

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**022305Orig1s000**

**PHARMACOLOGY REVIEW(S)**

**DEPARTMENT OF HEALTH AND HUMAN SERVICES  
PUBLIC HEALTH SERVICE  
FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH**

**PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION**

Application number: NDA 22-305  
Supporting Documents: S000  
Applicant's letter date: October 30, 2010  
CDER stamp date: November 1, 2010  
Product: Eye Wash<sup>1</sup>  
Indication: For cleansing the eye to help relieve irritation,  
(b) (4) burning, (b) (4) by  
removing loose foreign material, (b) (4)  
Applicant: Niagara Pharmaceuticals, Inc.  
Review Division: Division of Nonprescription Clinical Evaluation  
Reviewer: Wafa Harrouk, Ph.D., DNCE  
Secondary Reviewers: Paul Brown, Ph.D., ODE IV Associate Director for  
Pharmacology/Toxicology, OND  
Division Director: Andrea Leonard-Segal, M.D.  
Project Manager: Phong Do, Pharm. D.

**Disclaimer**

Except as specifically identified, all data and information discussed below and necessary for approval of the present New Drug Application (NDA) submission (NDA 22-305) are owned by Niagara Pharmaceuticals or are data for which Niagara has obtained a written right of reference. Any information or data necessary for approval of the present NDA submission that Niagara does not own or have a written right to reference constitutes one of the following: (1) published literature, or (2) a prior FDA finding of safety or effectiveness for a listed drug, as reflected in the drug's approved labeling. Any data or information described or referenced below from reviews or publicly available summaries of a previously approved application is for descriptive purposes only and is not relied upon for approval of the present NDA submission.

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<sup>1</sup> The sponsor had originally proposed (b) (4) the most recent proposed trade name is Pur-Wash

# 1 Executive Summary

## 1.1 Introduction

The sponsor is relying on the over-the-counter (OTC) monograph indication for water as a cleanser for debris in the eyes. This eyewash product consists of 98.3% purified water (b) (4). Eye wash products which meet the regulatory requirements of CFR 330.1 and 349.1 are recognized as safe and effective and can be marketed as OTC if there are no deviations from the established monograph. The current product is required to be submitted under an NDA since it deviates from the OTC monograph for eye wash products since it is sterilized (b) (4). This NDA does not require new nonclinical or clinical testing provided the (b) (4) does not change the chemistry specifications when comparing (b) (4) products. This product does not contain antimicrobial preservatives. The sponsor argues that a preservative agent should not be required since the product is to be used exclusively for a single use where the entire volume is expected to be used once the container is opened. The risk/benefit of eyewash products has been established for products that follow the OTC monograph.

## 1.2 Brief Discussion of Nonclinical Findings

As discussed above, no new nonclinical studies would be required for this NDA if no differences are noted in the product specifications (b) (4). Upon testing, the product did not show different specifications when comparing the (b) (4) products. As a result, no nonclinical studies were required and none were submitted for this NDA. The only nonclinical concern relates to the impurities, degradants and leachables profile from containers/labels and closure systems. Three separate lots of eye wash samples contained in two container systems (16 oz, 32oz HDPE bottles) were tested (b) (4) an impact on the level of leachables and degradants in the eye wash product. Purified water filled in plastic and glass bottles were used as controls. Bottles containing saline and borate buffer were used as test containers. No detectable change in the levels of saline or boric acid was noted in the tested samples.

(b) (4)

Some impurities/ degradants were found near the detection limit of 2 µg/ml but none were found above 10µg/mL (reporting threshold). A comparison of borate & chloride levels [REDACTED] (b) (4) did not show any significant changes.

### 1.3 Recommendations

#### 1.3.1 Approvability

NDA 22-305 Eye Wash is recommended for approval for the intended indication from the standpoint of pharmacology/toxicology.

#### 1.3.2 Additional Non Clinical Recommendations

None

#### 1.3.3 Labeling

None

## 2 Drug Information

### 2.1 Drug

Eye wash is listed in the monograph for eye wash in 21 CFR part 349-Ophthalmic Drug Products for Over-The-Counter Human Use, subpart B active Ingredients, Sec. 349.20 Eyewashes.

**Pharmacologic Class:** No specific activity, the solution contains 98.3% purified water (USP) which is used to physically dislodge debris from the eyes and to prevent eye irritation.

### 2.2 Relevant INDs, NDAs, and DMFs

PIND 77883

### 2.3 Drug Formulation

This eye wash solution contains purified water USP (98.3%), boric acid N.F./EP/USP [REDACTED] (b) (4), sodium chloride USP [REDACTED] (b) (4) and sodium borate N.F. [REDACTED] (b) (4). All ingredients are USP or NF specifications. The final drug product is [REDACTED] (b) (4) the primary reason for which this product was required to be reviewed under an NDA.

### Comments on Novel Excipients

None

2.5 Comments on Impurities/Degradants of Concern

Leachables from container closure: Stability testing after 1, 3 and 6 months of storage at 40°C/75% RH for different lots did not reveal any significant impurities or leachables that should present a toxicity issue for the 1 oz and 32 oz containers (see table below).



**TABLE 5**  
**Leachables in Irradiated Eyewash after One, Three and Six Months Storage at 40°C/75%RH**  
**(Results in µg/mL)**

Container	32oz HDPE	1oz HDPE
(b) (4)		

2.6 Proposed Clinical Population and Dosing Regimen

This product is recommended to wash debris from the eyes. No specific dosing regimen is provided.

2.7 Regulatory Background

This NDA was originally submitted on January 30, 2008 but was found to have insufficient information for filing purposes and thus was given a “refused to file” status due partly to the lack of non-clinical information provided and the lack of characterization of leachables and new impurities/degradants. In the new submission dated November 1, 2010, (b) (4) the formulation and information on leachables/impurities was provided.

**3 Studies Submitted**

3.1 Studies Reviewed

No new nonclinical studies were required or submitted for the approval of this eye wash product.

3.2 Studies Not Reviewed

None.

3.3 Previous Reviews Referenced

None.

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/s/  
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WAFA HARROUK  
06/07/2011

PAUL C BROWN  
06/07/2011

I concur with the recommendation that this NDA can be approved from a pharm/tox perspective.

# PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR A NEW NDA/BLA

**NDA Number:** 22-305

**Applicant:** Niagra Pharmaceuticals

**Stamp Date:** March 3, 2008

**Drug Name:** (b) (4)  
(b) (4) eye wash

**NDA Type:** new NDA

**Background:** Eyewash produced by Niagra Pharmaceuticals Inc., is a sterile aqueous solution that is isotonic and buffered to mimic actual lacrimal fluids intended for washing, bathing and flushing the eye and/or skin. The active ingredient is Purified Water USP and comprises 98.3% of the drug product which was developed in compliance with the monograph for eyewash (21 CFR 349.20). Inactive ingredients are boric acid (b) (4), sodium chloride (b) (4) and sodium borate (b) (4) all of which are in compliance with the maximum potencies listed for similar FDA-Approved products in the inactive ingredients list. The pH specifications imposed on the drug product are in accordance with those of the USP monograph for purified water, namely (b) (4). No preservatives were added to this eyewash as the sterility of the product is achieved (b) (4). This NDA was refused to be filed (RTF) the last time it was submitted (March 2008) due partly to the lack of non-clinical information provided and the lack of characterization of leachables and new impurities/degradants.

**Impurities & degradants and leachables from containers/labels and closure systems:** Three separate lots of eye wash samples in two container systems (32oz HDPE bottles) were tested (b) (4) impact on the level of leachables and degradants in the eye wash product. Purified water filled in plastic and glass bottles were used as controls. Product container containing saline and borate buffer were used as test containers. No detectable level of change occurred in the test samples with respect to borate and chloride content.

(b) (4)

Some impurities/ degradants were found near the detection limit of 2 µg/ml but none were found above 10µg/mL (reporting threshold). A comparison of borate & chloride levels (b) (4) did not show any significant changes.

On **initial** overview of the NDA application: The sponsor addressed the issues raised after the 2008 RTF letter, namely, the characterization of leachables from the closure container systems and the presence of new impurities/degradants.

	Content Parameter	Yes	No	Comment
1	On its face, is the pharmacology/toxicology	x		

## PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR A NEW NDA/BLA

	Content Parameter	Yes	No	Comment
	section of the NDA organized (in accord with 21 CFR 314 and current guidelines for format and content) in a manner to allow substantive review to begin?			
2	Is the pharmacology/toxicology section of the NDA indexed and paginated in a manner allowing substantive review to begin?	x		
3	On its face, is the pharmacology/toxicology section of the NDA legible so that substantive review can begin?	x		
4	Are all required (*) and requested IND studies (in accord with 505 b1 and b2 including referenced literature) completed and submitted in this NDA (carcinogenicity, mutagenicity*, teratogenicity*, effects on fertility, juvenile studies, acute and repeat dose adult animal studies*, animal ADME studies, safety pharmacology, etc)?			N/A
5	If the formulation to be marketed is different from the formulation used in the toxicology studies, have studies by the appropriate route been conducted with appropriate formulations? (For other than the oral route, some studies may be by routes different from the clinical route intentionally and by desire of the FDA).			N/A
6	On its face, does the route of administration used in the animal studies appear to be the same as the intended human exposure route? If not, has the sponsor <u>submitted</u> a rationale to justify the alternative route?			N/A
7	Has the sponsor <u>submitted</u> a statement(s) that all of the pivotal pharm/tox studies have been performed in accordance with the GLP regulations (21 CFR 58) <u>or</u> an explanation for any significant deviations?			N/A
8	Has the sponsor submitted all special studies/data requested by the Division during pre-submission discussions with the sponsor?	x		
9	Are the proposed labeling sections relative to pharmacology/toxicology appropriate (including human dose multiples expressed in either mg/m <sup>2</sup> or comparative serum/plasma levels) and in accordance with 201.57?			N/A

**PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR A  
NEW NDA/BLA**

	<b>Content Parameter</b>	<b>Yes</b>	<b>No</b>	<b>Comment</b>
10	If there are any impurity – etc. issues, have these been addressed? (New toxicity studies may not be needed.)	x		
11	Has the sponsor addressed any abuse potential issues in the submission?			N/A
12	If this NDA is to support a Rx to OTC switch, have all relevant studies been submitted?			N/A
13	From a pharmacology/toxicology perspective, is the NDA fileable? If ``no`` please state below why it is not.	x		

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/s/  
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WAFA HARROUK  
12/15/2010

## PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR A NEW NDA/BLA

**NDA Number:** 22-305

**Applicant:** Niagra Pharmaceuticals

**Stamp Date:** March 3, 2008

**Drug Name:** (b) (4)  
eye wash

**NDA Type:** new NDA

On **initial** overview of the NDA application: The sponsor did not address the issues discussed at the pre-IND meeting (PIND 77,883) regarding the non-clinical portion of this NDA. The sponsor asked whether the Agency can waive the non-clinical section (module 4) at the time of the NDA submission. The Agency responded that if review of chemistry issues does not reveal any difference in data from the monograph product, then Niagra Pharma can make a reference to the monograph to support the NDA. However, the chemistry review for this NDA seems to indicate that there are a number of differences between the proposed (b) (4) eye wash and the (b) (4) product listed in the monograph (see CMC filing review). It appears that new impurities/degradants may be present that the sponsor should characterize. The only information relevant to module 4 (non-clinical section) included in this submission is a single line stating that "because this is a monographed drug and the monograph requirements have been met, no additional nonclinical work is required".

	Content Parameter	Yes	No	Comment
1	On its face, is the pharmacology/toxicology section of the NDA organized (in accord with 21 CFR 314 and current guidelines for format and content) in a manner to allow substantive review to begin?		x	
2	Is the pharmacology/toxicology section of the NDA indexed and paginated in a manner allowing substantive review to begin?		x	
3	On its face, is the pharmacology/toxicology section of the NDA legible so that substantive review can begin?			N/A
4	Are all required (*) and requested IND studies (in accord with 505 b1 and b2 including referenced literature) completed and submitted in this NDA (carcinogenicity, mutagenicity*, teratogenicity*, effects on fertility, juvenile studies, acute and repeat dose adult animal studies*, animal ADME studies, safety pharmacology, etc)?			N/A
5	If the formulation to be marketed is different from the formulation used in the toxicology studies, have studies by the appropriate route been conducted with appropriate formulations? (For other than the oral route, some studies may be by routes different from the clinical route intentionally and by desire of the FDA).			N/A

## PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR A NEW NDA/BLA

	Content Parameter	Yes	No	Comment
6	On its face, does the route of administration used in the animal studies appear to be the same as the intended human exposure route? If not, has the sponsor <u>submitted</u> a rationale to justify the alternative route?			N/A
7	Has the sponsor <u>submitted</u> a statement(s) that all of the pivotal pharm/tox studies have been performed in accordance with the GLP regulations (21 CFR 58) <u>or</u> an explanation for any significant deviations?			N/A
8	Has the sponsor submitted all special studies/data requested by the Division during pre-submission discussions with the sponsor?		x	No data were submitted
9	Are the proposed labeling sections relative to pharmacology/toxicology appropriate (including human dose multiples expressed in either mg/m <sup>2</sup> or comparative serum/plasma levels) and in accordance with 201.57?			N/A
10	If there are any impurity – etc. issues, have these been addressed? (New toxicity studies may not be needed.)		x	
11	Has the sponsor addressed any abuse potential issues in the submission?			N/A
12	If this NDA is to support a Rx to OTC switch, have all relevant studies been submitted?			N/A
13	From a pharmacology/toxicology perspective, is the NDA fileable? If ``no`` please state below why it is not.		x	

Any Additional Comments: Complete lack of non-clinical information about new impurities/degradants.

Wafa Harrouk

April 16, 2008

\_\_\_\_\_  
Reviewing Pharmacologist

\_\_\_\_\_  
Date

Paul Brown

April 16, 2008

\_\_\_\_\_  
Team Leader/Supervisor

\_\_\_\_\_  
Date

Application  
Type/Number

Submission  
Type/Number

Submitter Name

Product Name

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NDA-22305

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ORIG-1

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NIAGARA  
PHARMACEUTICA  
LS INC

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 (b) (4) EYE WASH

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WAFI HARROUK  
03/15/2010

## PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR A NEW NDA/BLA

**NDA Number:** 22-305

**Applicant:** Niagra Pharmaceuticals

**Stamp Date:** March 3, 2008

**Drug Name:** (b) (4)  
(b) (4) eye wash

**NDA Type:** New IND

On **initial** overview of the NDA application: The sponsor did not address the issues discussed at the pre-IND meeting (PIND 77,883) regarding the non-clinical portion of this NDA. The sponsor asked whether the Agency can waive the non-clinical section (module 4) at the time of the NDA submission. The Agency responded that if review of chemistry issues does not reveal any difference in data from the monograph product, then Niagra Pharma can make a reference to the monograph to support the NDA. However, the chemistry review for this NDA seems to indicate that there are a number of differences between the proposed (b) (4) eye wash and the (b) (4) product listed in the monograph (see CMC filing review). It appears that new impurities/degradants may be present that the sponsor should characterize. The only information relevant to module 4 (non-clinical section) included in this submission is a single line stating that "because this is a monographed drug and the monograph requirements have been met, no additional nonclinical work is required".

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Any Additional Comments: Complete lack of non-clinical information about new impurities/degradants.

Wafa Harrouk

April 16, 2008

\_\_\_\_\_  
Reviewing Pharmacologist

\_\_\_\_\_  
Date

Paul Brown

April 16, 2008

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Team Leader/Supervisor

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Date

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Wafa Harrouk  
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Paul Brown  
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