CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-193

SUMMARY REVIEW

Division Director Summary Review

Date	July 23, 2008
From	Wiley A. Chambers, MD, Acting Director, DAIOP
Subject	Division Director Summary Review
NDA #	NDA 22-193
Proprietary / Established Names	NAVSTEL® Intraocular Irrigating Solution (balanced salt ophthalmic solution with hypromellose, dextrose and glutathione)
Dosage Forms	Ophthalmic solution
Proposed Indication(s)	For use as an intraocular irrigating solution during surgical procedures involving perfusion of the eye
Action:	*Approval*

1. Background/Regulatory History/Previous Actions/Foreign Regulatory Actions/Status

The drug product is identical to that of the same sponsor in NDA 18-469, with one difference. The present NDA includes enough hypromellose to [redacted] osmolality to 305 mOsm/kg and the viscosity to [redacted], making the solution more physiological to aqueous humor with respect to these parameters. Other than the one component, the composition, processes, analytical methods, container/closure systems, etc. are identical to the earlier product (Balanced Salt Solution Plus Parts I and II). Hypromellose (also known as hydroxypropylmethlcellulose) is present in a 2% concentration in Ocucoat, an ophthalmic viscoelastic agent for intraocular use.

b(4)

2. CMC

The drug product is provided in two containers which must be mixed before use.

Composition of Part 1

Component	Percent w/v	Function
Hypromellose[b]		
Sodium Chloride		
Potassium Chloride		
Sodium Phosphate dibasic, [redacted]		
Sodium Bicarbonate		
Hydrochloric acid or Sodium Hydroxide		
Water for injection		

b(4)

Composition Part 2

Component	Percent w/v	Function
Glutathione Disulfide		
Calcium Chloride, [redacted]		
Magnesium chloride, [redacted]		

b(4)

Dextrose,	
Water for Injection	

b(4)

Hypromellose — or equivalent, which meets both USP and PH. Eur. requirements and for which the apparent viscosity of a — solution is approximately — , is used to prepare a — solution. An appropriate amount (between —) of a — hypromellose solution is used in the manufacture of NGOIS Part I —

Calcium chloride, USP is the — form. b(4)

Magnesium Chloride, USP is the — form.

Composition of Reconstituted Irrigating Solution

Component	Percent w/v
Hypromellose	
Glutathione Disulfide	
Sodium Chloride	
Potassium Chloride	
Calcium Chloride	
Magnesium Chloride	
Sodium Bicarbonate	
Dextrose, —	
Sodium Phosphate dibasic, ? —	
Hydrochloric acid or Sodium Hydroxide	
Water	

b(4)

Fluid	Viscosity	Surface Tension
Reconstituted BSS Plus		
Reconstituted Navstel		
Human Aqueous Humor		

b(4)

Regulatory Specifications:

pH (bottle 1)
pH (bottle 2)
Osmolality
Viscosity
Subvisible Particles

b(4)

Sterility
Bacterial endotoxin

Review Comments: *Acceptable.*

3. Nonclinical Pharmacology/Toxicology

HPMC is a chemically modified cellulose polymer. According to the published literature and studies conducted for marketed viscoelastic products, HPMC has no known pharmacological action, no receptor site, is not metabolized in *vivo*, and is generally considered non-toxic and non-irritating. CFR 21 Part 349.12 (Ophthalmic demulcents for the ophthalmic over-the-counter ophthalmic drug product) has listed hypromellose (HPMC) 0.2 to 2.5% as the generally recognized safe and effective concentrations. The specific HPMC formulation (b(4) has been safely used intraocularly for over 10 years at a ten-fold higher concentration (2%) in the form of Ocucoat® (Bausch and Lomb) and Celoftal® (Alcon) viscoelastic products used during cataract surgery. Viscoelastic solutions help to push back the vitreous face, thus preventing formation of a flat chamber during surgery. The proposed HPMC concentration in NGOIS is fold less than the maximum accepted ocular OTC level.

According to the sponsor's estimate, the maximum amount of HPMC remaining in the eye at the b(4) end of surgery in clinics, assuming total absorption, is not expect to exceed 8.7 mg (assuming 5.0 mL retained volume in the posterior segment of HPMC in NGIOS). This amount is less than the HPMC exposure introduced by 0.5 mL of marketed 2.0% HPMC viscoelastic agent (10 mg). Approval is recommended.

Review Comments: *Agree.*

4. Clinical Pharmacology/Biopharmaceutics

The sponsor did not conduct any clinical pharmacology studies to assess the in vivo bioavailability of Navstel. All of the ingredients of Navstel Parts I and II are normally found in the aqueous humor with the exception of hypromellose. The specific hypromellose formulation was b(4) chosen because of its molecular weight ( ) . 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 Navstel.

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 Navstel is an irrigating solution during surgical procedures, all the ingredients of Navstel 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 Navstel.

Review Comments: *Agree.*

5. Clinical Efficacy and Safety

Anterior Segment			Posterior Segment
C-02-39	**C-03-33**	**C-04-14**	**C-04-18**
PRIMARY EFFICACY VARIABLE(S)			
• Phacoemulsification time (actual time phacoemulsification energy is applied)	• Turbulence (lens fragment or fluid) • Percent change in endothelial cell density	• Percent change in endothelial cell density	• Maintenance or improvement in best-corrected logMAR visual acuity
SECONDARY EFFICACY VARIABLE(S)			
• Surgeon's evaluation of lens fragment followability to the phacoemulsification tip • Video panel's evaluation of lens fragment followability to the phacoemulsification tip (observer-masked) • Surgeon's evaluation of lens fragment/fluid turbulence during phacoemulsification • Video panel's evaluation of lens fragment/fluid turbulence during phacoemulsification (observer-masked) • Surgeon's evaluation of viscoelastic retention immediately following phacoemulsification • Central corneal thickness • Average phacoemulsification energy • Phacoemulsification duration (elapsed time)	• Surgeon's evaluation of lens fragment followability to the phacoemulsification tip • Surgeon's evaluation of viscoelastic retention immediately following phacoemulsification • Central corneal thickness (measured by ultrasound pachymetry) • Average phacoemulsification energy • Average phacoemulsification time • Average phacoemulsification duration (elapsed time)	• Best-corrected logMAR visual acuity • Central corneal thickness • Surgeon questionnaire regarding flow characteristics of the irrigating solution (turbulence and followability to the phacoemulsification tip) • Retention of the viscoelastic	

Results:

C-02-39

The primary efficacy variable in C-02-39 was phacoemulsification time. There was no difference between groups (ITT).

NGOIS 5 cps	43.9 seconds	N=34
NGOIS 5 cps & BSS Plus	43.3 seconds	N=35
BSS Plus	37.9 seconds	N=33

C-03-33

The primary efficacy variable in C-03-33 was the investigator's assessment of turbulence (lens fragment or fluid) (ITT).

	None	Minimal	Moderate	p value
NGOIS 3 cps	21 (54%)	15 (39%)	3 (8%)	0.0005
NGOIS 4 cps	21 (62%)	12 (35%)	1 (3%)	< 0.0001
BSS Plus	7 (20%)	16 (46%)	12 (34%)	

Descriptive Statistics for Phacoemulsification Time (sec) in C-03-33 (ITT)

	N	**Mean**
NGOIS 3	36	73 seconds
NGOIS 4	31	80 seconds
BSS Plus	33	67 seconds

The differences are not statistically significant.

C-04-14

The primary efficacy variable in C-04-14 was percent change in endothelial cell density. This study was designed to demonstrate statistical non-inferiority of NGOIS 3 cps relative to BSS Plus for percent decrease in endothelial cell density at the post-operative Day 90 visit relative to baseline.

Mean Endothelial Cell Density Percent Change from Baseline to Day 90 in C-04-14 (PP)

	Baseline	Day 90	Mean Change	
NGOIS 3	2531	2335	-7.7%	
BSS Plus	2504	2270	-9.6%	
Difference			**1.9**	**95% Confidence Interval (-1.5 – 5.2)** **p-value = 0.27**

Descriptive Statistics for Turbulence by Treatment (PP) in C-04-14

	N	None	Minimal	Moderate	Pronounced	p-value
NGOIS	173	76 (44%)	89 (51%)	7 (4%)	1 (1%)	<0.0001
BSS Plus	171	18 (11%)	47 (28%)	86 (50%)	20 (12%)	

C-04-18

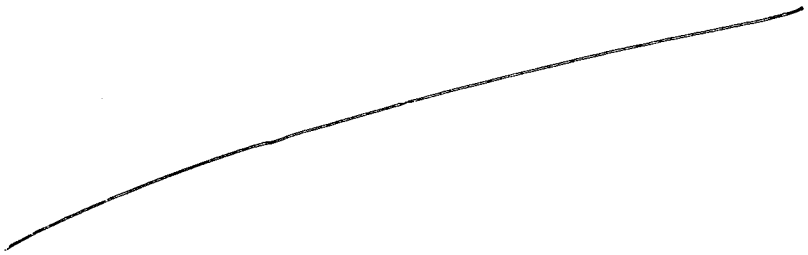
The primary efficacy variable in C-04-18 was maintenance or improvement in best-corrected visual acuity measured on the logMAR scale.

		Decrease from Baseline for the Study Eye	
		Exit visit ≥3 Line Decrease	Any visit ≥3 Line Decrease
NGOIS	N=168	14 (8%)	61 (36%)
BSS Plus	N=175	11 (6%)	54 (31%)

The differences are not statistically significant.

NAVSTEL™ Solution Labeling Claims

C-02-39
C-03-33
C-04-14



b(4)

6. **Advisory Committee Meeting**
   An advisory committee meeting has not been convened. The indication is not a new indication. The components in the formulation are not new to ophthalmic use and do not raise any new safety issues.

7. **Other Regulatory Issues**
   7.1. Application Integrity Policy (AIP) – *not invoked*
   7.2. Exclusivity/patent issues – *none identified*

8. **Financial Disclosure** – *Although no issues have been identified based on the information submitted.*

9. **Labeling**
   9.1. Proprietary name
   There is no USP monograph or USAN designated name. The following name is being used until such time as there is a USP monograph or USAN designated name: NAVSTEL® Intraocular Irrigating Solution (balanced salt ophthalmic solution with hypromellose, dextrose and glutathione).
   9.2. Labeling – *all issues resolved, see medical officer review. The final label is the result of negotiations between the Agency and Alcon. It includes the labeling revisions from the individual review disciplines.*

   9.3. Where appropriate, the DMETS labeling comments have been incorporated into the review. The bottles are packaged together, the Vacuum Transfer Device is now listed in the "How Supplied" Section, and the established name is at least one half the size of the trademark. The proprietary name, established name, volume, etc. were not repeated on the section of the Part I bottle label meant to be read upside down; this section still reads "Single Patient Use Only" because of the relative importance of this specific information. The volume of the irrigation solution utilized is determined by the amount visually observed in the bottle during the surgical case. The "Dosage and Administration" Section has been revised to include additional instructions formally found in the "Warnings and Precautions."

10. DSI Audits

Two of the investigational sites were inspected in connection with this application. In addition, some other investigational sites have been inspected in the past in connection with other ophthalmic applications. In general, the audited sites adhered to the applicable regulations and good clinical practices governing the conduct of clinical investigations. The inspection of documents supports that audited subjects exist, met eligibility criteria, received assigned study medication, adhered to protocol, and signed informed consent documents. The inspections documented minor regulatory violations at the site of Dr. Fishman regarding protocol adherence, recordkeeping, and informed consent violations. Although failure to keep electronic records in a protected state at the site raised the question of whether alterations may have been made in the endothelial cell photographs used to determine the primary efficacy endpoint, there is no evidence that such alterations occurred and no evidence that data integrity was impacted.

Review Comments: *Acceptable.*

11. Conclusions and Recommendations

11.1. Recommendations

The application has been recommended for approval by all disciplines and provides for a new drug product which will offer an alternative to currently marketed ophthalmic irrigating solutions. Less turbulence in the anterior chamber during phacoemulsification should result in less injury to structures, but these may not be noticed until many years after the surgical procedure. The use of this endpoint is supported by literature references identified in the medical officer's primary review.

11.2. Safety concerns to be followed postmarketing

The greatest concern with the addition of hypromellose is the risk of elevating the intraocular pressure (IOP) during the early post-operative period. IOP was measured in all patients following surgery and the product does not appear to lead to a significantly higher level of IOP than irrigating solutions without hypromellose. Never the less, warnings of elevated intraocular pressure have been included in the labeling.

11.3. Risk Minimization Action Plan – *None.*

11.4. Postmarketing studies – *None.*

12. Action

Approval of NDA 22-193, NAVSTEL® Intraocular Irrigating Solution (balanced salt ophthalmic solution with hypromellose, dextrose and glutathione) for use as an intraocular irrigating solution during surgical procedures involving perfusion of the eye.

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/s/

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