CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-193

PHARMACOLOGY REVIEW(S)

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

PHARMACOLOGY/TOXICOLOGY REVIEW AND EVALUATION

NDA NUMBER:	22-193
SERIAL NUMBER:	000
DATE RECEIVED BY CENTER:	09/24/07
DRUG NAME:	[redacted] [M] Sterile Intraocular Irrigating Solution
INDICATION:	For use as intraocular irrigating solution during intraocular surgical procedures involving perfusion of the eye
SPONSOR:	Alcon, Inc.
DOCUMENTS REVIEWED:	Module 2, Vol. 1; Module 4, Volume 1-3
REVIEW DIVISION:	Division of Anti-Infective and Ophthalmology Products
PHARM/TOX REVIEWER:	Conrad H. Chen, Ph.D.
ACTING PHARM/TOX TEAM LEADER:	Wendelyn Schmidt, Ph.D.
DIVISION DIRECTOR:	Wiley Chambers, M.D.
PROJECT MANAGER:	Lori Gorski

b(4)

Date of review submission to Division File System (DFS):

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EXECUTIVE SUMMARY

I. Recommendations

A. Recommendation on approvability
The approval of NDA 22-193 is recommended.

B. Recommendation for non-clinical studies
None

C. Recommendations on labeling
The following labeling as proposed by the sponsor appears acceptable:

Non-clinical toxicology

Carcinogenesis, Mutagenesis, Impairment of Fertility

The carcinogenicity potential of ——— Solution has not been investigated. The hypromellose in [———]4 Solution has been demonstrated to be non-mutagenic in the *in vitro* Ames assay and the bacterial reverse mutation assay. A similar modified cellulose polymer (methyl cellulose) was also non-mutagenic at concentrations up to 5,000 mg/kg in the rat bone marrow cytogenic assay. Fertility studies have not been conducted with hypromellose; however, rats fed a diet of up to 5% methylcellulose had no significant adverse effects relative to reproductive function. b(4)

II. Summary of nonclinical findings

A. Brief overview of nonclinical findings

The composition of Next Generation Ophthalmic Irrigating Solution (NGOIS) Part I is made up of various essential ions and buffer salts with hypromellose (also known as hydroxypropyl methylcellulose or HPMC) added as ——— The composition of NGOIS Part II consists of essential ions, dextrose and glutathione disulfide which is the same formula as Alcon's currently marketed BSS PLUS®A Part II, NDA 18-946. b(4)

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 (———) 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 —— to —— which is —— fold less than the maximum accepted ocular OTC level. b(4)

According to the sponsor's estimate, the maximum amount of HPMC remaining in the eye at the 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). b b(4)

B. Pharmacologic activity

HPMC has no known pharmacological action, no receptor site, is not metabolized in *vivo*, and is generally considered non-toxic and non-irritating.

C. Nonclinical safety issues relevant to clinical use

There are no safety issues for NGOIS relevant to clinical use.

2.6 PHARMACOLOGY/TOXICOLOGY REVIEW

2.6.1 INTRODUCTION AND DRUG HISTORY

NDA number: 22-193
Review number: No.1
Sequence number/date/type of submission: SN000/September 21, 2007/Original NDA Submission
Information to sponsor: Yes (x) No ( )
Sponsor and/or agent: Alcon, Inc., Hunenberg, Switzerland and Fort Worth, Texas
Reviewer name: Conrad H. Chen, Ph.D.
Division name: Division of Anti-Infective and Ophthalmology Products
Review completion date: February 19, 2008

Drug:

Trade name: [redacted] Sterile Intraocular Irrigating Solution b(4)
Generic name: Balanced Salt Intraocular Irrigating Solution with/[redacted] glutathione, hypromellose, sodium bicarbonate
Code name: NGOIS (Next Generation Ophthalmic Irrigating Solution)

Relevant INDs/NDAs/DMFs: IND 64,320, NDA 18-469 (BSS PLUS®)

Drug class: Sterile physiologically balanced salt solution for intraocular irrigation

Indication: For use as intraocular irrigating solution during intraocular surgical procedures involving perfusion of the eye

Clinical formulation: The composition of Next Generation Ophthalmic Irrigating Solution (NGOIS) Part I is made up of various essential ions and buffer salts with hypromellose (also known as hydroxypropyl methylcellulose or HPMC) added as a viscosity enhancing agent. The composition of NGOIS Part II consists of essential ions, dextrose and glutathione disulfide which is the same formula as Alcon's currently marketed BSS PLUS®A Part II, NDA 18-946.

Table 2.3.P.1-1

Composition of NGOIS Part I (FID [a] 106689)

Component	Percent w/v	Function	Compendial
Hypromellose [b]			
Sodium Chloride			
Potassium Chloride			
Dibasic Sodium Phosphate,			
Sodium Bicarbonate			
Hydrochloric Acid and/or Sodium Hydroxide			
Water for Injection			

b(4)

[a] FID = Formulation Identification Number.
[b] Hypromellose (HPMC) , or equivalent, which meets both USP and Ph. Eur. requirements and for which the apparent viscosity of a w/w solution is approximately , is used to prepare a w/v solution.
[c] An appropriate amount (between of a w/v HPMC solution is used in the manufacture of NGOIS Part I to achieve the

b(4)

Table 2.3.P.1-2

Composition of NGOIS Part II (FID 11229) [a]

Component	Percent w/v	Function	Compendial Designation
Glutathione Disulfide			
Calcium Chloride [c]			
Magnesium Chloride [d]			
Dextrose,			
Water for Injection			

b(4)

[a] This formulation is identical to BSS PLUS Part II.
[b] No official compendial designation; in-house standards are used.
[c] Calcium Chloride, USP is the form.
[d] Magnesium Chloride, USP is the form.

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ON ORIGINAL

Table 2.3.P.1-3

Composition of Reconstituted NGOIS (FID 107583)

Component	Percent w/v
Hypromellose	
Glutathione Disulfide	
Sodium Chloride	
Potassium Chloride	
Calcium Chloride	
Magnesium Chloride	
Sodium Bicarbonate	
Dextrose,	
Dibasic Sodium Phosphate,	
Hydrochloric Acid and/or Sodium Hydroxide	
Water for Injection	

b(4)

Route of administration: Intraocular irrigation

Proposed use: For use as intraocular irrigating solution during intraocular surgical procedures involving perfusion of the eye

2.6.2 PHARMACOLOGY

2.6.2.1 Brief summary: NGOIS is intended for use as an intraocular irrigating solution during surgical procedures involving perfusion of the eye. HPMC is added to the formulation . HPMC is a chemically modified cellulose polymer that has no known receptor affinity, pharmacological action or side effect potential. b(4)
The specific HPMC formulation ( ) has been safely used intraocularly for over 10 years at a ten-fold higher concentration 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.

2.6.4 PHARMACOKINETICS/TOXICOKINETICS

2.6.4.1 Brief summary: NGOIS is the same as Alcon's currently marketed BSS PLUS® with the addition of HPMC. Alcon has not conducted non-clinical pharmacokinetic studies in support of NGOIS.
The discussion of pharmacokinetics for HPMC is based on the following published literature:
1. Fernandez-Vigo J, Refojo MF, Jumblatt M. Elimination of hydroxypropyl methylcellulose from the anterior chamber of the rabbit J Cataract Refract Surg 1989; 15(2):191-5.

2. Gorzinski SJ, Takahashi IT, Hurst GH. The fate of ultra-low viscosity ^{14}C-hydroxypropyl methylcellulose in rats following gavage administration Drug Chem Toxicol 1986 ;(2):83-100.

The oral bioavailability of HPMC is low. In rats administered a much [redacted] molecular weight HPMC ([redacted] than used in NGOIS, only approximately 1% of the dose was absorbed with the remaining dose excreted in the feces. The absorption of [redacted] molecular weight HPMC used in NGOIS is expected to be negligible. b(4)

After intracameral administration, the elimination half life of HPMC from the anterior chamber was 3 hours in rabbits. They were administered 0.1 mL of solution containing 2% HPMC which had a molecular weight ([redacted]) and a viscosity ([redacted]) [redacted]. The concentration of HPMC in the anterior chamber diminished gradually, until at 24 hours it was at the lower limit of detectability of analytical procedure used. HPMC is considered to be metabolically inert. b(4)

2.6.6 TOXICOLOGY

2.6.6.1 Overall toxicology summary

General toxicology:
HPMC, used in NGOIS, is a modified cellulose polymer. Additional modified cellulose polymers used in pharmaceutical applications include hydroxypropyl cellulose (HPC), hydroxyethyl cellulose (HEC), methylcellulose (MC) and cellulose gum (CG). HPMC is currently used extensively as an excipient in ophthalmic viscosurgical device formulations, topical and oral pharmaceutical formulations, as well as food, consumer and cosmetic 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 proposed HPMC concentration in NGOIS is [redacted]%. b(4)
The information for single dose and repeat dose toxicity studies with HPMC is taken from the published literature: Final Report on the Safety Assessment of Hydroxylcellulose, Methylcellulose, Hydroxypropyl Methylcellulose, and Cellulose Gum Journal of the American College of Toxicology 1986;5(3):1-59.

Table 2.4.4-1 Summary of Acute Toxicity Studies with HPMC

Species and Strain	Method of Administration	Parameters / Result	Reference / GLP Status
Rat; Strain not reported	Oral gavage of HPMC	No toxic effects were noted in single oral doses up to 4g/kg	J Am Coll Toxicol, 1986 / non-GLP
Mouse; Strain not reported	Intraperitoneal injection of HPMC	138 mice had an approximate LD_{50} of 5g/kg	J Am Coll Toxicol, 1986 / non-GLP

In these studies rat oral NOEL of 4 g/kg and mouse intraperitoneal LD_{50} of 5 g/kg were demonstrated.

Table 2.4.4-2 Summary of Repeat Dose Toxicity Studies with HPMC

Species and Strain	Method of Administration	Exposure Duration	Parameters / Result	Reference / GLP Status
Rat; Strain not reported	Oral HPMC / 0%, 1%, 3%, 10% and 30% of diet	121 days	Marked decrease in growth at 30% level; slight growth decrease in 10% males; no pathological effects; slow growth attributed to nonnutritive bulk in diet.	J Am Coll Toxicol, 1986 / non-GLP
Rat; Strain not reported	Oral HPMC / 0%, 20% and 25% of diet	1 year	Growth retardation at 20% and 25% levels. No other toxic effects.	J Am Coll Toxicol, 1986 / non-GLP
Rat; Strain not reported	Oral HPMC / 0%, 1%, 5%, and 20% of diet	2 years	High-dose group showed growth reduction in first year; all others normal; slow growth trend continued in second year; no significant microscopic effects or tumors	J Am Coll Toxicol, 1986 / non-GLP
Dog; Strain not reported	Oral HPMC / 0, 0.1, 0.3, 1, and 3 g/kg per day in diet	1 year	No toxic effects	J Am Coll Toxicol, 1986 / non-GLP

In these studies, no significant toxic effects other than growth retardation at HPMC concentrations of 20 to 30% were noted. This was probably attributed to malnutrition due to the non-nutritive bulk content of the diet. No toxic effects were noted in gross or microscopic pathology.

Genetic toxicology:

Table 2.4.4-3 Summary of Genotoxicity Studies with HPMC

Type of Study	Species and Strain	Method of Administration	Test Article / Concentration / Dosage	Exposure Duration	Parameters / Result	Reference / GLP Status
Ames Mutagenicity Assay	*S. typhimurium (TA98, TA100, TA1535, TA1537, and TA1538)*	Plate incorporation method with and without S9 activation	HPMC [a] 100 mg/mL in H_2O (final HPMC concentration of 0.2%)	24 hours	Non-mutagenic in presence and absence of S9 activation	NAMSA MG019-211 / GLP
Ames Mutagenicity Assay	*S. typhimurium (TA98, TA100, TA1535, TA1537, and TA1538)*	Plate incorporation method with and without S9 activation	MC	~24 hours	Non-mutagenic in presence and absence of S9 activation	J Am Coll Toxicol, 1986 / non-GLP
Reverse Mutation Assay	*E. coli* WP2 *uvr*A	Plate incorporation method with and without S9 activation	HPMC [a] 100 mg/mL in H_2O (final HPMC concentration of 0.2%)	24 hours	Non-mutagenic in presence and absence of S9 activation	Alcon TR 104:38520:0796 / GLP
Chromosome Aberration Assay	Human Tissue Culture Cells	Media Incorporation	MC up to 800 µg/mL	~24 hours	No significant aberrations were noted in anaphase chromosomes	J Am Coll Toxicol, 1986 / non-GLP
Bone marrow Micronucleus Cytogenetic Assay	Rat; Strain not reported	Oral	MC up to 5000 mg/kg	~72 hours	No significant aberrations were noted in metaphase bone marrow chromosomes	J Am Coll Toxicol, 1986 / non-GLP

[a] CELLUGEL® (Alcon Laboratories, Inc.) – 2.0% HPMC (E10M & K100M in a ratio of 2:1)

b(4)

The combined data indicate that HPMC and other modified cellulose polymers are considered non-genotoxic.

The information shown above is taken from:

1. The Journal of the American College of Toxicology Volume 5, Number 3, 1986
2. Ames mutagenicity study of Cellugel VSF. [redacted] Sponsored by [redacted]
3. Wagner VO. *Escherichia coli* plate incorporation assay mutagenicity assay with Cellugel. Final Report. Fort Worth (TX): Alcon Laboratories, Inc.; 1996 Aug. Technical Report No.: 104:38520:0796

b(4)

Carcinogenicity: Not conducted.

Reproductive toxicology:

Table 2.4.4-4 Summary of Reproductive and Developmental Toxicity Studies of Methylcellulose

Type of Study	Species and Strain	Method of Administration	Test Article / Concentration / Dosage	Exposure Duration	Parameters / Result	Reference / GLP Status
Teratology Assay	Pregnant Mouse; CD/1	Oral gavage	MC / 0, 70, 153, 330, and 700 mg/kg	Animals dosed on days 6 – 15 of gestation / Animals euthanized and evaluated on day 17	Fetal abnormalities were determined by external, visceral and skeletal examinations. No significant teratogenic or toxic effects were noted	J Am Coll Toxicol, 1986 / non-GLP
Teratology Assay	Pregnant Rat; Sprague/ Dawley	Oral gavage	MC / 0, 120, 260, 556, and 1200 mg/kg	Animals dosed on days 6 – 15 of gestation / Animals euthanized and evaluated on day 20	Fetal abnormalities were determined by external, visceral and skeletal examinations. No significant teratogenic or toxic effects were noted	J Am Coll Toxicol, 1986 / non-GLP
Reproductive Toxicity Study	Rat (three consecutive generations); Strain not reported	Oral	Up to 5% MC in diet	Chronic exposure in diet.	Animals studied for three generations. No effects noted on reproductive function, and no gross or microscopic damage to tissues observed.	J Am Coll Toxicol, 1986 / non-GLP

The information obtained from the literature above indicated that modified cellulose polymer (methylcellulose) was non-teratogenic.
The information shown above is taken from the Journal of the American College of Toxicology Volume 5, Number 3, 1986.

Special toxicology:
Ocular Toxicity Study: These studies were previously conducted for the marketed viscoelastic products.

Table 2.4.4-7 Summary of Anterior Segment Ocular Toxicity Studies with NGOIS and HPMC

Type of Study	Species and Strain	Method of Administration	Test Article / Concentration / Dosage	Exposure Duration	Parameters / Result	Reference / GLP Status
Ocular Implant following Irrigation/ Aspiration	NZW Rabbit	Anterior chamber irrigation / aspiration (150 mL minimum flowthrough)	Reconstituted NGOIS —→HPMC — Part I conc.)	1 week	No difference in IOP or ocular toxicity potential vs. BSS PLUS®[a] control	Alcon TR 079:30:0702 / non-GLP
Ocular Implant following Phaco-emulsification	NZW Rabbit	100 mL minimum flowthrough during phaco-emulsification lensectomy procedure	Reconstituted NGOIS , HPMC Part I conc.)	1 week	Study Terminated - test article out of viscosity specification	Alcon TR TDOC-0005081 / GLP
Ocular Implant following Phaco-emulsification or Irrigation/ Aspiration	NZW Rabbit	90 mL minimum flowthrough during phaco-emulsification lensectomy procedure	Reconstituted NGOIS —, HPMC — Part I conc.)	1 week	No difference in IOP or ocular toxicity potential vs. BSS PLUS®[a] control	Alcon TR 080:30:0702 / non-GLP

[a] BSS PLUS® (Alcon Laboratories, Inc.)

b(4)

Table 2.4.4-7 (continued) Summary of Anterior Segment Ocular Toxicity Studies with NGOIS and HPMC

Type of Study	Species and Strain	Method of Administration	Test Article / Concentration / Dosage	Exposure Duration	Parameters / Result	Reference / GLP Status
Ocular Implant following Phaco-emulsification	NZW Rabbit	65 mL minimum flowthrough during phaco-emulsification lensectomy procedure	Reconstituted NGOIS — HPMC — Part I conc.)	1 month	No difference in IOP or ocular toxicity potential vs. BSS PLUS®[a] control	Alcon TR 078:30:0702 / GLP
Anterior Chamber Ocular Implant	NZW Rabbit	Single anterior (0.1 mL) chamber injection	HPMC —	1 month	Slit lamp, indirect and specular microscopy revealed no test article related findings. IOP response was similar to the marketed control (OCCUCOAT®)[b]. Histopathology revealed no ocular damage or irritation	Alcon TR 086:38520:079 / GLP

[a] BSS PLUS® (Alcon Laboratories, Inc.) [b] OCCUCOAT® (Bausch and Lomb)

b(4)

The first three studies were exploratory in nature. The concentrations of HPMC in these studies were higher than that in NGIOS. During a GLP anterior chamber injection study in rabbits with 2.0% HPMC and 1 month observation, HPMC was determined to be non-toxic and non-irritating to ocular tissue. In a GLP flow through study (65 mL) following phacoemulsification of crystalline lens in rabbits, NGIOS (— % HPMC) did not show any IOP or ocular toxicity different from that of marketed BSS PLUS® control.

b(4)

The information in the pivotal studies shown above is taken from:

1. Williams KK. Ocular evaluation of BSS PLUS® intraocular irrigating solution containing — hydroxypropyl methylcellulose (HPMC) following lensectomy by phacoemulsification in New Zealand white (NZW) rabbits. Final Report. Fort

b(4)

Worth (TX): Alcon Research Ltd.; 2002 Dec. Alcon Technical Report No.: 078:30:0702.

2. Carson DL, Hackett RB. Anterior and vitreal chamber toxicity evaluation of Celoftal in rabbits. Final Report. Fort Worth (TX): Alcon Laboratories, Inc.; 1997 Dec. Alcon Technical Report No.: 086:38520:1097.

Immunogenicity Study

Table 2.4.4-8 Summary of Immunogenicity Studies with HPMC

Species and Strain	Method of Administration	Exposure Duration	Parameters / Result	Reference / GLP Status
Guinea Pig; Hartley	Intradermal injection followed by single patch administration followed by single challenge administration 2.0% HPMC 2910[a] (Maximization Assay)	72 hours following challenge dose	Non-sensitizer	Alcon TR 204:38520:1197 / GLP

[a] CELOFTAL (Alcon Laboratories, Inc.)

b(4)

In this study, the marketed product CLEOFTAL® (2% HPMC) was used. The results showed that the test material was a non-sensitizer in the Guinea Pig model.
The information shown above is taken from Alcon Technical Report No. 204:38520:1197, 1998 March: Sensitization Study in the Guinea Pig Using Celoftal.

Ocular Retention Study

Table 2.4.4-10 Summary of Ocular Retention Study

Species and Strain	Method of Administration	Exposure Duration	Parameters / Result	Reference
Pigmented Rabbit	Single vitreal chamber injection (0.5 mL) HPMC (——→ following gas compression vitrectomy	10 weeks	HPMC levels in vitreous and aqueous humor were monitored for 10 weeks. Percent of initial concentrations in vitreous were: 48 hrs, 93%; 2 wks, 88%; 4 wks, 78%; 10 wks, 0%. Actual HPMC concentrations in the aqueous humor were: 0 hrs, 0%; 48 hrs, 0.002%; 1 wk, 0.004%; 2 wks, 0.001%; 4 wks, 0.0%.	Fernandez-Vigo, 1990 / non-GLP

b(4)

The non-GLP study above showed relatively rapid elimination rate of HPMC from the eye. This study utilized a ——→ solution of ——→ HPMC having approximately 14-fold increase in HPMC concentration over NGIOS (——→ HPMC).

b(4)

The above results are taken from Fernandez-Vigo et al., Retina 1990 Volume 10, Number 2, 148-52: Evaluation of a Viscoelastic Solution of Hydroxypropyl Methylcellulose as a Potential Vitreous Substitute.

OVERALL CONCLUSIONS AND RECOMMENDATIONS

Conclusions:
Next Generation Ophthalmic Irrigating Solution (NGOIS) is being developed for use as intraocular irrigating solution during intraocular surgical procedures involving perfusion of the eye. The composition of NGOIS Part I is made up of various essential ions and buffer salts with hypromellose (also known as hydroxypropyl methylcellulose or HPMC) added as a ——————. The composition of NGOIS Part II consists of essential ions, dextrose and glutathione disulfide which is the same formula as Alcon's currently marketed BSS PLUS® Part II, NDA 18-946. b(4)

HPMC is a chemically modified cellulose polymer. 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 (——————, has been safely used intraocularly for over 10 years at a —— higher concentration (2%) in the form of Ocucoat® (Bausch and Lomb) and Celoftal® (Alcon) viscoelastic products used during cataract surgery. b(4) 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 — to — % which is —— folds less than the maximum accepted ocular OTC level.

According to the published literature and studies conducted for marketed viscoelastic products, the absorption of higher molecular weight HPMC used in NGOIS is expected to be negligible. After intracameral administration, the elimination half life of HPMC from the anterior chamber was 3 hours in rabbits. The rat oral NOEL is 4 g/kg and the mouse intraperitoneal LD_{50} is 5 g/kg. In the repeat oral dose toxicity studies in animals, no significant toxic effects other than growth retardation was observed at HPMC concentrations up to 20 to 30%. The results from genotoxicity studies showed that HPMC and other modified cellulose polymers are considered non-genotoxic. The information obtained from the literature indicated that modified cellulose polymer (methylcellulose) was non-teratogenic. During a GLP anterior chamber injection study in rabbits with 2.0% HPMC and 1 month observation, HPMC was determined to be non-toxic and non-irritating to ocular tissue. In a GLP flow through study (65 mL) following b(4) phacoemulsification of crystalline lens in rabbits, NGIOS (— HPMC) did not show any IOP or ocular toxicity different from that of marketed BSS PLUS® control. In a guinea pig sensitization study, HPMC was shown to be a non-sensitizer.

According to the sponsor's estimate, the maximum amount of HPMC remaining in the eye at the 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). b(4)

Unresolved toxicology issues (if any): None

Recommendations: The approval of NDA 22-193 is recommended.

Suggested labeling:
The following labeling as proposed by the sponsor appears acceptable:
Non-clinical toxicology
Carcinogenesis, Mutagenesis, Impairment of Fertility
The carcinogenicity potential of [redacted] M Solution has not been investigated. The hypromellose in [redacted] M Solution has been demonstrated to be non-mutagenic in the *in vitro* Ames assay and the bacterial reverse mutation assay. A similar modified cellulose polymer (methyl cellulose) was also non-mutagenic at concentrations up to 5,000 mg/kg in the rat bone marrow cytogenic assay. Fertility studies have not been conducted with hypromellose; however, rats fed a diet of up to 5% methylcellulose had no significant adverse effects relative to reproductive function. b(4)

Signatures (optional):

Reviewer Signature _Conrad H. Chen, Ph.D._____

Team Leader Signature_Wendelyn Schmidt, Ph.D._____
Concurrence Yes _x_ No ___

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

/s/

Conrad Chen
3/19/2008 02:57:03 PM
PHARMACOLOGIST
The approval of NDA 22-193 is recommended.

Wendelyn Schmidt
4/8/2008 01:53:56 PM
PHARMACOLOGIST