CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 21-856

PROPRIETARY NAME REVIEW(S)

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Department of Health and Human Services
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Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Date:	December 5, 2008
To:	Bob Rappaport, MD Director, Division of Anesthesia, Analgesia, and Rheumatology Products
Thru:	Kellie Taylor, PharmD., MS, Team Leader Denise Toyer, PharmD., Deputy Director Carol Holquist, R.Ph., Director Division of Medication Error Prevention and Analysis
From:	Walter Fava, R.Ph., Safety Evaluator Division of Medication Error Prevention and Analysis
Subject:	Proprietary Name Review
Drug Name(s):	Uloric (febuxostat) tablets 40 mg and 80 mg
Application Type/Number:	NDA: 21-856
Applicant:	Takeda
OSE RCM #:	2008-1431

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EXECUTIVE SUMMARY

The results of the Proprietary Name Risk Assessment found that the proposed name, Uloric, is not vulnerable to name confusion that could lead to medication errors. Thus, the Division of Medication Error Prevention and Analysis does not object to the use of the proprietary name, Uloric, for this product. This is considered a final review, however, if approval is delayed beyond 90 days from the date of this review, the proprietary name should be resubmitted for re-review.

1 BACKGROUND

1.1 INTRODUCTION

This review was written in response to a request from the Division of Anesthesia, Analgesia, and Rheumatology Products, to evaluate the product for its potential to contribute to medication errors. The proposed name, Uloric, is evaluated to determine if the name could potentially be confused with other proprietary or established drug names. The proposed proprietary name, Uloric, was previously reviewed by DMEPA in 2004 (OSE Consult #: 04-0018) and in 2005 (OSE Consult # 04-0118-3) without objection. Container labels, carton and insert labeling were also provided to be evaluated from a medications errors perspective. Review comments will be provided under separate cover in a forthcoming review (OSE #: 2008-1936).

1.2 PRODUCT INFORMATION

Uloric (Febuxostat) is a non-purine selective inhibitor of xanthine oxidase (NP-SIXO) and is indicated for the treatment of hyperuricemia in patients with gout. The usual recommended adult dosage is 40 mg to 80 mg once a day. b(4)

Uloric will be available in 40 mg and 80 mg tablets.

2 METHODS AND MATERIALS

This section describes the methods and materials used by the Division of Medication Error Prevention and Analysis medication error staff 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. The Division of Medication Error Prevention and Analysis defines a medication error as any preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of the health care professional, patient, or consumer. [1]

2.1 PROPRIETARY NAME RISK ASSESSMENT

FDA's Proprietary Name Risk Assessment considers the potential for confusion between the proposed proprietary name, Uloric, 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, Uloric, the medication error staff of the Division of Medication Error Prevention and Analysis search a standard set of databases and information sources to identify names with orthographic and phonetic similarity (see Sections 2.1.1 for detail) and held an CDER Expert Panel discussion to gather professional opinions on the safety of the proposed proprietary name (see 2.1.1.2).

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

the Division of Medication Error Prevention also conducts internal CDER prescription analysis studies (see 2.1.2), and, when provided, external prescription analysis studies results are considered and incorporated into the overall risk assessment (see detail 2.1.4). In this case, an internal CDER prescription analysis study was conducted in OSE Review #: 04-0018, and was therefore not repeated for this review.

The Safety Evaluator assigned to the Proprietary Name Risk Assessment is responsible for considering the collective findings, and provides an overall risk assessment of the proposed proprietary name (see detail 2.1.4). The overall risk assessment is based on the findings of a Failure Modes and Effects Analysis (FMEA) of the proprietary name, and is focused on the avoidance of medication errors. FMEA is a systematic tool for evaluating a process and identifying where and how it might fail. [2] FMEA is used to analyze whether the drug names identified with look- or sound-alike similarity to the proposed name could cause confusion that subsequently leads to medication errors in the clinical setting. The Division of Medication Error Prevention and Analysis uses the clinical expertise of the medication error staff to anticipate the conditions of the clinical setting that the product is likely to be used in based on the characteristics of the proposed product.

In addition, the product characteristics provide the context for the verbal and written communication of the drug names and can interact with the orthographic and phonetic attributes of the names to increase the risk of confusion when there is overlap, or, in some instances, decrease the risk of confusion by helping to differentiate the products through dissimilarity. As such, the Staff consider the product characteristics associated with the proposed drug throughout the risk assessment, since the product characteristics of the proposed 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, the Division of Medication Error Prevention and Analysis considers the potential for confusion throughout the entire U.S. medication use process, including drug procurement, prescribing and ordering, dispensing, administration, and monitoring the impact of the medication.[3]

2.1.1 Search Criteria

The Medication Error Staff consider the spelling of the name, pronunciation of the name when spoken, and appearance of the name when scripted as outlined in Appendix A.

For this review, particular consideration was given to drug names beginning with the letter 'U' 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]

To identify drug names that may look similar to Uloric, the Staff also consider the other orthographic appearance of the name on lined and unlined orders. Specific attributes taken into consideration include the length of the name (6 letters), upstrokes (2, capital letter 'U' and lower case letter 'l'), downstrokes

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

[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

(none), cross-strokes (none), and dotted letters (one letter, 'i'). Additionally, several letters in Uloric may be vulnerable to ambiguity when scripted, including the letter 'U' which may appear as the letters 'V', 'W', 'Ci', 'Ce', 'Cl', 'A', or 'M', the lowercase letters 'b', or 'l', or the letter string 'ril'; the lower case letter 'o' may appear as a lower case 'a', or 'u'; and '-ric' may appear as '-rec', '-nic', '-nec', '-sic', '-sec', 'vic' or 'vec'. As such, the Staff also consider these alternate appearances when identifying drug names that may look similar to Uloric.

When searching to identify potential names that may look or sound similar to Uloric, the Medication Error Prevention and Analysis staff search for names with similar number of syllables (3), stresses (U-lor-IC or u-LOR-ic), and placement of vowel and consonant sounds. We also considered alternative pronunciations for the various portions of the name such as 'uh' instead of 'u' for the first syllable. The Applicant's intended pronunciation of the proprietary name could not be expressly taken into consideration, as this was not provided with the proposed name submission.

The Staff also consider the product characteristics associated with the proposed drug throughout the identification of similar drug names, since the product characteristics of the proposed drug ultimately determine the use of the product in the clinical practice setting. For this review, the Medication Error Prevention and Analysis staff were provided with the following information about the proposed product: the proposed proprietary name (Uloric), the established name (febuxostat), proposed indication (hyperuricemia), strength (40 mg, 80 mg), dose (one tablet daily), frequency of administration (daily), route (oral) and dosage form of the product (tablet). Appendix A provides a more detailed listing of the product characteristics the Medication Error Prevention and Analysis staff general take into consideration.

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

2.1.1.1 Database and Information Sources

The proposed proprietary name, Uloric, was provided to the medication error staff of the Division of Medication Error Prevention and Analysis to conduct a search of the internet, several standard published drug product reference texts, and FDA databases to identify existing and proposed drug names that may sound-alike or look-alike to Uloric using the criteria outlined in 2.1.1. A standard description of the databases used in the searches is provided in Section 7. To complement the process, the Division of Medication Error Prevention and Analysis 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 Division of Medication Error Prevention and Analysis staff review the United States Adopted Names (USAN) stem list to determine if any USAN stems are present within the proprietary name. The findings of the individual Safety Evaluators were then pooled and presented to the Expert Panel.

2.1.1.2 CDER Expert Panel Discussion

An Expert Panel Discussion is held by the Division of Medication Error Prevention and Analysis to gather CDER professional opinions on the safety of the product and the proprietary name, Uloric. Potential concerns regarding drug marketing and promotion related to the proposed names are also discussed. This group is composed of the Division of Medication Error Prevention and Analysis

(DMEPA) staff and representatives from the Division of Drug Marketing, Advertising, and Communications (DDMAC).

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

2.1.2 Safety Evaluator Risk Assessment of the Proposed Proprietary Name

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

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

In the initial stage of the Risk Assessment, the Safety Evaluator compares the proposed proprietary name to all of the names gathered from the above searches, expert panel evaluation, and studies, and identifies potential failure modes by asking: "Is the name Uloric convincing similar to another drug name, which may cause practitioners to become confused at any point in the usual practice setting?" An affirmative answer indicates a failure mode and represents a potential for Uloric 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.

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

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

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

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

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

Additionally, post-marketing experience has demonstrated that medication errors resulting from drug name confusion are notoriously difficult to remedy post-approval. Educational efforts and so on are low-leverage strategies that have proven to have limited effectiveness at alleviating the medication errors involving drug name confusion. Higher-leverage strategies, such as drug name changes, have been undertaken in the past; but at great financial cost to the 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 Applicants have changed a product's proprietary name in the post-approval phase, it is difficult to eradicate the original proprietary name from practitioner's vocabulary, and as such, the Agency has continued to receive reports of drug name confusion long after a

name change in some instances. Therefore, DMEPA believes that post-approval efforts at reducing name confusion errors should be reserved for those cases in which the potential for name confusion could not be predicted prior to approval (see limitations of the process).

If DMEPA objects to a proposed proprietary name on the basis that drug name confusion could lead to medication errors, the FMEA process is used to identify strategies to reduce the risk of medication errors. The Division of Medication Error Prevention and Analysis is likely to recommend that the Applicant select an alternative proprietary name and submit the alternate name to the Agency for DMEPA to review. However, in rare instances FMEA may identify plausible strategies that could reduce the risk of medication error of the currently proposed name, and so DMEPA may be able to provide the 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

This search identified 13 names as having some similarity to the name Uloric.

Eleven names were thought to look like Uloric, which include: Alocril, Urealac, Urocit-K, Aloxi, Urotrol, Valorin, Ultiva, Ulmus fulva, Ulran, Alrex, and Ulsanic. The remaining two names, Alora, and Zyloric, were thought to look and sound similar to Uloric. The proprietary name, Uloric, was also identified but was not included for evaluation since it is the trademark name for the same product in other countries.

Additionally, the Division of Medication Error Prevention and Analysis did not identify any United States Adopted Names (USAN) stems in the name Uloric, as of the last date searched on October 22, 2008.

3.1.2 Expert Panel Discussion

The Expert Panel reviewed the pool of names identified by the Division of Medication Error Prevention and Analysis staff (see section 3.1.1. above), and noted one additional name, Valproic acid, thought to have orthographic similarity to Uloric and have the potential for confusion. The Expert Panel also noted that despite orthographic similarity of the letter 'U' with the letter 'W'' in some handwriting samples, no names beginning with that letter were included in the pool. The Expert Panel recommended that independent searches consider the potential for confusion with drug names beginning with this letter.

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

3.1.3 Safety Evaluator Risk Assessment

Independent searches by the primary Safety Evaluator identified three additional names, Utira, Utira-C, and Celexa, thought to look similar to Uloric and represent a potential source of drug name confusion. Careful evaluation was afforded to drug names beginning with the letter 'W' in accordance with the Expert Panel's recommendations.

Because the product characteristics of Uloric have changed since the previous review (the withdrawal of the 120 mg tablet strength and the addition of the 40 mg tablet strength) the 17 names identified from the previous reviews 04-0118 and 04-0118-3, were re-evaluated. These names include Lasix, Mobic, ULR-LA, ULO, and U-lactin, Klotrix, Allerx, Vioxx, Artane, Sular, Coreg, Luvox, Luride, Clinoril, Lorcet-HD, Ultram, and Alorin. As such, a total of 34 proprietary names were analyzed to determine if the drug names could be confused with Uloric 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 Uloric, and thus determined to present some risk for confusion. Failure modes and effects analysis (FMEA) was then applied to determine if the proposed name, Uloric, could potentially be confused with any of the 34 names and lead to medication errors. This analysis determined that the name similarity between Uloric and the identified names was unlikely to result in medication errors for all 34 products identified (see Appendices B through G).

4 DISCUSSION

4.1 PROPRIETARY NAME

We evaluated 13 names for their similarity to the proposed name, Uloric. The FMEA indicates that the proposed name is not vulnerable to name confusion that could lead to medication errors. The findings of the Proprietary Name Risk Assessment are based upon current understanding of factors that contribute to medication errors involving name confusion. Although we believe the findings of the Risk Assessment to be robust, our findings do have limitations. First, because our assessment involves a limited number of practitoners, it is possible that the analysis did not identify a potentially confusing name. Also, there is some possibility that our Risk Assessment failed to consider a circumstance in which confusion could arise. However, the Division of Medication Error Prevention and Analysis believes that these limitations are sufficiently minimized by the use of an Expert Panel, the CDER Prescription Studies that involved 123 CDER practitioners, and, in this case, the data submitted by the Applicant from an independent proprietary name risk assessment firm, which included the responses of frontline practitioners.

However, our risk assessment also faces limitations beyond the control of the Agency. First, our risk assessment is based on current health care practices and drug product characteristics. future changes to either could increase the vulnerability of the proposed name to confusion. Since these changes cannot be predicted for or accounted by the current Proprietary Name Risk Assessment process, such changes limit our findings. To help counterbalance this impact, the Division of Medication Error Prevention and Analysis recommends that the proprietary name be re-submitted for review if approval of the product is delayed beyond 90 days.

5 CONCLUSIONS

The Proprietary Name Risk Assessment findings indicate that the proposed name, Uloric, is not vulnerable to name confusion that could lead to medication errors. As such, the Division of Medication Error Prevention and Analysis does not object to the use of the proprietary name, Uloric, for this product. However, 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. Additionally, if the product approval is delayed beyond 90 day from the date of this review, the proposed name must be resubmitted for evaluation.

6 RECOMMENDATIONS

6.1 COMMENTS TO THE DIVISION

We would appreciate feedback on the final outcome of this review. We would be willing to meet with the Division for further discussion, if needed. Please copy us on any communication to the Applicant with regard to this review. If you have further questions or need clarifications, please contact Chris Wheeler, at 301-796-0558.

6.2 COMMENTS TO THE APPLICANT

6.2.1 Proprietary Name

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

Uloric will be re-reviewed 90 days prior to approval of the NDA. If we find the name unacceptable following 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.

7 REFERENCES

1. ***OSE Reviews 04-0118 and 04-0118-3.*** *July 5, 2004 and May 15, 2006, respectively.*

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

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

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

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

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

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

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

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

6. ***Division of Medication Errors Prevention and Analysis proprietary name consultation requests***

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

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

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

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

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

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

Provides information regarding patent and trademarks.

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

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

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

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

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

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

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

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

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

List contains all the recognized USAN stems.

15. Red Book Pharmacy's Fundamental Reference

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

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

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

17. Medical Abbreviations Book

Contains commonly used medical abbreviations and their definitions.

APPENDICES

Appendix A:

The Medication Error Staff consider the spelling of the name, pronunciation of the name when spoken, and appearance of the name when scripted. The Division of Medication Error Prevention and Analysis also compare the spelling of the proposed proprietary name with the proprietary and established name of existing and proposed drug products because similarly spelled names may have greater likelihood to sound similar to one another when spoken or look similar to one another when scripted. The Medication Error Staff also examine the orthographic appearance of the proposed name using a number of different handwriting samples. Handwritten communication of drug names has a long-standing association with drug name confusion. Handwriting can cause similarly *and* dissimilarly spelled drug name pairs to appear very similar to one another and the similar appearance of drug names when scripted has lead to medication errors. The Medication Error Staff apply their expertise gained from root-cause analysis of such medication errors to identify sources of ambiguity within the name that could be introduced when scripting (i.e. "T" may look like "F," lower case 'a' looks like a lower case 'u,' etc), along with other orthographic attributes that determine the overall appearance of the drug name when scripted (see detail in Table 1 below). Additionally, since verbal communication of medication names is common in clinical settings, the Medication Error Staff compare the pronunciation of the proposed proprietary name with the pronunciation of other drug names. If provided, the Division of Medication Error Prevention 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, the Division of Medication Error Prevention and Analysis also considers a variety of pronunciations that could occur in the English language.

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

Type of similarity	Considerations when searching the databases		
	Potential causes of drug name similarity	Attributes examined to identify similar drug names	Potential Effects
Look-alike	Similar spelling	Identical prefix Identical infix Identical suffix Length of the name Overlapping product characteristics	• Names may appear similar in print or electronic media and lead to drug name confusion in printed or electronic communication • Names may look similar when scripted and lead to drug name confusion in written communication
	Orthographic similarity	Similar spelling Length of the name Upstrokes Downstrokes	• Names may look similar when scripted, and lead to drug name confusion in written communication

		Cross-strokes Dotted letters Ambiguity introduced by scripting letters Overlapping product characteristics	
Sound-alike	Phonetic similarity	Identical prefix Identical infix Identical suffix Number of syllables Stresses Placement of vowel sounds Placement of consonant sounds Overlapping product characteristics	• Names may sound similar when pronounced and lead to drug name confusion in verbal communication

Appendix B: Proprietary names with overlapping numerical strength or dose but lack orthographic similarity to contribute to confusion that may lead to medication errors

Proprietary Name	**Strength, Dosage form, Route of Administration**	**Usual Adult Dose**
Uloric	40 mg and 80 mg tablets oral	40 mg to 80 mg by mouth once a day
Klotrix	10 mEq extended-release tablets	20 mEq to 120 mEq by mouth once a day (40 mEq or 80 mEq by mouth daily may be prescribed)

Appendix C: Proprietary names with orthographic similarity to Uloric but no overlapping product characteristics

Proprietary Name	Strength, Dosage form, Route of Administration	Frequency of Administration
Uloric	40 mg and 80 mg tablets oral	Once a day
Alocril	2% ophthalmic suspension ocular	Twice a day
Alrex	0.2% ophthalmic suspension ocular	Four times a day
Urealac	35% lotion 50% ointment, suspension, gel, and cream topical	Twice a day
Alora	0.025 mg/24 hrs, 0.05 mg/24 hrs, 0.075 mg/24 hrs, 0.1 mg/24 hrs transdermal patch topical	Twice a week
Ultiva	1 mg, 2 mg, 5 mg injectable intravenous	Continuous IV infusion during general anesthesia

Appendix D: Foreign proprietary names with similar orthographic characteristics with Uloric

Proprietary Name (established name)	Country	Similarity to Uloric
Ulsanic (sucralfate)	Israel	Look-alike
Zyloric (allopurinol)	United Kingdom	Look-alike
Ulran (ranitidine)	Phillipines	Look-alike
Urotrol (oxybutynin)	Spain	Look-alike
Alorin (loratidine)	Italy	Look-alike

Appendix E: Proprietary names for over-the-counter and natural medicines with no overlapping strength or dose

Proprietary Name (established name)	**Strength/Dosage Form**	**Usual adult dose**
Uloric (febuxostat)	**40 mg and 80 mg tablets**	**40 mg to 80 mg by mouth once a day**
Valorin (acetaminophen)	325 mg tablets	1 – 2 tablets by mouth every 6 hours as needed for pain/fever
Ulmus fulva (slippery elm)	Powder (no strength)	4 grams in 500 mL boiling water three times a day as a nutritional supplement

Appendix F: Proprietary names for drug products with orthographic similarity to Uloric no longer manufactured

Proprietary Name (established name) dosage form	**Status**
Utira extended-release tablets (Hyoscyamine Sulfate Methenamine Phenyl Salicylate Sodium Phosphate Monobasic Methylene Blue)	Discontinued
ULR-LA sustained Action Tablets (Guaifenesin, Phenylpropanolamine)	Discontinued
ULO Syrup, Injection, Lozenge (Chlophedianol)	[redacted]
Vioxx (Rofecoxib)	Discontinued
Sular extended-release tablets (Nisoldipine) 10 mg, 20 mg, 30 mg, and 40 mg	Discontinued No generic equivalent available

b(4)

Appendix G: Proprietary names for prescription drugs with orthographic similarity to Uloric with no overlap in strength or dose

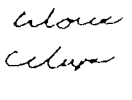
Product name with potential for confusion	**Similarity to Proposed Proprietary Name**	**Strength/Dosage Form**	**Usual Dose (if applicable)**
Uloric **(febuxostat)**		**40 mg and 80 mg tablets**	**40 mg to 80 mg once a day**
Utira-C (Hyoscyamine Sulfate Methenamine	Look-alike	 0.12mg 81.6 mg	1 tablet by mouth four times a day

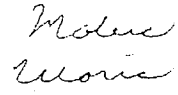
Phenyl Salicylate Sodium Phosphate Monobasic Methylene Blue)		36.2 mg 40.8 mg 10.8 mg	
Aloxi (palonosetron hydrochloride)	Look-alike	0.5 mg capsules injectable 0.075 mg/5 mL 0.25 mg/5 mL	0.5 mg by mouth one hour prior to chemotherapy 0.25 mg infused intravenously over 30 minutes before the start of chemotherapy
Valproic acid	Look-alike	250 mg and 500 mg capsules	1 capsule by mouth twice a day
Allerx (Chlorpheniramine, Pseudoephedrine and Methscopolamine)	Look-alike/Sound-alike	Dose Pack: AM Dose: 120 mg Pseudoephedrine and 2.5 mg methscopoloamine nitrate PM Dose: 8 mg chlorpheniramine and 2.5 mg methscopoloamine	One yellow tablet in the morning One blue tablet in the evening
Luvox (Fluvoxamine)	Look-alike	25 mg, 50 mg, 100 mg and 150 mg tablets	50 mg to 300 mg maximum daily dose. Doses over 100 mg should be given in two divided doses.
Luride (Sodium Fluoride)	Sound-alike	Drops: 0.125 mg/drop (0.5 mg/mL) Gel: 0.1%, 0.5%, 1.23% Gel Drops: 0.5% Rinse: 0.09% Tablets: 1 mg Chewable Tablets: 0.25 mg, 0.5 mg, and 1 mg	0.25 mg daily to 1 mg daily 5 mL to 10 mL daily (Rinse)
Coreg (Carvedilol)	Sound-alike	3.125 mg, 6.25 mg, 12.5 mg, and 25 mg tablets	Hypertension: Individualized 6.25 mg to a maximum of 25 mg by mouth twice a day. Heart Failure: Individualized 3.125 mg initially to a maximum dose for patients <85 kg is 25 mg by mouth twice a day. For patients >85 kg the dose is 50 mg by mouth twice a day.
Clinoril (sulindac)	Look-alike	150 mg and 200 mg tablets	150 mg to 200 mg by mouth twice a day
Lorcet-HD	Look-alike/Sound-	500 mg/5 mg capsules	Take one to two capsules by mouth every 4 to 6 hours as needed for pain

(Acetaminophen/Hydrocodone)	alike		not to exceed 4 grams of acetaminophen per day.
Ultram (Tramadol)	Look-alike/Sound-alike	50 mg tablets	50 mg to 100 mg by mouth every 4 to 6 hours. Maximum of 400 mg per day.
Artane (Trihexyphenidyl) Available as generic only	Look-alike	Extended-release Capsule: 5 mg Elixir: 2 mg/5 mL Tablets: 2 mg and 5 mg	1 mg to 15 mg divided three to four times a day with meals and last dose at bedtime.
U-Lactin (Lactic acid 2%/Urea 10%)	Look-like	Topical emollient	As needed

Appendix H: Proprietary names for prescription drugs with orthographic similarity to Uloric with numerical overlap in dose and/or strength

Uloric **(febuxostat)**	**40 mg and 80 mg tablets**	**Usual adult dose: 40 mg to 80 mg by mouth once a day**
Failure Mode: **Orthographic name confusion and overlapping product characteristics**	**Causes (could be multiple)**	**Effect**
Urocit-K (potassium citrate)	Orthographic similarities when scripted. Beginning letters of Urocit-K, 'Uro', may look similar to beginning letters of Uloric, 'Ulo' Urocit Uloric Potential numerical overlap in daily dose: Urocit-K is available as 5 mEq and 10 mEq extended-release tablets but the usual dose is 40 mEq to 80 mEq/day, which has numerical overlap with the usual daily dose range of Uloric: 40 mg to 80 mg per day.	Despite the orthographic similarity between the names when scripted, there are orthographic differences which minimize the potential that could lead to medication errors. *Rationale:* The ending portion of Urocit-K, 'cit-K' looks different from the ending portion of Uloric, 'ric'. Even if the '-K' is omitted from Urocit-K, the letter string 'cit' with the crossed letter at the end appears very different from the letter string 'ric'. Additionally, potential confusion caused by the numerical overlap in the daily dose is minimized by the different units of measure between the products:

		milligrams vs milliequivalents. It is also likely that prescribers will order Urocit-K by its product strength, either 5 mEq or 10 mEq, and indicate the number of tablets to take each day rather than indicating the daily dose (40 mEq or 80 mEq), which the patient may not clearly understand to achieve based on the strength of the product.
Celexa (citalopram)	Orthographic similarity between the names when scripted. Both names contain six letters making them appear similar in length when scripted, and the beginning three letters of Celexa, 'Cel', may look similar to the first two letters of Uloric, 'Ul' when scripted.  Product strength overlap: Uloric 40 mg vs Celexa 40 mg Overlapping usual adult doses: 40 mg or 80 mg per day Overlapping dosage forms: tablets	Despite some orthographic similarites between the names when scripted, the orthographic differences minimize the potential for look-alike confusion that could lead to medication errors. *Rationale:* The letter string, 'oric' in Uloric appears quite dissimilar from the corresponding letter string 'exa' when scripted. Additionally, the letter 'C' in Celexa would need to be scripted as a very open letter with no curve on the top to closely resemble the letter 'u' when scripted. Other differences include the dotted letter 'i' in Uloric which Celexa does not have, and the crossed letter 'x' in Celexa which Uloric does not have. These orthographic differences minimize the potential for confusion despite overlapping strengths, dosages, and dosage forms between these two products.
Lasix (Furosemide)	Orthographic similarity when scripted 	Despite some orthographic similarites between these two proprietary names, the orthographic differences will minimize the potential for confusion that may contribute to medication errors in the usual

	Overlapping strength/dose: 40 mg to 80 mg daily	practice setting. *Rationale:* Although the letter 'u' in Uloric may be scripted similarly to the letter 'l' in Lasix, the remaining portions of the names look different when scripted. The upstroke letter 'l' in Uloric is in a different position in the name 'Lasix'. The letters 'Las' in Lasix may appear similar to the letters 'lor' in Uloric, but the preceding letter 'u' helps to distinguish this letter string since no letters precede the letter 'l' in Lasix. Additionally, the crossed letter 'x' at the end of Lasix appears quite different from the letter 'c' at the end of Uloric. These orthographic differences will help to minimize the potential for confusion caused by the overlapping strengths and doses between the two products.
Mobic (Meloxicam)	Orthographic similarity when scripted 	Despite some orthographic similarities between the names, the orthographic differences and different product characteristics will help to minimize the potential for confusion between the names in the usual practice setting. *Rationale:* The beginning letters 'U' and 'M' may appear similar when scripted and both names end in the same two letters, 'ic'. However, the letters 'ob' in Mobic are positioned so that the upstroke letter 'b' appears in the middle of the name compared to the upstroke letter 'l' in Uloric which appears at the beginning of the name. Additionally, Mobic does not have any overlapping strengths or doses with Uloric (7.5 mg and 15 mg

		tablets; 7.5 mg/5 mL oral suspension versus 40 mg and 80 mg tablets).

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/s/

Walter Fava
12/5/2008 12:19:37 PM
DRUG SAFETY OFFICE REVIEWER

Kellie Taylor
12/5/2008 04:32:59 PM
DRUG SAFETY OFFICE REVIEWER

Denise Toyer
12/5/2008 05:15:07 PM
DRUG SAFETY OFFICE REVIEWER

Carol Holquist
12/5/2008 05:15:53 PM
DRUG SAFETY OFFICE REVIEWER

MEMORANDUM

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

To: Bob Rappaport, MD
Director, Division of Anesthesia, Analgesia, and Rheumatology Products, HFD-170

From: Tina M. Tezky, PharmD, Safety Evaluator
Division of Medication Errors and Technical Support, HFD-420

6/2/2006

Through: Alina R. Mahmud, RPh, MS, Team Leader
Denise Toyer, PharmD, Deputy Director
Carol Holquist, RPh, Director
Division of Medication Errors and Technical Support, HFD-420

Date: May 15, 2006

Re: ODS Consult #04-0118-3; Uloric (febuxostat) tablets; NDA 21-856

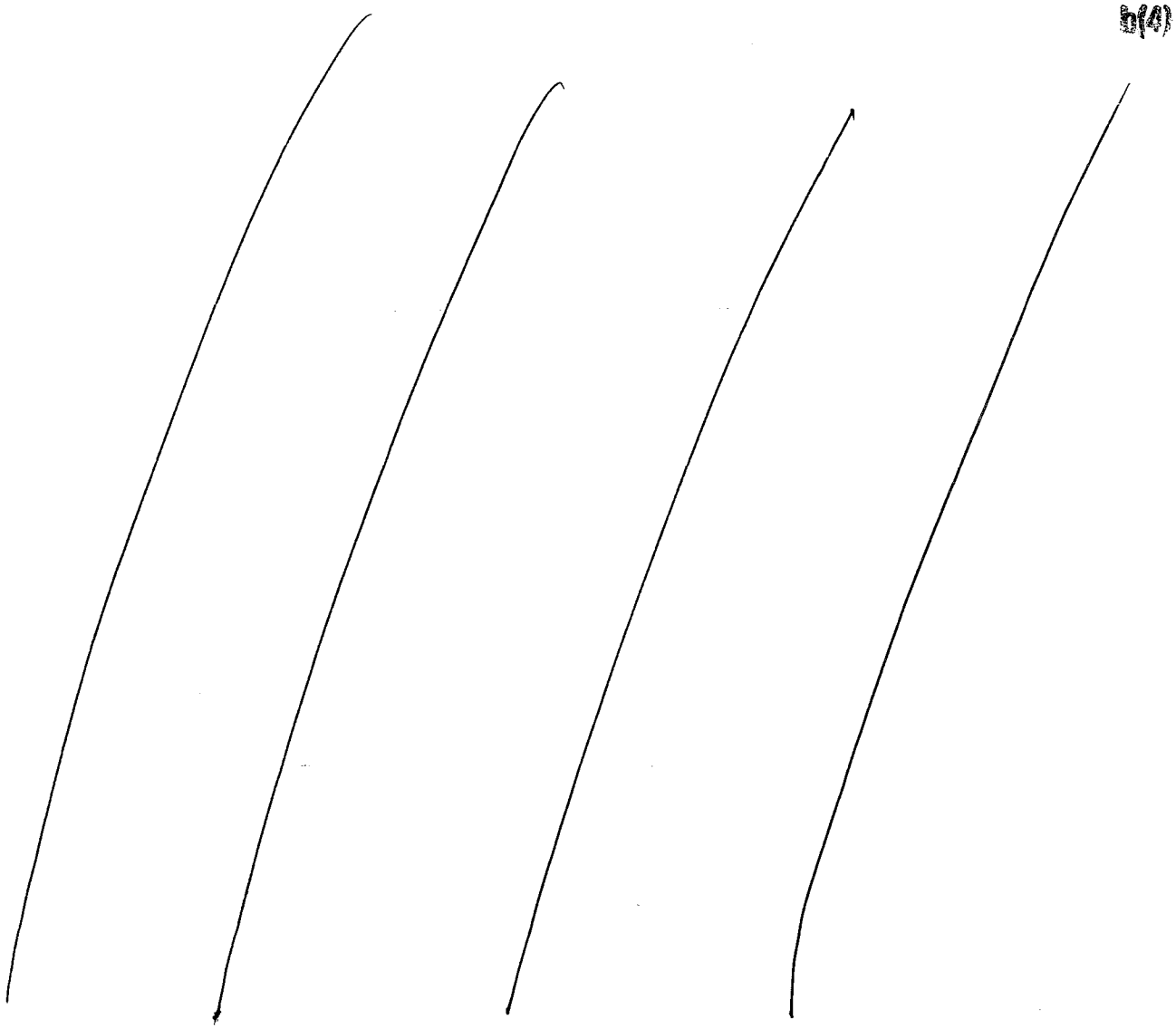
This memorandum is in response to the April 20, 2006 request from your Division for a re-review of the proprietary name, Uloric. The proposed proprietary name was previously found acceptable by the Division of Medication Errors and Technical Support (DMETS) on February 25, 2005 (ODS consult 04-0118). Additionally, DMETS provided label and labeling comments in our review dated February 25, 2005. The sponsor has submitted revised container labels, carton and package insert labeling for review and comment.

Since we conducted our previous review, DMETS has identified one additional proprietary name, Alorin which has the potential for look-alike confusion with Uloric. Alorin is a foreign (Italy) tradename for loratidine, an antihistamine agent indicated for the treatment of allergic rhinitis and chronic idiopathic urticaria. Alorin is available in the foreign market as 10 mg tablets, 10 mg effervescent tablets, and 1 mg/mL oral solution and the recommended dose is 10 mg daily as needed. Additional information related to this tradename is difficult to obtain, since it is not available in the U.S. The two names are identical, aside from the first and last letters (ALORIN vs. ULORIC). Additionally, the first letters (A- vs. U-) and last letters (-N vs. -C) can look similar when scripted (see sample below). With the available information, the two products have some overlapping product characteristics such as dosage form (tablet), route of administration (oral), and frequency of administration (once daily). However, they differ with respect to available strengths (80 mg, 120 mg vs. 10 mg, 1 mg/mL). The fact that both products are available in multiple strengths, dosage forms, and are in different areas of marketing will help minimize the potential for confusion between the two names.

Additionally, DMETS reviewed the container labels, carton and insert labeling of Uloric from a safety perspective. DMETS has identified the following areas of possible improvement, which might minimize potential user error.

A. GENERAL COMMENTS

b(4)



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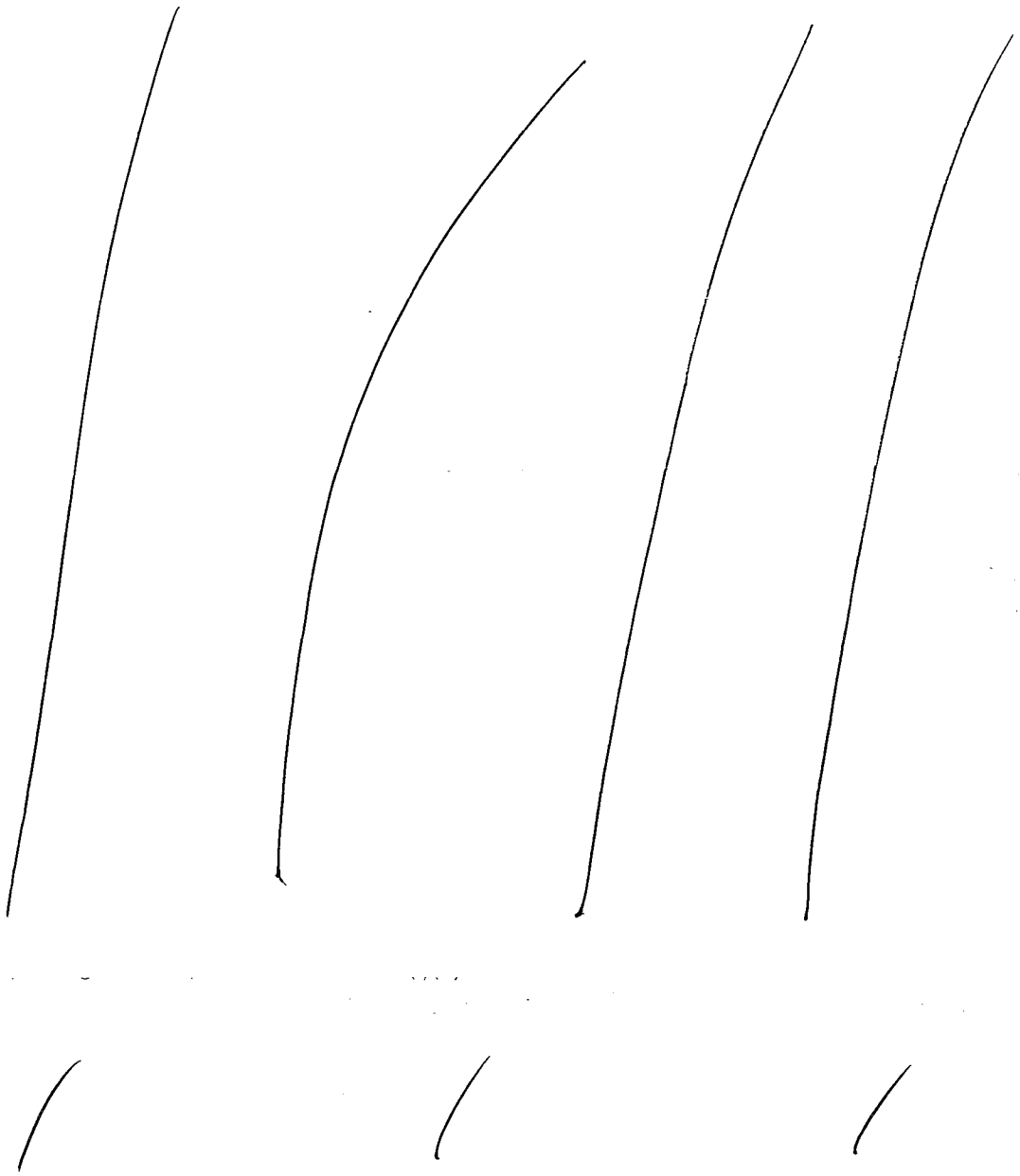
✓ Trade Secret / Confidential (b4)

_____ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

b(4)



In summary, DMETS does not have any objections to the use of the proprietary name Uloric. Additionally, DDMAC finds the proprietary name Uloric acceptable from a promotional perspective. DMETS recommends implementation of the label and labeling revisions outlined above. DMETS considers this a final review. However, if the 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. If you have any questions or need clarification, please contact Diane Smith at 301-796-0538.

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/s/

Tina Tezky
6/1/2006 04:11:32 PM
DRUG SAFETY OFFICE REVIEWER

Alina Mahmud
6/1/2006 04:51:47 PM
DRUG SAFETY OFFICE REVIEWER

Denise Toyer
6/2/2006 02:38:05 PM
DRUG SAFETY OFFICE REVIEWER

Carol Holquist
6/2/2006 03:59:21 PM
DRUG SAFETY OFFICE REVIEWER

2/25/05

Office of Drug Safety

MEMO

To: Brian Harvey, M.D., Ph.D.
Director, Division of Anti-Inflammatory, Analgesic, and Ophthalmologic Drug Products HFD-550

From: Denise P. Toyer, Pharm.D. Deputy Director
Carol Holquist, R.Ph., Director
Division of Medication Errors and Technical Support, HFD-420

cc: Jane Dean, Project Manager
Division of Anti-Inflammatory, Analgesic, and Ophthalmologic Drug Products HFD-550

Date: January 11, 2005

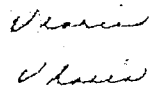
Re: ODS Consult 04-0118; Uloric 80 mg and 120 mg (Febuxostat Tablets) IND 58,229

This memorandum is written in response to the attached DMETS Proprietary Name Review conducted on Uloric for the Division of Reproductive and Urologic Drug Products (HFD-580). We have reviewed the safety evaluator's comments and disagree with the final conclusion. The review found that the proposed proprietary name was unacceptable due to the potential for confusion with Lasix. Specifically, the written review states:

> "Both names contain letters that look similar when scripted (lasix and loric). DMETS agrees with b(4) analysis that the "U" of Uloric may be misinterpreted as a check mark if the 'U' were separated from the rest of the letters, and if the name Uloric were included in a list of orders on an inpatient order sheet…An inpatient setting is the most likely location where this particular type of error might occur. Of particular concern is in a hospital that uses multi-part carbon-less order sheets."

Following discussion with the safety evaluator, the concerns surround the fact that the preceding letter 'U' in the name (Uloric) can look similar to a check mark "√" when scripted especially if the letter 'U' is separated from the rest of the letters of the name. The reviewer believes the potential for confusion will only occur in the pharmacy and not on the nursing unit. The order sheet is then sent to the pharmacy where the letter 'U' of the prescribed 'Uloric…' order is misinterpreted as '√ Lasix….' Thus, Lasix would be dispensed instead of Uloric. Although, not noted in the reviewer's written review, she indicated verbally that the potential for confusion could also result in an order for Lasix being misinterpreted as Uloric. Once a Lasix order is charted on the Medication Administration Record (MAR), the ward clerk/nurse etc may place a '√' (check mark) next to the medication. This serves as verification that the ward clerk has charted the order. A carbonless order sheet is then sent to the pharmacy. This may result in the '√' being interpreted as the letter 'U' leading the pharmacist to dispense Uloric rather than Lasix. Thus, the reviewer feels that under the aforementioned conditions there is a potential for Uloric to be dispensed as Lasix and for Lasix to be dispensed as Uloric.

We agree there is some similarity in the appearance of the names, Uloric and Lasix. The names are similar in length (six vs. five letters) and there are no upstroke or downstroke letters in the last five letters of each name, which contributes to the orthographic similarity. Additionally, there are product characteristics that overlap such as strength (80 mg), dose (80 mg and 120 mg), dosing interval (daily), and route of administration (oral). Moreover, the first letter 'U' of Uloric may be written separate from the remaining letters (loric) of the name (see below).



Despite some similarity in the appearance of the names and overlapping product characteristics, we believe that Uloric and Lasix can safely coexist in the marketplace for the following reasons.

- Although the reviewer specifically mentions the letter 'U' being misinterpreted as a check mark (or vice versa), we note that other stray marks may commonly appear on carbonless order sheets that are sent to the pharmacy. Any of these unintentional marks could interfere with the interpretation of any order. Thus, an unintentional consequence of using carbonless order sheets is the potential for stray marks to hinder or impede interpretation of pharmacy orders. Pharmacy personnel are cognizant that these stray marks, [e.g., '√' (check marks)] may affect the interpretation of any order and therefore routinely attempt to elucidate medical orders (pharmacy, laboratory, etc) from stray marks.

- We note that the Joint Commission for Accreditation of Hospitals (JCAHO), 2005 Hospitals National Patient Safety Goals includes the goal: Improve the effectiveness of communication among caregivers. A requirement to meet this goal is that each hospital must 'Standardize a list of abbreviations, acronyms and symbols that are not to be used throughout the organization.'[1] Other healthcare organizations have published articles on symbols that can lead to medication errors. For example, the Institute for Safe Medication Practices (ISMP) has published recommendations in their Medication Safety Alert pertaining to the use of check marks and transcribing of orders. With JCAHO's National Patient Safety Goals, ISMP's alerts, and other healthcare organizations drawing attention to these types of medication errors, healthcare practitioners (i.e., pharmacy personnel) are more aware of the potential for stray marks on an order to be misinterpreted resulting in a medication error. This awareness should help to minimize the potential for confusion to occur.

- The person (e.g., RN, LPN, Unit/Ward Clerk, Unit Secretary) initially transcribing the prescriber's order to the MAR is unlikely to misinterpret the letter 'U' as a 'check mark' since they can see the original order, and not a copy. Additionally, they would question why a physician would write an order that translates to "Check Lasix XX mg po QD". Moreover, if the transcriber makes a check mark on the original order they are likely to notice that the check mark has changed the appearance of the drug orders when they remove the copy from the chart before sending it to the pharmacy.

[1] http://www.jcaho.org/accredited+organizations/patient+safety/05+npsg/05_npsg_hap.htm

- In most facilities, orders are routinely removed from the chart and placed in the pharmacy outbox or transmitted to the pharmacy before they are transcribed to the Medication Administration Record (MAR). This procedure prevents the delay of medication delivery to the nursing unit (i.e., order transcribed then sent to pharmacy vs. order sent to pharmacy then transcribed). Thus, the Unit/Ward Clerk, etc is unlikely to "check-off" the order prior to the carbonless order being removed from the chart. This decreases the opportunity for a '√' check mark to be placed in front of a Lasix order resulting in the misinterpretation of the order as the proprietary name Uloric.

- In the inpatient setting many facilities use Computerized Physician Order Entry. Prescriptions entered via the computer would minimize any potential confusion with check marks.

- In the event the pharmacy believes that the beginning letter 'U' is a check mark, the pharmacy personnel would likely check to see if other orders written at the same time have check marks, thus potentially verifying their interpretation.

- The current recommendation is that Uloric treatment be initiated with a non-steroidal anti-inflammatory drug (NSAID) or colchicine [redacted] to prevent the onset of an acute gouty attack. Thus, the presence of an NSAID or colchicine order may also help the pharmacy differentiate an Uloric order from a Lasix order. b(4)

- The maximum single oral dose of Lasix is generally 80 mg per day, decreasing the potential for overlap at the 120 mg dosing level. Moreover, the most common dose of Lasix is 40 mg daily or two times a day. Doses in excess of 40 mg two times a day are generally written for short time periods (e.g., one time, for 4 doses, etc). b(4)

- [redacted] indicated that there could be slight look-alike similarity between Uloric and Lasix if the 'U' in Uloric was mistaken as a number or as a check mark on an order. However [redacted] conclusion was that the proprietary name, Uloric, could be considered for use with a medical product.

Based on the aforementioned reasons, we feel that the potential for name confusion between Uloric and Lasix is minimal and that these two agents can safely co-exist in the marketplace together. Therefore, DMETS has no objections to the use of the proposed name, Uloric. Please see the attached review for DMETS' label and labeling comments and for DDMAC comments.

CONSULTATION RESPONSE

DIVISION OF MEDICATION ERRORS AND TECHNICAL SUPPORT
OFFICE OF DRUG SAFETY
(DMETS; HFD-420)

DATE RECEIVED:	**DESIRED COMPLETION DATE:**	**ODS CONSULT #:** 04-0118
April 26, 2004	June 26, 2004	

TO: Brian Harvey, MD, PhD.
Acting Director, Division of Anti-Inflammatory, Analgesic, and Ophthalmologic Drug Products
HFD-550

THROUGH: Jane Dean
Project Manager
HFD-550

PRODUCT NAME:	**IND SPONSOR:** Tap Pharmaceuticals
Uloric (Febuxostat Tablets) 80 mg and 120 mg **IND#: 58,229**	

SAFETY EVALUATOR: Linda M. Wisniewski, RN

RECOMMENDATIONS:

1. DMETS does not recommend use of the proprietary name, Uloric.

2. DDMAC finds the proprietary name Uloric acceptable from a promotional perspective.

3. DMETS recommends submitting labels and labeling when available for review and comment.

Denise Toyer, PharmD
Deputy Director
Division of Medication Errors and Technical Support
Office of Drug Safety
Phone: (301) 827-3242

Carol Holquist, RPh
Director
Division of Medication Errors and Technical Support
Office of Drug Safety
Phone: (301) 827-3242 Fax: (301) 443-9664

Division of Medication Errors and Technical Support (DMETS)
Office of Drug Safety
HFD-420; PKLN Rm. 6-34
Center for Drug Evaluation and Research

PROPRIETARY NAME REVIEW

DATE OF REVIEW: July 5, 2004

IND#: 58,229

NAME OF DRUG: **Uloric** (Febuxostat Tablets) 80 mg and 120 mg

IND HOLDER: Tap Pharmaceuticals

I. INTRODUCTION:

This consult was written in response to a request from the Division of Anti-Inflammatory Analgesic and Ophthalmologic Drug Products (HFD-550), for assessment of the proprietary name "Uloric", regarding potential name confusion with other proprietary or established drug names. Draft container labels and carton labeling were not provided for review and comment. However, draft insert labeling was provided.

PRODUCT INFORMATION

Uloric is a non-purine, selective inhibitor of xanthine oxidase/dehydrogenase. The proposed indication is for the management of hyperuricemia in patients with gout. Uloric will be dosed as 80 mg or 120 mg taken orally as a single dose, once daily, in order to maintain serum uric acid below 6 mg/dL. Doses can be given without regard to timing of meals. In order to reduce the possibility of an acute gouty attack, it is recommended that febuxostat therapy begin with a concomitant low dose of either a non-steroidal anti-inflammatory drug (NSAID) or colchicine ——————. It is supplied in 80 mg and 120 mg tablets, each packaged in bottles of 30 and 90 tablets. It should be protected from light and stored at 25°C (77°F). b(4)

II. RISK ASSESSMENT:

The medication error staff of DMETS conducted a search of several standard published drug product reference texts[2,3] as well as several FDA databases[4] for existing drug names which sound-alike or look-alike to Uloric 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[5]. The Saegis[6] 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

[2] MICROMEDEX Integrated Index, 2004, MICROMEDEX, Inc., 6200 South Syracuse Way, Suite 300, Englewood, Colorado 80111-4740, which includes all products/databases within ChemKnowledge, DrugKnowledge, and RegsKnowledge Systems.
[3] Facts and Comparisons, online version, Facts and Comparisons, St. Louis, MO.
[4] AMF Decision Support System [DSS], the Division of Medication Errors and Technical Support [DMETS] database of Proprietary name consultation requests, Drugs@fda, and the electronic online version of the FDA Orange Book.
[5] WWW location http://www.uspto.gov/tmdb/index.html.
5-Data provided by Thomson & Thomson's SAEGIS ™ Online Service, available at www.thomson-thomson.com

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.

A. EXPERT PANEL DISCUSSION (EPD)

An Expert Panel discussion was held by DMETS to gather professional opinions on the safety of the proprietary name Uloric. 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 and 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 name Uloric acceptable from a promotional perspective.
2. The Expert Panel identified Alora and Mobic, as having potential for confusion with Uloric. These products are listed in Table 1 (see below), along with the dosage forms available and usual dosage.
3. Independent review identified ULR-LA, ULO, and U-Lactin as having potential orthographic similarity to Uloric. These products are listed in Table 1 (see below), along with the dosage forms available and usual dosage.

Table 1: Potential Sound-Alike/Look-Alike Names Identified by DMETS Expert Panel and through Independent Review

Product Name	**Dosage form(s), Established name**	**Usual adult dose***	**Other****
Uloric	Febuxostat 80 mg and 120 mg tablets	80 mg or 120 mg daily	N/A
Alora	Estradiol Extended Release Transdermal Film 0.025 mg/24 hr, 0.05 mg/24 hr, 0.075 mg/24 hr, 0.1 mg/24 hr	Administer twice weekly as instructed.	SA/LA
Mobic	Meloxicam Tablets: 7.5 mg and 15 mg Oral Suspension 7.5 mg/5 mL	7.5 mg to 15 mg once daily.	LA
ULR-LA***	Guaifenesin with Phenylpropanolamine (PPA) Sustained Action Tablets	As directed. Removed from market November 2000, secondary to safety of PPA.	SA/LA
ULO	Chlophedianol Syrup, Injection, Lozenge	No information available. [redacted]	SA
U-Lactin	Emollients Lotion	As needed.	LA

*Frequently used, not all-inclusive.
**L/A (look-alike), S/A (sound-alike)
*** No longer marketed.

b(4)

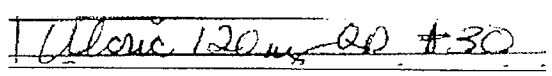
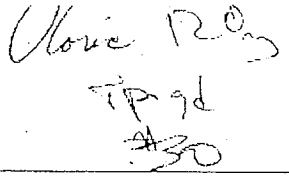
B. PHONETIC and ORTHOGRAPHIC COMPUTER ANALYSIS (POCA)

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. The phonetic search module returns a numeric score to the search engine based on the phonetic similarity to the input text. Likewise, an orthographic algorithm exists which operates in a similar fashion. The POCA did not identify any other names which were considered to have significant orthographic similarities to Uloric.

C. PRESCRIPTION ANALYSIS STUDIES

1. Methodology:

Three separate studies were conducted within the Centers of the FDA for the proposed proprietary name to determine the degree of confusion of Uloric with currently 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 124 health care professionals (pharmacists, physicians, and nurses). This exercise was conducted in an attempt to simulate the prescription ordering process. An inpatient and outpatient prescription were written, each consisting of a combination of marketed and unapproved drug products and a prescription for Uloric (see below). These prescriptions were optically scanned and one prescription was delivered to a random sample of the participating health professionals via e-mail. In addition, one inpatient order was recorded on voice mail. The voice mail messages were 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 sent their interpretations of the orders via e-mail to the medication error staff.

HANDWRITTEN PRESCRIPTION	VERBAL PRESCRIPTION
Inpatient RX#1: 	Uloric 120 mg QD #30
Outpatient RX: 	

2. Results:

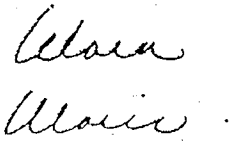
None of the interpretations of the proposed name overlap, sound similar, or look similar to any currently marketed U.S. product. See Appendix A for the complete listing of interpretations from the verbal and written studies.

D. SAFETY EVALUATOR RISK ASSESSMENT

In reviewing the proprietary name Uloric, the primary concerns related to look-alike and sound-alike confusion with Alora and Mobic. Similarly, through independent review, two additional names, ULR-LA and U-Lactin were determined to have potential for confusion with Uloric. Upon further review of the names gathered from EPD and independent review , the name ULO was not reviewed further due to inability to find further information in such commonly used references such as the Electronic Orange Book, Red Book, Drug Facts and Comparisons, Physicians' Desk Reference, and online databases such as DestinationRX.com and RX.com. The new drug applications (NDAs) for ULO, # 12-126, 12-135, and 12-136 were withdrawn on 3/2/94, 8/29/60, and 8/26/60, respectively. The active ingredient in ULO, (chlophedianol) is a USAN for an antitussive, however, it is no longer commercially available in the United States. ULR-LA was a combination product of guaifenesin with phenylpropanolamine (PPA) which was removed from the market by the Agency in November 2000 due to safety issues associated with PPA. Additionally, there is no information about ULR-LA as a non-PPA combination product available through such commonly used references such as the Red Book, DestinationRX.com, RX.com and Drugstore.com.

Additionally, DMETS conducted prescription studies to simulate the prescription ordering process. In this case, there was no confirmation that the proposed name could be confused with any of the aforementioned names. However, negative findings are not predicative as to what may occur once the drug is widely prescribed, as these studies have limitations primarily due to a small sample size. The majority of misinterpretations were misspelled/phonetic variations of the proposed name, Uloric.

1. Alora may look and sound similar to Uloric. Alora is indicated in the treatment of vasomotor symptoms associated with menopause and other gynecological problems. Both names begin with letters (a vs. u) that may look similar when scripted (see below). Additionally, the next three letters are the same (lor). The remaining letters may look similar, particularly if they are not clearly scripted (a vs. ic). If the 'u' of Uloric is pronounced using a short 'u', such as in 'hull', and the 'ic' is not clearly enunciated, both names may sound similar. Despite the orthographic and phonetic similarities, there are differences that may help to differentiate these two products. They are dose (80 mg and 120 mg vs. 0.025 mg/24hr, 0.05 mg/24 hr, 0.075 mg/24 hr, and 0.1 mg/24 hr), dosage form (tablet vs. transdermal film), strength (80 mg or 120 mg vs. 0.025 mg/24hr, 0.05 mg/24hr, 0.075 mg/24hr, and 0.1 mg/24hr), frequency (once daily vs. twice weekly), route of administration (oral vs. topical), indication of use (hyperuricemia vs. hormone replacement), and storage location (oral solids vs. transdermal). Despite the orthographic similarities, the product characteristics may help to differentiate the two products and minimize confusion.



2. Mobic may look similar to Uloric when scripted. Mobic is indicated for relief of the signs and symptoms of osteoarthritis. Both names contain letters that may look similar when scripted (mo vs. ulo). The 'b' in Mobic may look similar to an 'r', if it is not clearly scripted (see below). Additionally, both names end with the same two letters (ic). Although both products are tablets and dosed once daily, there are product characteristics that may differentiate them and help to minimize confusion, such as dose, and strength (80 mg and 120 mg vs. 7.5 mg and 15 mg). These differences will help to minimize confusion.

Mobic
Uloric

3. U-Lactin may look similar to Uloric when scripted. U-Lactin is an emollient that is used to help soften and moisture skin. Both names begin with the same two letters (ul), and contain letters that may look similar when scripted (ac vs. or and in vs ic). However, the upstroke for the 't' may help to differentiate the two names when scripted (see below). Despite the orthographic similarities, there are differentiating product characteristics, such as dose (80 mg or 120 mg vs. liberal amount), dosage form (tablet vs. lotion), frequency of administration (once daily vs. as needed), route of administration (oral vs. topical), indication of use (hyperuricemia vs. dry skin), and storage location (RX vs. over the counter). Thus, the product characteristics may help to minimize confusion involving these two products.

[redacted]

E. INDEPENDENT NAME ANALYSIS: [redacted] b(4)

1. The analysis conducted by [redacted] provided an analysis of twelve suggested proprietary names for this product. Although not all of the proposed names have similar spelling, three names were similar in spelling and pronunciation to Uloric. They are Ulorix, Ulore, and Loric. Thus, DMETS analyzed the results of the [redacted] Analysis associated with these three names in addition to the names identified as potential look-alikes and sound-alikes to Uloric. The following names were not identified by DMETS: Lasix, Klotrix, Allerx, Alrex, Vioxx, Artane, Sular, Coreg, Luvox, and Luride. These products are listed in Table 2 (see page 7), along with the dosage forms available and usual dosage.

b(4)

Table 2: Potential Sound-Alike/Look-Alike Names Identified by

Product Name	Dosage form(s), Established name	Usual adult dose*	Other**
Uloric	Febuxostat Tablets 80 mg and 120 mg	80 mg or 120 mg once daily.	N/A
Lasix	Furosemide Tablets: 20 mg, 40 mg, and 80 mg Solution: 10 mg/mL, 40 mg/5mL Injection: 10 mg/mL	20 mg to 120 mg daily. Adjust dose to response.	LA
Klotrix	Potassium Chloride Tablet: 10 mEq extended-release	20 mEq to 150 mEq. Adjust dose according to lab values.	LA
Allerx	Chlorpheniramine, Pseudoephedrine, and Methscopolamine Dose Pack: AM Dose: 120 mg Pseudoephedrine HCL and 2.5 mg methscopolamine nitrate PM Dose: 8 mg chlorpheniramine maleate and 2.5 mg methscopolamine nitrate	 One yellow tablet in AM. One blue tablet in PM.	SA/LA
Alrex	Loteprednol Ophthalmic Suspension 0.2%	One drop instilled into the affected eye(s) four times daily.	SA/LA
Vioxx	Rofecoxib Oral Suspension :12.5 mg/5 mL, and 25 mg /5 mL Tablet 12.5 mg, 25 mg, and 50 mg	The lowest dose possible. 12.5 mg to 50 mg maximum (not recommended beyond 5 days).	LA
Artane (Discontinued)	Trihexyphenidyl (available as generic) Extended Release Capsule: 5mg Elixir: 2mg/ 5mL Tablet: 2 mg, 5 mg	Total daily dose of 1 mg to 15 mg divided three or four times a day with meals and last dose at bedtime.	LA
Sular	Nisoldipine Extended-Release Tablet: 10mg, 20 mg, 30 mg, and 40 mg	20 mg to maximum of 60 mg daily.	SA
Coreg	Carvedilol Tablets 3.125 mg, 6.25 mg, 12.5 mg, and 25 mg	Hypertension: Individualized 6.25 mg to maximum of 25 mg PO bid. Heart Failure: Individualized 3.125 mg initially Maximum dose for patients <85 kg is 25 mg, PO, bid Maximum dose for patients >85 kg is 50 mg, PO, bid	SA
Luvox	Fluvoxamine Tablet: 25 mg, 50 mg, 100mg, and 150 mg	50 mg to 300 mg maximum daily. Doses over 100 mg should be given in two divided doses.	LA
Luride	Sodium Fluoride Drops: 0.125 mg/drop, 0.5 mg/mL Gel: 0.1%, 0.5%, 1.23 % Gel Drops: 0.5% Rinse: 0.09% Tablets: 1 mg Tablets (chewable): 0.25 mg, 0.5 mg, and 1 mg	 0.25 mg daily to 1 mg daily. 5 mL to 10 mL daily.	SA
*Frequently used, not all-inclusive. **L/A (look-alike), S/A (sound-alike)			

2. Following the review of the proprietary name analysis submitted by ——— b(4)
DMETS notes that the names Lasix and Klotrix warrant further review from a safety perspective.

a. DMETS agrees with ——— ...nalysis that Lasix has a look-alike similarity to Uloric, when scripted. Lasix is a diuretic indicated in the treatment of acute pulmonary edema, edema, hypertension, and hypercalcemia. Both names b(4)
contain letters that look similar when scripted (lasix and loric). DMETS agrees with ——— analysis that the "u" of Uloric may be misinterpreted as a checkmark if the 'u' were separated from the rest of the letters (see below), and if the name Uloric were included in a list of orders on an inpatient order sheet. This scenario is less likely to occur in an outpatient arena. An inpatient setting is the most likely location where this particular type of error might occur. Of particular concern is in a hospital that uses multi-part carbonless order sheets. The original order for Uloric may be clear. However, the presentation of the order on the carbonless copy that is sent to the pharmacy may be distorted due to handling of the paper, and as a result, it may be misinterpreted as Lasix with a checkmark in front of it. There are some overlapping product characteristics that may cause confusion, such as dose (80 mg or 120 mg), dosage form (tablet), strength (80 mg), frequency (once daily), route of administration (oral), and storage location (oral solids). Additionally, since diuretic therapy is patient response dependent, it would be possible for an 80 mg or 120 mg dose of Lasix to be ordered and administered, as in the treatment of chronic heart failure and hypercalcemia[7]. Although both products have different indications of use, the potential for orthographic similarities is problematic. If a patient not in need of diuretic therapy were to receive an 80 mg or 120 mg dose of Lasix, it might result in profound electrolyte and volume depletion which may precipitate circulatory collapse (i.e. hypokalemia)[8]. Thus, the orthographic similarities coupled with the overlapping product characteristics increase the potential for confusion involving Lasix and Uloric.

Uloric

Uloric

b. DMETS agrees with ——— analysis that Klotrix may look similar to b(4)
Uloric when scripted. Klotrix is a potassium supplement used for electrolyte balancing. Both names contain letters that may look similar (klo vs. ulo) when written, particularly if the two angle bars of the 'k' are not differentiated or connected to the vertical bar (see page 9). The last three letters may also look similar (rix vs. ric). However, the upstroke for the 't' in the middle of Klotrix may help to differentiate the two names when scripted. There are some overlapping product characteristics such as dosage form (tablet), frequency (once daily), route of administration (oral), and storage location (oral solids). Although the unit of measure is different (mg vs. mEq), the scripted presentations may look similar. Klotrix is usually dosed based upon lab values and as such may be dosed

[7] Wood, A. (1998). *Drug Therapy: Diuretic Therapy.* N Engl J Med 1998; 339:387-395, Aug 6, 1998 and Cohn, J. (1996). *The Management of Chronic Heart Failure*, N Engl J Med 1996; 335:490-498, Aug 15, 1996.
[8] AHFS Drug Handbook, Second Edition. Lippincott Williams, & Wilkins. 2003.

at either 80 mEq or 120 mEq as a total daily dose. However, at higher doses it would most likely be divided three or four times a day. Additionally, this higher dose would require a patient to take 8 or 12 tablets respectively. Thus, the frequency and number of tablets may help to minimize confusion and error involving Klotrix and Ulorix. Additionally, the 2004 IMS Health Data provided by Thomson and Thomson, indicates the _____ which would decrease the potential risk of a medication error even further. b(4)

Klotrix
Ulorix

3. Additionally, a Gout Name Validation Study was conducted by _____. This study identified the following names that were not identified by DMETS: Lasix, Lorcet, Ultram, and Clenaril. These products are listed in Table 3 (see below), along with the dosage forms available and usual dosage. No information on Clenaril is available in commonly used references such as Orange Book, NDC directory, Drug Facts and Comparison, Drugs@fda, and the Red Book. However, Clenaril sounds and looks similar to the product Clinoril. Information on this product is listed in Table 3 (see below). b(4)

Table 3: Names identified through _____ Gout Name Validation Study b(4)

Product Name	Dosage form(s), Established name	Usual adult dose*	Other**
Uloric	Febuxostat Tablets 80 mg and 120 mg	80 mg to 120 mg once daily.	N/A
Lasix	Furosemide Tablets: 20 mg, 40 mg, and 80 mg Solution: 10 mg/mL, 40 mg/5mL Injection: 10 mg/mL	20 mg to 120 mg daily. Adjust dose to response.	SA/LA
Clinoril	Sulindac Tablets 150 mg and 200 mg	150 mg to 200 mg, PO, bid.	LA
Lorcet-HD	Acetaminophen; Hydrocodone Bitartrate Capsule: 500 mg/5 mg	1 to 2 capsules every four to six hours with a maximum of 4 g of acetaminophen per day.	SA/LA
Ultram	Tramadol Hydrochloride Tablets 50 mg	50 mg to 100 mg orally every four to six hours. Maximum of 400 mg per day.	SA/LA
*Frequently used, not all-inclusive. **L/A (look-alike), S/A (sound-alike)			

After further evaluation of the list of names from the Gout Name Validation Study conducted by _____, DMETS believes that Lasix warrants further evaluation from a safety perspective. Lasix was discussed in section IIE2a above. DMETS believes that the remaining drug products do not pose a significant safety risk due to differentiating product characteristics. b(4)

In addition to the above mentioned drug products, the medical term "Pyloric" was identified as a potential sound-alike. However, the term 'pyloric' refers to the pylorus or to the pyloric part of the stomach (pars pylorica ventriculi), and as such would not normally be included in an order for a drug product[9].

[9] http://www.dorlands.com

III. COMMENTS TO THE SPONSOR:

DMETS does not recommend the use of the proprietary name Uloric. In reviewing the proprietary name, the primary concerns related to look-alike confusion with Lasix.

DMETS agrees with [redacted] analysis that Lasix has a look-alike similarity to Uloric, when scripted. Lasix is a diuretic indicated in the treatment of acute pulmonary edema, edema, hypertension, and hypercalcemia. Both names contain letters that look similar when scripted (lasix and loric). b(4
DMETS agrees with [redacted] analysis that the "u" of Uloric may be misinterpreted as a checkmark if the 'u' were separated from the rest of the letters (see below), and if the name Uloric were included in a list of orders on an inpatient order sheet. This scenario is less likely to occur in an outpatient arena. An inpatient setting is the most likely location where this particular type of error might occur. Of particular concern is in a hospital that uses multi-part carbonless order sheets. The original order for Uloric may be clear. However, the presentation of the order on the carbonless copy that is sent to the pharmacy may be distorted due to handling of the paper, and as a result, it may be misinterpreted as Lasix with a checkmark in front of it. There are some overlapping product characteristics that may cause confusion, such as dose (80 mg or 120 mg), dosage form (tablet), strength (80 mg), frequency (once daily), route of administration (oral), and storage location (oral solids). Additionally, since diuretic therapy is patient response dependent, it would be possible for an 80 mg or 120 mg dose of Lasix to be ordered and administered, as in the treatment of chronic heart failure and hypercalcemia[10]. Although both products have different indications of use, the potential for orthographic similarities is problematic. If a patient not in need of diuretic therapy were to receive an 80 mg or 120 mg dose of Lasix, it might result in profound electrolyte and volume depletion which may precipitate circulatory collapse (i.e. hypokalemia)[11]. Thus, the orthographic similarities coupled with the overlapping product characteristics increase the potential for confusion involving Lasix and Uloric.

Uloric

Uloric

IV. RECOMMENDATIONS:

1. DMETS does not recommend the use of the proprietary name, Uloric.

2. DMETS suggests submitting the labels and labeling for this product when available.

3. DDMAC finds the proprietary name Uloric 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. If you have further questions or need clarifications, please contact Sammie Beam, project manager, at 301-827-3242.

Linda M. Wisniewski, RN
Safety Evaluator
Division of Medication Errors and Technical Support
Office of Drug Safety

Wood, A. (1998). Drug Therapy: Diuretic Therapy. N Engl J Med 1998; 339:387-395, Aug 6, 1998 and Cohn, J. (1996). *The Management of Chronic Heart Failure.* N Engl J Med 1996; 335:490-498, Aug 15, 1996.

[11] AHFS Drug Handbook, Second Edition. Lippincott Williams, & Wilkins. 2003.

ODS: 04-0118

Appendix A: Uloric

.D#: 58,229

Inpatient	Outpatient	Verbal
Ulcric	Olovic	Euloric
Ulcric	Uloric	Euloric
Ulcric	Uloric	Euloric
Ulcric	Uloric	Eulort
Ulcric	Uloric	Ulorec
Ulcric	Uloric	Uloric
Ulcric	Uloric	Uloric
Ulcric	Ulovic	Uloric
Ulcric	Vloric	Uloric
Ulcric	Vloric	Uloric
Uloric	Vloric	Uloric
Uloric	Vloric	Uloric
Uloric	Vloric	Uloric
Uloric	Vloric	Uloric
Uloric	Vloric	Ulort
Uloric	Vloric	Ulort
Uloric	Vloric	Umoric
	Vloric	
	Vloric	

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/s/

Linda Wisniewski
2/25/05 01:14:21 PM
DRUG SAFETY OFFICE REVIEWER

Denise Toyer
2/25/05 02:32:15 PM
DRUG SAFETY OFFICE REVIEWER

Carol Holquist
2/25/05 03:57:36 PM
DRUG SAFETY OFFICE REVIEWER