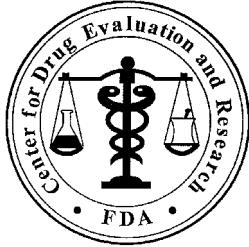


**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
200-890

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: March 22, 2010

To: Wiley Chambers, MD, Acting Director
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Division of Medication Error Prevention and Analysis

Subject: Proprietary Name Review

Drug Name(s): Isopto Carpine (Pilocarpine Hydrochloride) Ophthalmic Solution
1%, 2% and 4%

Application Type/Number: NDA 200890

Applicant: Alcon

OSE RCM #: 2010-84

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

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EXECUTIVE SUMMARY

Isopto Carpine is the proposed proprietary name for Pilocarpine Hydrochloride Ophthalmic Solution. Isopto Carpine is currently marketed “Grandfathered” pre-38 drug and is currently on FDA’s list of “Medically Necessary Unapproved Marketed Drugs”. 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, Isopto Carpine, 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 Alcon for an assessment of the proposed proprietary name, Isopto Carpine, regarding potential name confusion with other proprietary or established drug names in the usual practice settings.

Additionally, container labels and carton labeling were provided for review and comment and will be reviewed in a separate review.

1.2 REGULATORY HISTORY

Isopto Carpine (Pilocarpine Hydrochloride) ophthalmic solution is a currently marketed “Grandfathered” pre-38 drug and is currently on FDA’s list of “Medically Necessary Unapproved Marketed Drugs”. The Applicant has used the proprietary name, Isopto Carpine. The Review Division requested the Applicant to submit an NDA for this product.

1.3 PRODUCT INFORMATION

Isopto Carpine ophthalmic solution is indicated for the following indications: open-angle glaucoma or ocular hypertension; acute angle-closure glaucoma; prevention of (b)(4) post-operative elevated intraocular pressure; and induction of miosis. The recommended dose is 1 drop in the eye(s) up to four times daily. It is available in 1% (10 mg/mL), 2% (20 mg/mL) and 4% (40 mg/mL) strengths in 15 mL LDPC plastic DROP-TAINER dispenser with green LDPE tips and caps.

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 and 2.2 identify specific information associated with the methodology for the proposed proprietary name, Isopto Carpine.

2.1 SEARCH CRITERIA

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

For this review, particular consideration was given to drug names beginning with the letter ‘I’ 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}

DMEPA staff considers ‘Isopto Carpine’ as a complete name as well as ‘Isopto’ and ‘Carpine’ as separate names. To identify drug names that may look similar to Isopto Carpine, 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 (13 letters), upstrokes (three, capital letter ‘I’ and ‘C’ and lower case ‘t’); downstrokes (two, lower case ‘p’), cross-strokes (one, ‘t’), and dotted letters (one, lower case ‘i’). Additionally, several letters in Isopto Carpine may be vulnerable to ambiguity when scripted, including the capital letter ‘I’ may appear as ‘A,’ ‘E,’ ‘C,’ ‘J,’ ‘S’ or ‘T’; lower case ‘s’ may appear as ‘i’ or ‘s’; lower case ‘a,’ ‘e,’ ‘i’ and ‘o’ may appear as any of the vowels; lower case ‘p’ may appear as lower case ‘f,’ ‘g’ or scripted ‘z’; lower case ‘r’ may appear as ‘n’ or ‘i’; lower case ‘n’ may appear as ‘m’ or ‘r’; and lower case ‘t’ may appear as lower case lower case ‘h,’ ‘l’ or ‘x’. As such, the DMEPA staff also considers these alternate appearances when identifying drug names that may look similar to Isopto Carpine.

When searching to identify potential names that may sound similar to Isopto Carpine, DMEPA staff searches for names with similar number of syllables (five), stresses (i-SOP-to CAR-pine, I-sop-to CAR-pine, i-sop-TO CAR-pine, i-SOP-to car-PINE, I-sop-to car-PINE, i-sop-TO car-PINE), and placement of vowel and consonant sounds. Additionally, several letters in Isopto Carpine may be vulnerable to misinterpretation when spoken, including ‘I’ may be interpreted as ‘eye’ or ‘ee’; ‘-pine’ may be interpreted as ‘pin’ or ‘pah-in’; and ‘s’ may be interpreted as ‘c’. As such, the staff also considers these alternate pronunciations when identifying drug names that may sound similar to Isopto Carpine. The Applicant’s intended pronunciation of the proprietary name (i sop ‘to kar pen) was provided and taken into consideration.

2.2 MEDICATION ERROR RISK ASSESSMENT

DMEPA searched the FDA Adverse Event Reporting System (AERS) for medication errors involving Isopto Carpine. In addition, we requested data from the Institute of Safe Medication Practices (ISMP)^{*} databases.

2.2.1 AERS Search

Since Isopto Carpine is already marketed in the U.S., the FDA Adverse Event Reporting System (AERS) was searched for post-marketing safety reports concerning medication errors associated with use of the product. The search was conducted using the verbatim term “Isopto Carp%” and MedDRA Higher Level Group Term (HLGT) “Medication Errors” and “Product Quality Issues.”

The cases were manually reviewed to determine if a relevant medication error involving Isopto Carpine occurred. Duplicate cases and cases considered not relevant to this review were eliminated from further analysis.

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)

^{*} This document contains proprietary data from the Institute for Safe Medication Practices (ISMP) and Quantros which cannot be shared outside of the FDA. Users wanting this information must contact Matthew Grissinger, RPh, FISMP, FASCP, Director, Error Reporting Programs at (215) 947-7797.

2.2.2 ISMP* Databases

DMEPA requested a search of the ISMP's databases for medication error cases involving Isopto Carpine. The cases from one of the databases captures errors reported between September 2008 and February 2010 and another database captures errors reported between February 2009 and February 2010.

2.2.2.1 Quantros* Database

The cases from Quantros database captures errors reported with Pilocarpine and Pilocarpine Hydrochloride between from January 01, 2004 to January 25, 2010.

2.3 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 prescription was communicated during the FDA prescription studies.

Figure 1. Isopto Carpine Rx Study (conducted on January 26, 2010)

HANDWRITTEN REQUISITION MEDICATION ORDER	VERBAL PRESCRIPTION
<p><u>Inpatient Medication Order :</u> <i>“Isopto Carpine 1% instill one drop in right eye TID</i></p>	<p>Isopto Carpine 1% Instill one drop in right eye three times daily</p>
<p><u>Outpatient Prescription:</u> <i>Isopto Carpine #1 Instill 1 drop to right eye tid</i></p>	

3 RESULTS

3.1 DATABASE AND INFORMATION SOURCES

The searches yielded a total of 13 names as having some similarity to the name, Isopto Carpine.

Two of the 13 names were thought to look like Isopto Carpine. These names are (b) (4)*** and Carimune. The remaining 11 of 13 names (Isoptin, Isoptin SR, Isopto Alkaline, Isopto Atropine, Isopto Carbachol, Isopto Carpina, Isopto Cetamide, Isopto Cetapred, Isopto Homatropine, Isopto Hyoscine, Isopto Tears) were thought to both look and sound like Isopto Carpine.

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DMEPA staff did not identify any United States Adopted Names (USAN) stems in the proposed proprietary name, as of February 3, 2010.

3.2 EXPERT PANEL DISCUSSION

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

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 MEDICATION ERROR RISK ASSESSMENT

3.3.1 AERS Cases

The search did not result in any medication error cases associated with the use of Isopto Carpine in the FDA AERS database.

3.3.2 ISMP* Database

The search of the database did not result in any product selection errors with Isopto Carpine. However, the search resulted in eight medication errors with Pilocarpine but none were related to name confusion with Isopto Carpine. All eight cases were related to incorrect strength errors. The relevant cases will be reviewed and addressed in our forthcoming label and labeling review.

3.3.2.1 Quantros* Database

The search for medication error cases associated with “Pilocarpine” resulted in 45 cases all of which involved the branded product, Salagen, therefore were not further analyzed.

The search for medication error cases associated with “Pilocarpine Hydrochloride” resulted in 85 cases. Forty of the 85 cases involve the branded products, Pilocar or Pilopine HS, therefore, these cases were not further analyzed. The remaining 45 cases did not specify which branded Pilocarpine Hydrochloride product was involved. The 45 cases are categorized as the following:

- Prescribing error (missing strength, dose or direction on prescriptions): n=20
- Wrong strength (dispensed or typed): n=7
- Wrong drug: n=7
- Wrong dosage form: n=3
- Computer entry error (refill entered wrong): n=2
- Wrong directions during dispensing: n=1
- Wrong quantity/size dispensed: n=2
- NAI (used abbreviations, incorrect stop date, non-formulary drug): n=3

The 7 cases of wrong drug involved confusion with the following drugs: Aciphex (n=1), Carbachol (n=1), Mydriacyl + Neosynephrine (n=1), Tetracaine (n=2), Timoptic (n=1), and non-specific drug (n=1). Given

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the limited information provided and that the cases were not specific to Isopto Carpine, it is difficult to assess the significance of these name confusion, especially with regards to the proposed name, Isopto Carpine.

The other relevant medication error cases will be addressed in our forthcoming labels and labeling review.

3.4 FDA PRESCRIPTION ANALYSIS STUDIES

A total of 44 practitioners responded to the prescription analysis studies, but none of the responses overlapped with any existing or proposed drug names. Twenty-four respondents interpreted the name correctly as Isopto Carpine or Isoptocarpine. The remainder of the respondents (n=20) misinterpreted the drug name, primarily because ‘I’ was misinterpreted as ‘A’ in the verbal and written studies. The letter ‘t’ was misinterpreted as ‘l’ or ‘h’; ‘r’ was misinterpreted as ‘n’ or ‘i’; ‘n’ was misinterpreted as ‘r’; ‘e’ was misinterpreted as ‘a’ or ‘o’; and ‘o’ was misinterpreted as ‘i’ in the written studies. In the verbal study, ‘sop’ was misinterpreted as ‘sac’ or ‘ci’. See Appendix B for the complete listing of interpretations from the verbal and written prescription studies.

3.5 COMMENTS FROM THE REVIEW DIVISIONS

3.5.1 Initial Phase of Review

In response to the OSE January 22, 2010 e-mail, the Division of Anti-Infective and Ophthalmology Products (DAOP) did not object to the proposed proprietary name, Isopto Carpine.

3.5.2 Midpoint of Review

On February 25, 2010, DMEPA notified DAOP via e-mail that we had no objections to the proposed proprietary name, Isopto Carpine. Per e-mail correspondence from DAOP on March 18, 2010, they indicated that they concur with our assessment of the proposed proprietary name, Isopto Carpine.

3.6 SAFETY EVALUATOR RISK ASSESSMENT

Independent searches by the primary Safety Evaluator resulted in three additional names (Azopt, Isopto Frin and Isopto Plain) thought to look and sound similar to Isopto Carpine and represent a potential source of drug name confusion.

Upon further observation, one of the names, Isopto Carpina (Spain) is a foreign product; therefore, the name was eliminated from further analysis.

Thus, we evaluated a total of 15 names for their similarity to the proposed name.

4 DISCUSSION

4.1 ALCON’S USE OF THE PREFIX “ISOPTO”

Alcon uses the prefix “Isopto” in many of their proprietary names for ophthalmic products. According to the Applicant’s website, there are eight other “Isopto” products besides Isopto Carpine: Isopto Alkaline, Isopto Atropine, Isopto Carbachol, Isopto Carpine, Isopto Cetapred, Isopto Frin, Isopto Homatropine, Isopto Hyoscine, Isopto Plain, and Isopto Tears. DMEPA also identified Isopto Cetamide in Drugs@FDA website. According to the Applicant, only 6 of the Isopto products are currently marketed: Isopto Atropine, Isopto Carbachol, Isopto Carpine, Isopto Homatropine, Isopto Hyoscine, and Isopto Tears. The Applicant states the prefix “Isopto” is contrived from the name of the product vehicle which contains hypromellose and various salts.

Typically, DMEPA discourages the use of common prefixes such as “Isopto” because the proliferation of use may increase the risk of name confusion between all the “Isopto” products especially since they share many overlapping product characteristics such as dosage form, route of administration, strengths, and dose (see Appendix H). However, we were unable to identify any post marketing medication errors associated with the use of the proposed name, Isopto Carpine. Therefore, we believe that continued use of the proposed proprietary name is appropriate since there are no other Isopto products currently approved by the Agency.

Additionally, DMEPA notes that all the currently marketed Isopto products are pre-38, unapproved products. The two products that were approved by the Agency (Isopto Cetamide and Isopto Cetapred) were not reviewed by DMEPA and have been discontinued. Additionally, we noted that many of the Isopto products contain a portion of the active ingredient or the whole established name in the proprietary names. We discourage the use of the active ingredients in proprietary names since the active ingredients should only be reserved for use in the established name. Additionally, we discourage continue development of other product names using the same prefix “Isopto” because proliferation of this prefix will increase the look and sound alike similarity of your class of products that already have many overlapping product characteristics.

4.2 ISOPTO CARPINE SAFETY ASSESSMENT

Neither DDMAC nor the Division of Anti-Infective and Ophthalmology Products (DAOP) had concerns with the proposed name, Isopto Carpine.

DMEPA identified and evaluated 15 names for their potential similarity to the proposed name. One name lacked orthographic and/or phonetic similarity and was not evaluated further (see Appendix C). Failure mode and effect analysis (FMEA) was then applied to determine if the proposed proprietary name could potentially be confused with the remaining 14 names and lead to medication errors. This analysis determined that the name similarity between Isopto Carpine was unlikely to result in medication errors with 9 of the remaining 14 names for the reasons presented in Appendices D through G. Thus, DMEPA has no objection to the proprietary name, Isopto Carpine.

5 CONCLUSIONS AND RECOMMENDATIONS

The Proprietary Name Risk Assessment findings indicate that the proposed name, Isopto Carpine, is vulnerable to name confusion that could lead to medication errors with other Alcon’s “Isopto” products. Typically, DMEPA discourages the use of common prefixes such as “Isopto” because the proliferation of use may increase the risk of name confusion between all the “Isopto” products especially since they share many overlapping product characteristics such as dosage form, route of administration, strengths, and dose. However, we were unable to identify any post marketing medication errors associated with the use of the proposed name, Isopto Carpine. Therefore, we believe that continued use of the proposed proprietary name is appropriate since there are no other Isopto products currently approved by the Agency. Thus, the Division of Medication Error Prevention and Analysis (DMEPA) has no objection to the proprietary name, Isopto Carpine, for this product at this time. The name was not considered promotional.

However, if any of the proposed product characteristics as stated in this review are altered prior to approval of the product, 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 proprietary name must be re-reviewed 90 days before approval of the NDA. If you have further questions or need clarifications, please contact Brantley Dorch, OSE Project Manager, at 301-796-0150.

5.1 COMMENTS TO THE APPLICANT

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

However, we note that you have developed a naming convention for your product line that uses the prefix “Isopto” and in certain cases, contains the established name within the proprietary name. For future reference, we discourage the incorporation of established names in proprietary names and also discourage the use of the prefix “Isopto” for your other products because it will contribute to name similarity in a drug class with many overlapping product characteristics.

The proposed proprietary name, Isopto Carpine, will be re-reviewed 90 days prior to 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. ***FDA Document Archiving, Reporting & Regulatory Tracking System [DARRTS]***

DARRTS is a government database used to organize Applicant and Sponsor submissions as well as to store and organize assignments, reviews, and communications from the 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

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

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.

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 Sponsor’s intended pronunciation of the proprietary name. However, DMEPA also considers a variety of pronunciations that could occur in the English language because the Sponsor has little control over how the name will be spoken in clinical practice.

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.

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		
	<i>Potential causes of drug name similarity</i>	<i>Attributes examined to identify similar drug names</i>	<i>Potential Effects</i>
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/or 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

DMEPA requests the Office of New Drugs (OND) responsible for the application for its 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 is contacted a second time following our analysis of the proposed proprietary name. At this point, DMEPA conveys its decision to accept or reject the name. OND is requested to concur/not concur with DMEPA's final decision.

5. External Proprietary Name Risk Assessment

DMEPA conducts an independent analysis and evaluation of the data provided, and responds to the overall findings of the assessment. When the external proprietary name risk assessment identifies potentially confusing names that were not captured in 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 assessment of the proposed name, the Safety Evaluator compares the findings of the overall risk assessment to the findings of the proprietary name risk

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

6. 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:

“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:

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

- 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 Sponsor 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 Sponsor 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 Sponsor. 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, 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 Sponsor 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. Sponsors have undertaken higher-leverage strategies, such as drug name changes, 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 approving the error-prone proprietary name. Moreover, even after Sponsors' 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: FDA Prescription Study Responses (conducted January 26, 2010).

Written Outpatient	Written Inpatient	Verbal Prescription
Isoplo Canpire	asopt	Isoptocarpine
Isopto canpia	Asopto Carpine	Assactocarpine
Isopto Carpine	Isopto Carpine	Isoptocarpine
Isopto Carpine	Isopto Caipine	Acito carpine
Isopto Carpine	Isopto Carpine	Isoptocarpine
Isopto Canpio	Isoptic Caipine	Isoptocarpine
Isopto Carpine	Isopto Carpine	Isoptocarpine
Isopto Canpine	AsoptoCarpine	Isoptocarpine
Isoprh Canpia	Azopti Carpine	Isoptocarpine
Isopto Canpire	Isopto Carpine	Isoptocarpine
Isopto Canpiro	Isopto Carpine	Isoptocarpine
Isopto Campine	Isopto Carpine	Asoptocarpine
Isopto Carpine	Isopto Carpine	
Isoph carpine	Isopto Carpine	
Isopto Canpire	Isopto Carpine	
	Azopto Carpine	
	Isopto Carpine	

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

Proprietary Name	Similarity to Isopto Carpine
Carimune	Look

Appendix D: Discontinued branded generic products with no other generics available

Proprietary Name	Similarity to Isopto Carpine
Isopto Cetamide (Sulfacetamide Sodium)	Look and Sound
Isopto Cetapred (Prednisolone Acetate/ Sulfacetamide Sodium)	Look and Sound

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

Product name with potential for confusion	Similarity to Isopto Carpine	Dosage Form/ Strength	Usual Dose
Isopto Carpine (Pilocarpine Hydrochloride)	N/A	Ophthalmic Solution: 1%, 2%, 4%	Instill one drop in the eye(s) up to four times daily
(b) (4)			

Appendix F: Products with numerical similar or achievable dose with differentiating product characteristics

Product name with potential for confusion	Similarity to Isopto Carpine	Dosage Form/ Strength	Usual Dose (if applicable)	Differentiating Product Characteristics
Isopto Carpine (Pilocarpine Hydrochloride)	N/A	Ophthalmic Solution: 1%, 2%, 4%	Instill one drop in the eye(s) up to four times daily	N/A
Isoptin (Verapamil) <i>*Discontinued; Generics available</i>	Look and Sound	Tablet: 40 mg, 80 mg., 120 mg Injectable: 2.5 mg/mL	Tablet: 80 mg – 120 mg (1 tablet) three times daily orally Injectable: 5 mg to 10 mg intravenous bolus	Dosage form, route of administration, strength
Isoptin SR (Verapamil)	Look and Sound	Extended-release tablet: 120 mg, 180 mg, 240 mg	Initial dose: 180 mg every morning orally then up to 1 tablet (120 mg to 240 mg) once daily or twice daily	Dosage form, route of administration, strength

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

Appendix G: Products with numerical overlap in strength or achievable dose.

Failure Mode: Name confusion	Causes (could be multiple)	Effects
Isopto Carpine (Pilocarpine Hydrochloride)	Ophthalmic Solution: 1%, 2%, 4%	Usual dosage: Instill one drop in the eye(s) up to four times daily
Azopt (Brinzolamide) Ophthalmic suspension: 1%	<p>Orthographic similarity with the root name “Isopto”: ‘A’ and ‘I’ can appear similar; overlapping letters ‘opt’</p> <p>Phonetic similarity with the root name “Isopto”: ‘A’ and ‘I’ can sound similar; ‘zopt’ and ‘sopt’ can sound similar</p> <p>Overlapping strength (1%); dose (1 drop); frequency of administration (three times daily); route of administration (intraocular), dosage form (ophthalmic solution vs. ophthalmic suspension)</p>	<p>The orthographic differences in the names help to minimize the risk of medication errors in the usual practice setting.</p> <p><i>Rationale:</i></p> <p>There are some orthographic and phonetic similarities between Azopt and the root name “Isopto” of the proposed product. However, it is unlikely that Azopt will be confused with Isopto Carpine since the proposed product has a modifier “Carpine” following the root name that distinguishes the product from Azopt. The modifier is required on prescriptions of Isopto Carpine to differentiate the proposed product from the other “Isopto” products.</p> <p>Additionally, since Azopt is available in a single strength, the strength would often be omitted in the prescription. Since Isopto Carpine is available in 3 different strengths, the pharmacist would need to clarify the prescription with the prescriber before dispensing.</p> <p>Furthermore, postmarketing search did not result in any medication error cases between the name pair.</p> <p>For these reasons, the risk of error between the two products is minimal.</p>

Appendix H: Alcon’s “Isopto” Ophthalmic Product Line

Isopto Atropine (Atropine Sulfate)	Yes	Ophthalmic Solution: 1%	1-2 drops into eye(s) three times daily
Isopto Carbachol (Carbachol)	Yes	Ophthalmic Solution: 1.5%, 3%	2 drops into eye(s) three times daily
Isopto Homatropine (Homatropine Hydrobromide)	Yes	Ophthalmic Solution: 2%, 5%	1-2 drops into eye(s) twice or three times daily

Isopto Hyoscine (Hyoscine Hydrobromide)	Yes	Ophthalmic Solution: 0.25%	1-2 drops into eye(s) up to four times daily
Isopto Tears (Hypromellose) *Over-the-counter	Yes	Ophthalmic Solution: 0.5%	1-2 drops into eye(s) three to four times daily
Isopto Alkaline (Hypromellose)	No	N/A	N/A
Isopto Frin (Phenylephrine)	No	N/A	N/A
Isopto Plain	No	N/A	N/A

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-200890	ORIG-1	ALCON INC	PILOCARPINE HYDROCHLORIDE OPHTHALMIC SOLUTION, 1%, 2% AND 4%

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

/s/

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03/22/2010

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