

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

22-212

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: June 23, 2008

To: Wiley Chambers, M.D., Acting Director
Division of Anti-infective and Ophthalmology Products

Thru: Kellie Taylor, Pharm.D., MPH, Team Leader
Carol Holquist, RPh, Director
Division of Medication Error Prevention

From: Laura Pincock, RPh, Pharm.D., Safety Evaluator
Division of Medication Error Prevention

Subject: Memo regarding Durezol Review OSE RCM #2008-183

Drug Name(s): Durezol (Difluprednate Ophthalmic Emulsion) 0.05%

Application Type/Number: NDA 22-212

Applicant/sponsor: Sirion Therapeutics

OSE RCM #: 2008-183

1 INTRODUCTION

The Division of Medication Error Prevention completed a proprietary name, label, and labeling review for Durezol (OSE RCM #2008-183) on June 3, 2008 in which we recommended the proposed

_____ Subsequently, the Division of Anti-infective and Ophthalmology Products has clarified that the Applicant intends _____

_____ Additionally, per Dr. Chamber's email, the proposed dosing regimen when initiating therapy is four times daily, not twice a day as was our previous understanding. This new information has changed our overall risk assessment of this configuration as provided in our previous review.

2 MATERIAL REVIEWED

DMEDP has reviewed our initial proprietary name, label and labeling review for Durezol signed on June 3, 2008 in OSE RCM #2008-183. We have also reviewed the two emails from Dr. Wiley Chambers on June 23, 2008 that notified us of Sirion's intent to _____

3 DISCUSSION

As stated in our original review dated June 3, 2008 (page 14), DMEDP maintains that _____

However, Dr. Chambers' emails provided additional contextual information.

4 CONCLUSIONS AND RECOMMENDATIONS

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

/s/

Laura Pincock
6/23/2008 04:24:49 PM
DRUG SAFETY OFFICE REVIEWER

Kellie Taylor
6/23/2008 04:32:21 PM
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6/23/2008 04:34:35 PM
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**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: June 2, 2008

To: Janice Soreth, M.D., Director
Division of Anti-infective and Ophthalmology Products, HFD-520

Through: Kellie Taylor, Pharm.D., M.P.H., Team Leader
Carol Holquist, R.Ph., Director
Division of Medication Error Prevention, HFD-420

From: Laura Pincock, R.Ph., Pharm.D., Safety Evaluator
Division of Medication Error Prevention, HFD-420

Subject: Final Proprietary Name, Label, and Labeling Review

Drug Name(s): Durezol (Difluprednate ophthalmic emulsion) 0.05%

Application Type/Number: NDA 22-212

Applicant/sponsor: Sirion Therapeutics

OSE RCM #: 2008-183

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

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EXECUTIVE SUMMARY

The results of the Proprietary Name Risk Assessment found that the proposed name, Durezol, is vulnerable to name confusion that could lead to medication errors with the name _____ is not approved and it appears that the action date for _____ is scheduled after the action date for Durezol. If Durezol*** is approved first, DMEDP will recommend that the second product, _____ seek an alternate name. Thus at this time, the acceptability of the proprietary name, Durezol for this product is dependent on which application is approved first.

However, if the product approval is delayed beyond 90 days from the date of this review, the proposed name must be resubmitted for evaluation. Additionally, if any of the proposed product characteristics as stated in this review are altered prior to approval of the product, DMEDP rescinds this Risk Assessment finding, and recommends that the name be resubmitted for review.

The results of the Label and Labeling Risk Assessment found that the presentation of information and design of the proposed container labels and carton labeling appears to be vulnerable to confusion that could lead to medication errors. Specifically, DMEDP notes problems with the prominence, presentation, and consistency of information that is vital to the safe use of the product.

DMEDP believes the risks we have identified can be addressed and mitigated prior to drug approval, and provides recommendations in Section 6 that aim at reducing the risk of medication errors.

1 BACKGROUND

1.1 INTRODUCTION

This review is in response to a request from the Division of Anti-infective and Ophthalmology Products (HFD-520) for a final assessment of the proprietary name, Durezol, regarding potential name confusion with other proprietary or established drug names. DMEDP reviewed and did not recommend the use of the name the Sponsor previously proposed for this product, _____, in OSE review # 2007-472 dated March 22, 2007. That review noted the potential for look-alike confusion between _____ a medical device marketed in the U.S. Subsequently, the Sponsor had now proposed the alternate proprietary name, Durezol.

Additionally, the container labels, carton and insert labeling were provided for evaluation to identify areas that could lead to medication errors.

The product is proposed to be supplied in both multi-dose bottles. _____

Although this packaging is necessary from a chemistry and clinical perspective. _____

1.2 PRODUCT INFORMATION

Durezol (Difluprednate Ophthalmic Emulsion) 0.05%, is a topical steroid proposed to be indicated for the treatment of inflammation and pain associated with ocular surgery. The recommended dose is 1 drop instilled into the conjunctival sac of the affected eye(s) two times daily beginning 24 hours after surgery and continuing throughout the first 2 weeks of the postoperative period.

Durezol will be packaged in plastic bottles with a controlled drop top and cap in two sizes: mL fill in a 5 mL bottle and 5 mL fill in a 5 mL bottle. Additionally,

Durezol should be stored at room temperature (25 °C)

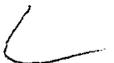
There are shapes of plastic dropper bottles (oval shaped) proposed for each size (and 5 mL) of Durezol, resulting in packing configurations for the bottles of Durezol.

¹ Drug Safety and Risk Management Advisory Committee, Meeting transcript, May 5, 2004,

² Guidance for Industry, Inhalation Drug Products Packaged in Semipermeable Container Closure Systems (Draft), Food and Drug Administration, Center for Drug Evaluation and Research, July 2002.

professional sample carton and one as a commercially available carton. In summary, there are proposed packaging configurations for Durezol.

- 
- Plastic Dropper Bottle, Oval Shaped, 7 mL size
- Plastic Dropper Bottle, Oval Shaped, 5 mL size

- 
- 

2 METHODS AND MATERIALS

This section consists of two sub-sections which describe the methods and materials used by DMEDP medication error staff conducting a proprietary name risk assessment (see 2.1 Proprietary Name Risk Assessment) and label, labeling, and/or packaging risk assessment (see 2.2 Container, Carton Label, and Insert Label Risk Assessment). The primary focus for both of the assessments is to identify and remedy potential sources of medication error prior to drug approval. DMEDP 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

2.1 PROPRIETARY NAME RISK ASSESSMENT

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

For the proprietary name, Durezol, the medication error staff of DMEDP 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). DMEDP normally conducts internal CDER prescription analysis studies and, when provided, external prescription analysis studies results are considered and incorporated into the overall risk assessment.

The Safety Evaluator assigned to the Proprietary Name Risk Assessment is responsible for considering the collective findings, and provides an overall risk assessment of the proposed proprietary name (see detail 2.1.2). 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.⁴ 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. DMEDP 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

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.

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

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

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 'D' 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.^{6,7}

To identify drug names that may look similar to Durezol, the Staff also consider the orthographic appearance of the name on lined and unlined orders. Specific attributes taken into consideration include the length of the name (seven letters), downstrokes (one, lower case scripted letter 'z'), and upstrokes (two, capital letter 'D' and lower case letter 'l'). Additionally, several letters in Durezol may be vulnerable to ambiguity when scripted, including the capital letter 'D' may appear as capital 'S'; lower case 'u' may look like lower case 'i', or 'n'; lower case 'r' may look like lower case 'n'; lower case letter 'e' may appear as lower case 'l' or 'i' or 'o'; lower case 'z' may appear as lower case 'g' or 'y' or 'm'; lower case 'o' may appear as lower case 'a' or 'e'; and lower case 'l' may appear as lower case 'e'. As such, the Staff also considers these alternate appearances when identifying drug names that may look similar to Durezol.

When searching to identify potential names that may sound similar to Durezol, the Medication Error Staff search for names with similar number of syllables (3), stresses (Dur-i-zahl or Dur-ah-zole), and placement of vowel and consonant sounds. The Sponsor's intended pronunciation of the proprietary name could not be expressly taken into consideration, as this was not provided with the proposed name submission.

The Staff also consider the product characteristics associated with the proposed drug throughout the identification of similar drug names, since the product characteristics of the proposed drug ultimately determine the use of the product in the clinical practice setting. For this review, the Medication Error Staff were provided with the following information about the proposed product: the proposed proprietary name (Durezol), the established name (Difluprednate ophthalmic emulsion), proposed indication (treatment of ocular pain and inflammation), strength (0.05%), dose (1 drop), frequency of administration (twice daily for about 2 weeks), route (topical ophthalmic), and dosage form (ophthalmic emulsion).

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

⁶ Institute for Safe Medication Practices. Confused Drug name List (1996-2006). Available at <http://www.ismp.org/Tools/confuseddrugnames.pdf>

⁷ Kondrack, G and Dorr, B. Automatic Identification of Confusable Drug Names. Artificial Intelligence in Medicine (2005)

Appendix A provides a more detailed listing of the product characteristics the Medication Error Staff generally take into consideration.

Lastly, the Medication Error Staff also consider the potential for the proposed name to inadvertently function as a source of error for reasons other than name confusion. 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 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, Durezol, was provided to the medication error staff of DMEDP 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 Durezol 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 Medication Error 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 Medication Error Staff review the USAN stem list to determine if any USAN stems are present within the proprietary name. The findings of the individual Safety Evaluators were then pooled and presented to the Expert Panel.

2.1.1.2 CDER Expert Panel Discussion

An Expert Panel Discussion is held by DMEDP to gather CDER professional opinions on the safety of the product and the proprietary name, Durezol. Potential concerns regarding drug marketing and promotion related to the proposed names are also discussed. This group is composed of the Division of Medication Errors Prevention 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, the Safety Evaluator Risk Assessment applies their individual expertise gained from evaluating medication errors reported to FDA to conduct a Failure Modes and Effects Analysis and provide an overall risk of name confusion. Failure Mode and Effects Analysis (FMEA) is a systematic tool for evaluating a process and identifying where and how it might fail.⁸ When applying FMEA to assess the risk of a proposed proprietary name, DMEDP seeks to evaluate the potential for a proposed name to be confused with another drug name as a result of the name confusion and cause errors to occur in the medication use system. FMEA capitalizes on the predictable and preventable nature of medication errors associated with drug name confusion. FMEA allows the Agency to identify the potential for medication errors due to look- or sound-alike drug names prior to approval, where actions to overcome these issues are easier and more effective than remedies available in the post-approval phase.

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

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

In the initial stage of the Risk Assessment, the Safety Evaluator compares the proposed proprietary name to all of the names gathered from the above searches, expert panel evaluation, and studies, and identifies potential failure modes by asking: "Is the name Durezol 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 Durezol 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 name possesses 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.

DMEDP 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. DMEDP identifies that the proposed proprietary name is misleading because of similarity in spelling or pronunciation to another proprietary or established name of a different drug or ingredient [CFR 201.10.(C)(5)].
3. FMEA identifies potential for confusion between the proposed proprietary name and other proprietary or established drug names, and demonstrates that medication errors are likely to result from the drug name confusion under the conditions of usual clinical practice.
4. The proposed proprietary name contains an USAN stem, particularly in a manner that is contradictory to the USAN Council's definition.
5. Medication Error Staff identify a potential source of medication error within the proposed proprietary name. The proprietary name may be misleading, or inadvertently introduce ambiguity and confusion that leads to errors. Such errors may not necessarily involve confusion between the proposed drug and another drug product.

In the event that DMEDP objects to the use of the proposed proprietary name, based upon the potential for confusion with another proposed (but not yet approved) proprietary name, DMEDP will provide a contingency objection based on the date of approval: whichever product is awarded approval first has the right to the use the name, while DMEDP will recommend that the second product to reach approval seek an alternative name.

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

Furthermore, DMEDP 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 Sponsor, 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 Sponsor's have changed a product's proprietary name in the post-approval phase, it is difficult to eradicate the original proprietary name from practitioner's vocabulary, and as such, the Agency has continued to receive reports of drug name confusion long after a name change in some instances. Therefore, DMEDP 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 DMEDP 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. DMEDP is likely to recommend that the Sponsor select an alternative proprietary name and submit the alternate name to the Agency for DMEDP 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 DMEDP may be able to provide the Sponsor with recommendations that reduce or eliminate the potential for error would render the proposed name acceptable.

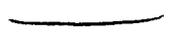
2.2 LABEL AND LABELING RISK ASSESSMENT

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

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

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

For this product the Sponsor submitted via e-mail on December 26, 2007, the following labels, carton, and insert labeling for DMEDP review (see Appendix H and I for images):

- Container Labels for Durezol Bottles ( bottle shapes in two sizes) 
- Carton Labeling for Durezol Bottles ( bottle shapes in two sizes) 
- Insert Labeling (no image)

3 RESULTS

3.1 PROPRIETARY NAME RISK ASSESSMENT

3.1.1 Database and information sources

DMEDP conducted a search of the internet, several standard published databases and information sources (see Section 7 References) for existing drug names which sound-alike or look-alike to Durezol to a degree where potential confusion between drug names could occur and result in medication errors in the usual clinical practice settings. Our search yielded a total of 17 names identified as having some similarity to the name Durezol.

Six of the 17 names were thought to look like Durezol. These include Diuril, Claripel, Donepezil, Clozarol, Diurex, and Divigel. Four names (Doral, Toradol, Duraclon, and Duragesic) were thought to sound like Durezol. The remaining seven names were thought to look and sound similar to Durezol (Ezol, Terazol, Dutoprol, Duricef, Danazol, Durasal II, and Duricol). A search of the United States Adopted Name stem list on May 12, 2008 identified no USAN stems within the proposed name, Durezol.

3.1.2 Expert panel discussion

The Expert Panel reviewed the pool of names identified by DMEDP staff (see section 3.1.1. above). 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 an additional six names that were thought to look similar to Durezol and represent a potential source of drug name confusion. The names are: Doryx, , Drysol, Droloxol, and Droxyl. A search of the United States Adopted Name stem list on April 22, 2008 identified no USAN stems within the proposed name, Durezol. As such, a total of 23 names were analyzed to determine if the drug names could be confused with Durezol and if the drug name confusion would likely result in a medication error.

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

All of the identified names were determined to have some orthographic and/or phonetic similarity to Durezol, and thus determined to present some risk of confusion. Failure mode and effect analysis was then applied to determine if the potential name, Durezol, could potentially be confused with any of the 23 names and lead to medication errors.

This analysis determined that the name similarity between Durezol and the identified names was unlikely to result in medication error for four of the 23 products. Two names (Droxyl and Drolox) were marketed outside the U.S. and both are no longer marketed (see Appendix B). Two names (Durasal II, and Dutoprol) are no longer marketed in the U.S. (See Appendix C).

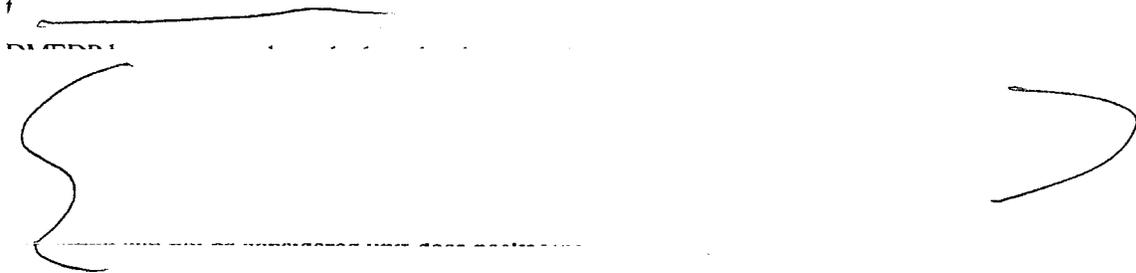
For 15 of the 23 names identified, FMEA determined that medication errors were unlikely because they do not overlap in strength or dose with Durezol and/or have minimal orthographic and/or phonetic similarity to Durezol (Appendix E). Two of the 23 names, (Claripel and Drysol) are available in one strength leading to the omission of the strength in a prescription or requisition for the product. However, FMEA determined the products contain multiple differentiating product characteristics such as dose, dosage form, route of administration, specialized area of use, indication, and prescribers which minimize the potential for confusion between these products (Appendix F)

The names having some numerical overlap with Durezol in either strength or dose include _____ and Divigel. However, analysis of the failure mode of these two product names determined the effect of this similarity to result in medication errors in the usual practice setting was likely for only one product, _____ (see Appendix G).

3.2 LABEL AND LABELING RISK ASSESSMENT

Review of the container labels and carton labeling identified several areas of vulnerability that could lead to medication error, specifically with respect to the proper use of the product, product strength, and route of administration.

In general, DMEDP is confused as to why _____ shapes of bottles (e.g., _____ oval shape) are proposed for each size of Durezol (_____ mL and 5 mL)? _____



3.2.1 Container Labels

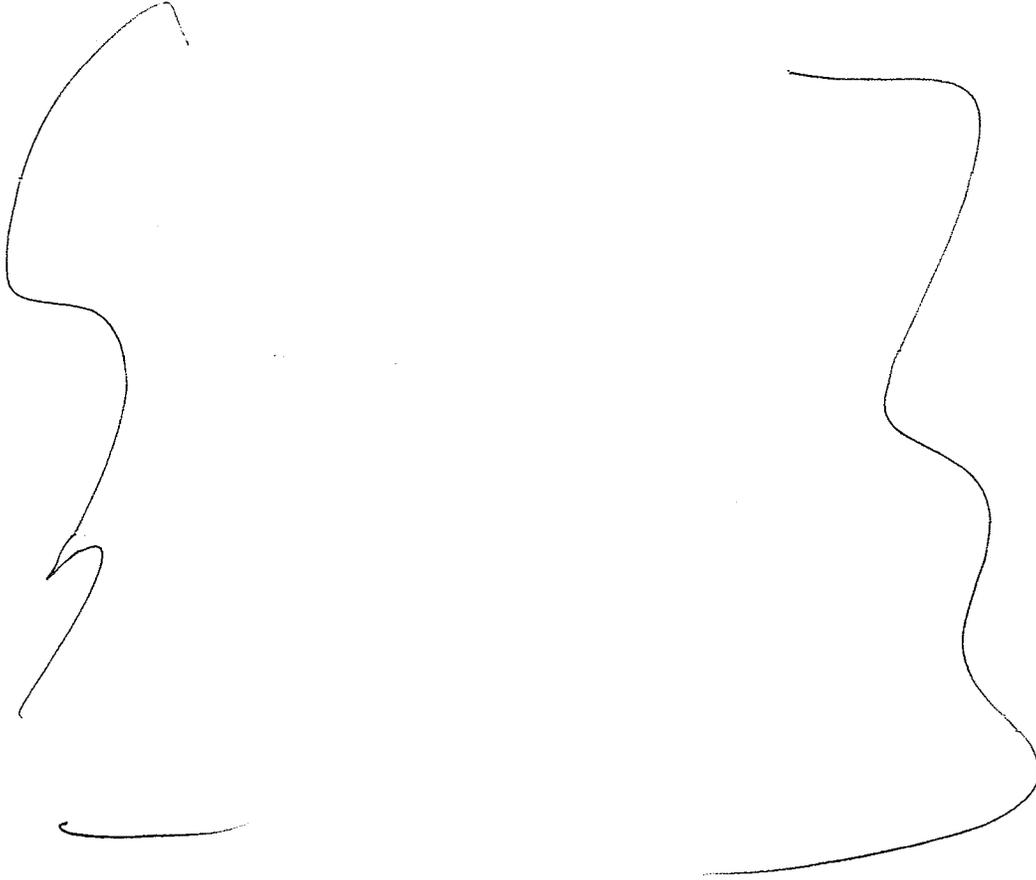
The established name does not appear to be at least one half the size of the proposed proprietary name, as required by 21 CFR 201.10(g)(2).

3.2.2 Carton Labeling

The established name does not appear to be at least one half the size of the proposed proprietary name, as required by 21 CFR 201.10(g)(2).

The net quantity on the bottle cartons (_____ mL and 5 mL) lacks differentiation between the two sizes.

4.2.2 Carton Labeling



4.2.3 Insert Labeling

When evaluating the insert labeling, we noted that the Patient Counseling Information section of the Full Prescribing Information does not state



5 CONCLUSIONS

The Proprietary Name Risk Assessment findings indicate that the proposed name, Durezol is vulnerable to name confusion that could lead to medication errors in the current marketplace. However, _____ is still under evaluation. Should both products and proposed names be approved, the potential for medications errors to occur is greatly increased. Therefore, whichever product is awarded approval first has the right to use the name, and DMEDP recommends that the second product seek an alternate name. It appears that the approval decision for _____ is scheduled after the action date for _____

Durezol. If Durezol is approved first, DMEDP will recommend that the second product, _____, seek an alternate name. Additionally, if any of the proposed product characteristics as stated in this review are altered prior to approval of the product; DMEDP 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 days from the date of this review, the proposed name must be resubmitted for evaluation.

The Label and Labeling Risk Assessment findings indicate that the presentation of information and design of the proposed container labels and carton labeling introduces vulnerability to confusion that could lead to medication errors. Specifically, DMEDP notes problems with the prominence, presentation, and consistency of information that is vital to the safe use of the product. DMEDP believes the risks we have identified can be addressed and mitigated prior to drug approval, and provides recommendations in Section 6 that aim at reducing the risk of medication errors.

 This conclusion is supported by the recommendations of the Drug Safety and Risk Management Advisory Committee (See Section 1.1 Introduction), as well as the findings of the Label and Labeling Risk Assessment. 

DMEDP 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 DMEDP on any communication to the sponsor with regard to this review. If you have further questions or need clarifications, please contact Cheryle Milburn, project manager, at 301-796-2084.

6 RECOMMENDATIONS FOR THE SPONSOR

6.1 Proprietary name:

DMEDP has determined the name Durezol is vulnerable to confusion with a product that is currently undergoing review by the Agency. In the event that the other application is awarded approval prior to your application, DMEDP recommends that you seek an alternate name for your product.

If the product approval is delayed beyond 90 days from the date of this review, the proposed name must be resubmitted for evaluation. Additionally, if any of the proposed product characteristics as stated in this review are altered prior to approval of the product, DMEDP rescinds this Risk Assessment finding, and recommends that the name be resubmitted for review.

6.2 Labels and Labeling:

6.2.1 General Comments

6.2.2 Container Labels

1. Revise the font of the proprietary and established names so that the established name is at least one half the size of the proprietary name per 21 CFR201.10(g)(2).

6.2.3 Carton Labeling

1. 
2. Revise the fonts of the proprietary and established names so that the established name is at least one half the size of the proprietary name per 21 CFR201.10(g)(2).
3. On the bottle cartons, differentiate between the  of bottles 7 mL and 5 mL) through the use of colored font or other prominent means of differentiation.

4.

5.

6.2.4 Insert Labeling

1.

Appears This Way
On Original

7 REFERENCES

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

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

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

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

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

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

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

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

5. ***Division of Medication Errors and Technical Support proprietary name consultation requests***

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

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

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

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

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

8. ***United States Patent and Trademark Office <http://www.uspto.gov>.***

Provides information regarding patent and trademarks.

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

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

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

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

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

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

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

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

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

List contains all the recognized USAN stems.

14. Red Book Pharmacy's Fundamental Reference

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

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

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

16. Medical Abbreviations Book

Contains commonly used medical abbreviations and their definitions.

APPENDICES

Appendix A:

The Medication Error Staff consider the spelling of the name, pronunciation of the name when spoken, and appearance of the name when scripted. DMEDP also compare the spelling of the proposed proprietary name with the proprietary and proper 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 (e.g., "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, DMEDP will consider the Sponsor's intended pronunciation of the proprietary name.

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

Appendix B: Proprietary names used only in Foreign Countries

Proprietary Name	Similarity to Durezol	Country
Droxyl	Look Sound	Thailand (no longer marketed)
Droxol	Look Sound	Argentina (no longer marketed)

Appendix C: Products no longer marketed. No generic equivalent products currently available or product was a generic equivalent.

Proprietary Name	Similarity to Durezol
Durasal II	Look Sound
Dutoprol	Look Sound

Appendix D: Proposed proprietary names for products not yet approved or approved with another name.

Proprietary Name	Similarity to Durezol
_____	Look
_____	Look Sound

***These names are proprietary and confidential information that should not be released to the public.

Appendix E: Products with no overlap in strength and dose.

Product name with potential for confusion	Similarity to Proposed Proprietary Name	Strength	Usual Dose (if applicable)
Durezol (Difluprednate Ophthalmic Emulsion)	N/A	0.05%	Usual dose: 1 drop into conjunctival sac of the affected eye(s) twice daily beginning 24 hours after surgery and continuing throughout the first 2 weeks of the postoperative period.
Diuril (Chlorothiazide)	Look	250 mg, 500 mg, 250 mg/5 mL	500 -1000 mg/day orally in 1-2 divided doses 500-1000 mg intravenously once or twice daily by intravenous infusion or slow intravenous injection
Donepezil	Look	5 mg, 10 mg	5 mg or 10 mg by mouth once a day
Clozaril (Clozapine)	Look	25 mg, 100 mg	1 tablet once daily (12.5-25 mg) titrated up daily (by 25 -50 mg increments) to 300-450 mg/day
Diurex product line (Various over-the-counter monographed drugs)	Look	50 mg (Aquagels) 50 mg (Water capsules) 50 mg (Maximum relief water caplets) 50 mg/192.5 mg (Water pills) 25 mg/500 mg/15 mg (PMS Formula caplets)	Aquagels, Water capsules, Water caplets: 1 pill after breakfast with a full glass of water. Dose may be repeated after 6 hours, not to exceed 4 pills in 24 hours. Water pills and PMS Formula caplets: 2 pills every 4 to 6 hours, not to exceed 8 pills in 24 hours
Doral	Sound	7.5 mg, 15 mg	7.5 or 15 mg orally once daily at bedtime.
Toradol (ketorolac)	Sound	10 mg, 15 mg/mL, 30 mg/mL	30 or 60 mg intramuscularly every 6 hours 15 or 30 mg intravenously every 6 hours 10-20 mg orally every 4 to 6 hours. Do not exceed 40 mg/day or use for longer than 5 days.
Duraclon (clonidine)	Sound	100 mcg/mL, 500 mcg/mL	The recommended starting dose for continuous epidural infusion is 30 mcg/hr. Although dosage may be titrated up or down depending on pain relief and occurrence of adverse events, experience with dosage rates above 40 mcg/hr is limited.
Duragesic (fentanyl)	Sound	12.5 mcg/hr, 25 mcg/hr, 50 mcg/hr, 75 mcg/hr,	Apply a new patch every 72 hours. Some patients may require a new patch every 48 hours.

		100 mcg/hr	
Ezol (Butalbital/Acetaminophen/Caffeine)	Look Sound	No information available, but multiple strength	One or 2 capsules every four hours as needed for headache. Do not exceed 6 capsules per day.
Terazol 3 Terazol 7 (terconazole)	Look Sound	0.4%, 0.8%, 80 mg	1 full 5 g applicator (20 mg terconazole for 0.4% vaginal cream; 40 mg terconazole for 0.8% vaginal cream) or 1 terconazole vaginal suppository (80 mg) should be administered intravaginally once daily at bedtime for 3 consecutive days.
Duricef (Cefadroxil)	Look Sound	500 mg, 1 g, 125 mg/5 mL, 250 mg/5 mL, 500 mg/5 mL	1 or 2 g per day in single (once daily) or divided doses (twice daily).
Danazol	Look Sound	50 mg, 100 mg, 200 mg	200 to 400 to 800 mg in 2 divided doses daily depending on severity of symptoms. Dose may be titrated to response.
Duricol (Chloramphenicol)	Look Sound	50 mg, 100 mg, 250 mg, 500 mg	Veterinary preparation Dogs: 25 mg per pound of body weight every 6 hours
Doryx (Doxycycline hyclate)	Look	75 mg, 100 mg	One capsule by mouth twice daily

Appendix F: Products with a single strength but have multiple differentiating product characteristics

Product name with potential for confusion	Similarity and Proposed Proprietary Name	Strength	Usual Dose (if applicable)	Other differentiating product characteristics (excluding dose and frequency)
Durezol (Brimonidine Ophthalmic Emulsion)	N/A	0.05%	Usual dose: 1 drop into conjunctival sac of the affected eye(s) 4 times daily beginning 24 hours after surgery and continuing throughout the first 2 weeks of the postoperative period.	N/A
Claripel (Hydroquinone Topical Cream with Sunscreen)	Look	4%	Apply to the affected area of skin twice daily	Dose Dosage form Route of administration Area of use Indication

Drysol (Aluminum chloride topical solution)	Look Sound	20%	Apply to the affected area (underarms, palms of feet and hands) once daily, only at bedtime.	Dose Dosage form Route of administration Area of use Indication
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Appendix G: Potential confusing name with numerical overlap in strength or dose

Durezol	0.05%	Usual dose: 1 drop into conjunctival sac of the affected eye(s) twice daily beginning 24 hours after surgery and continuing throughout the first 2 weeks of the postoperative period.
Failure Mode Name Confusion	Causes (could be multiple)	Effects

<p>Divigel (Estradiol topical gel)</p>	<p>Orthographic similarity. Each contains seven letters, starts and ends with the same letters "D" and "L". Letters "y" and "z" are similar when scripted and sit on the same position of the name. Share a similar strength/dose (0.05% vs 0.5 g/day). Same directions for use. Apply</p>	<p>Predict character sets minimize the likelihood of medication error in the usual practice setting.</p> <p><i>Rationale:</i></p> <p>Orthographic differences stem from the doubling of the two letters.</p> <p>Divigel prescriptions would have to specify a dose (X%) or number of packets applied per day. Divigel prescriptions may also contain the strength of the product (0.1%) or the net quantity of 30 packets per box.</p> <p>Durezol is for topical application to the eye after surgery, whereas Divigel is for topical application to the upper thigh. Application to such specific and separate areas of the body, well known to each patient, increases the detectability if an error were to occur.</p> <p>Divigel 0.1% supplied as 0.25 g/day packet, 0.5 g/day packet, and 1 g/day packet in boxes of 30 packets.</p> <p>Apply contents of unit dose packet to upper thigh once daily. Start with 0.25 g/day packet and titrate dose to desired response.</p>
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 § 552(b)(4) Trade Secret / Confidential

X § 552(b)(4) Draft Labeling

 § 552(b)(5) Deliberative Process

None I

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/s/

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