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| NDA# | 22-193 (N-000) |
| PRODUCT | Balanced salt intraocular irrigating solution (b) (4) |
| FORMULATION | Sterile solution |
| SUBMISSION DATE | September 21, 2007 |
| SUBMISSION TYPE | Original NDA |
| SPONSOR | Alcon Research, Ltd, Fort Worth, TX 76134-2099 |
| REVIEWER | Charles R. Bonapace, Pharm.D. |
| SECONDARY REVIEWER | John A. Lazor, Pharm.D. |

# CLINICAL PHARMACOLOGY REVIEW

**BACKGROUND:**

The sponsor submitted a New Drug Application for a balanced salt intraocular irrigating solution, also referred to as Next Generation Ophthalmic Irrigating Solution (NGOIS). NGOIS is a sterile, physiologically enhanced balanced salt solution based upon Alcon's currently marketed BSS PLUS® Sterile Intraocular Irrigating Solution (Balanced Salt Solution enriched with bicarbonate, dextrose, and glutathione). Like BSS PLUS, NGOIS is a two-part drug product which consists of NGOIS Part I and NGOIS Part II. Please refer to NDA 18-469 for further details of BSS PLUS Sterile Intraocular Irrigating Solution.

NGOIS Part II is identical to BSS Plus® Part II. The composition of NGOIS Part I (and thus reconstituted NGOIS) differs from BSS Plus® Part I only by addition of hypromellose (also known as hydroxypropy1 methycellulose or HPMC). The HPMC enhances the viscosity of NGOIS, leading to improved flow properties during intraocular surgery compared to BSS PLUS. In addition, the HPMC modifies the surface tension of NGOIS to closely approximate that of aqueous humor. None of the components of NGOIS have any pharmacological action. The compositions of NGOIS Part I and NGOIS Part II are shown in Tables 1 and 2, respectively.

**Table 1. Composition of NGOIS Part I**

| Component | Percent (W/V) | Function | Compendial Designation |
|---|---|---|---|
| Hypromellose[a] | (b) (4) | Viscosity Enhancer | USP |
| Sodium Chloride | | (b) (4) | USP |
| Potassium Chloride | | | USP |
| Dibasic Sodium Phosphate, (b) (4) | | | USP |
| Sodium Bicarbonate | | | USP |
| HCl or NaOH | | | NF |
| Water for Infection | | | USP |

a-Hypromellose (HPMC) (b) (4), or equivalent, which meets both USP and Ph. Eur. requirements and for which the apparent viscosity of a (b) (4) solution is approximately (b) (4), is used to prepare a (b) (4) solution.

b-An appropriate amount (between (b) (4) HPMC solution is used in the manufacture of NGOIS Part I to achieve the finished product target viscosity.

**Table 1. Composition of NGOIS Part II**

| Component | Percent (W/V) | Function | Compendial Designation |
|---|---|---|---|
| Glutathione disulfide | (b) (4) | | --- |
| Calcium Chloride[a] | | | USP |
| Magnesium Chloride[b] | | | USP |
| Dextrose, Anhydrous | | | USP |
| Water for Injection | | | USP |

a-Calcium Chloride, USP is the (b) (4) form.
b-Magnesium Chloride, USP is the (b) (4) form.

NGOIS Part I (480 or 240 mL) and NGOIS Part II (20 or 10 mL) are mixed aseptically immediately prior to use in a ratio of 24:1 (24 parts of Part I to one part of Part II). NGOIS is intended for use as an intraocular irrigating solution during intraocular surgical procedures involving perfusion of the eye, which is the same indication as BSS PLUS.

The sponsor did not conduct any clinical pharmacology studies to assess the in vivo bioavailability of NGOIS. All of the ingredients of NGOIS Parts I and II are normally found in the aqueous humor with the exception of hypromellose. The specific hypromellose (b) (4) formulation was chosen because of (b) (4) In addition, the systemic exposure of hypromellose will likely be less than that achieved by other currently marketed topical viscoelastic products (i.e., OCCUCOAT® [2% HPMC], CELOFTAL® [2% HPMC], and CELLUGEL® [2% HPMC]) which have HPMC concentrations approximately 10× that of NGOIS.

Although Alcon Research, Ltd. did not request a waiver of evidence of in vivo bioavailability for NGOIS, a full waiver is hereby granted based on 21 CFR 320.22(e). The sponsor meets the requirements for granting a waiver of evidence of in vivo bioavailability for topical products based on the fact that NGOIS is an irrigating solution during surgical procedures, all the ingredients of NGOIS Part I and Part II are normally found in the eye with the exception of hypromellose, hypromellose has no known receptor affinity, pharmacological action, or side effect potential, and distribution of hypromellose into ocular tissues is unlikely because of its molecular weight (b) (4) No further clinical pharmacology studies are necessary to support the in vivo bioavailability of NGOIS.

**LABELING RECOMMENDATIONS:**
Please refer to Appendix 1, Proposed Package Insert (Annotated) for the reviewer's labeling comments.

**RECOMMENDATIONS:**
This application was reviewed by the Office of Clinical Pharmacology, Division of Clinical Pharmacology 4 and found to be acceptable from a clinical pharmacology point of view.

The labeling comments provided in Appendix 1 should be forwarded to the reviewing medical officer and the sponsor.

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Charles R. Bonapace, Pharm.D.
Office of Clinical Pharmacology
Division of Clinical Pharmacology 4

RD/FT Initialed by John A. Lazor Pharm.D._____
Division Director, DCP4

cc:
Division File: NDA 22-193
HFD-520 (PM/Gorski)
HFD-520 (MO/Boyd)
HFD-880 (Division File, Lazor, Bonapace)
CDR (Clin. Pharm./Biopharm.)

3 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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Charles Bonapace
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3/20/2008 05:24:19 PM
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