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APPLICATION NUMBER:

022305Orig1s000

SUMMARY REVIEW

Summary Review for Regulatory Action

Date	September 1, 2011
From	Joel Schiffenbauer
Subject	Deputy Division Director Summary Review
NDA/BLA #	NDA 22-305
Supplement #	
Applicant Name	Niagara Pharmaceuticals
Date of Submission	November 1, 2010
PDUFA Goal Date	September 1, 2011
Proprietary Name / Established (USAN) Name	Purified water
Dosage Forms / Strength	Ophthalmic solution
Proposed Indication(s)	1. for cleansing eye to help relieve irritation etc 2. 3.
Action/Recommended Action for NME:	<i>Approval</i>

Material Reviewed/Consulted	Names of discipline reviewers
OND Action Package, including:	
Medical Officer Review	Victor Alexander, Jennifer Harris, William Boyd
Statistical Review	
Pharmacology Toxicology Review	Wafa Harrouk
CMC Review/OBP Review	Muthukumar Ramaswamy, Ali Al Hakim
Microbiology Review	Denise Miller
Clinical Pharmacology Review	
DDMAC	
DSI	
CDTL Review	Lesley Furlong
OSE/DMEPA	Yelena Maslov, Zachary Oleszczuk
OSE/DDRE	
OSE/DSRCS	
Other/labeling	Elaine Abraham, Marina Chang

OND=Office of New Drugs

DDMAC=Division of Drug Marketing, Advertising and Communication

OSE= Office of Surveillance and Epidemiology

DMETS=Division of Medication Errors and Technical Support

DSI=Division of Scientific Investigations

DDRE= Division of Drug Risk Evaluation

DSRCS=Division of Surveillance, Research, and Communication Support

CDTL=Cross-Discipline Team Leader

Signatory Authority Review Template

1. Introduction

The applicant submitted NDA 22-305 seeking approval for an OTC single use, sterile eyewash product for the OTC indications consistent with the OTC monograph 21 CFR 349 (for cleansing the eye to help relieve irritation etc by removing loose foreign material etc.). This eyewash product contains purified water as the active ingredient, contains no preservatives, and the drug product is (b) (4) sterilized (b) (4).

The applicant proposes to rely on the Ophthalmic Products for Over-the-Counter Human Use final monograph (21 CFR 349) for this eyewash product. The risk/benefit profile of eyewash products has been found acceptable for products that follow the OTC monograph.

However, the current product is sterilized by (b) (4) and does not contain any preservatives. Under 21 CFR 310 (b) (4), all drug products sterilized by (b) (4) require an NDA. This product also deviates from the OTC monograph for eyewash products since it does not contain (antimicrobial) preservatives. These changes therefore, necessitated that the applicant submit an NDA. The application otherwise meets the requirements of the OTC monograph for eyewashes.

This review will address the 2 main issues that impact the approvability of this product, chemistry (b) (4) and sterilization/microbiology, as well as briefly discuss the safety of eyewash products. For additional details on each topic, the reader is referred to the specific discipline reviews.

2. Background

This eyewash solution contains purified water USP (98.3%), boric acid N.F./USP (b) (4), sodium chloride USP (b) (4) and sodium borate N.F. (b) (4). The final drug product does not contain preservative and is sterilized by (b) (4), which are the primary reasons this product requires review under an NDA (see 21 CFR 310 (b) (4)).

The application is a resubmission responding to FDA's refusal to file the original application submitted on January 30, 2008. The refusal to file was prompted by inadequate testing and characterization of degradants after (b) (4) as well as multiple

required sections and forms were omitted in the original application. The current application provides all the required information in regards to chemistry and microbiology data to address the chemistry deficiencies and provides the missing NDA sections and forms.

In addition 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 (b) (4) products, as well as five GMP violations related to inadequate testing procedures and records. After the applicant addressed the deficiencies, FDA's Office of Compliance determined that the manufacturing sites were acceptable.

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

3. CMC/Device

I concur with the conclusions reached by the chemistry reviewer regarding the acceptability of the manufacturing of the drug product and drug substance. Manufacturing site inspections were acceptable. Stability testing supports an expiry of 24 months. There are no outstanding issues.

The CMC review team found the application approvable pending acceptable recommendations from the microbiology review and provided the following comments (excerpted from the CMC review):

The eyewash is a sterile, isotonic, aqueous solution. The eyewash contains a borate/boric acid (b) (4) sodium chloride (b) (4), and purified water as the active ingredient in the following amounts:

Purified Water (98.3%)

Boric acid (b) (4)

Sodium chloride (b) (4)

Sodium borate (b) (4)

The pH of the solution is between (b) (4).

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 packaged product is sterilized at a contract facility by (b) (4) and the sterilization process is validated per (b) (4). The adequacy of the sterilization process validation data will be evaluated by Microbiology reviewer.

The applicant conducted a study to compare extractables and degradants between the (b) (4) products. The study supported the similarity between (b) (4) 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 Firm has also completed a leachable assessment for the drug product stored under accelerated storage conditions (40°C ± 2°C at 75% RH ± 5%) for 6 months. The target leachables were present in these solutions at below detection limits. The Applicant provided adequate method validation information for the GC/MS method used for detecting leachables. The Firm has also completed an assessment on the levels of heavy metals present in the drug product by ICP-MS. Test results showed that heavy metal impurities (b) (4) are present at or below limits specified under USP <231>/<232> and the EP monograph for water for injection.

The NDA contains adequate in-process controls for bulk eye wash manufacturing, filling and packaging operations. The proposed final specification for the product meets the USP monograph specification for eye wash solution. The finished product is tested for various physical and chemical attributes (appearance, color, assay of sodium chloride and boric acid, osmolality, heavy metals, specific gravity, particulate matter); microbiological attributes (sterility and endotoxin), and packaging integrity. The NDA contains acceptable method validation for the assay used for the determination of borate and chloride content.

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. All packaging configurations have a tamper-evident seal. The packaged product is (b) (4) sterilized (b) (4).

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 (b) (4) closures. The components meet regulations for food contact materials. The NDA contains information on specification, material of construction, and engineering drawings for packaging components. The Applicant has also provided appropriate reference to the DMFs associated with the packaging components.

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 (b) (4).

Based on the above, the applicant has provided sufficient information to demonstrate that (b) (4) should not have an impact on the efficacy and safety of this product from a clinical perspective.

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 [REDACTED] (b) (4) products.”

5. Clinical Pharmacology/Biopharmaceutics

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

6. Clinical Microbiology

I concur with the conclusions reached by the clinical microbiology reviewer that there are no outstanding clinical microbiology or sterility issues for either the eye wash or the eye cups, that preclude approval.

7. Clinical/Statistical-Efficacy

Clinical studies should not be required to support this NDA. The drug product generally conforms to the requirements in 21 CFR 349 - Ophthalmic Drug Products for Over-The-Counter Human Use for eyewashes. Eyewash products which meet the regulatory requirements of the monograph are recognized as being safe and effective and can be marketed OTC. This product deviates from the monograph in that it lacks a preservative agent and is sterilized with [REDACTED] (b) (4) (which is not permitted under the monograph).

I agree that no efficacy information was required for this NDA as this product meets the conditions for use of an eyewash and these changes should not impact the efficacy or safety of this product.

8. Safety

This single use sterile product is not expected to pose any serious safety risk to consumers as long as product sterility is ensured and the [REDACTED] (b) (4) sterilization method is shown effective in maintaining product sterility for the proposed shelf life.

The sponsor has marketed more than [REDACTED] (b) (4) units of a comparable sterile eyewash, largely in Canada, since 2003 and received no reports of adverse effects. There have been no serious

adverse event reports nor product recalls.

Dr. Alexander, medical officer, performed searches in FDA AERS database on multiple occasions using the terms “Niagara”, “Niagara Pharmaceuticals”, “eyewash”, and “eye wash” in various AERS search fields with no positive results. Dr. Alexander further conducted an updated search in AERS on May 27, 2011 for all adverse events for the drug product term “Collyrium” (an eyewash product from Bausch and Lomb). A total of seven case reports were identified. He identified that none of the case reports included a narrative and therefore could not be further evaluated. In addition, he noted the cases might be confounded by indication, among other biases.

Dr. Alexander conducted another updated search in AERS on May 27, 2011 for all adverse events for the drug product term “purified water.” A total of seven case reports were identified. There was no overlap between the cases found in the AERS search for “Collyrium” and the AERS search for “purified water.” Dr. Alexander notes that most cases clearly were unrelated to possible drug toxicity due to topical exposure to purified water, or were confounded by pre-existing medical conditions, concomitant drug exposures, and non ophthalmic use. He further provides the following comments:

The striking feature of these AERS search results is the relative paucity of adverse event case reports for either eyewash products or the active ingredient purified water. There are no unequivocal case reports of serious adverse events for eyewash products in the AERS database, dating back at least 25 years. Nor are there any instances of systemic adverse events likely to be related to topical exposure to these products, despite millions of consumer exposures. The very limited data in AERS described here lends support for the safety of OTC eyewash products available under the final monograph.

Finally, Dr. Alexander performed a number of Medline searches to identify relevant papers. The terms “eyewash” and “eye wash” yielded a total of 47 citations in PubMed on May 27, 2011. None of the three publications reviewed in detail provided direct evidence for a safety hazard related to the applicant’s proposed product. The literature search did not provide evidence of safety hazards due to sterile eyewash solutions except when the drug product itself has become contaminated.

A PubMed search for the conjoint terms “purified water” and “adverse events” yielded two citations, neither of which was relevant. Dr. Alexander comments:

The rarity of readily identifiable publications about safety hazards associated with topical eyewash products is consistent with the lack of significant numbers 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.

Dr. Furlong the CDTL, performed independent searches of FDA’s Adverse Event Reporting System on 3-Dec-2010 using the search term “water” in the active ingredient field and did not identify any cases other than those identified by Dr. Alexander.

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

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.

I agree with Drs. Alexander and Furlong that there do not appear to be any significant safety issues related to the use of eyewash in general.

9. Advisory Committee Meeting

No advisory committee meeting was held for this product. This product deviates from the OTC monograph but did not raise any significant issues requiring advisory input.

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. Labeling for monograph eyewashes does not restrict the age for which this can be used, and therefore the label will allow for pediatric use.

11. Other Relevant Regulatory Issues

There are no other unresolved relevant regulatory issues.

12. Labeling

The reader is referred to the labeling reviews by Elaine Abraham and Yelena Maslov. The only unresolved issue regards the recommendation by Drs. Harris and Boyd, that the warning language about keeping out of reach of children and contacting a poison control center if swallowed, be removed. However, the DNCE clinical team rather found the language acceptable. Dr. Furlong provided a reasonable rationale for including such a statement, as follows:

The larger volumes of product may contain enough boric acid to produce toxicity in children. According to the Poisindex₁ 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.

I agree with Dr. Furlong's recommendations in this regard.

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. Directions for use are appropriate for the eyecup with nozzle features.

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 (b) (4).

DMEPA and DNRD have several labeling recommendations related primarily to formatting issues. I agree with these recommendations and they are to be conveyed to the applicant.

13. Decision/Action/Risk Benefit Assessment

The sponsor seeks approval for an OTC single use, sterile eyewash product for OTC use. This eyewash product contains 98.3% purified water as the active ingredient, contains no preservatives, and the drug product is (b) (4) sterilized (b) (4).

The sponsor proposes to rely on the Ophthalmic Products for Over-the-Counter Human Use final monograph (21 CFR 349) for safety and efficacy. The risk/benefit of eyewash products has been established for products that follow the OTC monograph.

The applicant has provided adequate CMC and microbiology data to support approval of this product. There are no unresolved issues that would preclude approval. There are no post-marketing commitments needed.

Therefore, this reviewer recommends that this NDA be approved.

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

/s/

JOEL SCHIFFENBAUER
09/01/2011