CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

022572Orig1s000

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:	22572
Supporting document/s:	Original application and SD 0004 (7/13/10)
Applicant's letter date:	June 21, 2010
CDER stamp date:	June 21, 2010
Product:	Optomycin Kit for Ophthalmic use
Indication:	Treatment of refractory glaucoma as an adjunct to ab externo glaucoma surgery by topical application to the exposed site of a filtering bleb during trabeculectomy surgery to prolong the closing of the surgically created fistula.
Applicant:	Mobius Therapeutics LLC
Review Division:	Division of Anti-Infective and Ophthalmology Products
Reviewer:	Amy C. Nostrandt, DVM, PhD
Supervisor/Team Leader:	Wendelyn J. Schmidt, PhD
Acting Division Director:	Wiley Chambers, MD
Project Manager:	Alison K. Rogers

Template Version: December 7, 2009

Disclaimer

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approved application) is for descriptive purposes only and is not relied upon for approval of NDA 22-572.

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1 Executive Summary

1.1 Recommendations

1.1.1 Approvability

From a nonclinical standpoint, the application is approvable.

1.1.2 Additional Non Clinical Recommendations

None

1.1.3 Labeling

The following excerpts are the Applicant's proposed wording for the nonclinical sections for the label. Reviewer recommendations are made in subsequent comments.

Under "Highlights", (b) (4)

(b) (4)

Under Section 4 CONTRAINDICATIONS

(b) (4) Mitomycin administered parenterally has been shown to be teratogenic in mice and rats when given at doses equivalent to the usual human intravenous dose. (b) (4)

Under Section 8.1 Pregnancy

Pregnancy: Teratogenic Effects: Pregnancy Category X: See CONTRAINDICATIONS section.

(b) (4)

Reviewer's comment: The label for the reference listed drug (RLD), Mutamycin®, does not specify a pregnancy category but does state that teratological changes have been noted in animal studies. In the absence of a known NOAEL exposure in teratogenicity studies, this category would be appropriate. Wording regarding use in pregnancy in Sections 4 and 8.1 is consistent with that found in the label for the reference listed drug (RLD), Mutamycin®. (b) (4)

(b) (4)

If the Medical Officer considers this information to be needed, perhaps it should be re-worded and/or included in the Highlights, Precautions, or Warnings.

(b) (4)

Intravenous administration of mitomycin has been found to be carcinogenic in rats and mice. At doses approximating the recommended clinical injectable dose in man, mitomycin produces a greater than 100 percent increase in tumor incidence in male Sprague-Dawley rats, and a greater than 50 percent increase in tumor incidence in female Swiss mice.

Reviewer's comment: This should be moved to Section 13 NONCLINICAL TOXICOLOGY.

Under Section 13. NONCLINICAL TOXICOLOGY

13.1Carcinogenesis, Mutagenesis, Impairment of Fertility

Adequate long-term studies in animals to evaluate carcinogenic potential have not been conducted with (b) (4).

Reviewer's comment: This statement is not consistent with the label for the RLD, (b) (4) *The following wording is recommended:*

13.1Carcinogenesis, Mutagenesis, Impairment of Fertility

Intravenous administration of mitomycin has been found to be carcinogenic in rats and mice. At doses approximating the recommended clinical injectable dose in man, mitomycin produces a greater than 100 percent increase in tumor incidence in male Sprague-Dawley rats, and a greater than 50 percent increase in tumor incidence in female Swiss mice.
Adequate long-term studies in animals to evaluate carcinogenic potential have not been conducted with (b) (4)
The effect of (b) (4) on fertility is unknown.

1.2 Brief Discussion of Nonclinical Findings

For the proposed ophthalmic indication, mitomycin acts an antiproliferative, suppressing cell proliferation that would take place in wound healing and scarring. Specifically, DNA replication is inhibited in fibroblasts and vascular endothelial cells, decreasing cellularity and fibrosis of the surgical bleb. Mitomycin (0.2 mg) is administered topically to the eye as a single dose for 2 minutes followed by copious site irrigation.

The Applicant has submitted a number of published articles describing *in vivo* animal studies and *in vitro* cell culture experiments that have evaluated a range of potential toxicities to the ciliary body, trabecular meshwork, subconjunctiva, cornea, sclera and capillary endothelium. Additionally, fluorophotometry has been utilized to evaluate the potential of mitomycin to induce hypotony as a result of impaired aqueous humor production. Review and clinical articles indicate that adverse effects known to occur in humans include chronic effects that can occur for years after a single topical application, such as endophthalmitis and hypotony.

Nonclinical studies appear to have been conducted to investigate adverse events already known to occur in human patients. The Applicant has provided a review by Abraham et al. (2006) which indicates that a single application of mitomycin may result in prolonged cytotoxicity that can have sight-threatening complications, including endophthalmitis and hypotony. Mietz (1996) noted that hypotony was likely due to decreased production of aqueous humor by the adversely affected ciliary body epithelium. Mitomycin has been shown in multiple published articles to improve the success of glaucoma filtering surgery by inhibiting wound healing and scarring.

The Applicant concluded that the preclinical toxicology literature has demonstrated adverse cytotoxic effects of mitomycin on the ciliary body, trabecular meshwork, fibroblasts, and corneal endothelial cells. Potential risks of mitomycin in the eye include inadequate control of aqueous humor, hypotony, damage to the cornea, and endophthalmitis.

2 Drug Information

2.1 Drug

2.1.1 CAS Registry Number (Optional)

Mitomycin C: [50-07-7]

2.1.2 Generic Name

Mitomycin

2.1.3 Code Name

Not applicable

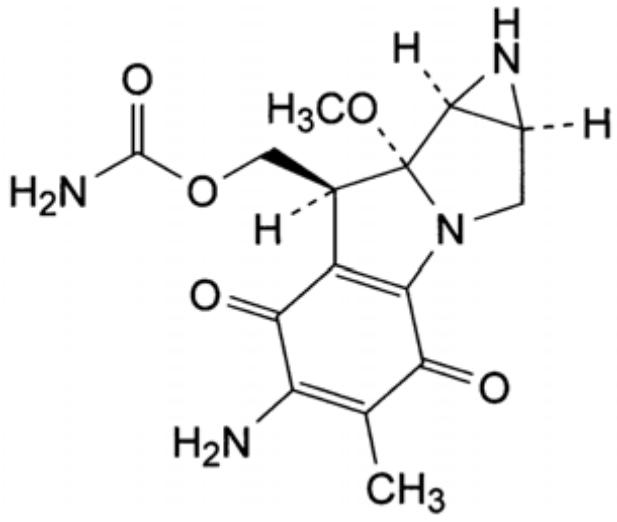
2.1.4 Chemical Name

1. Azirino[2',3':3,4]pyrrolo[1,2-*a*]indole-4,7-dione,6-amino-8-[[(aminocarbonyl)oxy]methyl]-1,1a,2,8,8a,8b-hexahydro-8a-methoxy-5-methyl-, [1a*R*-(1a*α*,8*β*,8a*α*,8b*α*)]-.
2. 6-Amino-1,1a,2,8,8a,8b-hexahydro-8-(hydroxymethyl)-8a-methoxy-5-methylazirino[2',3': 3,4]-pyrrolo[1,2-*a*]indole-4,7-dione carbamate(ester).
3. (1a*S*,8*S*,8a*R*,8b*S*)-6-Amino-8a-methoxy-5-methyl-4,7-dioxo-1,1a,2,4,7,8,8a,8b-octahydroazirino[2',3': 3,4]pyrrolo[1,2-*a*]-indol-8-yl]methyl carbamate.

2.1.5 Molecular Formula/Molecular Weight

$C_{15}H_{18}N_4O_5$
MW = 334.3

2.1.6 Structure



2.1.7 Pharmacologic class

DNA alkylating agent

2.2 Relevant IND/s, NDA/s, and DMF/s

The Applicant is using a contract manufacturer that produces the drug product in 5 and 20 mg vials for the approved oncology indication under ANDA 64-144. That ANDA is cross-referenced for CMC information.

In the nonclinical section, the Applicant references ANDA 62-336 for mitomycin (Bristol Myers Squibb) for systemic nonclinical toxicology information

2.3 Clinical Formulation

2.3.1 Drug Formulation

Each vial contains 0.2 mg of lyophilized mitomycin and 0.4 mg mannitol. (b) (4) Water for injection is added to make a total volume of 1 mL.

The proposed kit product, OptomycinTM Kit for Ophthalmic Use (Rx Only), contains the following components:

(b) (4)

2.3.2 Comments on Novel Excipients

None

2.3.3 Comments on Impurities/Degradants of Concern

None

2.4 Proposed Clinical Population and Dosing Regimen

In patients undergoing filtering surgery for glaucoma, mitomycin (0.2 mg) is administered topically (using sponges) to the eye intra-operatively as a single dose for 2 minutes followed by copious site irrigation.

2.5 Regulatory Background

The Applicant states that mitomycin has been used off-label for this indication in this manner, using diluted product that has been approved and marketedfor oncology indications.

3 Studies Submitted

3.1 Studies Reviewed

No original studies were performed or submitted. This application is made under 505(b)(2), and published literature references are provided. This review is based upon the Applicant's summaries and overviews. Submitted literature references were evaluated to establish the accuracy of the Applicant's summaries, but are not reviewed individually below in detail.

3.2 Studies Not Reviewed

All of the published studies were read and evaluated but none are reviewed individually below in detail.

3.3 Previous Reviews Referenced

The Applicant references ANDA 64-144 for CMC information and ANDA 62-336 for mitomycin (Bristol Myers Squibb) for systemic nonclinical toxicology information. Studies related to systemic nonclinical toxicology were reviewed with applications for mitomycin for oncology indications.

4 Pharmacology

4.1 Primary Pharmacology

Mitomycin is an alkylating agent isolated from *Strep. Caespitosus*. It forms stable cross-links between DNA strands at guanine residues, inhibiting DNA synthesis and cell proliferation, and promoting apoptosis. This action is independent of the phase of the cell cycle. This activity is used for anti-tumor activity by inhibiting DNA synthesis in rapidly proliferating neoplastic cells.

For the proposed ophthalmic indication, mitomycin acts an antiproliferative, suppressing cell proliferation that would take place in wound healing and scarring. Specifically, DNA replication is inhibited in fibroblasts and vascular endothelial cells, decreasing cellularity and fibrosis of the surgical bleb. Mitomycin (0.2 mg) is administered topically to the eye as a single dose for 2 minutes followed by copious site irrigation. The Applicant states, "By suppression of wound healing processes following filtering surgery for glaucoma, Mitomycin helps maintain surgically-created subconjunctival blebs that provide the channel from the aqueous humor to the subconjunctival space. Preventing scarring and

flattening of the subconjunctival blebs allows aqueous humor flow to stay optimized, thus maintaining the post-operative lowering of intraocular pressure."

Mitomycin is approved in larger quantities for systemic administration for oncology indications.

4.2 Secondary Pharmacology

The Applicant states that, at higher concentrations (30-100 times those inhibiting DNA synthesis), mitomycin can suppress RNA and protein synthesis and have antimicrobial activity. The Applicant also states that mitomycin decreases aqueous humor flow.

4.3 Safety Pharmacology

The Applicant states that, "The usual focus of safety pharmacology assessments (e.g., cardiovascular, respiratory, or central nervous system functions for Mitomycin 5 mg, 20 mg or 40 mg for Injection) are not relevant for very low-dose, short-duration, topical applications to the eye. Mitomycin Injection (ANDA 62-336) is referenced for systemic pharmacology information with injectable cancer indications."

Published studies of mitomycin used in animals as adjunctive therapy in trabeculectomy and other ocular surgical procedures as single-dose administrations between 0.002-1.0 mg/mL solution applied to the eye via soaked sponge, film, contact lens, or subconjunctival injection are discussed in the Toxicology section.

5 Pharmacokinetics/ADME/Toxicokinetics

5.1 PK/ADME

The Applicant refers to the Reference Listed Drug (RLD) Mitomycin for Injection ANDA 62-336 for systemic pharmacokinetics of mitomycin. The Applicant also references a clinical article (Crooke et al., 1976) for information regarding oral, intraperitoneal, intramuscular, and intravenous administrations of mitomycin in animals. They state that absorption is extensive regardless of route of systemic administration. Clearance is stated to be rapid, with approximately 90% of an intravenous dose in dogs cleared after 80 minutes. They state that broad distribution of injectable mitomycin to multiple organs has been shown in mice, rats, guinea pigs, dogs and monkeys, with kidney showing the greatest tissue concentration in guinea pigs. They state that urinary excretion of mitomycin is low, with 7% and 30% of the total dose in dogs being excreted in urine after 0.5 mg/kg and 2 mg/kg doses, respectively. It is suggested that mitomycin is cleared via metabolism, with pathways including activation via NADPH-dependent reduction and inactivation by liver, spleen, brain and heart.

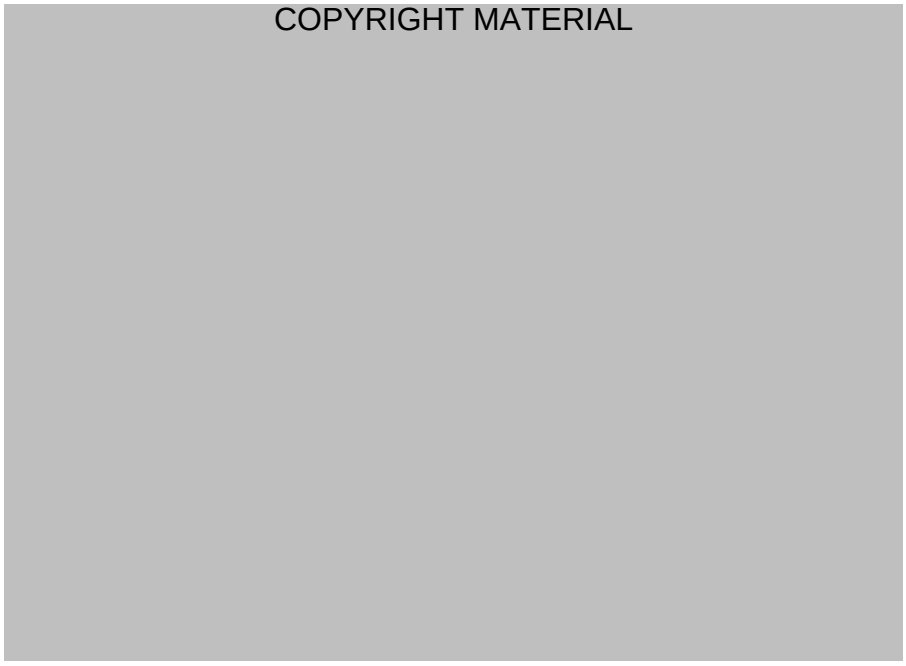
No data were provided regarding systemic exposure following topical ocular administration.

To support the proposed clinical use, the Applicant discusses data from several published investigations of local ocular pharmacokinetics in animal models. They state that, in studies in rabbits, intraocular penetration of mitomycin has been demonstrated via a variety of application devices, including regular surgical sponge, scleral shield, soft contact lenses and via subconjunctival injection. In the aforementioned, ocular penetration was similar regardless of the device used for topical administration, but higher ocular concentrations were achieved by subconjunctival injection (Mietz, et al., 1998). Studies, in which mitomycin was applied between the conjunctiva and the sclera demonstrated rapid uptake into ocular tissues, with measurable concentrations in the µg/mL range in conjunctiva, sclera, cornea, vitreous and aqueous humor. Concentrations correlated with the dose and duration of exposure before irrigation (Hara et al., 1998).

A 1993 study in rabbits (Sarraf et al., 1993) compared the pharmacokinetics of topically applied mitomycin in rabbits following posterior sclerectomy vs. untreated eyes. Peak concentrations were seen in aqueous and vitreous compartments within 1-2 hours, and the drug was cleared within 4 hours. There was no difference in ocular pharmacokinetics between surgically treated eyes and untreated eyes.

When doses of 0.002-0.2 mg mitomycin were administered to rabbits by subconjunctival injection, drug levels were readily measurable then decreased relatively rapidly in the conjunctiva, sclera and aqueous humor as shown below for the 0.2 mg administered dose (Figure 1). The half-life of mitomycin (determined from the 0.2 mg dose) in these tissues ranged from 0.18 hours to 0.45 hours. The mean peak ocular concentration, 8.4 µg/g, was reported to be similar to levels seen in human eyes after intraoperative application of 0.2 mg/0.5 mL followed by irrigation (Kawase et al., 1992).

Figure 1 Mitomycin concentration in rabbit ocular tissues following a single subconjunctival injection, 0.2 mg (0.4 mg/mL) (data from Kawase et al., 1992)



6 General Toxicology

6.1 Single-Dose Toxicity

The Applicant has submitted a number of published articles describing *in vivo* animal studies and *in vitro* cell culture experiments that have evaluated a range of potential toxicities to the ciliary body, trabecular meshwork, subconjunctiva, cornea, sclera and capillary endothelium. Additionally, fluorophotometry has been utilized to evaluate the potential of mitomycin to induce hypotony as a result of impaired aqueous humor production. Review and clinical articles indicate that adverse effects known to occur in humans include chronic effects that can occur for years after a single topical application, such as endophthalmitis and hypotony.

Nonclinical studies appear to have been conducted to investigate adverse events already known to occur in human patients. The Applicant has provided a review by Abraham et al. (2006) which indicates that a single application of mitomycin may result in prolonged cytotoxicity that can have sight-threatening complications, including endophthalmitis and hypotony. Mietz (1996) noted that hypotony was likely due to decreased production of aqueous humor by the adversely affected ciliary body epithelium. Mitomycin has been shown in multiple published articles to improve the success of glaucoma filtering surgery by inhibiting wound healing and scarring.

Nonclinical studies that investigated potential toxicity of mitomycin to the ciliary body demonstrated decreased ciliary body epithelial thickness, microscopic degenerative changes highlighted by intracellular vacuolization, degeneration of the basal surface and pigmentation loss (Hong et al., 2001; Akyol et al., 2003). *In vitro*, these adverse effects were dose-dependent and more prominent than similar effects in trabecular meshwork cells. Adverse effects included DNA fragmentation and changes in cAMP and intracellular calcium. The adverse effects on cell viability and proliferation *in vitro* were most clearly observed at concentrations >10 µg/mL (Hong et al., 2001).

An independent study of the adverse effects of mitomycin on bovine trabecular meshwork cells in culture, based on cytologic evaluation of apoptosis, also identified cytotoxicity at doses >10 µg/mL (Sibayan et al., 1998). A study was performed in monkeys to determine whether cytotoxicity to ciliary epithelium might contribute to the risk of hypotony. Sponge application of mitomycin (0.5 mg/mL) generated a transient, modest reduction in aqueous humor flow, with a decrease to 80% of control after 2 weeks and normalization by 4 weeks (Kee and Youn, 1995). The Applicant concluded that this also suggested that mitomycin may have a demonstrable effect on the ciliary body.

Potentially toxic effects of mitomycin on fibroblasts have been evaluated *in vitro* and *ex vivo* from explanted tissues. Cytotoxicity to cultured 3T3 fibroblasts and bovine capillary endothelial cells, including impaired proliferation, was demonstrated after exposure to mitomycin (Jampel, 1992; Khaw et al., 1993; Smith et al. 1994). Capillary endothelial cells were shown to have similar sensitivity to mitomycin in culture as fibroblasts, suggesting that therapy directed at the pharmacodynamic target (fibroblasts) may inadvertently compromise tissue vascularity. Antiproliferative effects and mitomycin dose-dependent apoptosis were demonstrated in cultured human Tenon's capule fibroblasts (Crowston, 1998). Effects in cells examined *ex vivo* were localized to the treatment area, which was consistent with pharmacokinetics studies that showed highest ocular tissue concentrations nearest the site of application (Khaw et al., 1993).

Examination of effects on corneal endothelial cells demonstrated mitomycin-induced cytotoxicity, suggesting potential risks from inadvertent access of drug to the anterior chamber. Findings have included apoptosis of the corneal stroma, corneal neovascularization, opacification, or haze, and conjunctival epithelial defects (Bergstrom et al., 1991; Khaw et al., 1993; Hyung, et al., 1994; Buffenn et al., 1997; Wong et al., 2005; Song et al., 2007).

The Applicant concluded that the preclinical toxicology literature has demonstrated adverse cytotoxic effects of mitomycin on the ciliary body, trabecular meshwork, fibroblasts, and corneal endothelial cells. Potential risks of mitomycin in the eye therefore include inadequate control of aqueous humor, hypotony, damage to the cornea, and endophthalmitis.

7 Genetic Toxicology

No genetic toxicity studies were provided. Mitomycin is a known DNA alkylating agent so may be considered positive for genetic toxicity.

8 Carcinogenicity

No carcinogenicity data were provided. Since the proposed clinical use is for a single topical application, no carcinogenicity studies to support this application are necessary. The approved label for the RLD indicates that systemic mitomycin is carcinogenic.

9 Reproductive and Developmental Toxicology

No reproductive or developmental toxicity data were provided. It is unlikely that systemic exposure would be high enough after single topical ocular use to affect a developing embryo or fetus, but no NOAEL for developmental toxicity has been provided, nor have any comparative systemic exposure data been provided. The approved label for the RLD indicates that teratogenicity has been noted in animal studies and that the effects of mitomycin on fertility are unknown. The Applicant has proposed Pregnancy Category X, which would be consistent with the label for the RLD.

10 Special Toxicology Studies

No special toxicology studies were provided.

11 Integrated Summary and Safety Evaluation

The Applicant concluded that the preclinical toxicology literature has demonstrated adverse cytotoxic effects of mitomycin on the ciliary body, trabecular meshwork, fibroblasts, and corneal endothelial cells. Potential risks of mitomycin in the eye therefore include inadequate control of aqueous humor, hypotony, damage to the cornea, and endophthalmitis. These findings have been noted clinically.

12 Appendix/Attachments

None

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

/s/

AMY C NOSTRANDT
10/25/2010

WENDELYN J SCHMIDT
10/28/2010

Division of Anti-Infective Drug Products (HFD-520)
Pharmacology/Toxicology Forward Planning Meeting

NDA Number: 22-572 **Date**: 6/29/2010
Drug Name: Optomycin Kit for Opthalmic use (mitomycin C)
Reviewer: Amy Nostrandt
CAS Number: 50-07-7
Drug Type: New formulation, new indication
Drug Class: Antibiotic, antimetabolite
Indication: For treatment of refractory glaucoma as an adjunct to trabeculectomy surgery
Route of Administration: Topical to the exposed site of a filtering bleb during trabeculectomy surgery
Date CDER Received: 6/21/2010
User Fee Date: 12/21/2010
Expected Date of Draft Review: August 2010
Sponsor: Mobius Therapeutics, LLC
Fileability:

On initial overview of the NDA application:	YES	NO
(1) On its face, is the pharmacology/toxicology section of the NDA organized in a manner to allow substantive review to begin?	_X__	____
Comments?		
(2) Is the pharm/tox section of the NDA indexed and paginated in a manner to allow substantive review to begin?	____	____
Comments? Not applicable. This is an electronic submission.		
(3) On its face, is the pharm/tox section of the NDA legible so that substantive review can begin?	___	__X_
Comments?		

This is an electronic submission with journal articles submitted as .pdf files. These scanned files appear to be legible with the exception of at least two that are not in English. One of them appears to have an abstract in English. The other file (4.3.1.37) is completely blank. In addition, reference 4.3.1.38 is listed (and is in Chinese), but is not provided.

(4) Are all required (*) and requested IND studies completed and submitted in this NDA (carcinogenicity, mutagenicity, teratogenicity*, effects on fertility*, juvenile studies, acute studies*, chronic studies*, maximum tolerated dosage determination, dermal irritancy, ocular irritancy, photocarcinogenicity, animal pharmacokinetic studies, etc)?	_X__	___
Comments? No new studies were requested. This is a 505(b)(2) application.		
(5) If the formulation to be marketed is different from the formulation		

used in the toxicology studies, has the Sponsor made an appropriate effort to either repeat the studies using the to be marketed product or to explain why such repetition should not be required? ____ ____

Comments?

The proposed formulation contains 0.2 mg mitomycin C with mannitol and sterile water for injection. It is unclear at this time how this may differ from formulations used in published nonclinical and clinical studies.

(6) Are the proposed labeling sections relative to pharm/tox appropriate (including human dose multiples expressed in either mg/m^2 or comparative serum/plasma levels) and in accordance with 201.57? _X__ ____

Comments?

The nonclinical sections of the labeling do not describe parenteral doses at which effects were seen, however, these do not appear to be necessary for this product and single dose indication.

(7) Has the Sponsor submitted all special studies/data requested by the Division during pre-submission discussions with the Sponsor? ____ ____

Comments?

Not applicable

(8) 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 submitted a rationale to justify the alternative route? __X_ ____

Comments?

The published studies do describe application to eyes in nonclinical studies, even if not using the same application method.

(9) Has the Sponsor submitted a statement(s) that all of the pivotal pharm/tox studies have been performed in accordance with the GLP regulations (21 CFR 58) or an explanation for any significant deviations? ____ ____

Comments?

Not applicable

(10) Has the Sponsor submitted the data from the nonclinical carcinogenicity studies, in the STUDIES electronic format, for the review by Biometrics? ___ ____

Comments?

Not applicable

(11) Has the Sponsor submitted a statement(s) that the pharm/tox studies have been performed using acceptable, state-of-the-art protocols which also reflect agency animal welfare concerns? ____ ____

Comments?
Not applicable

(12) From a pharmacology perspective, is this NDA fileable? If "no", please state below why it is not. __X_ ____

(13) If the NDA is fileable, are there any issues that need to be conveyed to Sponsor? If so, specify: __X_ ___

To be conveyed to the Sponsor:

Nonclinical references 4.3.1.37 and 4.3.1.38 are not provided in the electronic submission. Please be sure to provide the abstract, if not the whole article, in English.

(14) Issues that should not be conveyed to the Sponsor:
None

_____
Reviewing Pharmacology Officer

_____
Pharmacology Supervisor

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22572	ORIG-1	MOBIUS THERAPEUTICS	Optomycin Kit for Ophthalmic Use

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/s/

AMY C NOSTRANDT
07/07/2010

WENDELYN J SCHMIDT
07/07/2010