APPLICATION NUMBER:

022305Orig1s000

CROSS DISCIPLINE TEAM LEADER REVIEW
Cross-Discipline Team Leader Review

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<tr>
<td>From</td>
<td>Lesley-Anne Furlong</td>
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<td>Subject</td>
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<td>NDA/BLA #</td>
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<td>Applicant</td>
<td>Niagara Pharmaceuticals, Inc.</td>
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<td>Date of Submission</td>
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<td>PDUFA Goal Date</td>
<td>9/1/2011</td>
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<tr>
<td>Proprietary Name / Established (USAN) names</td>
<td>Pur-Wash Eyewash/Purified water</td>
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<td>Dosage forms / Strength</td>
<td>Sterile solution</td>
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<td>Proposed Indication(s)</td>
<td>For cleansing the eye to help relieve irritation, by removing loose foreign material</td>
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Recommended: *Approval pending an approval recommendation from the microbiology reviewer and satisfactory negotiation of final labeling.*
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1. Introduction

This summary review evaluates a marketing application for a buffered, sterile, single-use, saline eyewash. Pur-Wash meets the requirements for eyewash set forth in the over-the-counter (OTC) monograph in 21 CFR Part 349, with two exceptions: Pur-Wash does not contain preservative(s), and Pur-Wash is sterilized.

The OTC monograph requires that multiple-dose ophthalmic products contain one or more preservatives (21 CFR 200.50). Because Pur-Wash is a single-use and sterile product, the applicant contends that a preservative is unnecessary. The lack of preservative is a deviation from the OTC monograph, and an OTC drug deviating in any respect from a final monograph is marketed through the NDA (new drug application) process (21 CFR 330.11).

Pur-Wash is sterilized as required for ophthalmic preparations (21 CFR 200.50); however, sterilization is accomplished. A drug that is sterilized is marketed through the NDA process (21 CFR 310.502).

The application consists primarily of chemistry and microbiology data to support that the product is sterile, stable, and unchanged in any clinically important manner as a result of.

2. Background

The application is a resubmission responding to FDA’s refusal to file the original application submitted on January 30, 2008. The main issues prompting the refusal to file were inadequate testing and characterization of degradants after. In addition, various required sections and forms were omitted in the original application. Dr. Alexander’s primary clinical review provides further details. After the refusal-to-file and discussion with the FDA chemistry team, the applicant. The current application provides chemistry and microbiologic data to address the chemistry deficiencies, it also provides the missing NDA sections and forms.

In addition, the applicant had problems with its manufacturing sites. An FDA inspection in September 2006 revealed deficiencies that were the subject of an FDA Form 483. The deficiencies included the need for a new drug application for products, as well as five GMP violations related to inadequate testing procedures and records. After applicant addressed the deficiencies, FDA re-inspected the manufacturing sites in September 2010. On January 18, 2011, FDA’s Office of Compliance determined that the manufacturing sites were acceptable.

According to the ophthalmic monograph (21 CFR 349), eyewash is a “sterile aqueous solution intended for washing, bathing, or flushing the eye.” The active ingredient is water, and the product “also contains suitable tonicity agents to establish isotonicity with tears, suitable
agents for establishing pH and buffering to achieve the same pH as tears, and a suitable preservative agent.” The proposed product contains sodium chloride and boric acid.

The regulations further specify requirements for ophthalmic preparations and dispensers (21 CFR 200.50). Preparations must be sterile and the containers must be sealed so that the contents cannot be used without destroying the seal. Although "one or more suitable and harmless substances that will inhibit the growth of microorganisms" are required for multi-dose containers, the regulations are silent on preservative(s) for products like Pur-Wash that are packaged in single-use containers. OTC products should have tamper-evident packaging (21 CFR 211.132).

There were no clinical trials performed for the application; the applicant is relying on FDA’s previous findings of safety and efficacy as stated in the monograph.

I consulted the following FDA reviews when writing this summary review:
- Clinical review from the Division of Nonprescription Clinical Evaluation (DNCE)
- Clinical review from the Division of Transplant and Ophthalmology Products (DTOP)
- Pharmacology/toxicology review
- Chemistry, Manufacturing, and Controls (CMC) review
- Division of Medication Error Prevention and Analysis (DMEPA) review
- Division of Nonprescription Regulation Development (DNRD) review
- DNCE regulatory correspondence and reviews

At the time this review was finalized, the microbiology review was pending; although no microbiology issues had been identified, the applicant had not yet submitted sterility validation data for the eyecups (expected at the end of July 2011).

3. CMC/Device

The CMC review team found the application approvable pending acceptable recommendations from the microbiology review. The following is a summary of the CMC review; details may be found in Dr. Ramaswamy’s primary CMC review.

The eyewash is a sterile, isotonic, aqueous solution. The eyewash contains a boric acid buffer, sodium chloride and purified water as the active ingredient in the following amounts:
- Purified Water (98.3%)
- Boric acid
- Sodium chloride
- Sodium borate

The pH of the solution is between 7.0.
The inactive ingredients in Pur-Wash are compendial grade excipients and the proposed specification for these ingredients meet USP/NF monograph specifications. The active ingredient, purified water, is manufactured using a qualified water purification system. The proposed specification for purified water meets the USP monograph requirement. Storage stability data is unnecessary for the purified water as the water purification system generates purified water on demand. Test results for 3 stability batches met the proposed product release specification. The applicant provided 6 months of accelerated stability data and 12 months of real-time stability data for 3 batches of eyewash solution; the stability results were acceptable. The CMC team recommended a shelf-life of 24 months for the proposed product. The applicant has provided a post-approval stability protocol and committed to evaluating post-approval stability. The applicant has claimed categorical exemption for environmental assessment under 21 CFR 25.31 (b) and (c); the CMC team concurs.

The product is packaged in five different-sized container closure systems: 1, 4, 8, 16, and 32 ounce high density polyethylene resin (HDPE) bottles with closures. The components meet regulations for food contact materials.

21 CFR 349.78(d) requires that the directions for use for eyewash direct the consumer to use either a nozzle applicator or an eyecup. All five containers have either a “nozzle equivalent” or are co-packaged with a sterile eyecup. There are two different configurations for the 16-oz container: a cylinder bottle with a “natural plug” and a round bottle with a sterile eyecup. The 1-oz and 4-oz containers have a “natural dropper tip.” The 8-oz container has a “natural plug.” The 32-oz bottle is packaged with a sterile eyecup. All packaging configurations have a tamper-evident seal. The packaged product is.

The applicant conducted a study to compare extractables and degradants between the products. The study supported the similarity between products. Leachables data for the product stored under accelerated storage conditions indicated that the leachable compounds were present at or below detection levels. Three batches were tested for heavy metals. The data were deemed acceptable by the CMC review team.

The Office of Compliance has issued an acceptable recommendation for the purified water manufacturing sites from a quality system perspective.

The CMC team recommends that the product be labeled for storage under USP controlled room temperature (20 to 25 degrees C, or 68 to 77 degrees F) because the postapproval stability study does not include intermediate storage conditions.

4. Nonclinical Pharmacology/Toxicology

The pharmacology/toxicology review team recommended approval of the application from the standpoint of pharmacology/toxicology. No new pharmacology/toxicology data were submitted; because the applicant was able to show that the product “did not show different
 specifications when comparing the products,” no nonclinical studies were required.

5. Clinical Pharmacology/Biopharmaceutics

No new clinical pharmacology/biopharmaceutics data were submitted, nor were any required.

6. Clinical Microbiology

No new clinical microbiology data were submitted, nor were any required. Product sterility will be addressed in the microbiology review that has not been finalized.

7. Clinical/Statistical- Efficacy

The applicant relied on the monograph (21 CFR 349) to establish efficacy.

Comment: I agree with reliance on the monograph to establish efficacy because neither absence of a preservative nor the method of sterilization should affect the ability of the product to flush foreign material from the eye.

8. Safety

The applicant relied on the monograph (21 CRF 349) to establish safety. In addition, the applicant provided postmarketing safety summary that did not detect any new signals for eyewash.

The proposed product has not been marketed. A similar product (called the “original product” in the application) is currently legally marketed only in Canada. The original product has three preservative agents, but otherwise contains the same ingredients as the proposed product. There are no applications pending for the original product.

The applicant provided a postmarketing summary for the original product. From June 3, 2008 through November 25, 2010, approximately [redacted] units were sold in the United States and Canada. After spring 2007, all sales were in Canada because the company had been told they needed an NDA to support U.S. sales. The total U.S. sales were [redacted] units.

No adverse drug reactions have been reported and no recalls have occurred. In 2008, a complaint was brought from Health Canada regarding the yellowness of the eyewash solution. The complainant was a salesman from a competitor. According to the applicant, the yellowing “Furthermore it was tested independently by Health Canada and proved that all testing passed the prescribed specifications.”
I searched FDA’s Adverse Event Reporting System on 3-Dec-2010 using the search term “water” in the active ingredient field. There was one report of an adverse event associated with misuse of a different eyewash product. The product was Collyrium eyewash, currently manufactured by Bausch & Lomb, and containing water, boric acid, sodium borate, sodium chloride and benzalkonium chloride. A 51-year old soaked his contact lens in expired Collyrium eyewash and subsequently went to the in the emergency room for “chemical burns of eye.” He was treated and the problem resolved. It is difficult to make much of this single case as the product was misused (for cleaning a contact lens), and the product contains benzalkonium chloride, which is not an ingredient in the proposed eyewash.

I then searched AERS using “eyewash” in the verbatim substance name field. I retrieved no additional adverse events. Also on 3-Dec-10, I checked the FDA document archive (DARRTS) for safety issues for water or eyewash and found none.

Dr. Alexander, primary DNCE clinical reviewer, also performed multiple independent searches of FDA’s AERS database and the literature. Details of his findings may be found in his review. In his review he comments, “The rarity of readily identifiable publications about safety hazards associated with topical eyewash products is consistent with the lack of significant number of reports in FDA AERS database, despite the widespread use of these products over decades. It provides further support that OTC eyewash products marketed under the final monograph are safe and effective.”

Comment: There do not appear to be any significant safety signals for marketed eyewashes. I would expect a similar safety profile for the proposed eyewash.

The absence of a preservative should not affect safety for a sterile, single-use product that is used according to labeling; therefore, I agree that Pur-Wash may rely on the monograph to support safety.

9. Advisory Committee Meeting

Not applicable.

10. Pediatrics

The application does not trigger the Pediatric Research Equity Act (PREA) because it does not propose a new active ingredient, new indication, new dosage form, new dosing regimen, or new route of administration.

11. Other Relevant Regulatory Issues

The firm does not appear on FDA’s application integrity list (checked 16-Dec-10).
The applicant has certified that there are no relevant patents that claim the active ingredient, drug product, or methods of use. There were no clinical trials to audit. On January 18, 2011, FDA’s Office of Compliance determined that the manufacturing sites were acceptable.

12. Labeling

At the time this review was completed, final labeling had not been negotiated. The Division of Medication Error Prevention and Analysis (DMEPA) and the Division of Nonprescription Regulation Development (DNRD) provided labeling reviews.

The applicant submitted the proprietary name (b)(4) for review; Pur-Wash was the applicant’s alternate proprietary name. The applicant withdrew (b)(4) after DMEPA informed them that there were two other international products with the same name. DMEPA found “Pur-Wash” acceptable.

Initially the proposed label was not in compliance with Drug Facts labeling format and monograph labeling as described in 21 CFR. In addition, the applicant had the statement (b)(4) under the “Warning” heading of Drug Facts labeling. The monograph does not restrict use of eyewashes in children. General regulatory requirements were communicated to the applicant in May 2011. In addition, the applicant was asked to remove the age restriction or provide a rationale for the age restriction. The applicant responded with revised labeling that removed the age restriction and addressed the general regulatory requirements. The DTOP team had also recommended removing warning language about keeping out of reach of children and contacting a poison control center if swallowed; however, the DNCE clinical team found the language acceptable.

Comment: The larger volumes of product may contain enough boric acid to produce toxicity in children. According to the Poisindex summary, death has resulted from boric acid ingestions of 2 to 3 grams in infants, 5 to 6 grams in children, and 15 to 20 grams in adults although there have been reports of survival after an estimated 10 gram ingestion by an infant; the lethal dose is not well-established. As the proposed product contains (b)(4) of boric acid per 100 ml, it is possible, albeit unlikely, to ingest a toxic amount. For this reason, retaining the applicant’s cautionary language about keeping the product out of reach of children and contacting poison control for accidental ingestions was acceptable to the DNCE clinical team.

The monograph provides for two different directions for use, depending on whether the product is packaged with an eyecup or a nozzle. The applicant has appropriately chosen the directions for a nozzle for the smaller containers. The larger containers are packaged with an eyecup that has side ports. The eyecup replaces the bottle cap when in use. The affixed eyecup with side ports allow for continuous flow of solution, in much the same way as a nozzle allows for continuous flow. Directions for use are appropriate for the eyecup with nozzle features.

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1 Borates, Poisindex Management, Micromedex 2.0, last modified 24-Sep-2010, Thomson Reuters

Reference ID: 2976033
The CMC team recommends that the product be labeled for storage under USP controlled room temperature (20 to 25 degrees C, or 68 to 77 degrees F) because the postapproval stability study does not include intermediate storage conditions. 

DMEPA and DNRED have several labeling recommendations related primarily to formatting issues; these recommendations are to be conveyed to the applicant.

Comment: The review team’s labeling recommendations are acceptable to me.

13. Recommendations/Risk Benefit Assessment

Recommended Regulatory Action

I concur with the review team and recommend approval pending:
- Final microbiology review supporting approval
- Final agreement on labeling

Risk Benefit Assessment

Pur-Wash should have the same safety and efficacy profiles as other eyewashes approved under the OTC monograph. There are no unexpected safety signals in the application or discovered by the review team. The risk/benefit assessment is therefore acceptable.

Recommendation for Postmarketing Risk Evaluation and Management Strategies

None

Recommendation for other Postmarketing Requirements and Commitments

None. Routine postmarketing pharmacovigilance should be adequate.

Recommended Comments to Applicant

None
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

LESLEYANNE A FURLONG
07/20/2011