

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

22-430

PROPRIETARY NAME REVIEW(S)



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

Date: September 22, 2009

To: Scott Monroe, M.D., Director
Division of Reproductive and Urology Products

Through: Melina Griffis, R.Ph., Acting Team Leader
Denise Toyer, PharmD, Deputy Director
Carol Holquist, RPh, Director
Division of Medication Error Prevention and Analysis (DMEPA)

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

Subject: Proprietary Name Review

Drug Name(s): Lysteda (Tranexamic Acid) Tablet, 650 mg

Application Type/Number: NDA 022430

Applicant: Xanodyne

OSE RCM #: 2009-1283

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1 INTRODUCTION

This re-assessment of the proprietary name is written in response to a notification that NDA 022430 may be approved within 90 days. The Division of Medication Error Prevention and Analysis (DMEPA) found the proposed proprietary name, Lysteda, acceptable in OSE Review #2009-429, dated May 28, 2009. The Division of Reproductive and Urology Products did not have any concerns with the proposed name, Lysteda, and the Division of Drug Marketing, Advertising and Communications (DDMAC) found the name acceptable from a promotional perspective on May 28, 2009.

2 METHODS AND RESULTS

For the proposed proprietary name, DMEPA staff search a standard set of databases and information sources (see section 4) to identify names with orthographic and/or phonetic similarity to the proposed name that have been approved since the previous OSE proprietary name review. We used the same search criteria that were used in OSE Review# 2009-429 for the proposed proprietary name, Lysteda. None of the proposed product characteristics were altered, thus, we did not re-evaluate previous names of concern. Additionally, DMEPA searched the USAN stem list to determine if the name contains any USAN stems as of the last USAN updates. DMEPA bases the overall risk assessment on the findings of a Failure Mode and Effects Analysis¹ (FMEA) of the proposed proprietary name, and focuses on the avoidance of medication errors

The searches of the databases referenced in Section 4 yielded no additional new names which were thought to have some look-alike or sound-alike similarity to the name, Lysteda.

DMEPA staff did not identify any United States Adopted Names (USAN) stems in the proposed proprietary name, Lysteda, as of September 11, 2009.

3 CONCLUSIONS AND RECOMMENDATIONS

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

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

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

4 REFERENCES

1. OSE review # 2009-429 Proprietary Name Review of Lysteda; Crandall, Anne K.

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

Drugs@FDA contains most of the drug products approved since 1939. The majority of labels, approval letters, reviews, and other information are available for drug products approved from 1998 to the present.

Drugs@FDA contains official information about FDA approved brand name, generic drugs, therapeutic biological products, prescription and over-the-counter human drugs and discontinued drugs and “Chemical Type 6” approvals.

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

The FDA Orange Book provides a compilation of approved drug products with therapeutic equivalence evaluations.

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

USAN Stems List contains all the recognized USAN stems.

5. ***CDER Proposed Name List***

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

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

/s/

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**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
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Date: May 28, 2009

To: Scott Monroe, M.D., Director
Division of Reproductive and Urology Products

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Carol Holquist, RPh, Director
Division of Medication Error Prevention and Analysis

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

Subject: Proprietary Name Review

Drug Name: Lysteda (Tranexamic Acid) Modified-release Tablets, 650 mg

Application Type/Number: NDA 22-430

Applicant: Xanodyne Pharmaceuticals

OSE RCM #: 2009-429

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

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EXECUTIVE SUMMARY

This review is in response to a request from Xanodyne Pharmaceuticals on March 2, 2009 for an evaluation of the proposed proprietary name, Lysteda. Lysteda is the proposed proprietary name for Tranexamic acid tablets. This is an extended-release formulation for a product that was previously marketed by a different Applicant as an immediate-release tablet and intravenous formulation for a different indication of use. This product is being developed for the treatment of menorrhagia and amelioration of associated symptoms. The proposed name was evaluated from both a safety and promotional perspective giving consideration to all review disciplines (e.g., DDMAC, clinical and DMEPA). The Proprietary Name Risk Assessment did not identify concerns that would render the name unacceptable based on product characteristics and safety profile known at the time of this review.

Thus the Division of Medication Error Prevention and Analysis (DMEPA) has no objection to the proprietary name, Lysteda, for this product.

However, if any of the proposed product characteristics as stated in this review are altered prior to approval of the product, DMEPA rescinds the Risk Assessment findings and recommends that the name be resubmitted for review. In the event that our Risk Assessment finding is rescinded, the evaluation of the name on resubmission is independent of the previous Risk Assessment, and as such, the conclusions on re-review of the name are subject to change.

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

1 BACKGROUND

1.1 INTRODUCTION

This review is in response to a request from the Applicant, Xanodyne Pharmaceuticals, for an assessment of the proposed proprietary name Lysteda, regarding potential name confusion with other proprietary or established drug names. The Applicant also submitted container labels, and carton labeling which will be reviewed separately in OSE Review # 2009-430.

1.2 REGULATORY HISTORY

Lysteda is a pending NDA application with an anticipated action date of November 30, 2009. A different applicant (Pharmacia and Upjohn) held the NDA for the regular release oral formulation of Tranexamic acid (Cyklokapron) which was approved for the indication for the treatment of patients with hemophilia for short-term use to reduce or prevent hemorrhage and reduce the need for replacement therapy during and following tooth extraction. The regular release oral formulation was pulled from the market in 2003 however, the NDA for the injectable formulation is still currently marketed but for a different indication. Lysteda will be the first extended-release formulation of Tranexamic acid.

1.3 PRODUCT INFORMATION

Lysteda is a modified release formulation of Tranexamic acid, an antifibrinolytic drug, indicated for the treatment of heavy menstrual bleeding (menorrhagia) and the amelioration of symptoms associated with heavy menstrual bleeding, including limitations on social, leisure and physical activities.

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

The recommended dose of Lysteda is two 650 mg taken three times daily (3.9 g/day) for up to 5 days during menstruation. Lysteda will be available as a 650 mg modified release tablet in bottles of 30, 100 and 500. Lysteda will also be available in a 30 tablet carton containing 5 blister cards, each containing 6 tablets.

2 METHODS AND MATERIALS

This section describes the methods and materials used by DMEPA staff conducting a proprietary name risk assessment (see 2.1 Proprietary Name Risk Assessment). The primary focus for this assessment is to identify and remedy potential sources of medication error prior to drug approval. The Division of Medication Error Prevention and Analysis (DMEPA) defines a medication error as any preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of the health care professional, patient, or consumer.¹

2.1 PROPRIETARY NAME RISK ASSESSMENT

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

For the proprietary name, Lysteda, DMEPA searches a standard set of databases and information sources to identify names with orthographic and phonetic similarity (see Sections 2.1.1 for detail) and held a CDER Expert Panel discussion to gather professional opinions on the safety of the proposed proprietary name (see 2.1.2). We also conduct internal CDER prescription analysis studies (see 2.1.3), and, when provided, external prescription analysis studies results are considered and incorporated into the overall risk assessment (see detail 2.3).

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 2.1.6). The overall risk assessment is based on the findings of a Failure Mode and Effects Analysis (FMEA) of the proprietary name, and is focused on the avoidance of medication errors.

FMEA is a systematic tool for evaluating a process and identifying where and how it might fail.¹ FMEA is used to analyze whether the drug names identified with look- or sound-alike similarity to the proposed name could cause confusion that subsequently leads to medication errors in the clinical setting. We define 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.² We use the clinical expertise of our 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.

² National Coordinating Council for Medication Error Reporting and Prevention. <http://www.nccmerp.org/aboutMedErrors.html>. Last accessed 10/11/2007.

As such, DMEPA considers the product characteristics associated with the proposed drug throughout the risk assessment, since the product characteristics of the proposed name may provide a context for communication of the drug name and ultimately determine the use of the product in the *usual* clinical practice setting.

Typical product characteristics considered when identifying drug names that could potentially be confused with the proposed drug name include, but are not limited to established name of the proposed product, the proposed indication, dosage form, route of administration, strength, unit of measure, dosage units, recommended dose, typical quantity or volume, frequency of administration, product packaging, storage conditions, patient population, and prescriber population.

Because drug name confusion can occur at any point in the medication use process, we consider the potential for confusion throughout the entire U.S. medication use process, including drug procurement, prescribing and ordering, dispensing, administration, and monitoring the impact of the medication.³

2.1.1 Search Criteria

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

For this review, particular consideration was given to drug names beginning with the letter ‘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.^{4,5}

To identify drug names that may look similar to Lysteda, DMEPA also consider the other orthographic appearance of the name on lined and unlined orders. Specific attributes taken into consideration include the length of the name (seven letters), upstrokes (three, capital letter ‘L’, ‘t’, ‘d’), downstrokes (one, ‘y’), cross-strokes (one, ‘t’), and dotted letters (none). Additionally, several letters may be vulnerable to ambiguity when scripted, including the letter ‘L’ which may appear similar to ‘F’, ‘Z’, ‘C’, ‘h’ or ‘e’; the letter ‘y’ may appear as ‘g’ or ‘ij’; lower case ‘s’ may appear as ‘n’ or ‘r’; lower case ‘t’ may appear as ‘f’ or ‘l’; lower case ‘e’ may appear as a lower case ‘i’; lower case ‘d’ may appear as a lower case ‘cl’ and lower case ‘a’ may appear as ‘e’, ‘o’ or ‘u’. As such, DMEPA also considers these alternate appearances when identifying drug names that may look similar to Lysteda.

When searching to identify potential names that may sound similar, DMEPA searches for names with similar number of syllables (three), stresses (LY-sted-a, ly-STED-a, or ly-sted-A), and placement of vowel and consonant sounds. In addition, several letters may be subject to interpretation when spoken, including the letters ‘Ly’ may be interpreted as ‘Li’ or Lie; ‘ste’ may be interpreted as ‘stea’ and the letter ‘d’ may be interpreted as ‘t’. As such, DMEPA also considers these alternate pronunciations when identifying drug names that may sound similar to Lysteda.

³ Institute of Medicine. Preventing Medication Errors. The National Academies Press: Washington DC. 2006.

⁴ Institute for Safe Medication Practices. Confused Drug name List (1996-2006). Available at <http://www.ismp.org/Tools/confuseddrugnames.pdf>

⁵ Kondrack, G and Dorr, B. Automatic Identification of Confusable Drug Names. Artificial Intelligence in Medicine (2005).

The Applicant's intended pronunciation of the proprietary name, *lye-stead-a*, is taken into consideration, however DMEPA has no control over how practitioners pronounce the name and must take into consideration that individual practitioners will pronounce the name as they interpret what they read or see, additionally, many foreign accents can alter pronunciations of names, in an unpredictable manner.

DMEPA also considers the product characteristics associated with the proposed drug throughout the identification of similar drug names, since the product characteristics of the proposed drug ultimately determine the use of the product in the clinical practice setting.

For this review, the DMEPA staff were provided with the following information about the proposed product: the proposed proprietary name (Lysteda), the established name (Tranexamic acid), proposed indication (treatment of heavy menstrual bleeding and the amelioration of symptoms associated with heavy menstrual bleeding), strength (650 mg), dose (two tablets), frequency of administration (three times daily for up to 5 days during menstruation), route of administration (oral) and dosage form of the product (modified-release tablet).

Lastly, DMEPA staff also considers the potential for the proposed name to inadvertently function as a source of error for reasons other than name confusion. Post-marketing experience has demonstrated that proprietary names (or components of the proprietary name) can be a source of error in a variety of ways.

As such, these broader safety implications of the name are considered and evaluated throughout this assessment and 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, Lysteda, was provided to 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 using the criteria outlined in 2.1.1. A standard description of the databases used in the searches is provided in Appendix A. To complement the process, DMEPA staff uses a computerized method of identifying phonetic and orthographic similarity between medication names. The program, Phonetic and Orthographic Computer Analysis (POCA), uses complex algorithms to select a list of names from a database that have some similarity (phonetic, orthographic, or both) to the trademark being evaluated. Lastly, DMEPA staff reviews the USAN stem list to determine if any USAN stems are present within the proprietary name. The findings of the individual Safety Evaluators were then pooled and presented to the Expert Panel.

2.1.3 CDER Expert Panel Discussion

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

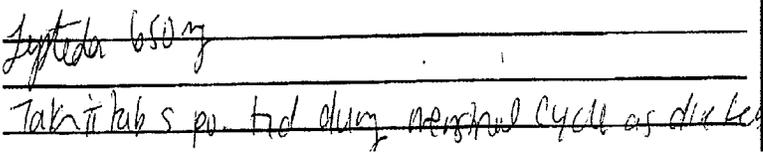
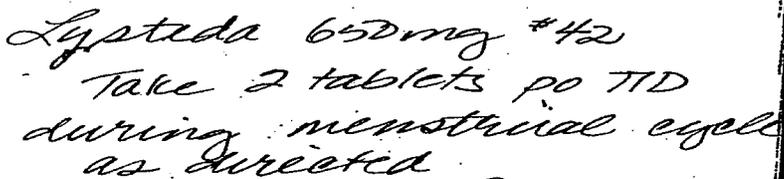
The pooled results of the DMEPA staff were presented to the Expert Panel for consideration. Based on the clinical and professional experiences of the Expert Panel members, the Panel may recommend the addition of names, additional searches by the Safety Evaluator to supplement the pooled results, or general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

2.1.4 FDA Prescription Analysis Studies

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

In order to evaluate the potential for misinterpretation of Lysteda in handwriting and verbal communication of the name, inpatient medication orders are written, each consisting of a combination of marketed and unapproved drug products, including the proposed name. These prescriptions are optically scanned and one prescription is delivered to a random sample of 123 participating health professionals via e-mail. In addition, a verbal prescription is recorded on voice mail. The voice mail messages are then sent to a random sample of the participating health professionals for their interpretations and review. After receiving either the written or verbal prescription orders, the participants send their interpretations of the orders via e-mail to the DMEPA staff.

Figure 1. Study 0416 (conducted on April 16, 2009)

HANDWRITTEN PRESCRIPITON AND MEDICATION ORDER	VERBAL PRESCRIPTION
<p><u>Inpatient Written Prescription:</u></p> 	<p>Lysteda 650 mg # 42 Take 2 tablets by mouth three times daily during menstrual cycle as directed</p>
<p><u>Outpatient Written Prescription:</u></p> 	

2.1.5 Comments from the Office of New Drug Division or the Office of Generic Drugs

DMEPA requests the regulatory division in the Office of New Drugs responsible for the application for their comments or concerns with the proposed proprietary name and any clinical issues that may impact the DMEPA review during the initial phase of the name review. Additionally, when applicable, at the same time DMEPA requests concurrence/non-concurrence with DDMAC's decision on the name. Any comments or concerns are addressed in the safety evaluator's assessment.

The regulatory division is contacted a second time following our analysis of the proposed proprietary name. At this point, DMEPA conveys their decision to accept or reject the name. The regulatory division is requested to concur/not concur with DMEPA's final decision.

2.1.6 External Proprietary Name Risk Assessment

For this product, the Applicant submitted a name validation study conducted by Addison Whitney to evaluate the proposed proprietary name Lysteda. DMEPA conducts an independent analysis and evaluation of the data provided, and responds to the overall findings of the assessment. When the external proprietary name risk assessment identifies potentially confusing names that were not captured in the DMEPA database searches or in the Expert Panel Discussion, these names are included in the Safety Evaluator's Risk Assessment and analyzed independently by the Safety Evaluator to determine if the potentially confusing name could lead to medication errors in usual practice settings.

After the Safety Evaluator has determined the overall risk assessment of the proposed name, the Safety Evaluator compares the findings of their overall risk assessment with the findings of the proprietary name risk assessment submitted by the Applicant. The Safety Evaluator then determines whether the DMEPA's risk assessment concurs or differs with the findings. When the proprietary name risk assessments differ, DMEPA provides a detailed explanation of these differences.

2.1.7 Safety Evaluator Risk Assessment of the Proposed Proprietary Name

Based on the criteria set forth in Section 2.1.1, the Safety Evaluator 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.⁶ When applying FMEA to assess the risk of a proposed proprietary name, the DMEPA staff 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 mode.

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 Lysteda convincingly similar to another drug name, which may cause practitioners to become confused at any point in the usual practice setting?”

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

An affirmative answer indicates a failure mode and represents a potential for Lysteda 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.

We 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.©(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 we object to the use of the proposed proprietary name, based upon the potential for confusion with another proposed (but not yet approved) proprietary name, we will provide a contingency objection based on the date of approval: whichever product is awarded approval first

has the right to the use the name, while we will recommend that the second product to reach approval seek an alternative name.

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

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

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

If we object to a proposed proprietary name on the basis that drug name confusion could lead to medication errors, the FMEA process is used to identify strategies to reduce the risk of medication errors. We are likely to recommend that the Applicant select an alternative proprietary name and submit the alternate name to the Agency for us to review. However, in rare instances FMEA may identify plausible strategies that could reduce the risk of medication errors 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 and render the proposed name acceptable.

3 RESULTS

3.1 PROPRIETARY NAME RISK ASSESSMENT

3.1.1 Database and Information Sources

For this review, DMEPA identified 22 names as having some similarity to the name Lysteda. The names Lyrica, Luter, Glyburide, Dyazide, Lysodren, Byetta, Bystolic, Zyrtec (D), Cystadane, Tyrisa, Listica; Lysodase, Lysadam, Lystin, Lysotan, Cysteine, Zyprexa, and Lipitor were thought to look like Lysteda. The name Tyzeka was thought to sound like Lysteda and the names Lusedra and Lunesta were thought to look and sound like Lysteda.

b(4)

A search of the United States Adopted Name (USAN) stem list on May 18, 2009 identified no USAN stem names within the proposed name, Lysteda.

3.1.2 CDER Expert Panel Discussion

The Expert Panel reviewed the pool of names identified by DMEPA (see section 3.1 above), and noted no additional names.

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

3.1.3 FDA Prescription Analysis Studies

A total of 32 practitioners responded to Rx Study 0416. None of the responses overlapped with any existing drug names. About 60 percent of the participants (n=19) interpreted the name correctly as "Lysteda". In this Rx study, correct interpretation occurred more frequently in the outpatient study, with only one misinterpretation involving 'a' for 'e'. The majority of misinterpretations occurred in the inpatient and the voice study, with the first component 'Lys' being misinterpreted as 'Lep' or 'Lyp' in the inpatient study and Lis in the voice study, and the last component of the name 'da' was misinterpreted as 'dor' in the inpatient study and 'tta' in the voice study. See Appendix B for the complete listing of interpretations from the verbal and written prescription studies.

3.1.4 Comments from the Division

In response to the OSE e-mail sent March 20, 2009, the Division of Reproductive and Urologic Products (DRUP) did not forward any comments and or concerns on the proposed proprietary name at the initial phase of the name review.

DMEPA notified DRUP, via e-mail, that we had no objections to the proposed proprietary name, Lysteda, on May 1, 2009. Per e-mail correspondence from the DRUP on May, 1, 2009, they indicated they concur with our assessment of the proposed proprietary name, Lysteda.

3.1.5 External Name Study

In the submission the Applicant provided a proposed name validation study conducted by _____ which identified 10 names that look or sound alike to the proposed name, Lysteda. Five of the 10 names (Lyrica, Lunesta, Byetta, Lysodren and Zyprexa) were also identified by DMEPA. The remaining names Lisinopril, Levitra and Nystatin were thought to sound-like Lysteda and Lybrel and Cytoxan were thought to look-like Lysteda.

b(4)

3.1.6 Safety Evaluator Risk Assessment

Independent searches by the primary Safety Evaluator identified three additional names; Leustatin, which was thought to sound similar to Lysteda and Bystolic and Hystolan which were thought to look like Lysteda. As such, a total of 30 names were analyzed for look-alike and sound- alike similarity.

The term Modified-release chosen by the Applicant to describe the release process of this tablet, is not recognized by USP as a recognized dosage form nor is it listed in the Center for Drug Evaluation and Research Data Standards Manual (CDER DSM) as an accepted or recognized dosage form.

4 DISCUSSION

DMEPA identified a total of thirty names for their potential similarity to the proposed name, Lysteda. Failure Mode and Effect Analysis (FMEA) was then applied to determine if the proposed name could potentially be confused with the 30 names and lead to medication errors. This evaluation determined that the name similarity between Lysteda was unlikely to result in

medication errors with any of the 30 products for the reasons presented in Appendices C through I. This finding was consistent with and supported by an independent risk assessment of the proprietary name submitted by the Applicant.

Neither DDMAC nor the review Division raised concerns with the proposed name.

Our evaluation also noted that the Applicant refers to this particular formulation of Tranexamic acid as a modified-release tablet. The designation of modified release is not recognized by USP as a dosage form nor does it appear in the CDER Standard DSM and should be deleted. However, DMEPA defers to CMC and Labeling and Nomenclature Committee (LNC) for the final determination of the dosage formulation for this product.

5 CONCLUSIONS

The Proprietary Name Risk Assessment findings indicate that the proposed name, Lysteda, is acceptable. As such, the Division of Medication Error Prevention and Analysis does not object to the use of the proprietary name, Lysteda, for this product.

If any of the proposed product characteristics as stated in this review are altered prior to approval of the product, the Division of Medication Error Prevention and Analysis rescinds this Risk Assessment finding, and recommends that the name be resubmitted for review. In the event that our Risk Assessment finding is rescinded, the evaluation of the name on resubmission is independent of the previous Risk Assessment, and as such, the conclusions on re-review of the name are subject to change. If the approval of this application is delayed beyond 90 days from the signature date of this review, the proposed name must be resubmitted for evaluation.

5.1 COMMENTS TO THE DIVISION

The use of the term “modified-release” is not acceptable because it is not recognized by the United States Pharmacopeia (USP) as a dosage form, nor is it listed in the CDER DSM. We recommend the Division refer to CMC and that LNC is consulted for further guidance, if necessary, to determine the appropriate dosage form designation for this product.

We would be willing to meet with the Division for further discussion, if needed. If you have any questions or need clarification, contact Darrell Jenkins, OSE Project Manager, at 301-796-0558.

5.2 COMMENTS TO THE APPLICANT

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

Lysteda will be re-reviewed 90 days prior to the approval of the NDA. If we find the name unacceptable following the re-review, we will notify you.

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

6 REFERENCES

1. MICROMEDEX INTEGRATED INDEX ([HTTP://WEBLERN/](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 orthographic algorithm is a database which was created for the Division of Medication Error Prevention, FDA.

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

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

4. AMF Decision Support System [DSS]

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

5. Division of Medication Error Prevention proprietary name consultation requests

This is a list of proposed and pending names that is generated by the Division of Medication Error Prevention from the Access database/tracking system.

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

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

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

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

8. US Patent and Trademarks Office <http://www.uspto.gov>.

Provides information regarding patent and trademarks.

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

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

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

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

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

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

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

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

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

List contains all the recognized USAN stems.

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

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

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

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

16. **Medical Abbreviations Book**

Contains commonly used medical abbreviations and their definitions.

APPENDICES

Appendix A:

The DMEPA staff considers the spelling of the name, pronunciation of the name when spoken, and appearance of the name when scripted. We also compare the spelling of the proposed proprietary name with the proprietary and established name of existing and proposed drug products because similarly spelled names may have greater likelihood to sound similar to one another when spoken or look similar to one another when scripted. DMEPA also examines the orthographic appearance of the proposed name using a number of different handwriting samples. Handwritten communication of drug names has a long-standing association with drug name confusion. Handwriting can cause similarly *and* dissimilarly spelled drug name pairs to appear very similar to one another and the similar appearance of drug names when scripted has led to medication errors. DMEPA applies their expertise gained from root-cause analysis of such medication errors to identify sources of ambiguity within the name that could be introduced when scripting (i.e. “T” may look like “F,” lower case ‘a’ looks like a lower case ‘u,’ etc), along with other orthographic attributes that determine the overall appearance of the drug name when scripted (see detail in Table 1 below). Additionally, since verbal communication of medication names is common in clinical settings, DMEPA compares 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 source 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	<ul style="list-style-type: none"> Names may look similar when scripted, and lead to drug name confusion in written communication

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

Appendix B: CDER Prescription Study 0416 Responses

Original	Correction?	Notes
Lysteda	Lysteda	Lystetta
Lystedor	Lysteda	Lysteda
Lepteda	Lysteda	Lystetta
Lysteda	Lysteda	Lysteda
Lepteda	Lysteda	Listeda
Lysteda	Lystada	Lystetta
Lysteda	Lysteda	
Lysteder	Lysteda	
Lypteda	Lysteda	
Lystedor	Lysteda	
Lysteda	Lysteda	
Lepteda	Lysteda	
Lysteda		
Lepteda		

Appendix C: Names of withdrawn drug products

Name	Status
Listica (no established name listed)	Withdrawn by Commissioner 1972

Appendix D: Proprietary name associated with drug on foreign market

Proprietary Name	Established Name	Country
Lysadam	Calcium	Philippines
Lystin	Nystatin	Hong Kong, Thailand
Lysotan	Unable to locate	Italy
Hystolan	Isoxsuprine	Indonesia

Appendix E: Drug name found on Orphan Drug List, not found in other commonly used drug references (still in developmental stage)

Proprietary Name	Established Name
Lysodase	PEG-glucocerebrosidase

Appendix F: NDA approved with different proprietary name

Denied Proprietary Name	Established Name	Approved Proprietary Name
	Lisdexamfetamine dimesylate	Proposed name turned down, approved as Vyvanse (NDA # 21-977)

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

Product name with potential for confusion	Similarity to Proposed Product Name	Strength	Usual Dose (if applicable)
Lysteda (Tranexamic acid)		650 mg Modified-release tablet	Two tablets by mouth three times daily during menstruation
Glyburide	Look	1.25 mg, 2.5 mg, 5 mg oral tablets	1.25 mg to 20 mg by mouth daily in single or divided doses
Dyazide (Hydrochlorothiazide/Triamterene)	Look	25 mg/50 mg, 25 mg/37.5 mg oral capsule	One capsule once daily
Byetta (Exenatide synthetic)	Look	5 mcg per dose, 60 doses, 1.2 mL, 10 mcg per dose, 60 doses, 2.4 mL	5 mcg to 10 mcg subcutaneously twice daily within 60 minutes of morning and evening meals
Bystolic (Nebivolol hydrochloride)	Look	2.5 mg, 5 mg, 10 mg, 20 mg oral tablet	5 mg to 40 mg by mouth once daily
Zyrtec (Cetirizine) +/- Pseudoephedrine	Look	5 mg, 10 mg oral tablet 5 mg, 10 mg chewable tablets 5 mg/5 mL oral syrup 5 mg/120 mg pseudoephedrine oral tablet	2.5 mg to 10 mg by mouth once daily 1 tablet by mouth twice daily
Zyprexa (Olanzapine)	Look	2.5 mg, 5 mg, 7.5 mg, 10 mg oral tablets 5 mg, 10 mg, 15 mg, 20 mg orally disintegrating tablets 10 mg vial for reconstitution (5 mg/mL)	2.5 mg to 20 mg by mouth once daily 2.5 mg to 10 mg intramuscularly per day
Lipitor (Atorvastatin calcium)	Look	10 mg, 20 mg, 40 mg, 80 mg oral tablets	10 mg to 80 mg by mouth at bedtime

Product name with potential for confusion	Similarity to Proposed Proprietary Name	Strength	Usual Dose (if applicable)
Lysteda (Tranexamic acid)		650 mg Modified-release tablet	Two tablets by mouth three times daily during menstruation
Lunesta (Eszopiclone)	Both	1 mg, 2 mg, 3 mg oral tablets	1 mg to 3 mg by mouth right before bedtime
Lisinopril	Sound	2.5 mg, 5 mg, 10 mg, 20 mg, 30 mg, 40 mg oral tablet	2.5 mg to 40 mg by mouth once daily
Levitra (Vardenafil hydrochloride)	Sound	2.5 mg, 5 mg, 10 mg, 20 mg oral tablet	2.5 mg to 20 mg by mouth 60 minutes prior to sexual activity
Nystatin	Sound	100,000 international units vaginal insert 500,000 international units oral tablet 100,000 international units per gram; cream, ointment, topical powder	One insert vaginally once daily for 2 weeks 1 to 2 tablet by mouth 3 times daily 200,000 – 600,000 international units by mouth 4 times daily Apply liberally 2 to 3 times daily
Cytosan (Cyclophosphamide)	Look	25 mg, 50 mg oral tablet 0.5 g, 1 g, 2 g single dose vial for injection	1 mg to 5 mg/kg/day by mouth 40 mg to 50 mg/kg intravenously in divided doses over 2 to 5 days or 10 mg to 15 mg/kg intravenously every 7 to 10 days or 3 mg to 5 mg/kg intravenously twice weekly
Bystolic (Nebivolol hydrochloride)	Look	2.5 mg, 5 mg, 10 mg, and 20 mg oral tablet	2.5 mg to 40 mg by mouth once daily

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Appendix H: Single strength products with multiple differentiating product characteristics

Product name with preferred formulation	Similarity to product being	Strength	Usual Dose (if applicable)	Other Differentiating Product Characteristics
Lysteda (Tranexamic acid)		650 mg modified-release oral tablet	Two tablet by mouth three times daily during menstruation	
Lutera (Ethinyl estradiol/Levonorgestrel)	Look	20 mcg/0.1 oral tablets, 28 day pack	One table by mouth once daily	Frequency of administration (three times a day vs. once daily) Dose (2 tablets vs. 1 tablet) Length of therapy (up to 5 days per month vs. chronic therapy)
Cysteine hydrochloride	Look	0.5 grams (50 mg/mL), 10 mL syringe	To be used only after dilution in Aminosyn. Combine 10 mL of Cysteine with 12.5 g of amino acids. Dosage is based on nutritional need of patient.	Dosage form (tablet vs. intravenous fluid) Route of administration (oral vs. intravenous) Context of use (Cysteine must be diluted with Aminosyn and then further diluted and then administered within 1 hour after mixing)
Cystadane (Betaine)	Look	Anhydrous powder for oral solution	6 grams per day by mouth in divided doses of 3 grams twice a day	Frequency of administration (three time a day vs. twice daily) Dosage form (tablets vs. scoop) 1 scoop is equal to 1 gram-each administration of Cystadane must be diluted and then ingested immediately.
Leustatin (Cladribine)	Sound	10 mg (1 mg/mL) vial	Continuous intravenous infusion for 7 days at dose of 0.09 mg/kg/day	Frequency of administration (three times daily vs. continuous infusion) Route of administration (oral vs. intravenous) Dosage form (tablet vs. intravenous infusion)
Lusedra (Fospropofol)	Both	25 mg/mL (total 1,050/30 mL) single use vial	Bolus intravenous injection of 6.5 mg/kg followed by a supplemental infusion of 1.6 mg/kg intravenous as needed to achieve sedation	Route of administration (oral vs. intravenous) Dose (2 tablet vs. weight based mg/kg bolus, then infusion) Dosage form (tablet vs. intravenous infusion)

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Appendix I: Potential confusing name with single strength dose and multiple overlapping product characteristics

Lysteda (Ethinamate orally)	650 mg oral tablet	Usual dose: Two tablets by mouth three times daily during menstruation
Failure Mode: Name Confusion	Causes (could be multiple)	Rationale
<p>Lysodren (Mitotane) 500 mg oral tablet 2 grams to 19 grams orally per day divided in 3 to 4 doses, with treatment continuing as long as clinical benefits are observed.</p>	<p>Orthographic (Both begin with 'Lys', similar length) Frequency of administration (three times daily) Route of administration (oral) Dosage form (tablet) Both are single strength</p>	<p>Medication errors are unlikely due to the orthographic differences as well as differentiating product characteristics. Orthographically Lysteda contains a cross stroke 't' vs. no cross strokes in Lysodren, the 't' in Lysteda also provides another upstroke for a total of 3 upstrokes vs. 2 upstrokes in Lysodren. Lysteda has only one letter that follows the last upstroke 'd' vs. 3 letters which follow the last upstroke in Lysodren. The following characteristics will help differentiate between Lysteda and Lysodren; Lysteda is available in 650 mg strength while Lysodren is available in 500 mg. The typical dose of Lysodren is 9 grams to 10 grams per day or 4 to 6 tablets per dose vs. Lysteda, which is 2 tablets per dose. Lysodren is a chemotherapeutic agent. Per the package insert, it is highly recommended that therapy is initiated in the hospital, where the patient is titrated and then subsequently stabilized on a dose and then released from the hospital. Lysteda will be used on an outpatient basis and only taken by females. Additionally, Lysteda will be only be taken for 1 week per month vs. continual use of Lysodren for 3 months with continual follow up by an oncologist.</p>
<p>Tyzeka (Telbivudine) 600 mg oral tablets 600 mg by mouth once daily</p>	<p>Orthographic (both have 'y' as second letter, upstroke as second to last letter and both end in 'a') Route of administration (oral) Dosage form (tablet) Strength (both single strength)</p>	<p>Medication errors are unlikely due to the orthographic differences as well as differentiating product characteristics. Orthographically; Tyzeka begins with a 'T' which provides a cross-stroke vs. 'L' of Lysteda. The third letter of Tyzeka will either provide a downstroke or a cross-stroke, depending on how it is written vs. 's' of Lysteda. The fourth letter of Lysteda, 't' provides an up-stroke and a cross-stroke vs. 'e' of Tyzeka. Total up-strokes of Lysteda are three vs. two upstrokes in Tyzeka. The following characteristics will help differentiate between Lysteda and Tyzeka; The dose of Lysteda is two tablets vs. one tablet for Tyzeka. Lysteda is taken 3 times daily for a maximum of 5 days only during menstruation. Tyzeka is taken once daily, chronically. Tyzeka is used for long term treatment for Hepatitis B as with any anti-viral, patients must be compliant and take consistently every day to ensure that resistance does not occur. A 5 day supply of Tyzeka is extremely unlikely.</p>

Lysteda (Piroxicam acid)	650 mg modified release oral tablet	Usual dose: Two tablets by mouth three times daily during menstruation
Failure Mode: Name Confusion	Causes (could be multiple)	Rationale
<p>Lybrel (Ethinyl estradiol/ Levonorgestrel)</p> <p>20 mcg Ethinyl estradiol/0.09 mg levonorgestrel oral tablet</p> <p>One tablet one daily</p>	<p>Orthographic (both begin with 'Ly')</p> <p>Route of administration (oral)</p> <p>Dosage form (tablet)</p> <p>Strength (both single strength)</p> <p>Similar population (women of child-bearing age)</p>	<p>Medication errors are unlikely due to the orthographic differences differentiating product characteristics.</p> <p>Orthographically; Lysteda contains an 's' in between the downstroke 'y' and upstroke of 't' vs. nothing in between the downstroke 'y' and upstroke 'b'. Lybrel has two letters, 're' in between the two upstrokes of 'b' and 'l' vs. one letter, 'e' in between the up-strokes of 't' and 'd'. Lysteda ends with an 'a' that is preceded by the upstroke of 'd' vs. Lybrel ends with the up-stroke of 'l'.</p> <p>The following characteristics will help differentiate between Lysteda and Lybrel; Lysteda is taken 3 times daily for a maximum of 5 days vs. Lybrel is once daily for either 21 days or 28 days. Lysteda dose is two tablets vs. one tablet for Lybrel.</p>
<p>Lyricea (Pregabalin)</p> <p>25 mg, 50 mg, 75 mg, 100 mg, 150 mg, 200 mg, 225 mg, 300 mg oral capsule</p> <p>Starting dose: 150 mg/day in 2 to 3 divided doses. Maximum daily dose is 600 mg per day.</p>	<p>Orthographic (both begin w/ 'Ly', similar length)</p> <p>Route of administration (oral)</p> <p>Dosage form (tablet)</p> <p>Frequency (three times daily vs. two to three times daily)</p>	<p>Medication errors are unlikely due to the orthographic differences as well as differentiating product characteristics.</p> <p>Orthographically; Lysteda contains 3 upstrokes ('L', 't', 'd') vs. one upstroke 'L' in Lyricea. Lyricea contains one dotted 'i' vs. no dotted letters in Lysteda. Lysteda contains a cross-stroke provided by 't' vs. no cross-strokes in Lyricea.</p> <p>The following characteristics will help differentiate between Lysteda and Lyricea; Lyricea maximum strength per dose is 300 mg vs. dose of Lysteda is 1300 mg. Maximum daily dose of Lyricea is 600 mg vs. Lysteda is only available as a 650 mg tablet.</p>

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