

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

22548Orig1s000

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: April 7, 2010

To: Wiley Chambers, MD, Acting Director
Division of Anti-infective and Ophthalmologic Products

Through: Todd Bridges, RPh, Team Leader
Denise Toyer, Pharm.D., Deputy Director
Division of Medication Error Prevention and Analysis (DMEPA)

From: Denise V. Baugh, PharmD, BCPS, Safety Evaluator
Division of Medication Error Prevention and Analysis (DMEPA)

Subject: Proprietary Name Review

Drug Name(s): Zymaxid (Gatifloxacin) Ophthalmic Solution 0.5%

Application Type/Number: NDA# 022548

Applicant: Allergan, Inc.

OSE RCM #: 2009-2231

1 INTRODUCTION

This re-assessment of the proprietary name is written in response to the anticipated approval of this NDA within 90 days from the date of this review. The Division of Medication Error Prevention and Analysis (DMEPA) found the proposed proprietary name, Zymaxid, acceptable in OSE Reviews #2009-1534, dated November 13, 2009. The Division of Anti-infective and Ophthalmologic Products did not have any concerns with the proposed name, Zymaxid, and the Division of Drug Marketing, Advertising and Communication (DDMAC) found the name acceptable from a promotional perspective on November 2, 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 proprietary name review. We use the same search criteria previously used in the above stated review. Since none of the proposed product characteristics were altered we did not re-evaluate previous names of concern. Additionally, DMEPA searches the United States Adopted Names (USAN) stem list to determine if the name contains any USAN stems as of the last USAN updates. The overall risk assessment is based on the findings of a Failure Mode and Effects Analysis (FMEA) of the proposed proprietary name, and focuses on the avoidance of medication errors.

DMEPA staff did not identify any United States Adopted Names (USAN) stems in the proposed proprietary name, Zymaxid, as of April 6, 2010.

The searches of the databases yielded no new names which look or sound similar to Zymaxid and represent a potential source of drug name confusion.

3 CONCLUSIONS AND RECOMMENDATIONS

The proprietary name risk assessment findings indicate that the proposed name, Zymaxid, 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 (DMEPA) has no objection to the proprietary name, Zymaxid, 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 Anti-infective and Ophthalmologic Products should notify DMEPA because the proprietary name must be re-reviewed prior to the new approval date.

We are willing to meet with the Division for further discussion, if needed. If you have further questions or need clarifications, please contact OSE Project Manager, Brantley Dorch, at 301-796-0150.

4 REFERENCES

1. OSE review #2009-1534, dated November 13, 2009; Proprietary Name Review of Zymaxid; Denise V. Baugh, PharmD, BCPS, Safety Evaluator.

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

USAN Stems List contains all the recognized USAN stems.

4. **CDER Proposed Names 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.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22548	ORIG-1	ALLERGAN	GATIFLOXACIN OPHTHALMIC SOLUTION 0.5%

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

/s/

DENISE V BAUGH
04/07/2010

TODD D BRIDGES
04/07/2010

DENISE P TOYER
04/13/2010



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: November 13, 2009

To: Wiley Chambers, MD, Acting Director
Division of Anti-infective and Ophthalmologic Products

Through: Todd Bridges, RPh, Team Leader
Denise Toyer, Pharm.D., Deputy Director
Carol Holquist, RPh, Director
Division of Medication Error Prevention and Analysis (DMEPA)

From: Denise V. Baugh, PharmD, BCPS, Safety Evaluator
Division of Medication Error Prevention and Analysis (DMEPA)

Subject: Proprietary Name Review

Drug Name(s): Zymaxid (Gatifloxacin) Ophthalmic Solution 0.5%

Application Type/Number: NDA# 022548

Applicant: Allergan, Inc.

OSE RCM #: 2009-1534

CONTENTS

EXECUTIVE SUMMARY	3
1 BACKGROUND	3
1.1 Introduction.....	3
1.2 Product Information	3
2 METHODS AND MATERIALS	4
2.1 Search Criteria.....	4
2.2 FDA Prescription Analysis Studies.....	5
2.3 External Proprietary Name Risk Assessment	5
3 RESULTS.....	6
3.1 Database and Information Sources.....	6
3.2 CDER Expert Panel Discussion.....	6
3.3 FDA Prescription Analysis Studies.....	6
3.4 External Proprietary Name Risk Assessment	6
3.5 Comments from the Division of Anti-infective and Ophthalmologic Products (DAIOP)	6
3.6 Safety Evaluator Risk Assessment.....	7
4 DISCUSSION	7
5 CONCLUSIONS AND RECOMMENDATIONS	8
5.1 Comments To The Applicant.....	8
6 REFERENCES	9
APPENDICES	11

EXECUTIVE SUMMARY

The findings of the Proprietary Name Risk Assessment indicate the use of an alternate proprietary name rather than a modified proprietary name product line extension is reasonable for this formulation of Gatifloxacin Ophthalmic Solution 0.5%. (b) (4)

(b) (4), we would have concern that medication errors may occur if the strength is misinterpreted (i.e., 0.3% is misread as 0.5%) and the wrong concentration is dispensed and administered at the wrong frequency and for the wrong duration. Another option would be to use the name Zymar with a modifier to further distinguish the proposed product. However, because these products are initially dosed the same (every 2 hours) and then differently (four times daily versus (b) (4)) it would be challenging to identify a suitable modifier that clearly communicates the differences between the proposed product and the existing product, Zymar. Therefore, in light of the medication error concerns associated with the use of the Zymar name or Zymar name plus modifier, the use of a different proprietary name may represent a reasonable option.

This proposed name was evaluated from a safety and promotional perspective based on the product characteristics provided by the Applicant. We sought input from pertinent disciplines involved with the review of this application and considered it accordingly. Our evaluation did not identify concerns that would render the name unacceptable based on the product characteristics and safety profile known at the time of this review. Thus, DMEPA finds the proposed proprietary name Zymaxid conditionally acceptable for this product. The proposed proprietary name must be re-reviewed 90 days before approval of the NDA.

Additionally, if any of the proposed product characteristics as stated in this review are altered, DMEPA rescinds this finding and the name must be resubmitted for review. The conclusions upon re-review are subject to change

1 BACKGROUND

1.1 INTRODUCTION

This review is written in response to a request from Allergan, Inc., received on August 21, 2009, for an assessment of the proposed proprietary name, Zymaxid. The proposed product represents a higher concentration of the currently marketed product, Zymar.

1.2 REGULATORY HISTORY

Zymar (gatifloxacin ophthalmic solution) was approved March 28, 2003 (NDA# 021493). Zymar is marketed by the same Applicant as the product under review. Comparison of the product characteristics for Zymar and Zymaxid are detailed in Table 1, Section 1.3.

1.3 PRODUCT INFORMATION

Zymaxid (gatifloxacin ophthalmic solution) is a topical fluoroquinolone anti-infective indicated for the treatment of bacterial conjunctivitis caused by susceptible strains. The recommended dose is:

Day 1: Instill one drop every two hours in the affected eye(s) while awake, up to 8 times.

Days 2 through (b) (4) Instill one drop two times daily in the affected eye(s) while awake, (b) (4)

Zymaxid will be supplied in the following sizes: 2.5 mL in 5 mL bottle (b) (4)

Table 1. Comparison of product characteristics for Zymaxid and Zymar

	Zymaxid	Zymar
Active ingredient	Gatifloxacin	Gatifloxacin
Dosage form	Ophthalmic solution	Ophthalmic solution
Strength	0.5%	0.3%
Indication	Treatment of bacterial conjunctivitis	Treatment of bacterial conjunctivitis
Directions for use	Day 1: one drop every 2 hours in the affected eye(s) up to 8 times daily Day 2 through (b) (4) one drop two times daily in the affected eye(s) (b) (4)	Days 1 and 2: one drop every 2 hours in the affected eye(s) up to 8 times daily Days 3 through 7: one drop up to four times daily in the affected eye(s)
How supplied	2.5 mL, (b) (4) in 5 mL bottle	5 mL in 10 mL bottle

2 METHODS AND MATERIALS

Appendix A describes the general methods and materials used by the Division of Medication Error Prevention and Analysis (DMEPA) when conducting a proprietary name risk assessment for all proprietary names. Sections 2.1, 2.2 and 2.3 identify specific information associated with the methodology for evaluating the proposed proprietary name, Zymaxid.

2.1 SEARCH CRITERIA

For this review, particular consideration was given to drug names beginning with the letter ‘Z’ 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.^{1,2}

To identify drug names that may look similar to Zymaxid, the DMEPA staff also consider the orthographic appearance of the name on lined and unlined orders. Specific attributes taken into consideration include the length of the name (7 letters), upstrokes (2, capital letter ‘Z’ and lower case ‘d’), downstrokes (1, lower case ‘y’), cross-strokes (1, lower case ‘x’), and dotted letters (1, lower case ‘i’). Additionally, several letters in Zymaxid may be vulnerable to ambiguity when scripted (see Appendix B). As such, the DMEPA staff also considers these alternate appearances when identifying drug names that may look similar to Zymaxid.

When searching to identify potential names that may sound similar to Zymaxid, the DMEPA staff search for names with similar number of syllables (3), stresses (ZY-max-id, zy-MAX-id or zy-max-ID), and placement of vowel and consonant sounds. Additionally, the DMEPA staff considers that pronunciation of parts of the name can vary (See Appendix B). Moreover, names are often mispronounced and/or spoken with regional accents and dialects, so other potential pronunciations of the name are considered.

¹ Institute for Safe Medication Practices. Confused Drug name List (1996-2006). Available at <http://www.ismp.org/Tools/confuseddrugnames.pdf>

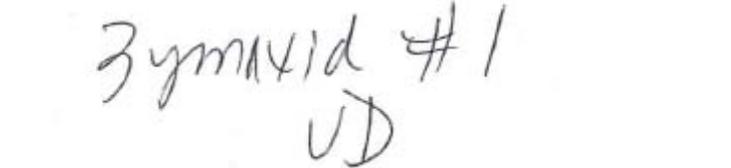
² Kondrack, G and Dorr, B. Automatic Identification of Confusable Drug Names. Artificial Intelligence in Medicine (2005)

The Applicant did not provide their intended pronunciation of the proprietary name in the proposed name submission and, therefore, it could not be taken into consideration.

2.2 FDA PRESCRIPTION ANALYSIS STUDIES

In order to evaluate the potential for misinterpretation of the proposed proprietary name in handwriting and verbal communication of the name, the following inpatient medication order, outpatient and verbal prescriptions were communicated during the FDA prescription studies.

Figure 1. Zymaxid Prescription Study (conducted on September 4, 2009)

HANDWRITTEN MEDICATION ORDER	VERBAL PRESCRIPTION
<u>Inpatient Medication Order:</u> <hr/>  <hr/>	"Zymaxid Dispense #1 Take as directed."
<u>Outpatient Prescription:</u> 	

2.3 EXTERNAL PROPRIETARY NAME RISK ASSESSMENT

For this product, the Applicant submitted an external evaluation of the proposed proprietary name. The Division of Medication Error Prevention and Analysis 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 DMEPA's 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 associated with 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 DMEPA's risk assessment concurs or differs with the findings of the external risk assessment. When the proprietary name risk assessment differs, the Division of Medication Error Prevention and Analysis provides a detailed explanation of these differences.

3 RESULTS

3.1 DATABASE AND INFORMATION SOURCES

The searches yielded a total of sixteen names as having some similarity to the proposed proprietary name Zymaxid.

Nine of the names were thought to look like Zymaxid. These include Zymar, Zymine, Zyvox, Lymerix, Tylox, Zegerid, Zymecot, Symax SL, and Gynecort. Three of the names (Axid, Biacid, and Primaxin) were thought to sound like Zymaxid. The remaining four names were thought to look and sound similar to Zymaxid: Zymax, Zymaxx, Zymaxid, and Zymad.

Additionally, DMEPA staff did not identify any United States Adopted Names (USAN) stems in the proposed proprietary name, as of November 10, 2009.

3.2 CDER EXPERT PANEL DISCUSSION

The Expert Panel reviewed the pool of names identified by DMEPA staff (See Section 3.1 above) and noted no additional names thought to have orthographic or phonetic similarity to Zymaxid.

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

3.3 FDA PRESCRIPTION ANALYSIS STUDIES

A total of thirteen practitioners responded but none of the responses overlapped with any existing or proposed drug names. Seven of the participants interpreted the name correctly as "Zymaxid," with correct interpretation occurring in the inpatient written study (n = 6) and the outpatient written study (n = 1). The remainder of the responses misinterpreted the drug name. See Appendix C for the complete listing of interpretations from the verbal and written prescription studies.

3.4 EXTERNAL PROPRIETARY NAME RISK ASSESSMENT

In the proposed name risk assessment submitted by the Applicant, the Drug Safety Institute (DSI) Inc., a subsidiary of Brand Institute, Inc., identified and evaluated a total of nineteen drug names (Axid, Lanoxin, Maxair, Maxidex, Maxzide, Primaxin, Robaxin, Symax, Synercid, Xifaxan, Z-Pak, Zantac, Zilactin, Zithromax, Zmax, Zymar, Zymine, Zyprexa, and Zymase) thought to have some potential for confusion with the name Zymaxid. Five of these names (Axid, Primaxin, Symax, Zymar, and Zymine) were also identified by DMEPA during the database searches. It is noted that DSI did not evaluate the potential for confusion related to the use of the dual trade names (Zymaxid and Zymar) for the active ingredient and dosage form, gatifloxacin ophthalmic solution. The fourteen remaining names were evaluated as part of the Safety Evaluator Risk Assessment.

3.5 COMMENTS FROM THE DIVISION OF ANTI-INFECTIVE AND OPHTHALMOLOGIC PRODUCTS (DAIOP)

In response to an e-mail from OSE dated September 03, 2009, the Division of Anti-infective and Ophthalmologic Products forwarded the following comment:

"The name Zymaxid sounds like the "maxi" of Zymar."

A meeting was held October 7, 2009, between DDMAC, DMEPA, and DAIOP to discuss the Division's concern with the proposed name from a promotional perspective. The outcome of the meeting was a consensus that the Agency would not object to the name, Zymaxid, from a promotional perspective and that DMEPA would continue their safety review of the proposed name.

DMEPA notified the Division of Anti-infective and Ophthalmologic Products via e-mail that we had no objections to the proposed proprietary name, Zymaxid, on November 5, 2009. Per e-mail correspondence from the Division of Anti-infective and Ophthalmologic Products on November 6, 2009, they indicated they concur with our assessment of the proposed proprietary name, Zymaxid.

3.6 SAFETY EVALUATOR RISK ASSESSMENT

The Applicant believes a new name for this formulation is appropriate because if there was confusion and the 0.3% strength was dosed only twice daily, instead of four times daily as labeled, the patient would not receive the anti-infective benefits of the product. Furthermore, if the newly proposed 0.5% strength was dosed four times daily, instead of the intended twice daily dosing, the patient would unnecessarily receive an overdose of the antibiotic. Therefore, in order to limit confusion among prescribers, the Applicant believes this proposed product would be best managed under a separate brand name. We considered this rationale in our overall risk assessment.

Independent searches by the primary Safety Evaluator did not identify any additional names which were thought to look or sound similar to Zymaxid and represent a potential source of drug name confusion. Thus, a total of thirty names were evaluated for their similarity to the proposed name, Zymaxid.

The name Zymaxid was identified in our database searches but eliminated from further analysis because it is the subject of this review.

4 DISCUSSION

Zymaxid (gatifloxacin ophthalmic solution) will be an extension of the Zymar product line. Both are manufactured by Allergan and contain the same active ingredient. In addition to having the same active ingredient as Zymar, Zymaxid will also have the same indication: treatment of bacterial conjunctivitis. Zymaxid and Zymar differ with respect to product concentration and dose. Zymaxid contains a higher concentration of gatifloxacin ophthalmic solution (0.5% versus 0.3%). Initially, Zymar and Zymaxid are dosed with the same frequency (every 2 hours, up to 8 times in a day). However, starting on day two, Zymaxid is dosed less frequently than Zymar (twice daily versus up to four times daily) (b) (4)

See chart in Section 1.3 (Product Information) for a comparison of Zymaxid and Zymar product characteristics.

The Applicant proposes a new and different proprietary name for the proposed strength. In evaluating this proprietary name, we considered whether the product could be safely managed using the name, Zymaxid, and considered the risk of inadvertent concomitant administration of the gatifloxacin products.

4.1 ZYMAR PRODUCT LINE EXTENSION

Currently, gatifloxacin ophthalmic solution is marketed under the proprietary name, Zymar. Zymar was originally approved in 2003. Typically the introduction of a new strength of a product can be successfully managed under the existing name since the product strength differentiates the products. Also, multiple indications of use and dosing can be managed under a single name. However, in this case the treatment regimens have a common initial dosing regimen (i.e., every 2 hours on day 1) but differ thereafter in dosing frequency and therapy duration. If the proposed product were to be marketed using the Zymar name and strength alone to differentiate the products, we would have concern that medication errors may occur if the strength is misinterpreted (i.e., 0.3% is misread as 0.5%) and the wrong concentration is dispensed and administered at the wrong frequency and for the wrong duration.

Given the concern about confusion between Zymar 0.3% and the proposed 0.5% product, another option would be to use the name Zymar with a modifier to further distinguish the proposed product. However,

because these products are initially dosed the same (every 2 hours) and then differently (four times daily versus (b) (4) it would be challenging to identify a suitable modifier that clearly communicates the differences between the proposed product and the existing product, Zymar. Therefore, in light of the medication error concerns associated with the use of the Zymar name or Zymar name plus modifier, the use of a different proprietary name may represent a reasonable option.

4.2 RISK ASSESSMENT OF ZYMAXID OUTSIDE OF THE PRODUCT LINE

Neither DDMAC nor the review Division had any concerns with the proposed name.

DMEPA identified and evaluated twenty-nine (29) names for their potential similarity to the proposed name, Zymaxid. Fifteen (15) names lacked orthographic and/or phonetic similarity to Zymaxid and were not evaluated further (see Appendix D).

Failure Mode and Effects Analysis was then applied to determine if the proposed name, Zymaxid, could potentially be confused with any of the remaining fourteen (14) names and lead to medication errors. This analysis determined that the name similarity between Zymaxid and these fourteen (14) names was unlikely to result in medication errors for the reasons presented in Appendices E through I.

Additionally, DMEPA did not identify any other factors that would render the name unacceptable at this time.

5 CONCLUSIONS AND RECOMMENDATIONS

The Proprietary Name Risk Assessment findings indicate that the use of an alternate proprietary name rather than a modified proprietary name product line extension is reasonable for this formulation of gatifloxacin ophthalmic solution. Therefore, DMEPA finds that the proposed name, Zymaxid, 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 (DMEPA) has no objection to the proprietary name, Zymaxid, for this product at this time.

However, if any of the proposed product characteristics as stated in this review are altered, DMEPA rescinds this Risk Assessment finding and the name must 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 re-reviewed 90 days before approval of the NDA. For questions or clarifications, please contact OSE Project Manager, Brantley Dorch, at 301-796-0150.

5.1 COMMENTS TO THE APPLICANT

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

The proprietary name, Zymaxid, 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.

6 REFERENCES

1. *Micromedex Integrated Index* (<http://csi.micromedex.com>)

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

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

POCA is a database which was created for the Division of Medication Error Prevention and Analysis, FDA. 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.

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

Drug Facts and Comparisons is a compendium organized by therapeutic course; it 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 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.

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](#), [generic drugs](#), [therapeutic biological products](#), [prescription](#) and [over-the-counter](#) human drugs and [discontinued drugs](#) and “[Chemical Type 6](#)” approvals.

7. *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.

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

USPTO provides information regarding patent and trademarks.

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

Clinical Pharmacology contains full monographs for the most common drugs in clinical use, plus mini monographs covering investigational, less common, combination, nutraceutical and nutritional products. It also 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 trade names that are used in about 50 countries worldwide. The data is provided under license by IMS HEALTH.

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

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

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

Stat!Ref contains full-text information from approximately 30 texts; it 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>)

USAN Stems List contains all the recognized USAN stems.

14. Red Book Pharmacy's Fundamental Reference

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

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

Lexi-Comp is a web-based searchable version of the Drug Information Handbook.

16. Medical Abbreviations Book

Medical Abbreviations Book contains commonly used medical abbreviations and their definitions.

APPENDICES

Appendix A:

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 IND, NDA, BLA, and ANDA products currently under review by the Center. DMEPA defines a medication error as any preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of the health care professional, patient, or consumer.³

For the proposed proprietary name, DMEPA staff search a standard set of databases and information sources to identify names with orthographic and phonetic similarity and hold a Center for Drug Evaluation and Research (CDER) Expert Panel discussion to gather professional opinions on the safety of the proposed proprietary name. DMEPA staff also conducts internal CDER prescription analysis studies. When provided, DMEPA considers external prescription analysis study results and incorporate into the overall risk assessment.

The Safety Evaluator assigned to the Proprietary Name Risk Assessment is responsible for considering the collective findings, and provides an overall risk assessment of the proposed proprietary name. DMEPA bases the overall risk assessment on the findings of a Failure Mode and Effects Analysis (FMEA) of the proprietary name, and focuses on the avoidance of medication errors.

FMEA is a systematic tool for evaluating a process and identifying where and how it might fail.⁴ DMEPA uses FMEA to analyze whether the drug names identified with orthographic or phonetic similarity to the proposed proprietary name could cause confusion that subsequently leads to medication errors in the clinical setting. DMEPA uses the clinical expertise of its staff to anticipate the conditions of the clinical setting where the product is likely to be used 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. Accordingly, the DMEPA staff considers the product characteristics associated with the proposed drug throughout the risk assessment because the product characteristics of the proposed may provide a context for communication of the drug name and ultimately determine the use of the product in the *usual* clinical practice setting.

Typical product characteristics considered when identifying drug names that could potentially be confused with the proposed proprietary name include, but are not limited to; established name of the proposed product, proposed indication of use, 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, DMEPA staff 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.⁵ DMEPA provides the product characteristics considered for this review in section one.

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

⁴ Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

⁵ Institute of Medicine. Preventing Medication Errors. The National Academies Press: Washington DC. 2006.

The Division of Medication Error Prevention and Analysis considers the spelling of the name, pronunciation of the name when spoken, and appearance of the name when scripted. DMEPA also compares the spelling of the proposed proprietary name with the proprietary and established name of existing and proposed drug products because similarly spelled names may have greater likelihood to sound similar to one another when spoken or look similar to one another when scripted. DMEPA staff 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 even dissimilarly spelled drug name pairs to appear very similar to one another. The similar appearance of drug names when scripted has led to medication errors. The DMEPA staff applies expertise gained from root-cause analysis of such medication errors to identify sources of ambiguity within the name that could be introduced when scripting (e.g., “T” may look like “F,” lower case ‘a’ looks like a lower case ‘u,’ etc). Additionally, other orthographic attributes that determine the overall appearance of the drug name when scripted (see Table 1 below for details). In addition, the DMEPA staff compares the pronunciation of the proposed proprietary name with the pronunciation of other drug names because verbal communication of medication names is common in clinical settings. If provided, DMEPA will consider the Applicant’s intended pronunciation of the proprietary name. However, DMEPA also considers a variety of pronunciations that could occur in the English language because the Applicant has little control over how the name will be spoken in clinical practice.

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

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

Lastly, the DMEPA staff also considers the potential for the proposed proprietary 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. Consequently, DMEPA considers and evaluates these broader safety implications of the name throughout this assessment and the medication error staff provides additional comments related to the safety of the proposed proprietary name or product based on professional experience with medication errors.

1. Database and Information Sources

DMEPA staff conducts searches 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 the proposed proprietary name using the criteria outlined in Section 2.1. Section 6 provides a standard description of the databases used in the searches. To complement the process, the DMEPA staff use a computerized method of identifying phonetic and orthographic similarity between medication names. The program, Phonetic and Orthographic Computer Analysis (POCA), uses complex algorithms to select a list of names from a database that have some similarity (phonetic, orthographic, or both) to the trademark being evaluated. Lastly, the DMEPA staff review the USAN stem list to determine if any USAN stems are present within the proprietary name. The individual findings of multiple safety evaluators are pooled and presented to the CDER Expert Panel.

2. CDER Expert Panel Discussion

DMEPA conducts an Expert Panel Discussion to gather CDER professional opinions on the safety of the proposed product and the proposed proprietary name. The Expert Panel is composed of Division of Medication Errors Prevention (DMEPA) staff and representatives from the Division of Drug Marketing, Advertising, and Communications (DDMAC). The Expert Panel also discusses potential concerns regarding drug marketing and promotion related to the proposed names.

The primary Safety Evaluator presents the pooled results of the DMEPA staff 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 primary Safety Evaluator to supplement the pooled results, or general advice to consider when reviewing the proposed proprietary name.

3. 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 the proposed proprietary name 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 healthcare professionals (pharmacists, physicians, and nurses), and attempts to simulate the prescription ordering process. The primary Safety Evaluator uses the results to identify orthographic or phonetic vulnerability of the proposed name to be misinterpreted by healthcare practitioners.

In order to evaluate the potential for misinterpretation of the proposed proprietary name in handwriting and verbal communication of the name, inpatient medication orders and outpatient prescriptions are written, each consisting of a combination of marketed and unapproved drug products, including the proposed name. These orders are optically scanned and one prescription is delivered to a random sample of the 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 DMEPA.

4. Comments from the OND Review Division or Office of Generic Drugs

DMEPA requests the Office of New Drugs (OND) or Office of Generic Drugs (OGD) Regulatory Division 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. The primary Safety Evaluator addresses any comments or concerns in the safety evaluator's assessment.

The OND or OGD 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 OND or OGD Regulatory Division is requested to concur/not concur with DMEPA's final decision.

5. Safety Evaluator Risk Assessment of the Proposed Proprietary Name

The primary Safety Evaluator applies his/her individual expertise gained from evaluating medication errors reported to FDA, conducts a Failure Mode and Effects Analysis, and provides an overall risk assessment 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, DMEPA seeks to evaluate the potential for a proposed proprietary name to be confused with another drug name because of name confusion and, thereby, 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 orthographically or phonetically similar 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 primary Safety Evaluator must analyze the use of the product at all points in the medication use system. Because the proposed product is has not been marketed, the primary Safety Evaluator anticipates the use of the product in the usual practice settings by considering the clinical and product characteristics listed in Section one. 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 Discussion, and prescription studies, external studies, and identifies potential failure modes by asking:

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

An affirmative answer indicates a failure mode and represents a potential for the proposed proprietary name 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, thus the name is eliminated from further review.

In the second stage of the Risk Assessment, the primary Safety Evaluator evaluates all potential failure modes to determine the likely *effect* of the drug name confusion, by asking:

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

“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 not ultimately be a source of medication errors in the usual practice setting, the primary Safety Evaluator eliminates the name 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 the use of an alternate proprietary name.

DMEPA will object to the use of proposed proprietary name when the primary Safety Evaluator identifies one or more of the following conditions in the Risk Assessment:

- a. 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 PROPRIETARY name or otherwise [21 U.S.C 321(n); See also 21 U.S.C. 352(a) & (n)].
- b. DMEPA identifies that the proposed proprietary name is misleading because of similarity in spelling or pronunciation to another proprietary or established name of a different drug or ingredient [CFR 201.10.(C)(5)].
- c. FMEA identifies the potential for confusion between the proposed proprietary name and other proprietary or established drug name(s), and demonstrates that medication errors are likely to result from the drug name confusion under the conditions of usual clinical practice.
- d. The proposed proprietary name contains an USAN (United States Adopted Names) stem.
- e. DMEPA identifies a potential source of medication error within the proposed proprietary name. For example, 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.

If DMEPA objects to a proposed proprietary name on the basis that drug name confusion could lead to medication errors, the primary Safety Evaluator uses the FMEA process to identify strategies to reduce the risk of medication errors. DMEPA 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. In that instance, DMEPA may be able to provide the Applicant with recommendations that reduce or eliminate the potential for error and, thereby, would render the proposed name acceptable.

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, DMEPA will provide a contingency objection based on the date of approval. Whichever product, the Agency approves first has the right to use the proprietary name, while DMEPA will recommend that the second product to reach approval seek an alternative 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 a through e are supported either by FDA regulation or by external healthcare authorities, including the Institute of Medicine (IOM), World Health Organization (WHO), The Joint Commission (TJC), and the Institute for Safe Medication Practices (ISMP). These organizations have examined medication errors resulting from look- or sound-alike drug names and called for regulatory authorities to address the issue prior to approval. Additionally, DMEPA contends that the threshold set for the Proprietary Name Risk Assessment is reasonable because proprietary drug name confusion is a predictable and

a preventable source of medication error that, in many instances, the Agency and/or Applicant can identify and rectify prior to approval to avoid patient harm.

Furthermore, post-marketing experience has demonstrated that medication errors resulting from drug name confusion are notoriously difficult to rectify post-approval. Educational and other post-approval efforts are low-leverage strategies that have had limited effectiveness at alleviating medication errors involving drug name confusion. Applicants have undertaken higher-leverage strategies, such as drug name changes, 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 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 practitioners’ vocabulary, and as a result, 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.

Appendix B: Letters with possible orthographic or phonetic misinterpretation

Letters in proposed name, Zymaxid	Scripted may appear as	Spoken may be interpreted as
Capital ‘Z’	T, L	S, X
lower case ‘y’	g, j, u	Any vowel
lower case ‘m’	n	n
lower case ‘a’	c, ‘ci’, ‘ce’, o, u, ‘el’	Any vowel
lower case ‘x’	t, f, k, a, r, p	Combination letters ‘-cks-’ or ‘-ks-’, ‘s’, ‘z’
lower case ‘i’	c, e, u, a	Any vowel
lower case ‘d’	‘cl’, ‘ci’, ‘ce’, a	T

Appendix C: FDA Prescription Study Responses for Zymaxid.

Inpatient Medication Order	Outpatient Medication Order	Voice Prescription
Zymaxid	Zymaxid	Zymcrid
Zymaxid		Zymcrid
Zymaxid		Zymcicriel
Zymaxid		Zymorxid
Zymaxid		Zymcrid
Zymaxid		Zymcrid

Appendix D: Names Lacking Orthographic and/or Phonetic Similarity.

Name	Similarity to Zymaxid
Tylox	Look
Symax SL	Look
Axid	Sound
Zymar	Look
Maxidex (DSI)	Look
Maxair (DSI)	Look and/or Sound
Robaxin (DSI)	Look and/or Sound
Xifaxan (DSI)	Look and/or Sound
Z-Pak (DSI)	Look and/or Sound
Zantac (DSI)	Look and/or Sound
Zilactin (DSI)	Look and/or Sound
Zithromax (DSI)	Look and/or Sound
Zmax (DSI)	Look and/or Sound
Zyprexa (DSI)	Look and/or Sound
Zymase (DSI)	Look and/or Sound

Appendix E: Proprietary or Established Name used only in Foreign Countries

Proprietary Name	Similarity to Zymaxid	Country
Zymad (colecalfiferol) - DSI	Look and Sound	France

Appendix F: Drug names not found in Micromedex, Drugs@FDA, Orange Book, Clinical Pharmacology Online, Lexi-Comp, Facts and Comparisons Online and Natural Medicines Database

Name	Similarity to Zymaxid	Comments
Zymecot	Look	Contains dehydrocholic acid and enzymes (per Redbook); used as a GI agent (exact indication not stated); product characteristics not available
Zymax (ephedra, 5-htp, L-carnitine, chromium picolinate, garcinia cambogia and other ingredients) Source: dogpile	Look and Sound	Herbal diet pill available for on-line purchase in the over-the-counter, self care marketplace.
Zimaxx (tyrosone Gyo Guram, Lycium fruit, Proline, Epimadium, glutamine Acid, Cistanche, Phenylalanine) Source: dogpile	Look and Sound	An oral product used for penis enhancement in the non-prescription, self-care marketplace.

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

Product name with potential for confusion	Similarity to Zymaxid	Strengths	Usual Dose
Zymaxid (gatifloxacin ophthalmic solution)	N/A	0.5%	Day 1: One drop every 2 hours in the affected eye(s) while awake up to 8 times. Days 2 through 5: One drop two times daily in the affected eye(s) approximately 12 hours apart
Zymine (triprolidine)	Look	1.25 mg per 5 mL oral liquid 2.5 mg per 5 mL oral suspension	10 mL every 4 to 6 hours not to exceed 40 mL in 24 hours
Zegerid (omeprazole and sodium bicarbonate)	Look	<u>Immediate release capsules:</u> 20 mg omeprazole and 1,100 mg sodium bicarbonate, 40 mg omeprazole and 1,100 mg sodium bicarbonate <u>Powder for oral suspension:</u> 20 mg omeprazole and 1,680 mg sodium bicarbonate, 40 mg omeprazole and 1,680 mg sodium bicarbonate	20 mg to 40 mg orally once daily for 4 to 8 weeks depending upon the diagnosis
Biaxin (clarithromycin)	Sound	250 mg, 500 mg oral tablets 125 mg per 5 mL, 250 mg per 5 mL oral granules for suspension	250 mg to 500 mg orally every 12 hours for 7 to 14 days
Primaxin (imipenem and cilastatin)	Sound	250 mg imipenem and 250 mg cilastatin powder for injection 500 mg imipenem and 500 mg cilastatin powder for injection	Intravenous: 250 mg to 1000 mg every 6 hours depending upon diagnosis Intramuscular: 500 mg to 750 mg every 12 hours depending upon diagnosis
Zyvox (linezolid) tablet, powder for oral suspension, injection	Look	Tablet: 600 mg Powder for oral suspension: 100 mg/5 mL Injection: 2 mg/mL	600 mg IV or oral every 12 hours

Appendix H: Single strength products with different product characteristics which will minimize the potential for medication errors with Zymaxid.

Product name with potential for confusion & Similarity to Zymaxid	Strengths	Usual Dose (if applicable)	Factors which make confusion with Zymaxid unlikely (Zymaxid vs. Product)
Zymaxid (gatifloxacin ophthalmic solution)	0.5%	Day 1: One drop every 2 hours in the affected eye(s) while awake up to 8 times. Days 2 through 5: One drop two times daily in the affected eye(s) approximately 12 hours apart	Dosage form: ophthalmic solution Dose: one drop Route of administration: ocular Frequency of administration: every 2 hours or every 12 hours
Gynecort (hydrocortisone acetate) cream	1%	Apply externally to the affected area (anus) no more than 3 to 4 times daily	Dosage form: cream Route of administration: topical Frequency of administration: 3 to 4 times daily
Maxzide (triamterene and hydrochlorothiazide) tablet (DSI)	75 mg/50 mg	Take one tablet daily	Dosage form: tablet Route of administration: oral Frequency of administration: daily
Synercid (quinupristin and dalfopristin) lyophilized injection	150 mg quinupristin and 350 mg dalfopristin	7.5 mg per kg intravenously every 8 to 12 hours depending upon diagnosis	Dosage form: lyophilized powder for injection Dose: 7.5 mg per kilogram Route of administration: intravenous
Lymerix (Lyme Disease Vaccine) Suspension for injection	30 mcg/0.5 mL	Give 0.5 mL intramuscularly as a 3-dose series on a 0, 1, 12-month schedule	Dosage form: suspension for injection Route of administration: intramuscularly Frequency of administration: 0, 1, and 12 months from tick exposure (as 3 shot series) Per Micromedex and Clinical Pharmacology, this drug product is no longer available in the United States.

Product I: Products with numerically similar or overlapping strengths but differentiating product characteristics.

Product name with potential for confusion	Similarity to Proposed Proprietary Name	Strength	Usual Dose	Differentiating Product Characteristics
Zymaxid (gatifloxacin ophthalmic solution)		0.5%	<p>Day 1: One drop every 2 hours in the affected eye(s) while awake up to 8 times.</p> <p>Days 2 through 5: One drop two times daily in the affected eye(s) approximately 12 hours apart</p>	<p>Dose form: ophthalmic solution</p> <p>Route of administration: ocular</p> <p>Strength: One strength available</p> <p>Frequency of administration: every 2 hours or every 12 hours</p>
Lanoxin (digoxin) tablet, injection, oral elixir (DSI)	Look or Sound	<p>Tablet: 0.125 mg, 0.25 mg</p> <p>Oral elixir: 0.05 mg/mL</p> <p>Injection: 0.25 mg/mL, 0.1 mg/mL</p>	Take 0.125 mg to 0.25 mg orally once daily	<p>Dosage form: tablet, oral solution, injection</p> <p>Route of administration: oral, intravenous</p> <p>Frequency of administration: once daily</p>

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22548	ORIG-1	ALLERGAN	GATIFLOXACIN OPHTHALMIC SOLUTION 0.5%

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

/s/

DENISE V BAUGH
11/13/2009

TODD D BRIDGES
11/13/2009

DENISE P TOYER
11/13/2009

CAROL A HOLQUIST
11/13/2009