CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-228

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:	August 31, 2009
To:	Wiley Chambers, M.D., Acting Director Division of Anti-Infective & Ophthalmology Products
Through:	Laura Pincock, Pharm.D., Acting Team Leader Denise Toyer, Pharm.D., Deputy Director Carol Holquist, RPh, Director Division of Medication Error Prevention and Analysis
From:	Raichell S. Brown, Pharm.D., J.D., Safety Evaluator Division of Medication Error Prevention and Analysis
Subject:	Proprietary Name Review
Drug Name(s):	Bepreve (Bepotastine Besilate) Ophthalmic Solution 1.5%
Application Type/Number:	NDA 22-288
Applicant:	ISTA Pharmaceuticals
OSE RCM #:	2009-260

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

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1 INTRODUCTION

This review is written in response to the anticipated approval of this NDA within 90 days from the date of this review. DMEPA found the proposed name, Bepreve, acceptable in OSE Review #2008-1987, dated February 9, 2009. Since that review, none of Bepreve's product characteristics have been altered. Additionally, the Division of Drug Marketing, Advertising and Communications (DDMAC) found the name acceptable from a promotional perspective on June 16, 2009. Furthermore, the Review Division did not have any concerns with the proposed name, Bepreve, during our initial review.

2 METHODS AND RESULTS

For the proposed proprietary name, DMEPA staff searched a standard set of databases and information sources (see Section 4) to identify names with orthographic and/or phonetic similarity to the proposed name that have been approved since the previous OSE proprietary name review. Because none of the proposed product characteristics were altered, we did not re-evaluate previous names of concern. Additionally, DMEPA searched the USAN stem list to determine if the name contains any USAN stems as of the last USAN update. DMEPA bases the overall risk assessment on the findings of a Failure Mode Effects Analysis (FMEA) of the proposed proprietary name, and focuses on the avoidance of medication errors.

The searches of the databases yielded three new names, Agenerase, Hepsera, and Hiprex, thought to look similar to Bepreve and represent a potential source of drug name confusion. These names were evaluated using FMEA. The findings of the FMEA indicate that the proposed name, Bepreve, is not likely to result in name confusion with Agenerase, Hepsera, and Hiprex for the reasons presented in Appendices A and B.

3 CONCLUSIONS AND RECOMMENDATIONS

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

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

4 REFERENCES

1. OSE Review # 2008-1987. Proprietary Name Review of Bepreve, Raichell S. Brown. February 5, 2009.

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

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

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

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

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

USAN Stems List contains all the recognized USAN stems.

APPENDICES

Appendix A: Products that lack convincing orthographic or phonetic similarity to Bepreve.

Product Name Identified to have Potential for Confusion	**Similarity to Bepreve.**
Agenerase	orthographic

Appendix B: Single strength products with multiple differentiating product characteristics.

Product name with potential for confusion	**Similarity to Bepreve**	**Strength**	**Indication for Use**	**Usual Dose (if applicable)**	**Differentiating Product Characteristics (Bepreve vs. Product)**
Bepreve (Bepotastine) Ophthalmic Solution	**N/A**	**1.5%**	**Itching associated with allergic conjunctivitis**	**One drop in affected eye(s) twice a day**	**N/A**
Hiprex (Methenamine) Tablet	orthographic	1 gram	Prophylactic or suppressive treatment or frequently recurring urinary tract infections	1 gram by mouth twice daily	DOSAGE FORM: **Bepreve**- Ophthalmic Drop **Hiprex**- Oral Tablet ROUTE OF ADMINISTRATION: **Bepreve**- Topical to the eye(s) **Hiprex**- Oral
Hepsera (Adefovir) Tablet	orthographic	10 mg	Treatment of chronic Hepatitis B in patients 12 years of age or older	10 mg by mouth once daily	DOSAGE FORM: **Bepreve**- Ophthalmic Drop **Hepsera**- Oral Tablet ROUTE OF ADMINISTRATION: **Bepreve**- Topical to the eye(s) **Hepsera**- Oral FREQUENCY OF ADMINISTRATION: **Bepreve**- Twice daily **Hepsera**- Once daily

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/s/

RAICHELL S Brown
09/01/2009

LAURA L PINCOCK
09/01/2009

CAROL A HOLQUIST
09/01/2009

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:	February 5, 2009
To:	Wiley Chambers, M.D., Acting Director Division of Anti-Infective & Ophthalmology Products
Through:	Todd Bridges, R.Ph., Team Leader Denise Toyer, Pharm.D., Deputy Director Carol Holquist, RPh, Director Division of Medication Error Prevention and Analysis (DMEPA)
From:	Raichell S. Brown, Pharm.D., J.D., Safety Evaluator Division of Medication Error Prevention and Analysis (DMEPA)
Subject:	Proprietary Name Review
Drug Name(s):	Bepreve (Bepotastine Besilate Ophthalmic Solution) 1.5%
Application Type/Number:	NDA 22-288
Applicant:	ISTA Pharmaceuticals
OSE RCM #:	2008-1987

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CONTENTS

EXECUTIVE SUMMARY

Our Proprietary Name Risk Assessment considered the potential similarity of 39 names to the proposed name, Bepreve. However, we concluded that these names would not render the proposed name, Bepreve, vulnerable to name confusion that could lead to medication errors. Thus, DMEPA has no objection to the use of the proprietary name Bepreve for this product. The Division of Anti-Infective & Ophthalmology Products concurs with this assessment.

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 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.

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

1 BACKGROUND

1.1 INTRODUCTION

This review is in response to a request from the Division of Anti-Infective & Ophthalmology Products for an assessment of the proposed proprietary name, Bepreve, regarding potential name confusion with other proprietary or established drug names in normal practice settings. Labels and labeling were also submitted and will be evaluated in separate forthcoming review (OSE Review 2008-1998).

1.2 PRODUCT INFORMATION

Bepreve is the proposed proprietary name for bepotastine besilate ophthalmic solution 1.5%. Bepreve is intended for treatment of itching associated with allergic conjunctivitis in patients 3 (three) years of age or older. Bepreve is dosed as one drop into affected eye(s) twice a day. Bepreve is proposed to be marketed in plastic squeeze bottles in the following sizes: 2.5 mL, 5 mL, and 10 mL. The recommended storage condition is 15 degrees Celsius to 25 degrees Celsius (59 degrees Fahrenheit to 77 degrees Fahrenheit).

2 METHODS AND MATERIALS

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

[1] National Coordinating Council for Medication Error Reporting and Prevention. http://www.nccmerp.org/aboutMedErrors html. Last accessed 12/22/2008.

2.1 PROPRIETARY NAME RISK ASSESSMENT

FDA's Proprietary Name Risk Assessment considers the potential for confusion between the proposed proprietary name, Bepreve, 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 CDER.

For the proprietary name, Bepreve, the DMEPA staff searched a standard set of databases and information sources to identify names with orthographic and phonetic similarity (See 2.1.1 for details) and held a CDER Expert Panel discussion to gather professional opinions on the safety of the proposed proprietary name (See 2.1.1.2). DMEPA also conducts internal CDER prescription analysis studies. 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 2.1.2 for details). The overall risk assessment is based on the findings of a Failure Mode and Effects Analysis (FMEA) of the proprietary name, and is focused on the avoidance of medication errors.

FMEA is a systematic tool for evaluating a process and identifying where and how it might fail. [2] FMEA is used to analyze whether the drug names identified with orthographic or phonetic similarity to the proposed name could cause confusion that subsequently leads to medication errors in the clinical setting. DMEPA uses the clinical expertise of the medication error 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 medication error 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 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, DMEPA considers the potential for confusion throughout the entire U.S. medication use process, including drug procurement, prescribing and ordering, dispensing, administration, and monitoring the impact of the medication.[3]

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

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

2.1.1 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 'Bb' when searching to identify potentially similar drug names, as 75% of the confused drug names reported by the USP-ISMP Medication Error Reporting Program involve pairs beginning with the same letter.[4,5]

To identify drug names that may look similar to Bepreve, the staff also considered the orthographic appearance of the name on lined and unlined orders. Specific attributes taken into consideration include the length of the name (seven letters), upstrokes (one, capital and lower case letter 'Bb'), downstrokes (one, lower case 'p'), cross-strokes (none), and dotted letters (none). In addition, several letters in Bepreve may be vulnerable to ambiguity when scripted, including the capital letter 'B' may appear as capital letters 'P', 'D', or 'R'; lower case 'b' may look like lower case 'l' or 'h'; lower case 'e' may look like lower case 'a' or 'i'; lower case 'p' may look like lower case 'j' or 'q'; lower case letters 're' together may appear as lower case 'u'; and lower case 'v' may appear as lower case 'u', 'a', 'r', or 'n'. As a result, the medication error staff considers these alternate appearances when identifying drug names that may look similar to Bepreve.

When searching to identify potential names that may sound similar to Bepreve, the DMEPA staff searched for names with similar number of syllables (two), stresses (BE-preve or Be-PREVE), and placement of vowel and consonant sounds. Additionally, the medication error staff considers that pronunciation of parts of the name can vary such as 'Be-' may sound like 'Bi-', 'Ba-', or 'Bu-'. The Applicant's intended pronunciation of the proprietary name, Bepreve, was not provided with the proposed name submission and, therefore, could not be taken into consideration. Moreover, names are often mispronounced and/or spoken with regional accents and dialects, so other potential pronunciations of the name are considered.

The DMEPA staff also considers the product characteristics associated with the proposed drug throughout the identification of similar drug names because the product characteristics of the proposed drug ultimately determine the use of the product in the clinical practice setting. For this review, the DMEPA staff was provided with the following information about the proposed product: proposed proprietary name (Bepreve); proposed established name (bepotastine besilate ophthalmic solution); proposed indication of use (itching associated with allergic conjunctivitis); strength (1.5%); dose (one drop in affected eye); frequency of administration (twice daily); route (ophthalmic); and dosage form (solution). Appendix A provides a more detailed listing of product characteristics that the medication error staff generally takes into consideration.

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

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

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

2.1.1.1 Database and Information Sources

The proposed proprietary name, Bepreve, was provided to the DMEPA staff to conduct a search of the internet, several standard published drug product reference texts, and FDA databases to identify existing and proposed drug names that may sound-alike or look-alike to Bepreve 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 DMEPA staff used 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. The medication error staff also reviewed the USAN stem list to determine if any USAN stems are present within the proprietary name. The individual findings of multiple safety evaluators were then pooled and presented to the CDER Expert Panel.

2.1.1.2 CDER Expert Panel Discussion

An Expert Panel Discussion was held to gather CDER professional opinions on the safety of the product and the proprietary name, Bepreve. The Expert Panel is composed of staff of the Division of Medication Error Prevention and Analysis (DMEPA) and representatives from the Division of Drug Marketing, Advertising, and Communications (DDMAC). Potential concerns regarding drug marketing and promotion related to the proposed names were also discussed.

The pooled results of the DMEPA staff are 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 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 Bepreve with marketed U.S. drug names (proprietary and established) due to similarity in visual appearance with handwritten prescriptions or verbal pronunciation of the drug name. The studies employ a total of 123 (one hundred twenty-three) healthcare professionals (pharmacists, physicians, and nurses), and attempts to simulate the prescription ordering process. The results are used by the Safety Evaluator to identify any orthographic or phonetic vulnerability of the proposed name to be misinterpreted by healthcare practitioners.

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

Figure 1. Bepreve Study (conducted on December 31, 2008)

HANDWRITTEN PRESCRIPTION AND MEDICATION ORDER	VERBAL PRESCRIPTION
Inpatient Medication Order: Bepreve instill 1 gtt into both eyes BID	"Bepreve, number one, instill 1 drop into both eyes bid"
Outpatient Prescription: Bepreve #1 1 gtt into both eyes bid	

2.1.3 Comments from the Division of Anti-Infective & Ophthalmology Products

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

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

2.1.4 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 Mode and Effects Analysis and provide an overall risk of name confusion. Failure Mode and Effects Analysis (FMEA) is a systematic tool for evaluating a process and identifying where and how it might fail.[6] When applying FMEA to assess the risk of a proposed proprietary name, DMEPA seeks to evaluate the potential for a proposed name to be confused with another drug name as a result of the name confusion and cause errors to occur in the medication use system. FMEA capitalizes on the predictable and preventable nature of medication errors associated with drug name confusion. FMEA allows the Agency to identify the potential for medication errors due to look- or sound-alike drug names prior to approval, where actions to overcome these issues are easier and more effective then remedies available in the post-approval phase.

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

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

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 Bepreve 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 Bepreve to be confused with another proprietary or established drug name because of orthographic or phonetic similarity. If the answer to the question is no, the Safety Evaluator is not convinced that the names posses similarity that would cause confusion at any point in the medication use system, then 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; for example, 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.

DMEPA will object to the use of proposed proprietary name when the one or more of the following conditions are identified in the Safety Evaluator's Risk Assessment:

1. DDMAC finds the proposed proprietary name misleading from a promotional perspective, and the Review Division concurs with DDMAC's findings. The Federal Food, Drug, and Cosmetic Act provides that labeling or advertising can misbrand a product if misleading representations are made or suggested by statement, word, design, device, or any combination thereof, whether through a trade name or otherwise. [21 U.S.C 321(n); see also 21 U.S.C. 352(a) & (n)].
2. DMEPA identifies that the proposed proprietary name is misleading because of similarity in spelling or pronunciation to another proprietary or established name of a different drug or ingredient [CFR 201.10.(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. DMEPA staff 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.

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 is awarded approval first has the right to the use the name, while DMEPA will recommend that the second product to reach approval seek an alternative name.

If none of these criteria are met, then DMEPA will not object to the use of the proprietary name. If any of these criteria are met, then DMEPA will object to the use of the proposed proprietary name. The threshold set for objection to the proposed proprietary name may seem low to the Applicant; however, the safety concerns set forth in criteria 1 through 5 are supported either by FDA regulation or by external healthcare authorities, including the IOM, WHO, 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, DMEPA contends that the threshold set for the Proprietary Name Risk Assessment is reasonable because proprietary drug name confusion is a predictable and preventable source of medication error that, in many instances, can be identified and remedied prior to approval to avoid patient harm.

Additionally, post-marketing experience has demonstrated that medication errors resulting from drug name confusion are notoriously difficult to remedy post-approval. Educational and other post-approval efforts are low-leverage strategies that have proven to have limited effectiveness at alleviating medication errors involving drug name confusion. Higher-leverage strategies, such as drug name changes, have been undertaken in the past but at great financial cost to the Applicant and at the expense of the public welfare, not to mention the Agency's credibility as the authority responsible for the approving the error-prone proprietary name. Moreover, even after Applicants have changed a product's proprietary name in the post-approval phase, it is difficult to eradicate the original proprietary name from 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. (See Section 4 for limitations of the process).

If DMEPA objects to a proposed proprietary name on the basis that drug name confusion could lead to medication errors, the FMEA process is used to identify strategies to reduce the risk of medication errors. DMEPA is likely to recommend that the Applicant select an alternative proprietary name and submit the alternate name to the Agency for DMEPA to review. However, in rare instances FMEA may identify plausible strategies that could reduce the risk of medication error of the currently proposed name. In that instance, DMEPA may be able to provide the Applicant with recommendations that reduce or eliminate the potential for error and, thereby, would render the proposed name acceptable.

3 RESULTS

3.1 PROPRIETARY NAME RISK ASSESSMENT

3.1.1 Database and Information Sources

The search yielded a total of 38 (thirty-eight) names as having some similarity to the name Bepreve.

Thirty-three of the thirty-eight names were thought to look like Bepreve. These include Bepadin, Bepreve, Bepricor, Bepridil, (b) (4) (b) (4)***, Biprin, Buprenex, Bupropion, Buprovan, Byetta, Depacon, Depodur, Diaprene, Diprivan, Diprolene, Heparin, Lupron, Lyrica, Pagene DPS, Papaverin, Propecia, (b) (4)***, (b) (4)***, Reorexain, Repliva, Reponex, Reprexian, Repronex, (b) (4), Requia, Zyprexa, (b) (4)***. One name, Aleve, was thought to sound similar to Bepreve. Four names, Beprane, Lipreve, Repreve, and Reprieve, were thought to both look and sound like Bepreve.

Additionally, DMEPA did not identify any United States Adopted Names (USAN) stems in the name, Bepreve, as of December 22, 2008.

3.1.2 Expert Panel Discussion

The Expert Panel reviewed the pool of names identified by DMEPA staff (See Section 3.1.1) and noted one additional name thought to have orthographic similarity to Bepreve; that name was Requip.

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 FDA Prescription Analysis Studies

A total of 29 practitioners responded. Three of the 29 responses overlapped with the proprietary name of a product marketed in Australia (Repreve). Thirteen of the participants interpreted the name correctly as "Bepreve," with correct interpretation occurring in both the inpatient written studies (n=2) and the outpatient written studies (n=9). The remainder of the written responses misinterpreted the drug name. In the verbal studies, one response was a misspelled phonetic variation of the proposed name, Bepreve. See Appendix B for the complete listing of interpretations from the verbal and written prescription studies.

3.1.4 Comments from the Division of Anti-Infective & Ophthalmology Products

In response to the OSE December 19, 2008 e-mail, the Division of Anti-Infective & Ophthalmology Products did not forward any comments and/or clinical/other concerns on the proposed name at the initial phase of the name review.

DMEPA notified the Division of Anti-Infective & Ophthalmology Products via e-mail that we had no objections to the proposed proprietary name, Bepreve, on January 27, 2009. Per e-mail correspondence from the Division of Anti-Infective & Ophthalmology Products on January 29, 2009, they indicated they concur with our assessment of the proposed name, Bepreve.

3.1.5 Safety Evaluator Risk Assessment

Independent searches by the primary Safety Evaluator resulted in no additional names which were thought to look or sound similar to Bepreve and represent a potential source of drug name confusion.

Thirty-nine names were analyzed to determine if the drug names could be confused with Bepreve and if the drug name confusion would likely result in a medication error. All of the identified names were determined to have some orthographic and/or phonetic similarity to Bepreve, and thus determined to present some risk of confusion.

Failure mode and effect analysis (FMEA) was then applied to determine if the potential name, Bepreve, could potentially be confused with any of the 39 names and lead to medication errors. This analysis determined that the name similarity between Bepreve and the identified names was unlikely to result in medication errors with any of the 39 products identified for the reasons presented in Appendices C through G.

4 DISCUSSION

4.1 PROPRIETARY NAME RISK ASSESSMENT

Our evaluation identified 39 (thirty-nine) names as having some similarity to the proposed name, Bepreve. However, FMEA findings indicate that the proposed name is not likely to be vulnerable to name confusion that could lead to medication errors for the reasons outlined in Appendices C through G.

5 CONCLUSIONS AND RECOMMENDATIONS

The Proprietary Name Risk Assessment findings indicate that the proposed name, Bepreve, is not likely to be vulnerable to name confusion that could lead to medication errors in the current marketplace. Thus DMEPA has no objections to the name, Bepreve, for this product at this time. This decision was shared with the Division of Anti-Infective & Ophthalmology Products who concurred with our findings.

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 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.

In addition, the proposed name must be re-evaluated 90 days before approval of the NDA, even if the proposed product characteristics as stated in this review are not altered.

5.1 COMMENTS TO THE DIVISION

We would appreciate feedback on the final outcome of this review. We are willing to meet with the Division for further discussion, if needed. Please copy DMEPA on any communication to the Applicant with regard to this review. If you have further questions or need clarifications, please contact Marlene Hammer, project manager, at 301-796-0757.

5.2 COMMENTS TO THE APPLICANT

We have completed our review of the proposed proprietary name, Bepreve, and have concluded that it is acceptable. The proprietary name, Bepreve, will be re-reviewed 90 days prior to the approval of the NDA. If we find the name unacceptable following the re-review, we will notify you.

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

6 REFERENCES

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

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

2. Phonetic and Orthographic Computer Analysis (POCA)

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

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

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

4. AMF Decision Support System [DSS]

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

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

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

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

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

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

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

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

USPTO provides information regarding patent and trademarks.

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

Clinical Pharmacology contains full monographs for the most common drugs in clinical use, plus mini monographs covering investigational, less common, combination, nutraceutical and nutritional products. It also provides a keyword search engine.

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

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

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

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

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

Stat!Ref contains full-text information from approximately 30 texts; it includes tables and references. Among the database titles are: Handbook of Adverse Drug Interactions, Rudolphs Pediatrics, Basic Clinical Pharmacology, and Dictionary of Medical Acronyms Abbreviations.

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

USAN Stems List contains all the recognized USAN stems.

14. Red Book Pharmacy's Fundamental Reference

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

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

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

16. Medical Abbreviations Book

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

APPENDICES

Appendix A:

The medication error staff 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 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 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 and the similar appearance of drug names when scripted has lead to medication errors. The medication error 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), along with other orthographic attributes that determine the overall appearance of the drug name when scripted (see Table 1 below for details). In addition, the medication error staff compares the pronunciation of the proposed proprietary name with the pronunciation of other drug names because verbal communication of medication names is common in clinical settings. If provided, DMEPA will consider the Applicant's intended pronunciation of the proprietary name. However, DMEPA also considers a variety of pronunciations that could occur in the English language because the Applicant has little control over how the name will be spoken in clinical practice.

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

Type of similarity	**Considerations when searching the databases**		
	Potential causes of drug name similarity	*Attributes examined to identify similar drug names*	*Potential Effects*
Look-alike	Similar spelling	Identical prefix Identical infix Identical suffix Length of the name Overlapping product characteristics	• 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 Upstokes Downstrokes Cross-stokes	• Names may look similar when scripted, and lead to drug name confusion in written communication

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

Appendix B: **FDA Prescription Study Responses**

Inpatient Medication Order	Outpatient Medication Order	Voice Prescription
Bepreve	Beprene	Bepreve
Bepreve	Beprene	Bepreve
Prepeve (not sure of spelling from handwriting here)	Bepreva	Beprieve
Repreve	Bepreve	Reprive
Repreve	Bepreve	Retrive
Repreve	Bepreve	
	Bepreve	
	Bepreve	
	Bepreve	
	Bepreve	
	Bepreve	
	Bepreve	

Appendix C: Products that lack convincing orthographic or phonetic similarity to Bepreve.

Product Name Identified to have Potential for Confusion	Similarity to Bepreve.
Bepadin	orthographic
Bepridil	orthographic
(b) (4)	orthographic
Bupropion	orthographic
Byetta	orthographic
Depacon	orthographic
Depodur	orthographic
Diaprene	orthographic
Diprolene	orthographic
Lyrica	orthographic
Pagene DPS	orthographic
Papaverin	orthographic
Propecia	orthographic
(b) (4)	orthographic
(b) (4)	orthographic
Reorexain	orthographic
Repliva	orthographic
Reponex	orthographic
Reprexian	orthographic
Repronex	orthographic
(b) (4)	orthographic
Requia	orthographic
Requip	orthographic
Zyprexa	orthographic
(b) (4)	orthographic

Appendix D: Proprietary name subject of this review.

Proprietary Name
Bepreve

Appendix E: Proprietary names of products marketed in foreign countries.

Proprietary Name	Similarity to Bepreve	Country
Beprane	orthographic and phonetic	France
(b) (4)	orthographic	UK
Biprin	orthographic	Venezuela
Repreve*	orthographic and phonetic	Australia

* Although three of the FDA Prescription Study Responses interpreted the proprietary name that is the subject of this review, Bepreve, as Repreve, risk of medication errors is minimal because Repreve is an Australian proprietary name not used in the United States.

Appendix F: Names that were not found in commonly used drug references as marketed drugs.

Proprietary Name	Similarity to Bepreve
Bepricor	orthographic
Buprovan	orthographic
Reprieve	orthographic and phonetic

Appendix G: Proprietary names with no numerical overlap in strength and/or dose.

Product name with potential for confusion	Similarity to Proposed Proprietary Name	Dosage Form & Strength	Usual Dose
Bepreve (Bepotastine Besilate)	**N/A**	**Ophthalmic Solution 1.5%**	**One drop in affected eye twice a day.**
Diprivan (Propofol)	orthographic	IV Injection: 10mg/mL (1%)	0.05 microgram per kilogram per minute to 200 microgram per kilogram per minute.
Heparin	orthographic	Solution for Injection: 1 unit/mL; 2 units/mL; 10 units/mL; 40 units/mL; 50 units/mL; 100 units/mL; 1,000 units/mL; 2,000 units/mL; 2,500 units/mL; 5,000 units/mL; 10,000 units/mL; 20,000 units/mL	8,000 to 20,000 units Subcutaneously every 8 to 12 hours; 5,000 to 10,000 units Intravenously every 4 to 6 hours; 20,000 to 40,000 units per day Continuous Infusion.
Lipreve (Arsenicum album/Natrum muriaticum/Sepia)	orthographic and phonetic	Oral capsules (Homeopathic)	2 capsules twice daily x 2 days.
Lupron (Leuprolide Acetate)	orthographic	Subcutaneous or Intramuscular Injection: 5 mg/mL; 22.5 mg (3-month depot); 30 mg (4-month depot); 45 mg (6-month depot) Powder for Injection, lyophilized: 7.5 mg Microspheres for Injection, lyophilized: 3.75 mg, 7.5 mg, 11.25 mg, 15 mg, 22.5 mg, 30 mg	(Subcutaneous) 1 mg once daily. (Intramuscular) 3.75 mg or 7.5 mg monthly; 11.25 mg or 22.5 mg every 3 months; 30 mg every 4 months; or 45mg every 6 months.
Aleve (Naproxen Sodium)	phonetic	Oral Tablet, Oral Capsule, Oral Gelcap: 220 mg	220 mg twice daily.
Buprenex (Buprenorphrine Hydrochloride)	orthographic	Intramuscular or Intravenous Injection: 0.324 mg/mL (equivalent to 0.3 mg of buprenorphine)	0.3 mg of buprenorphine every 6 hours as needed. May repeat once within 30 to 60 minutes of initial dose if needed.

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

/s/

Raichel Brown
2/5/2009 02:00:42 PM
DRUG SAFETY OFFICE REVIEWER

Todd Bridges
2/5/2009 02:10:29 PM
DRUG SAFETY OFFICE REVIEWER

Denise Toyer
2/5/2009 04:36:37 PM
DRUG SAFETY OFFICE REVIEWER

Carol Holquist
2/5/2009 04:58:00 PM
DRUG SAFETY OFFICE REVIEWER

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADM NISTRATION

REQUEST FOR CONSULTATION

TO *(Division/Office)*:
Director, Medication Error Prevention
Office of Post Marketing Drug Risk Assessment

FROM:
Wiley Chambers, MD, Acting Director, DAIOP
Raphael Rodriguez, RPM phone 796-0798

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
11/20/2008	66,864	22-288	Trade Name Review	11/12/08

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
bepotastine besilate ophthalmic solution 1.5%	Standard Review	5HT antagonist ophthalmics	6/1/09

NAME OF FIRM: Ista Pharmaceuticals, Inc.

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE--NDA MEETING
- ☐ END OF PHASE 2
- ☐ RESUBMISSION
- ☐ SAFETY/EFFICACY
- X TRADE NAME REVIEW
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- X ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☐ OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW ☐ END OF PHASE II MEETING ☐ CONTROLLED STUDIES ☐ PROTOCOL REVIEW ☐ OTHER (SPECIFY BELOW):	☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE IV STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL-BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ PRECLINICAL

COMMENTS:
Please provide a trade name reviews for the Bepreve (bepotastine besilate ophthalmic sol) 1.5%. This is an NME and anticipating for Advisory Committee.

This entire submission was sent via Electronic Submissions Gateway (ESG), eCTD which means there are NO jackets to distribute.

Please let me know if you need any additional information to complete this trade name review.

Thanks in advance. Raphael

SIGNATURE OF REQUESTER	METHOD OF DELIVERY (Check one)
Raphael Rodriguez 11/20/08	Via: Interoffice Mail
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

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/s/

Raphael Rodriguez
11/20/2008 11:19:55 AM