

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

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PROPRIETARY NAME REVIEW(S)



**Department of Health and Human Services
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Subject: Proprietary Name, Label, and Labeling Review for
MembraneBlue

Drug Name(s): MembraneBlue (Trypan Blue Ophthalmic Solution) 0.15%

**Application
Type/Number:** NDA 22-278

Applicant: Dutch Ophthalmic Research Center International, B.V.

OSE RCM #: 2007-2337

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EXECUTIVE SUMMARY

The Proprietary Name, Labels and Labeling Risk Assessments and FMEA findings indicate that the proposed name, MembraneBlue, appears to be vulnerable to product confusion with VisionBlue that could lead to medication errors. The Division of Medication Error Prevention believes that the risk may be mitigated by differentiating the proposed labels and labeling of MembraneBlue from the labels and labeling of the existing product VisionBlue. If the appropriate changes have been made, the Division of Medication Error Prevention may not object to the use of the proprietary name, MembraneBlue, for this product. Such changes would also be required to mitigate the risks identified in our Label and Labeling Risk Assessment which indicates that the presentation of information and design of the proposed carton and container labels introduces vulnerability to confusion that could lead to selection errors. Recommendations are provided in Section 5 that aim at reducing the risk of medication errors.

1 BACKGROUND

1.1 INTRODUCTION

This consult was written in response to a request from the Division of Anti-Infective and Ophthalmology Products (DAIOP) to evaluate the product for its potential to contribute to medication errors. The proposed proprietary name, MembraneBlue, was evaluated to determine if the name could be potentially confused with other proprietary or established drug names.

Additionally, the product design, container label, carton, and insert labeling were evaluated to identify areas that could lead to medication errors.

1.2 REGULATORY HISTORY

The applicant, Dutch Ophthalmic Research Center International, B.V., currently markets a trypan blue ophthalmic solution 0.06%, under a different application (NDA 21-670) using the proprietary name VisionBlue. This application was originally approved on December 16, 2004 for use as aid an ophthalmic surgery by staining the anterior capsule of the lens.

1.3 PRODUCT INFORMATION

MembraneBlue is the proposed name for trypan blue ophthalmic solution 0.15%. Trypan blue selectively stains membranes during ophthalmic surgical vitrectomy procedures. MembraneBlue is intended to be applied directly on the areas where membranes could be present, staining any portion of the membrane which comes in contact with the dye. Excess dye is washed out of the posterior chamber. The dye does not penetrate the membrane, permitting visualization of the membrane in contrast to the non-stained retina.

MembraneBlue is indicated for use as an aid in ophthalmic surgery by staining the epiretinal membranes during ophthalmic surgical vitrectomy procedures, facilitating removal of the tissue

The recommended dose is as follows:

Before injection of MembraneBlue, perform a 'fluid-air exchange', i.e. filling the entire vitreous cavity with air, to prevent aqueous dilution of MembraneBlue. MembraneBlue is carefully applied to the retinal membrane using a blunt cannula, without allowing the cannula

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to contact or damage the retina. Sufficient staining is achieved as soon as MembraneBlue has come in contact with the membrane. Remove all excess dye from the vitreous cavity before performing an air-fluid exchange, to prevent unnecessary spreading of the dye. The procedure can now proceed as a routine vitrectomy procedure.

MembraneBlue can also be injected directly in a buffered saline solution (BSS) filled vitreous cavity (instead of injecting under air).

MembraneBlue is supplied in 2.25 mL syringes filled to a volume of 0.5 mL. A thin blunt cannula has to be attached to each syringe. Five pouched products are packed in one distribution box. MembraneBlue is stored at 15-25°C and should be protected from direct sunlight.

2 METHODS AND MATERIALS

This section consists of two sections which describe the methods and materials used by the Division of Medication Error Prevention medication error staff conducting a proprietary name risk assessment (see 2.1 Proprietary Name Risk Assessment) and label, labeling, and/or packaging risk assessment (see 2.2 Container, Carton Label, and Insert Label Risk Assessment). The primary focus for both of the assessments is to identify and remedy potential sources of medication error prior to drug approval. The Division of Medication Error Prevention defines a medication error as any preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of the health care professional, patient, or consumer.¹

2.1 PROPRIETARY NAME RISK ASSESSMENT

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

For the proprietary name, MembraneBlue, the medication error staff of the Division of Medication Error Prevention search a standard set of databases and information sources to identify names with orthographic and phonetic similarity (see Sections 2.1.1 for detail) and held an CDER Expert Panel discussion to gather professional opinions on the safety of the proposed proprietary name (see 2.1.1.2). The Division of Medication Error Prevention also conducts internal CDER prescription analysis studies (see 2.1.2), and, when provided, external prescription analysis studies results are considered and incorporated into the overall risk assessment (see detail 2.1.4).

The Safety Evaluator assigned to the Proprietary Name Risk Assessment is responsible for considering the collective findings, and provides an overall risk assessment of the proposed proprietary name (see detail 2.1.4). The overall risk assessment is based on the findings of a Failure Modes and Effects Analysis (FMEA) of the proprietary name, and is focused on the avoidance of medication errors. FMEA is a systematic tool for evaluating a process and

¹ National Coordinating Council for Medication Error Reporting and Prevention.
<http://www.nccmerp.org/about/MedErrors.html>. Last accessed 10/11/2007.

identifying where and how it might fail.² FMEA is used to analyze whether the drug names identified with look- or sound-alike similarity to the proposed name could cause confusion that subsequently leads to medication errors in the clinical setting. The Division of Medication Error Prevention uses the clinical expertise of the medication error staff to anticipate the conditions of the clinical setting that the product is likely to be used in based on the characteristics of the proposed product.

In addition, the product characteristics provide the context for the verbal and written communication of the drug names and can interact with the orthographic and phonetic attributes of the names to increase the risk of confusion when there is overlap, or, in some instances, decrease the risk of confusion by helping to differentiate the products through dissimilarity. As such, the Staff considers the product characteristics associated with the proposed drug throughout the risk assessment, since the product characteristics of the proposed may provide a context for communication of the drug name and ultimately determine the use of the product in the *usual* clinical practice setting.

Typical product characteristics considered when identifying drug names that could potentially be confused with the proposed drug name include, but are not limited to established name of the proposed product, the proposed indication, dosage form, route of administration, strength, unit of measure, dosage units, recommended dose, typical quantity or volume, frequency of administration, product packaging, storage conditions, patient population, and prescriber population. Because drug name confusion can occur at any point in the medication use process, the Division of Medication Error Prevention considers the potential for confusion throughout the entire U.S. medication use process, including drug procurement, prescribing and ordering, dispensing, administration, and monitoring the impact of the medication.³

2.1.1 Search Criteria

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

For this review, particular consideration was given to drug names beginning with the letter 'M' 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 MembraneBlue, the Staff also consider the other orthographic appearance of the name on lined and unlined orders. Specific attributes taken into consideration include the length of the name (12 letters), upstrokes (4, 'b', 'l' and capital letters 'M', 'B'), downstrokes (none), cross-strokes (none), and dotted letters (none). Additionally, several letters in MembraneBlue may be vulnerable to ambiguity when scripted, including the

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

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

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

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

letter 'M' may appear as 'N'; lower case 'e' appear as a lower case 'a' or 'i'; and 'b' may appear as a 'u' or 'v'. As such, the Staff also considers these alternate appearances when identifying drug names that may look similar to MembraneBlue. We also consider that the name may be written as two separate words or written together (e.g. "Membrane" and "Blue" or "MembraneBlue"), especially in cases where the proposed name encompasses words from the standard English language.

When searching to identify potential names that may sound similar to MembraneBlue, the Medication Error Staff search for names with similar number of syllables (three), stresses (MEM-brane-blue or MEM-brane-BLUE), and placement of vowel and consonant sounds. Additionally, several letters in MembraneBlue may be pronounced similarly to other letters, 'M' may sound like 'N', 'B' like 'G' or 'L'. Therefore, the Staff considers names with these alternative sounds when identifying drug names that sound similar to MembraneBlue.

The Staff also consider the product characteristics associated with the proposed drug throughout the identification of similar drug names, since the product characteristics of the proposed drug ultimately determine the use of the product in the clinical practice setting. For this review, the Medication Error Staff were provided with the following information about the proposed product: the proposed proprietary name (MembraneBlue), the established name (trypan blue), proposed indication (facilitates removal of tissue during ophthalmic posterior surgery), strength (0.15%), dose (apply to the retinal membrane using a blunt cannula or inject directly in a buffered saline solution (BSS)-filled vitreous cavity), frequency of administration (per ophthalmic surgery), route (ophthalmic) and dosage form of the product (ophthalmic solution). Appendix A provides a more detailed listing of the product characteristics the Medication Error Staff general take into consideration.

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

2.1.1.1 Databases and information sources

The proposed proprietary name, MembraneBlue, was provided to the medication error staff of the Division of Medication Error Prevention 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 MembraneBlue using the criteria outlined in 2.1.1. A standard description of the databases used in the searches is provided in Section 7. To complement the process, the Medication Error Staff use a computerized method of identifying phonetic and orthographic similarity between medication names. The program, Phonetic and Orthographic Computer Analysis (POCA), uses complex algorithms to select a list of names from a database that have some similarity (phonetic, orthographic, or both) to the trademark being evaluated. Lastly, the Medication Error Staff review the USAN stem list to determine if any USAN stems are present within the proprietary name. The findings of the individual Safety Evaluators were then pooled and presented to the Expert Panel.

2.1.1.2 CDER Expert Panel Discussion

An Expert Panel Discussion is held by the Division of Medication Error Prevention to gather CDER professional opinions on the safety of the product and the proprietary name, MembraneBlue. Potential concerns regarding drug marketing and promotion related to the proposed names are also discussed. This group is composed of the Division of Medication Error Prevention Staff and representatives from the Division of Drug Marketing, Advertising, and Communications (DDMAC).

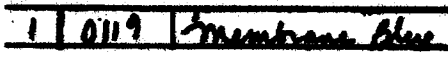
The pooled results of the medication error staff were presented to the Expert Panel for consideration. Based on the clinical and professional experiences of the Expert Panel members, the Panel may recommend the addition of names, additional searches by the Safety Evaluator to supplement the pooled results,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

2.1.2 CDER 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 MembraneBlue 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 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 MembraneBlue 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 prescriptions are optically scanned and one prescription is delivered to a random sample of 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 medication error staff.

Figure 1. MembraneBlue Study (conducted on January 08, 2008)

HANDWRITTEN PRESCRIPTION AND MEDICATION ORDER	VERBAL PRESCRIPTION
Pharmacy Requisition #1: 	Pharmacy Requisition: Order code 0119 MembraneBlue #1
Pharmacy Requisition #2: 	

2.1.3 Safety Evaluator Risk Assessment of the Proposed Proprietary Name

Based on the criteria set forth in Section 2.1.1, the Safety Evaluator Risk Assessment applies their individual expertise gained from evaluating medication errors reported to FDA to conduct a Failure Modes and Effects Analysis and provide an overall risk of name confusion. Failure Mode and Effects Analysis (FMEA) is a systematic tool for evaluating a process and identifying where and how it might fail.⁶ When applying FMEA to assess the risk of a proposed proprietary name, the Division of Medication Error Prevention seeks to evaluate the potential for a proposed name to be confused with another drug name as a result of the name confusion and cause errors to occur in the medication use system. FMEA capitalizes on the predictable and preventable nature of medication errors associated with drug name confusion. FMEA allows the Agency to identify the potential for medication errors due to look- or sound-alike drug names prior to approval, where actions to overcome these issues are easier and more effective than remedies available in the post-approval phase.

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

In the initial stage of the Risk Assessment, the Safety Evaluator compares the proposed proprietary name to all of the names gathered from the above searches, expert panel evaluation, and studies, and identifies potential failure modes by asking: "Is the name MembraneBlue 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 MembraneBlue to be confused with another proprietary or established drug name because of look- or sound-alike similarity. If the answer to the question is no, the Safety Evaluator is not convinced that the names possess similarity that would cause confusion at any point in the medication use system and the name is eliminated from further review.

In the second stage of the Risk Assessment, all potential failure modes are evaluated to determine the likely effect of the drug name confusion, by asking "Could the confusion of the drug names conceivably result in medication errors in the usual practice setting?" The answer to this question is a central component of the Safety Evaluator's overall risk assessment of the proprietary name. If the Safety Evaluator determines through FMEA that the name similarity would ultimately not be a source of medication errors in the usual practice setting, the name is eliminated from further analysis. However, if the Safety Evaluator determines through FMEA that the name similarity could ultimately cause medication errors in the usual practice setting, the Safety Evaluator will then recommend that an alternate proprietary name be used. In rare instances, the FMEA findings may provide other risk-reduction strategies, such as product reformulation to avoid an overlap in strength or an alternate modifier designation may be recommended as a means of reducing the risk of medication errors resulting from drug name confusion.

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

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

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

In the event that the Division of Medication Error Prevention objects to the use of the proposed proprietary name, based upon the potential for confusion with another proposed (but not yet approved) proprietary name, the Division of Medication Error Prevention 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 the Division of Medication Error Prevention will recommend that the second product to reach approval seek an alternative name.

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

Additionally, post-marketing experience has demonstrated that medication errors resulting from drug name confusion are notoriously difficult to remedy post-approval. Educational efforts and so on are low-leverage strategies that have proven to have limited effectiveness at alleviating the

medication errors involving drug name confusion. Higher-leverage strategies, such as drug name changes, have been undertaken in the past; but at great financial cost to the applicant, and at the expense of the public welfare, not to mention the Agency's credibility as the authority responsible for the approving the error-prone proprietary name. Moreover, even after Applicant's have changed a product's proprietary name in the post-approval phase, it is difficult to eradicate the original proprietary name from practitioner's vocabulary, and as such, the Agency has continued to receive reports of drug name confusion long after a name change in some instances. Therefore, the Division of Medication Error Prevention believes that post-approval efforts at reducing name confusion errors should be reserved for those cases in which the potential for name confusion could not be predicted prior to approval (see limitations of the process).

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

2.2 LABEL AND LABELING RISK ASSESSMENT

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

Given the critical role that the label and labeling has in the safe use of drug products, it is not surprising that 33 percent of medication errors reported to the USP-ISMP Medication Error Reporting Program may be attributed to the packaging and labeling of drug products, including 30 percent of fatal errors.⁷

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

For this product the Applicant submitted on January 8, 2008 the following labels and insert labeling for the Division of Medication Error Prevention review (see Appendix F, G, H, and I for images):

⁷ Institute of Medicine. Preventing Medication Errors. The National Academies Press: Washington DC. 2006. p275.

- Container (Syringe label)
- Carton (Box & Peel Pouch Labeling)
- Patient Record Labeling
- Prescribing Information (no image)
- VisionBlue labels (these are being included because they share the same applicant, established name, and contain the word "Blue" in the proprietary name)

3 RESULTS

3.1 PROPRIETARY NAME RISK ASSESSMENT

3.1.1 Database and information sources

The Division of Medication Error Prevention conducted a search of the internet, several standard published databases and information sources (see Section 6 References) for existing drug names which sound-alike or look-alike to MembraneBlue to a degree where potential confusion between drug names could occur and result in medication errors in the usual clinical practice settings. In total, six names were identified as having some similarity to the name MembraneBlue.

Two of the six names were thought to look like MembraneBlue, which include: Marcaine, Matulane. The four remaining names, Methylene Blue, VisionBlue, Prussian Blue, Evans Blue, were thought to look and sound similar to MembraneBlue.

As of March 18, 2008, the proposed name, MembraneBlue, did not contain a U.S. Adopted Name (USAN) stem.

3.1.2 Expert panel discussion

The Expert Panel reviewed the pool of names identified by the Division of Medication Error Prevention staff (see section 3.1.1. above), and noted an additional name, _____, thought to have orthographic similarity to MembraneBlue. The Expert Panel also wondered whether MembraneBlue and VisionBlue were marketed by the same applicant and expressed concerns that the labels and labeling of these products may be problematic if they looked similar.

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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 Prescription analysis studies

A total of 36 practitioners responded, but none of the responses overlapped with any existing or proposed drug names. About eighty percent of the participants (n=29) interpreted the name correctly, however, all of these participants interpreted the name as two words not one, as the applicant is proposing. The interpretation "Membrane Blue," occurred more frequently in the written studies. The remainder of the responses misinterpreted the drug name. The majority of misinterpretations occurred in the phonetic prescription study, with the first consonant 'B' in the second word Blue reported as 'g' and 'Blue' interpreted as 'Lube' in one instance. Some of the participants capitalized the second word and others did not. Only one participant in the written

prescription study misinterpreted 'Membrane' as 'Membrane'. See Appendix A for the complete listing of interpretations from the verbal and written prescription studies.

3.1.4 Safety Evaluator Risk Assessment of Proposed Proprietary Name

Independent searches by the primary Safety Evaluator did not identify additional names thought to look similar to MembraneBlue and represent a potential source of drug name confusion. Careful evaluation was afforded to drug names that had the name 'Blue'. Thus, a total of seven names were analyzed to determine if the drug names could be confused with MembraneBlue, 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 MembraneBlue, and thus determined to present some risk for confusion. Failure modes and effects analysis was then applied to determine if the proposed name, MembraneBlue, could potentially be confused with any of the seven names and lead to medication error.

This analysis determined that the name similarity between MembraneBlue and the identified names was unlikely to result in medication errors for five of the seven products [Marcaine, _____ Matulane, Methylene Blue, Radiogardase (Prussian Blue)]. One proprietary name (Evans Blue) is a generic product that has been withdrawn from the market (see Appendix C).

b(4)

MembraneBlue is proposed in one strength, thus recommended or ordered without a strength. Additionally, this product will most likely only be used in an operating room, thus prescriptions for patient use will most likely not be written. The analysis of products available in only one strength resulted in five products that the strength could be omitted in an order (_____ Marcaine, Matulane, Methylene Blue, Prussian Blue). These names have minimal orthographic and/or phonetic similarity to MembraneBlue and also have multiple differentiating product characteristics to minimize the potential for medication errors (see Appendix D).

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However, the remaining and seventh name, VisionBlue, was found to likely result in medication errors due to the identical established names, the use of the word 'Blue' in the second part of the name, overlapping product characteristics, and the visual similarity in the labels and labeling. In addition, these products are both indicated for ophthalmic surgical patients (see Appendix E).

3.2 LABEL AND LABELING RISK ASSESSMENT

Upon review of the carton and container labels for MembraneBlue, the Division of Medication Error Prevention's primary concern is the visual similarity between the labels of the proposed product and the labels of the currently marketed product, VisionBlue. It appears that the applicant is using some sort of identical template to present the product information. Moreover, it is not clear whether the applicant intends on using color to differentiate their products since the container labels and carton labeling were submitted in black and white presentation. We are also concerned about the similarity in packaging between the proposed product and the existing product, VisionBlue (e.g. both products are marketed in a 2.25 mL syringe although the actual volume is 0.5 mL).

Part of the established name appears immediately following and under the proprietary name while the strength appears immediately before the established name.

The route of administration and usual dose statement are absent on the carton labeling.

The net quantity statement appears immediately below the strength statement.

The box labeling makes reference to the size of the syringe (e.g., "5 Luer Lok Syringes 2.25 mL of 0.5 mL) volume of the product on one line.

The manufacturer's name, "DORC", appears prominently in blocked, bold font letters on the label, immediately above the proprietary and established names.

The Division of Medication Error Prevention notes that the applicant has included a patient record label.

4 DISCUSSION

The results of the Proprietary Name Risk Assessment found that the proposed name, MembraneBlue, is vulnerable to name confusion with VisionBlue which could result in medication errors due to the use of the word 'Blue' in the second part of the name, their identical established names, and overlapping product characteristics. The concerns identified regarding the proprietary name are further augmented by the findings of the Label and Labeling Risk Assessment.

Although the two products share the same established name, Trypan Blue, the Chemistry, Manufacturing, and Controls (CMC) Review determined that MembraneBlue and VisionBlue are two different products. According to the applicant, the concentration may be higher due to the higher purity of the trypan blue. Therefore, the two products can not be managed under one name with two strengths and must have separate names.

The applicant submitted labels and labeling that bear a remarkable similarity to the labels and labeling of their already existing product, VisionBlue, which further increases the risk of confusion among their products. While applicants typically prefer to use a common layout for their products, we are particularly concerned about the use of visually similar layouts for these two products because they have the same established name, include the name 'Blue' as part of their proprietary name, and are packaged in similar configurations (both 2.25 mL glass syringes with 0.5 mL volume). The two products share a common patient and prescribing population (ophthalmic surgical) and both are available in one strength only, which may lend itself to error since the strength does not have to be specified when ordered. Additionally, since both products will most likely be used in an operating room, prescriptions for patient use are unlikely to be written. However, we do not dismiss the fact that confusion and error could still arise from interpreting requisition orders for the product. And although this lessens one potential source of error, this increases our concerns regarding selection error since both products will most likely be stored in close proximity to one another (i.e. PYXIS or medication shelf). It is not uncommon to have products stored by established name and should the labels and labeling overlap in any way, we have concerns that confirmation bias may also contribute to the potential that the healthcare provider will select the wrong product.

Because the labels and labeling were submitted in black and white presentation, we are unable to evaluate if the use of colors, color fonts, and/or the graphics affect the readability of the labels and labeling or add visual distinction between VisionBlue and MembraneBlue.

Other areas noted in the review were the inconsistency of how the strength appears on the proposed labels. The applicant has placed the product strength immediately following the proprietary name and preceding part of the established name. This formatting is unconventional

and is different than how other products are presented rendering the product vulnerable to confusion because the healthcare provider is unfamiliar with the format and this information may be difficult to locate.

The proprietary and established names, strength and dosage form typically appear as follows:

MembraneBlue
(Trypan Blue) Solution 0.15%
Or
MembraneBlue
(Trypan Blue) Solution
0.15%

We also noted the applicant has omitted the route of administration and usual dose statement from the carton labeling as required per 21 CFR 201.100 (b)(3) and 21 CFR 201.55, respectively.

b(4)

To minimize the potential for confusion, the strength and net quantity statements usually appear away from one another on the labels and labeling. However, in the applicant's proposed labels and labeling, _____ This is problematic because our post-marketing surveillance shows that having these statements in close proximity with each other increases the probability that they will be confused with one another. Moreover, we believe referencing the size of the syringe (2.25 mL) may be confusing to practitioners and may mislead them to think that 2.25 mL of trypan blue is the amount of drug contained in the syringe when only 0.5 mL is in the syringe. We question why the product is marketed in a 2.25 mL syringe since the actual volume is 0.5 mL.

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The manufacturer name, "DORC", is prominently present in blocked, bolded letters which competes with the presentation of the proprietary and established names. The font size is also inappropriate as it appears to be larger than the proprietary and established names. The proprietary and established names, along with the strength, should be the most prominent information on the labels and labeling.

A Patient Record Label is included in the labels/labeling. How will this Patient Record Label be used? Is this label to be placed in the patients' chart to indicate that a patient has been treated with trypan blue? Also, there are no references or directions pertaining to this label on the carton or in the insert labeling.

The Division of Medication Error Prevention believes the risks we have identified can be addressed and mitigated prior to drug approval, and provides recommendations in Section 5 that aim at reducing the risk of medication errors.

Overall, our Risk Assessment is limited by our current understanding of medication errors and causality. The successful application of Failure Modes and Effect Analysis depends upon the learning gained for a spontaneous reporting program. It is quite possible that our understanding of medication error causality would benefit from unreported medication errors; and, that this understanding could have enabled the Staff to identify vulnerability in the proposed name, packaging, and labeling that was not identified in this assessment. To help minimize this

limitation in future assessments, we encourage the Applicant to provide the Agency with medication error reports involving their marketed drug products regardless of adverse event severity.

5 CONCLUSIONS AND RECOMMENDATIONS

The Proprietary Name, Labels and Labeling Risk Assessments and FMEA findings indicate that the proposed name, MembraneBlue, appears to be vulnerable to product confusion with VisionBlue that could lead to medication errors. The Division of Medication Error Prevention believes that the risk may be mitigated by differentiating the proposed labels and labeling of MembraneBlue from the labels and labeling of the existing product VisionBlue. If the appropriate changes have been made, the Division of Medication Error Prevention may not object to the use of the proprietary name, MembraneBlue, for this product. Such changes would also be required to mitigate the risks identified in our Label and Labeling Risk Assessment which indicates that the presentation of information and design of the proposed carton and container labels introduces vulnerability to confusion that could lead to selection errors. Recommendations are provided in Section 5 that aim at reducing the risk of medication errors.

5.1 COMMENTS TO THE DIVISION

The Proprietary Name, Label and Labeling Risk Assessment findings indicate that the proposed name, MembraneBlue, may appear to be vulnerable to product confusion with VisionBlue that could lead to medication errors. We are particularly concerned about the overlapping "Blue" ending, product characteristics, patient population, and the similar appearance of MembraneBlue labels and labeling to those of VisionBlue, a product marketed by the same applicant. The Division of Medication Error Prevention believes that this risk can be mitigated through differentiation between the proposed product and the currently marketed VisionBlue, avoiding the use of similar color, scheme, layout, font and images. If the appropriate changes are made, the Division of Medication Error Prevention may not have objections to the use of the proprietary name, MembraneBlue, for this product.

The Division of Medication Error Prevention would appreciate feedback of the final outcome of this consult. We would be willing to meet with the Division for further discussion, if needed. We have provided recommendations in section 5.2 and request this information be forwarded to the Applicant. Please copy the Division of Medication Errors Prevention on any communication to the applicant with regard to this review. If you have further questions or need clarifications, please contact Cheryle Milburn, OSE Project Manager, at 301-796-2084.

5.2 COMMENTS TO THE APPLICANT

The Proprietary Name Risk Assessment findings indicate that the proposed name, MembraneBlue, for this product may be vulnerable to product confusion that could lead to medication errors. However, the Division of Medication Error Prevention believes that this risk can be mitigated through the use of an alternate proprietary name or by differentiating the proposed labels and labeling from the labels and labeling of the applicant's existing product, VisionBlue. Once we review the changes and determine the labels/labeling are well differentiated, the Division of Medication Error Prevention may not have objections to the use of the proprietary name, MembraneBlue.

The labels and labeling closely resemble the currently marketed VisionBlue product. This similarity contributes to the potential for these products to be confused with one another. In addition, established and proprietary names, the dosage form, indication for use, and packaging of the product potentially add to this confusion. We believe that confirmation bias related to the similarity in name and packaging contributes to the potential a provider selecting the wrong product.

To minimize the risk of medication errors with this product, the Division of Medication Error Prevention makes the following recommendations:

1. Ensure that the labels and labeling for MembraneBlue are differentiated from their currently marketed product, VisionBlue (i.e. different font type, colors, formatting etc).
2. Revise the labels and labeling so that the established name, strength, and dosage form appear in conjunction with the proprietary name. For example:

MembraneBlue

(trypan blue) solution 0.15%

3. Ensure that the route of administration and usual dose statement are present on the carton labeling.
4. Explain why the product is packaged in a 2.25 mL syringe when the actual volume is 0.5 mL. Additionally, ensure that the strength is expressed in terms of mg/0.5 mL.
5. Ensure that the net quantity statement appears away from the product strength.
6. Remove reference to the size of the syringe (2.25 mL) from the "# Luer Lok Syringes 2.25 mL of 0.5 mL" statement.
7. Decrease the prominence of the manufacturer name, "DORC", and place it away from the proprietary and established names.
8. Comment on how the patient record label will be placed on the chart and how practitioners will know what the label will represent.

6 REFERENCES

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

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

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

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

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

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

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

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

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

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

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

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

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

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

8. ***WWW location*** <http://www.uspto.gov>.

Provides information regarding patent and trademarks.

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

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

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

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

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

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

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

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

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

List contains all the recognized USAN stems.

14. Red Book Pharmacy's Fundamental Reference

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

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

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

16. Medical Abbreviations Book

Contains commonly used medical abbreviations and their definitions.

Use standard format for citations for previous OSE reviews; literature.

APPENDICES

Appendix A:

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

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

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

		Upstrokes Downstrokes Cross-strokes Dotted letters Ambiguity introduced by scripting letters Overlapping product characteristics	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	• Names may sound similar when pronounced and lead to drug name confusion in verbal communication

Appendix B:

Prescription Study Responses

Membrane Blue	Membrane Blue	Membrane Blue
Membrane Blue	Membrane blue	Membrane Blue
Membrane Blue	Membraneglu	Membrane Blue
Membrane Blue	Membrane Lube	Membrane blue
Membrane Blue	Membrane Blue	Membrane Blue
Membrane Blue	Membrane glue	Membrane Blue

Membrane Blue	?	Membrane Blue
Membrane Blue	Membrane Blue	Membrane Blue
Membrane Blue	Membrane Blue	Membrane Blue
Membrane Blue	Membrane Blue	Membrane Blue
Membrane Blue	Membrane Blue	
Membrane Blue	Membrane blue	
	Membrane B	
	Membrane Blue	

Appendix C: Proprietary names of generic products withdrawn from the market by manufacturer

Proprietary Name	Similarity to Membrane Blue
Evans Blue	Look and Sound

Appendix D: Products with no numerical overlap in strength and dose.

Product name with potential for confusion	Similarity to Proposed Proprietary Name	Strength	Usual Dose (if applicable)
MembraneBlue® (Trypan Blue)		0.15%	Usual dose: 1. Attach a thin blunt cannula to the syringe; first perform a 'fluid-air exchange'; carefully apply to the retinal membrane using a blunt cannula; sufficient staining is achieved at contact with the membrane; remove all excess dye from the vitreous cavity. 2. Inject directly in a buffered saline solution (BSS) filled vitreous cavity; sufficient staining is achieved after 30 seconds of application under BSS; remove all excess dye from the vitreous cavity.
Marcaine	Look	0.25%, 0.5%, 0.75%, 0.25% with 1:200,000 epinephrine, 0.5% with 1:200,000 epinephrine, 0.75% with 1:200,000 epinephrine	Varies with anesthetic procedure.

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

Product name with potential for confusion	Similarity to Proposed Proprietary Name	Strength	Usual Dose (if applicable)	Other differentiating product characteristics (excluding dose and frequency)
MembraneBlue® (Trypan Blue)		0.15%	Usual dose: 1. Attach a thin blunt cannula to the syringe; first perform a 'fluid-air exchange'; carefully apply to the retinal membrane using a blunt cannula; sufficient staining is achieved at contact with the membrane; remove all excess dye from the vitreous cavity. 2. Inject directly in a buffered saline solution (BSS) filled vitreous cavity; sufficient staining is achieved after 30 seconds of application under BSS; remove all excess dye from the vitreous cavity.	
	Look	1%	Apply 5 to 10 mL to wet scalp and massage in. Leave on for 2 to 3 minutes. Rinse thoroughly and repeat. Two applications weekly for 2 weeks usually brings control, followed with 1 application every 1 to 4 weeks as needed.	Route of administration, indication for use, prescriber.
Matulane	Look	50 mg	Single or divided doses of 2 to 4 mg/kg/day for the first week. Maintenance	Route of administration, indication for use,

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			dose of 4 to 6 mg/kg/day.	prescriber.
Methylene Blue	Look and Sound	1%	0.1 to 0.2 mL/kg of body weight. Inject intravenously very slowly over a period of several minutes.	Route of administration, indication for use, prescriber.
Radiogardase (Prussian Blue)	Look and Sound	500 mg	3 grams by mouth three times daily for a minimum of 30 days. After 30 days, the patient should be reassessed for the amount of residual whole body radioactivity. When the internal radioactivity is substantially decreased the dose may be decreased to 1 or 2 grams by mouth three times daily to improve GI intolerance. The duration of treatment is dictated by the level of contamination.	Route of administration, indication for use, prescriber.

Appendix F: Product identified as resulting in medication errors

MembraneBlue® (Trypan Blue)	0.15%	Usual dose: 1. Attach a thin blunt cannula to the syringe; first perform a 'fluid-air exchange'; carefully apply to the retinal membrane using a blunt cannula; sufficient staining is achieved at contact with the membrane; remove all excess dye from the vitreous cavity. 2. Inject directly in a buffered saline solution (BSS) filled vitreous cavity; sufficient staining is achieved after 30 seconds of application under BSS; remove all excess dye from the vitreous cavity.
Failure Mode: Name confusion	Causes (could be multiple)	Effects
VisionBlue (Trypan Blue)	Established names are identical. Products share the name "Blue" in the second half of their respective names. Products are both used in ophthalmic surgery patients. Products share the same applicant. Both would probably only be used in the operating room and prescriptions for patient use are unlikely to be written. Both may be written without a strength. Identical established names and an overlap in the second half of the proprietary name	Medication error is likely to occur given that the established names are identical and the proprietary names both contain the word 'Blue' in them. Additionally, these products will most likely be stored in the same area. The similarity of the labels and labeling for MembraneBlue and the already existing product, VisionBlue, compounds this problem, as confirmation bias related to the similarity in name and packaging contributes to the potential a caregiver selecting the wrong product.

	(VisionBlue vs. MembraneBlue). The labels and labeling for both products look similar. The packaging configuration is identical.	
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 § 552(b)(4) Trade Secret / Confidential

√ § 552(b)(4) Draft Labeling

 § 552(b)(5) Deliberative Process

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