mg, and 50 mg	10 mg twice daily.	LA
Levetiracetam (Keppra)	Levetiracetam Tablets: 250 mg, 500 mg, 750 mg, and 1000 mg Oral Solution: 100 mg/mL Injection: 500 mg/5 mL	Adults: 500 mg to 1500 mg twice daily. Children: 10 mg/kg to 30 mg/kg twice daily. Injection: 500 mg to 1500 mg IV over 15 minutes.	LA
(b) (4)		N/A	LA/SA
Sanctura XR	Trospium Chloride Extended-release Capsules, 30 mg and 60 mg	60 mg daily on an empty stomach	LA

*Frequently used, not all-inclusive.
**LA (look-alike)/SA (sound-alike)

B. PRESCRIPTION ANALYSIS STUDIES

1. Methodology:

Three separate studies were conducted within the Centers of the FDA for each of the proposed proprietary names to determine the degree of confusion of Lamictal XR with marketed U.S. drug names (proprietary and established) due to similarity in visual appearance with handwritten prescriptions or verbal pronunciation of the drug name. These studies employed a total of 123 health care professionals (pharmacists, physicians, and nurses). The exercise was conducted in an attempt to simulate the prescription ordering process. An inpatient order and an outpatient prescription were written, each consisting of a combination of marketed and unapproved drug products with a prescription for Lamictal XR (see below). These prescriptions were optically scanned and one prescription was delivered to a random sample of participating health professionals via e-mail. In addition, the outpatient orders were recorded on voice mail and sent to a random sample of participating health professionals for their interpretation and review. After receiving either written or verbal prescription orders, the participants sent their interpretations of the orders via e-mail to the medication error staff.

HANDWRITTEN PRESCRIPTION	VERBAL PRESCRIPTION
<p data-bbox="298 176 493 205"><u>Outpatient RX:</u></p> 	<p data-bbox="1003 300 1406 396">Lamictal XR Quantity of 15 Take one tablet by mouth daily</p>
<p data-bbox="298 527 469 556"><u>Inpatient RX:</u></p> 	

2. Results for Lamictal XR:

None of the interpretations of the proposed name overlap, sound similar, or look similar to any currently marketed U.S. product. One respondent from the inpatient study omitted the proposed modifier of “XR.” In addition, there was one participant of the voice study who interpreted the modifier as “SR.” See Appendix A for complete listing of interpretations from the verbal and written studies.

C. CONTINUED POST-MARKETING SUREVEILLANCE

Lamictal XR is an addition to the Lamictal product line, consisting of Lamictal tablets (approved 1994) and Lamictal chewable dispersible tablets (approved 1998). Name confusion with Lamictal is well recognized by the Agency, the sponsor, and practitioners. This confusion has been reviewed by the Agency and the sponsor has subsequently initiated an educational program that includes computer software updates in retail pharmacies. In addition, the sponsor submits quarterly reports of errors with Lamictal. Current searches of the Agency’s safety databases found continuing errors with Lamictal and various other drug products (e.g. Lamisil, Labetolol, etc) that will be reviewed in detail in a post-marketing analysis (OSE# 2007-350). We anticipate continued confusion with Lamictal/Lamisil, in addition to the introduction of product line confusion between Lamictal and Lamictal XR.

D. SAFETY EVALUATOR RISK ASSESSMENT

To evaluate the potential of medication error with the proposed name of Lamictal XR, DMETS reviewed three aspects that commonly lead to error when product extensions are introduced in the marketplace that include: the modifier “XR”, the potential for confusion with the currently marketed Lamictal product line, and the potential for proprietary name confusion with drug products currently marketed.

1. Examination of the “XR” modifier

When comparing the proposed “XR” modifier, DMETS must not only evaluate the orthographic or phonetic similarity between the currently marketed products and the proposed modifier, but also examine if the meaning of the modifier is consistent with current “XR” products, if “XR” can look like a number, be interpreted as directions for use or is similar to a medical abbreviation, and evaluate if the addition of the modifier makes the name look similar to another drug name.

- a. In analysis of the potential for the “XR” modifier to resemble any numbers, dosing instructions, or medical abbreviation, post-marketing reporting has found that “XR” has been misinterpreted as “x 2.” This confusion occurred when the first XR suffix was approved; we have not seen recent confusion and the abbreviation does not appear on the dangerous abbreviations list. Additionally, the modifier “XR” is identified by standard references^{vii} as extended-release, X-linked recessive, X-ray, and Xeroradiography. These interpretations should not result in confusion. Moreover, the “X” of XR is associated with the Roman numeral “ten” and “R” could be misinterpreted as the Roman numeral “L”; thus, XL or “40”. However, we have not had such reports of confusion. Despite the potential for the “XR” modifier to look or be defined as above, DMETS does not believe this would prohibit the use of this modifier.
- b. When evaluating the appropriateness of the modifier and the intended meaning, we discovered twenty prescription products listed in the Orange Book, drugs@FDA, and DSS that use the “XR” modifier [Adderall XR, Augmentin XR, (b) (4)^{***} XR, Cipro XR, Dilacor XR⁺⁺, Dilt-XR⁺, Effexor XR, Focalin XR, Glucophage XR, Lodrane XR⁺, (b) (4)^{***}, Proquin XR⁺, Sanctura XR^{***}, Seroquel XR^{***}, Tanacof XR⁺, Tegretol XR, Tusso-XR⁺, Voltaren XR, Xanax XR, and Zerit XR (discontinued)].

Most of the “XR” drugs that represent product line extensions are dosed once daily (n=14) with the remaining five dosed twice daily/three times daily (n=5). Of the five drug products not dosed once daily, three were monograph drug products (Tanacof XR, Tusso-XR, Lodrane XR), and one (Tegretol XR) was approved in 1996 and thus not reviewed by DMETS. The remaining name, Augmentin XR, was reviewed by DMETS and approved by the Agency in 2002. Unfortunately, the name Augmentin XR was reviewed prior to the release of the Institute of Medicine report “Preventing Medication Errors” (2006)^{viii} or the National Coordinating Council for Medication Error Reporting and Prevention (NCC MERP) meeting on “Drug Name Suffixes and Medication Errors” (2005)^{ix} which identified safety concerns with modifiers. Since this, DMETS is addressing these issues in current review practices.

Despite the fact that 5 products have twice-daily dosing and use the ‘XR’ modifier, in DMETS opinion, the XR modifier adequately captures the most notable difference between Lamictal XR and the existing Lamictal, which is the dosing interval. As such, DMETS concludes that the ‘XR’ modifier is an acceptable choice for the proposed product.

^{vii} <http://www.pharma-lexicon.com/>, 02May2007.

^{***} Proprietary and confidential information that should not be released to the public.

⁺ No immediate release product is available on the market.

^{viii} July 20, 2006, Institute of Medicine (IOM) Report “Preventing Medication Errors” recommendation number four

^{ix} NCC MERP meeting “Drug Name Suffixes and Medication Errors: Exploring the Relationship and Minimizing the Risk”. October 2005.

2. Potential for Product Line Confusion

Post-marketing experience has shown that the introduction of product line extensions result in medication errors especially when there is any overlap in product characteristics and a knowledge deficit with respect to the introduction of the new extended-release formulation. Errors introduced by product line extensions are known to occur at all points in the medication use process. With respect to Lamictal, DMETS is concerned with the potential omission of the ‘XR’ modifier, overlapping strengths, and shelf/computer selection errors.

a. Omission of the “XR” modifier

Post-marketing experience has shown that the introduction of product line extensions result in medication errors when the modifier is omitted^x. In this case, if the XR modifier is omitted it is almost certain that Lamictal will be dispensed because of the overlapping product characteristics. Lamictal XR and Lamictal overlap in established name (lamotrigine), indication of use (adjunctive therapy for partial onset seizures), product strength (25 mg, 100 mg, and 200 mg), route of administration (oral), and dosage form (tablet). They also share a numerically similar strength (50 mg and 5 mg) and potential for overlapping dosing frequency depending on concurrent drug therapy (daily).

By choosing to develop a extended-release formulation of lamotrigine tablets that overlaps with three strengths of the currently marketed immediate-release formulation (25 mg, 100 mg, and 200 mg), the Sponsor has eliminated a potentially valuable error-reduction strategy that has been employed in other product line extensions. This sponsor, GlaxoSmithKline, took an alternative approach for the Paxil CR line with strengths of 12.5 mg, 25 mg, 37.5 mg compared to the existing Paxil strengths of 10 mg, 20 mg, 30 mg, and 40 mg. Thus, if the modifier were omitted or overlooked, the difference introduced by the strength offer an opportunity for an error to be caught before it reaches the patient. In the case of Lamictal, there will be nothing to distinguish these products. DMETS acknowledges that the sponsor developed the strengths to “allow patients to titrate to the optimal maintenance dose in the most convenient way.” However, the sponsor could and should have chosen a small deviation in strength similar to Paxil CR to lessen confusion.

If Lamictal and Lamictal XR confusion were to occur, the outcome must be considered. The likely cause of this confusion would be due to the omission of the modifier or knowledge deficit that the new formulation exists, which would result in the patient receiving an immediate-release tablet daily. Thus, the patient would not receive the expected total day lamotrigine coverage with potential fluctuations in blood levels resulting in adverse events.

Thus, we believe this confusion will occur based on the possibility of omission of the suffix, product characteristic overlap, and a knowledge deficit of the new product. Education alone will not fully address this confusion and we strongly recommend the sponsor revise the product strengths so that they do not overlap.

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

b. Shelf and Computer Selection Errors

Typically, pharmaceutical products are organized alphabetically by proprietary name, established name, or sorted by manufacturer. Since these attributes are identical with the currently marketed Lamictal product line and the proposed Lamictal XR, it is likely that the products will be stored near one another in virtually any organization carrying both product lines. Thus, this proximity could lead to selection errors, especially if the container labels look the same. Additionally, due to the shared root name of “Lamictal”, there is a possibility for computer selection errors.

There is currently post-marketing errors with incorrect drug selection between the currently marketed strengths of Lamictal. For example, the overlapping 25 mg strength of the tablets and chewable tablets has resulted in error. Adding additional overlapping strengths will contribute to further error. Shelf proximity was also implicated in error with other drug products (e.g. Lamisil, lamivudine). In order to minimize this potential source of confusion, differentiation in the packaging and labeling of Lamictal and Lamictal XR is essential. This also pertains to the various strengths of the proposed Lamictal XR product.

The sponsor has a computer monitoring tool, “Rx Safety Advisor”, currently in place in a small number of pharmacies to help prevent and monitor medication errors with Lamictal. The sponsor should assure that this tool encompassed this new formulation and be initiated in the target number of pharmacies in a timely fashion. In addition, post-marketing reporting should continue to be monitored for errors in order to determine if changes or updates to this tool are necessary or if other activities are required.

Overall, DMETS believes that labeling and packaging differentiation will help to minimize the potential for product selection errors, but will not be able to fully avoid confusion between Lamictal and Lamictal XR. Thus, DMETS believes that it is imperative that healthcare practitioners are educated about the existence of this extended-release formulation to avoid overdosing (and subsequent adverse events). In addition, to avoid ambiguity over the dosing regimen, it is imperative that the “Once Daily Dosing” statement be prominently presented on all Lamictal XR labels and labeling, and as well as any related marketing material, in order to prevent confusion.

3. Look-Alike And Sound-Alike Concerns

In reviewing the proprietary name, Lamictal XR, the primary concerns relate to look-alike and sound-alike confusion with Campral, Lamisil, Lamivudine, Epivir HBV, Labetalol, Seroquel, Cymbalta, Loxitane/Loxitane C/Loxitane IM, Levetiracetam, (b) (4) Lomotil, and Sanctura XR. Although Lamisil, labetalol, lamivudine, Lomotil, Seroquel, levetiracetam, and Cymbalta were identified as potential look-alike and sound-alike drug names, DMETS has received post-marketing report of confusion between these drugs and Lamictal. Errors in post-marketing could extrapolate to Lamictal XR, if the modifier is omitted.

DMETS conducted prescription studies to simulate the prescription ordering process. In this case, there was confirmation that modifier “XR” could be omitted from interpretation as demonstrated by one participant from the inpatient study. The remaining of the misinterpretations were misspelled/phonetic variations of the proposed name, Lamictal XR.

Of the twelve names identified, the following three names will not be reviewed further due to weak orthographic similarities and/or lack of overlapping products characteristics such as dosage form, strength, and/or directions for use: Campral, Loxitane, (b) (4)

The potential similarity of the remaining names Lamictal, Lamisil, Lamivudine, Epivir HBV, Labetalol, Seroquel, Cymbalta, Levetiracetam, Lomotil, and Sanctura XR are discussed in detail below.

a. Sanctura XR

Sanctura XR^{***} may look similar to Lamictal XR when scripted. Sanctura XR^{***} contains trospium chloride in an extended-release formulation to be used in the treatment of overactive bladder with symptoms of urge incontinence, urgency, and urinary frequency. Sanctura XR^{***} will be available in 30 mg and 60 mg capsules. Recommended dosing is 60 mg daily on an empty stomach.

Look-alike similarities between Lamictal XR and Sanctura XR may be attributed primarily to the limited potential for the leading “L” and “S” to resemble, shared central “t”, and shared “XR” modifier. However, the upstroke of the ending “L” of Lamictal should serve to differentiate the names upon scripting.



Sanctura XR and Lamictal XR share the overlapping characteristics of oral dosage form, daily dosing frequency, and the possibility of the 30 mg and 50 mg strengths to have a resemblance. Post-marketing reports found no confusion with the currently marketed Sanctura immediate-release drug product and Lamictal. Furthermore, the likelihood of simultaneous misinterpretation of the name and strength is limited. Thus, DMETS believes the likelihood of confusion is minimal.

b. Known Drug Name Confusion in the Lamictal Product Line

Post-marketing reports have found Lamictal to be confused with multiple drug names including Lamisil, labetalol, lamivudine (Epivir HBV), Lomotil, Seroquel, levetiracetam, and Cymbalta as having the potential for confusion.

Since the proposed product overlaps with the current Lamictal products in all product characteristics, DMETS suspects the same confusion will occur especially if the modifier is overlooked or omitted. However, if not omitted then the addition of the “XR” modifier may serve to differentiate Lamictal XR on interpretation of verbal or written orders for these names known to cause confusion (e.g. Lamisil, lamivudine).

However, computer selection errors have also been identified as an etiology for confusion. From the perspective of the leading “Lam” on selection from a list, this modifier will provide

^{***} Proprietary and confidential information that should not be released to the public.

no difference as the “XR” will likely make it last in the selection line (after Lamictal and Lamictal chewables). Additionally, the quick codes assigned to a drug product to allow for keystroke entry (thus, avoiding drop-down selection) may or may not alleviate confusion, depending on how assigned. For example, an assignment of LamX100 or LamXR100 could help, but Lam100X could result in proliferation of the confusion.

Lastly, if any of the drug names known to result in confusion were to add a modifier (e.g. Lomotil, Loxitane), this would likely lead to confusion. However, at this time, the only modifier is the “HPV” of Epivir, which does not have look-alike or sound-alike similarities to “XR.”

In light of the history of medication error with the Lamictal, DMETS will continue to monitor this product line.

III. LABELING, PACKAGING, AND SAFETY RELATED ISSUES

In review of the container labels, carton and insert labeling of Lamictal XR, DMETS has focused on safety issues relating to medication errors and has identified several areas of improvement to minimize potential user error.

A. GENERAL COMMENTS

1. Unit dose/blister labels were not provided for review and comment. However, in light of the errors found in current post-marketing reporting in the hospital or clinical setting, DMETS recommends the sponsor assure the Unit dose labeling is unique and easily identifiable from the current Lamictal product line. Many of the post-marketing reports noted errors in the Pyxis and pharmacy bins, which suggest the labels are similar in appearance and that distinguishable packaging/labeling may help to minimize this type of confusion.
2. This sponsor currently has an educational program in place and DMETS acknowledges the sponsors “comprehensive communication” program for Lamictal XR. However, the techniques described in this communication are similar to those used in the Lamictal name confusion. This technique has not been fully successful at minimizing error. The sponsor should consider many alternate pathways to limit confusion in the marketplace, which could include, but are not limited to, advertising in pharmacy and physician oriented journals (these advertisements could include reference to known confusion with the Lamictal product line) and pre-printed prescriptions pads. Further comments will be forwarded upon review of the proposed “comprehensive communication.”

B. CONTAINER LABEL

1. The sponsor has attempted to differentiate the Lamictal XR from the immediate-release Lamictal by the use of color caps, bottle size, and color placement. However, the 100 mg strengths for both Lamictal and Lamictal XR appear to be packaged in the same size bottle and use the same yellow color scheme as seen on the Lamictal XR 25 mg bottle. By using these similar features described above, it diminishes the intended purpose of differentiation between Lamictal and Lamictal XR and differentiation within the Lamictal XR line. Additionally, the redundancy of the yellow color diminishes the power of the Caution statement.

The sponsor also proposes to display all Lamictal XR strengths in a blue font. Placing these different strengths in blue may lead to selection error within the Lamictal XR product line. We note the immediate-release Lamictal product line utilizes a yellow container closure on the retail bottles in contrast to the proposed orange of the extended-release Lamictal XR product. This provides a good differentiation to the eye. However, caps are easily misplaced so to best achieve differentiation between the immediate-release formulation of Lamictal, Lamictal chewable dispersible tablets and extended-release Lamictal XR, DMETS recommends the sponsor continue the orange theme on the Lamictal XR labels. This can be achieved primarily by the removal of all yellow from the Lamictal XR labels. DMETS offers the following to help better distinguish these two dosage forms.

- a. Delete the yellow highlighting of the “ICTAL” as this causes a direct association with the immediate release product. In reference to the concern of potential confusion with other drug products, the “XR” on the label should serve to distinguish this formulation. If the sponsor would like to continue use of color on the “ICTAL” portion of the name, consider using orange as the highlight color. This will help distinguish this “XR” formulation from the immediate release product.
- b. DMETS would recommend that the Sponsor display the proprietary name in mixed case letters. For example, use upper and lower case letters (i.e. “LamICTAL”). This will minimize confusion between Lamictal/Lamisil and serve to further distinguish the visual similarities of the container labels of Lamictal and Lamictal XR.
- c. Change the internal coloring of the block letters of “XR” from yellow to orange. This serves to carry over the orange theme for the XR product line.
- d. We note, the sponsor uses a color scheme on the NDC number and caution statement that corresponds to the Lamictal XR tablet color. However, in two of the overlapping strengths (i.e. 100 mg and 200 mg), the colors are similar to that of the immediate-release Lamictal tablets. Thus, this will not likely serve to associate the tablet color as the sponsor may have intended. Instead, the color matching may lead to confusion and cause selection errors because this similarity. For example, as currently presented, the Lamictal XR 25 mg yellow color overlaps with the immediate-release color scheme and the yellow on yellow coloration diminishes the warning of the Caution statement (see below).



Additionally, the pink/peach of the Lamictal XR 100 mg and orange of the Lamictal 150 mg are too similar (see below).



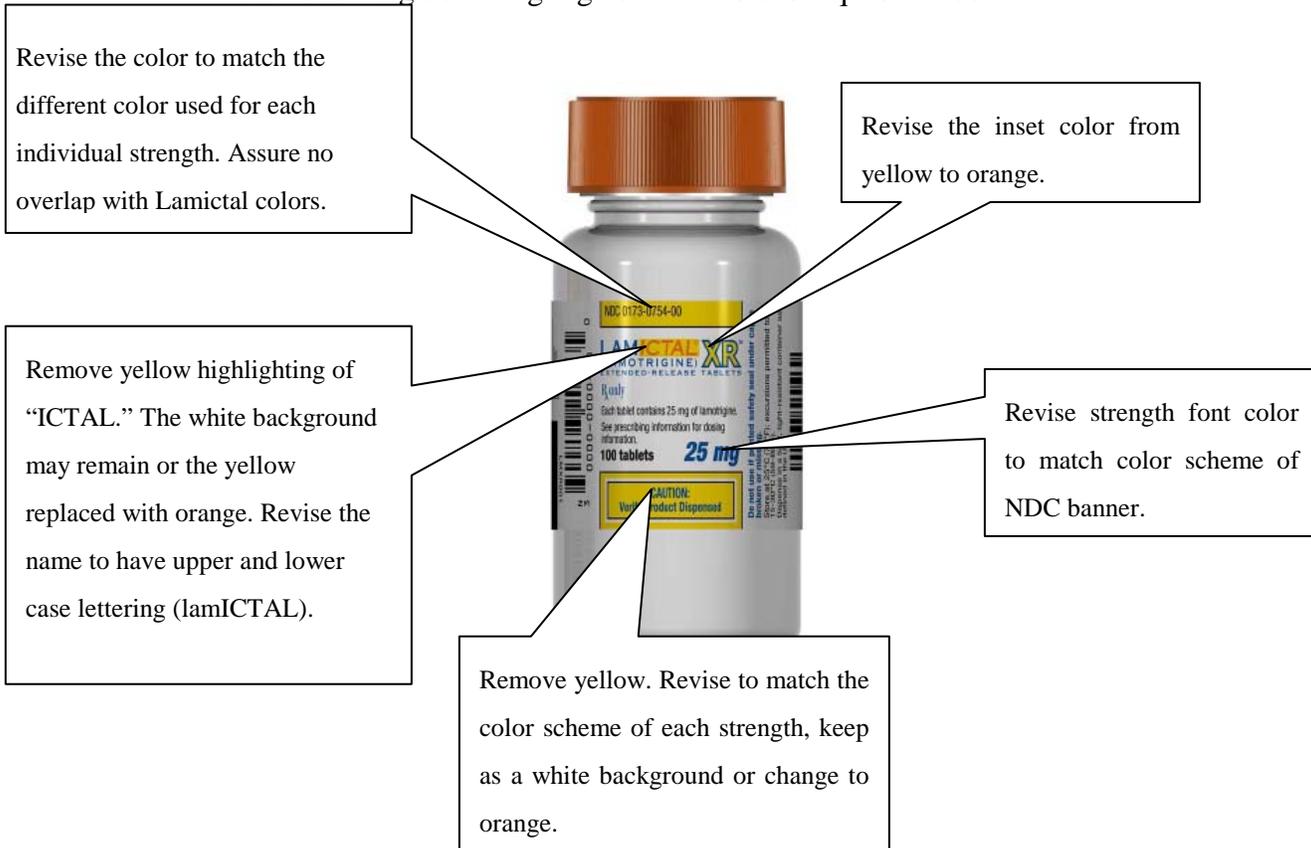
Lastly, a change of the color of the 200 mg strength may be required to assure differentiation from Lamisil (see below).



When considering your color scheme, the strength font color should match the chosen color scheme. This will help to minimize the errors we predict within the XR product line because of the similar appearance of all strengths in blue. Revising the font of each strength within the XR line to match the color banner/wrap of the NDC number could lead to more differentiation and less selection error within the Lamictal XR product line and between Lamictal and Lamictal XR products. However, the sponsor must assure the color provides sufficient contrast and readability against the text used in the strength to confirm prominence on the label.

- e. Delete the yellow background color of the Caution statement. The sponsor may present the warning on a white background, orange background or have the single box or double boxing reflect the color scheme for each strength. DMETS recommends the sponsor display this caution statement in colors that provide good visual contrast to increase readability and prominence of this information, but not in color used on immediate release Lamictal.

The following bottle highlights the revisions requested above in text.



2. Include a prominent statement referring to the drug product dosing frequency on the principle display panel to help educate practitioners and serve as a visual cue to alleviate confusion and error. For example, “Once Daily Dosing.”
3. Since the color of the bottle cap will help to differentiate the Lamictal products, assure the bottle caps for Lamictal and Lamictal XR are not interchangeable.
4. Relocate the net quantity statement away from the product strength. The net quantity appears bolded and has increased prominence, which draws your eye to the number rather than the strength. This may result in confusion with the product strength.
5. Correct the NDC count for the 50 mg strength. The current display is duplicative of the 25 mg strength.

C. INSERT LABELING

In the Dosage and Administration highlights section, please add the conversion statement from immediate-release tablets: “For patients being converted from immediate-release lamotrigine to Lamictal XR, the initial dose of Lamictal XR should match the total daily dose of the immediate-release lamotrigine.”

Appendix A: Prescription Study Results for Lamictal XR

Inpatient	Outpatient	Voice
Lamictal XR	Lamictal XR	Lamictal XR
Lamictal XR	Lamictal XR	LAMICTAL XR
Lamictal XR	Lamictal xr	Lamictil XR
Lamictal XR	Lamictal XR	Lamictal XR
Lamital XR	Lamictal XR	Lamictal XR
Lamictal XR	Lamictal XR	Melix Elixir XR
Lamictal XR	Lamictal XR	Mixilex R
Lamictal XR	Lamictal XR	Lamictal XR
Lamictal XR		Lamictal XR
Lamictal XR		Emixulex R
Lamictal		Lamictal SR
Lamictal XR		Mixilar
Lamictal XR		Lamictal XR

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this page is the manifestation of the electronic signature.**

/s/

Kimberly Culley-Pedersen
5/2/2007 09:57:25 PM
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Denise Toyer
5/3/2007 07:45:43 AM
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