CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

50-810

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:	**50-810**
SERIAL NUMBER:	**000**
DATE RECEIVED BY CENTER:	**6/28/06**
PRODUCT:	**AzaSite™**
INTENDED CLINICAL POPULATION:	**Adult and Pediatric Patients (≥ 1 year of age) with bacterial conjunctivitis**
SPONSOR:	**InSite Vision Inc.**
DOCUMENTS REVIEWED:	-000 (in **EDR**)
REVIEW DIVISION:	**DAIOP**
PHARM/TOX REVIEWER:	**Amy L. Ellis**
PHARM/TOX TEAM LEADER:	**Terry S. Peters**
DIVISION DIRECTOR:	**Janice Soreth**
PROJECT MANAGER:	**Raphael Rodriguez**

Date of review submission to Division File System (DFS): 2/5/07

TABLE OF CONTENTS

EXECUTIVE SUMMARY

I. Recommendations

A. Recommendation on approvability

The pharmacologist has no objection to the approval of this NDA.

B. Recommendation for nonclinical studies

No additional nonclinical studies are recommended.

C. Recommendations on labeling

The AzaSite™ label should be consistent with those for systemic azithromycin products, as applicable. Some minor editing of the sponsor's proposed label is recommended, including removal of the dose multiples calculated for the systemic products in the *Pregnancy* section.

II. Summary of nonclinical findings

A. Brief overview of nonclinical findings

Daily topical ocular application of AzaSite™ to rabbits for up to one month caused neither ocular irritation nor toxicity. Microvacuolation in the corneal epithelium and corneal stromal cells associated with application of azithromycin is likely a manifestation of phospholipidosis. This finding was associated with neither inflammation nor tissue damage, and it was reversible after the application of AzaSite™ was discontinued.

B. Pharmacologic activity

Azithromycin exerts its antimicrobial activity by binding to the 50S ribosomal subunit, thus inhibiting protein synthesis in susceptible bacteria.

C. Nonclinical safety issues relevant to clinical use

None.

2.6 PHARMACOLOGY/TOXICOLOGY REVIEW

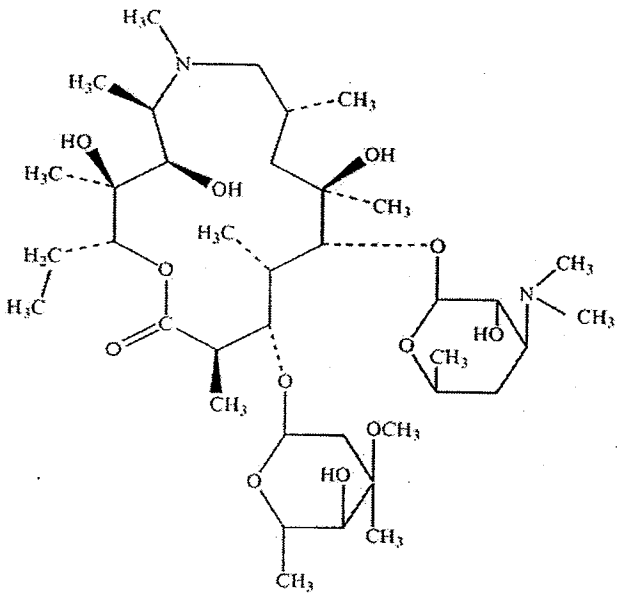
2.6.1 INTRODUCTION AND DRUG HISTORY

NDA number: 50-810
Review number: 1
Sequence number/date/type of submission: 000/28 JUN 2006/original NDA
Information to sponsor: Yes (X) No ( ) Labeling recommendations should be conveyed.
Sponsor and/or agent: InSite Vision Inc. (Alameda, CA)
Manufacturer for drug substance: [redacted] b(4)

Reviewer name: **Amy L. Ellis**
Division name: **Anti-Infective and Ophthalmology Products**
Review completion date: 2/2/07

Drug:

Trade name: AzaSite™
Generic name: 1% azithromycin solution in DuraSite® delivery vehicle
Code name: ISV-401
Chemical name: (2R,3S,4R,5R,8R,10R,11R,12S,13S,14R)-13-[(2,6-dideoxy-3-C-methyl-3-O-methyl-α-L-ribohexopyranosyl)oxy]-2-ethyl-3,4,10-trihydroxy-3,5,6,8,10,12,14-heptamethyl-11-[[3,4,6-trideoxy-3-(dimethylamino)-β-D-xylo-hexopyranosyl]oxy]-1-oxa-6-aza-cyclopentadecan-15-one monohydrate
CAS registry number: 83905-01-5
Molecular formula/molecular weight: $C_{38}H_{72}N_2O_{12} \cdot H_2O$
Structure:



$\cdot H_2O$

Relevant INDs/NDAs/DMFs: DMF [redacted] IND 62,873; NDA 50-670 (but the sponsor has no right of reference for this Pfizer NDA for azithromycin capsules) b(4)

Drug class: Azalide/Macrolide Antimicrobial

Intended clinical population: Adult and pediatric patients (≥ 1 year of age) with bacterial conjunctivitis

Clinical formulation:

From the NDA:

INGREDIENT	%W/W
Azithromycin Monohydrate, USP	1.0
Mannitol, USP	[redacted] b(4)
Citric Acid Anhydrous, USP	
Sodium Citrate Dihydrate, USP	
Poloxamer 407, NF	
Benzalkonium Chloride, NF	0.003
Polycarbophil, USP	[redacted]
Sodium Chloride, USP	
Edetate Disodium Dihydrate, USP	
Sodium Hydroxide, 2N, NF	adjust to pH 6.3
Water For Injection, USP	[redacted]

Route of administration: Topical ocular

Disclaimer: Tabular and graphical information are constructed by the reviewer unless cited otherwise.

Data reliance : Except as specifically identified below, all data and information discussed below and necessary for approval of NDA 50-810 are owned by InSite Vision Inc. or are data for which InSite Vision Inc. has obtained a written right of reference. Any information or data necessary for approval of NDA 50-810 that InSite Vision Inc. 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 described in the drug's approved labeling. Any data or information described or referenced below from a previously approved application that InSite Vision Inc. does not own (or from FDA reviews or summaries of a previously approved application) is for descriptive purposes only and is not relied upon for approval of NDA 50-810.

2.6.2.2 Primary pharmacodynamics

Mechanism of action: Azithromycin inhibits bacterial protein synthesis by binding to the 50S ribosomal subunit.

Drug activity related to proposed indication: Antimicrobial

2.6.2.3 Secondary pharmacodynamics

Nothing to report.

2.6.2.4 Safety pharmacology

Not relevant for this product. Systemic exposure to azithromycin should be very low following topical ocular administration to the human eye. The sponsor was not required to conduct human biopharmaceutics studies for this product.

2.6.2.5 Pharmacodynamic drug interactions

Not relevant for this product.

2.6.3 PHARMACOLOGY TABULATED SUMMARY

Not relevant for this product.

2.6.4 PHARMACOKINETICS/TOXICOKINETICS

2.6.4.1 Brief summary

When azithromycin is administered systemically, it is widely distributed to tissues and is generally present at higher levels in tissues than in plasma because it concentrates in phagocytes and fibroblasts. Azithromycin is not metabolized significantly and undergoes biliary and, to a lesser extent, renal excretion primarily as unchanged drug. Systemic availability of azithromycin following clinical ocular administration is expected to be very low. The sponsor was not required to conduct human biopharmaceutics for AzaSite™. Pharmacokinetic studies in rabbits showed that ocular absorption of azithromycin was limited, with plasma levels much lower than those found in ocular tissues (bulbar conjunctiva, cornea, or eyelids) and tears.

2.6.4.2 Methods of Analysis

A validated HPLC/MS/MS method was used to quantify azithromycin in plasma, tears, and other ocular tissues. The lower limit of detection for plasma was 0.1 ng/g and for other tissues was 0.01 μg/g.

2.6.4.3 Absorption

Absorption of azithromycin is limited following ocular administration to rabbits. Although the drug was detected in plasma, the plasma levels were much lower than those measured in tears and ocular tissues such as the bulbar conjunctiva, cornea, or eyelids.

2.6.4.4 Distribution

Systemic distribution of azithromycin is not relevant for this product due to limited total body exposure following ocular administration. Pharmacokinetic studies of AzaSite™ in rabbits showed that the drug distributed to ocular tissues (see above).

2.6.4.5 Metabolism

Not relevant for this product due to limited total body exposure following ocular administration. Studies with systemic azithromycin have demonstrated that the compound is not significantly metabolized.

2.6.4.6 Excretion

Not relevant for this product due to limited total body exposure following ocular administration. Studies with systemic azithromycin show that the drug is excreted unchanged primarily through biliary excretion with some renal excretion.

2.6.4.7 Pharmacokinetic drug interactions

Not relevant for this product.

2.6.4.8 Other Pharmacokinetic Studies

None

2.6.4.9 Discussion and Conclusions

Pharmacokinetic studies in rabbits showed that measurable amounts of azithromycin were found in ocular tissues and tears as long as 24 hours after instillation. The highest concentrations were found in tears, then eyelids, with similar levels detected in the bulbar conjunctiva and cornea. Azithromycin levels fell more quickly in tears than in the other tissues. Ocular concentrations of azithromycin were greater following instillation of a 1% formulation than a 0.5% formulation. Although azithromycin is detectable in rabbit plasma following ocular instillation, plasma levels of the drug are much lower than those measured in tears and ocular tissues. Substantial accumulation of azithromycin did not occur in tears, ocular tissues, or plasma following 5 daily doses to rabbits.

2.6.4.10 Tables and figures to include comparative TK summary

Not relevant for this product.

2.6.5 PHARMACOKINETICS TABULATED SUMMARY

As provided in the NDA:

Study Type	Species/ Strain	# Animals Per Time Point; Time Points	Route of Admin.	Doses; Formulation	Duration	Laboratory; Rpt. No.; Study Start Date	Results and Conclusions
Ocular Pharmaco-kinetics	New Zealand albino rabbits	6 males; 0.5, 1, 2, 4, 8, 12, 24 hours post-instillation	Topical ocular	One 25 µL eye drop; 0.5% AzaSite eye drop formulation	Single Dose	[redacted] 107U0506; 6/14/2000	Azithromycin distributed well into various ocular tissues. The highest concentrations were seen between the 0.5-hour and 2-hour time-point. The compartment with the highest concentration was tears (180.2 µg/g), followed by eyelid (50.7 µg/g), conjunctiva (20.0 µg/g), and cornea (17.4 µg/g). b(4)

Tissues	C_{max} (µg/g)	T_{max} (h)	K_{el} (h^{-1})	$t_{1/2}$ (h)	AUC [(µg/g) x h]
Tear	180.2	0.5	0.083	8.4	277.9
Conjunctiva	20.0	2.0	0.015	46	213.4
Cornea	17.4	0.5	0.0095	72	222.5
Eyelid	50.7	1.0	0.0063	110	345.9

Study Type	Species/ Strain	# Animals Per Time Point; Time Points	Route of Admin.	Doses; Formulation	Duration	Laboratory; Rpt. No.; Study Start Date	Results and Conclusions
Ocular Pharmaco-kinetics	New Zealand albino rabbits	6 males; 0.5, 1, 2, 4, 8, 12, 24 hours post-instillation	Topical ocular	One 25 µL eye drop; 0.5% and 1.0% AzaSite eye drop formulation	Single Dose	[redacted] 107U0101; 3/5/2001	The tear azithromycin levels of both 0.5% and 1.0% AzaSite reached their respective C_{max} within an hour, then dropped sharply during the next 4 hours. The levels then stayed essentially flat for the rest of observation period, resulting in a terminal elimination constant of zero b(4)

Formulation	C_{max} (µg/g)	T_{max} (h)	K_{el} (h^{-1})	$t_{1/2}$ (h)	AUC [(µg/g) x h]
0.5% AzaSite	87.1	1	0	ND*	413.0
1.0% AzaSite	288.4	0.5	0	ND*	632.8

* not determined

The conjunctival azithromycin levels of both formulations reached C_{max} at 0.5 hour, followed by a bi-exponential dec y. The levels achieved by 1.0% AzaSite were approximately twice those achieved by 0.5% ISV-401 at most of the time points, indicating linearity within these two formulation concentrations

Formulation	C_{max} (µg/g)	T_{max} (h)	K_{el} (h^{-1})	$t_{1/2}$ (h)	AUC [(µg/g) x h]
0.5% AzaSite	30.1	0.5	0.049	14.1	394.1
1.0% AzaSite	82.7	0.5	0.051	13.5	830.5

Study Type	Species/ Strain	# Animals Per Time Point; Time Points	Route of Admin.	Doses; Formulation	Duration	Laboratory; Rpt. No.; Study Start Date	Results and Conclusions
Ocular Pharmaco-kinetics	New Zealand albino rabbits	6 males; 0.5, 1, 2, 4, 8, 12, 24 hours post-instillation	Topical ocular	One 25 µL eye drop; 0.5% and 1.0% AzaSite eye drop formulation	Single Dose	[redacted] 107U0301; 03/30/2001	The plasma azithromycin levels of both formulations reached C_{max} at 0.5 hour, followed by a bi-exponential decay. The levels achieved by 1.0% AzaSite were approximately twice those achieved by 0.5% AzaSite at most of the time-points, indicating linearity within these two formulation concentrations.

b(4)

Tissues	C_{max} (ng/g)	T_{max} (h)	K_{el} (h^{-1})	$t_{1/2}$ (h)	AUC [(ng/g) x h]
0.5% AzaSite	2.2	0.5	0.053	13.1	12.1
1.0% AzaSite	4.4	0.5	0.073	9.5	22.8

Study Type	Species/ Strain	# Animals Per Time Point; Time Points	Route of Admin.	Doses; Formulation	Duration	Laboratory; Rpt. No.; Study Start Date	Results and Conclusions
Ocular Pharmaco-kinetics	New Zealand albino rabbits	6 males; 0.5, 1, 2, 4, 12, 24, 24.5, 25, 48, 48.5, 49, 72, 72.5, 73, 96, 96.5, 97, 120 hours following first instillation	Topical ocular	One 25 µL eye drop; 0.5% AzaSite eye drop formulation	Multiple-Dose. One drop of 0.5% AzaSite everyday for 5 days	[redacted] 107U1000; 11/17/2000	Over the five days of dosing, there appeared to be no accumulation of azithromycin in the tear or conjunctiva. The pharmacokinetic measures based upon on data obtained in the first 24 hours of dosing is shown in the table below:

b(4)

Tissue	C_{max} (µg/g)	T_{max} (h)	K_{el} (h^{-1})	$t_{1/2}$ (h)	AUC [(µg/g) x h]
Tear	101.1	1	0.054	12.8	286.6
Conjunctiva	36.1	1	0.049	14.2	290.4

Peak azithromycin plasma levels after a single instillation and multiple instillations were approximately 2 ng/g and 3 ng/g respectively.

2.6.6 TOXICOLOGY

2.6.6.1 Overall toxicology summary

Topical ocular application of up to 1% azithromycin was associated with neither irritation nor toxicity when applied to rabbit eyes twice daily for 30 days or 4 times daily for 2 weeks. Dose-related microvacuolation (generally slight to moderate and likely a manifestation of phospholipidosis) was observed in the corneal epithelium and corneal stromal cells at the end of dosing. Microvacuolation was less severe and present at lower incidence at the end of a 30 recovery period and it resolved completely after 60 days. The ocular toxicity of AzaSite™ was unchanged by the presence of the degradation product [redacted] In a separate study, the AzaSite™ vehicle, DuraSite®, did not cause ocular toxicity or irritation in rabbit eyes when applied 3 times daily for 52 weeks.

b(4)

Azithromycin is not genotoxic and it was not a reproductive toxicant in rats or mice when administered orally at doses up 200 mg/kg/day.

Studies reviewed within this submission:

Chronic Ocular Toxicity Study in Rabbits (Study No. 2584-100; this was a study of the Poloxamer and Polycarbophil vehicle components- not azithromycin)

Studies not reviewed within this submission:

These studies were reviewed under IND 62, 873-001:

14-Day Ocular Toxicity Study of ISV-401 Eye Drop Formulations in Rabbits (Study No. 6435-106)

0.5% Azithromycin Eye Drop. Ocular Distribution After a Single Instillation into the Conjunctival Sac of Albino Rabbits (Study No. I07U0500)

0.5% and 1.0% Azithromycin Eye Drop. Comparison of Ocular Distribution after a Single Instillation into the Conjunctival Sac of Albino Rabbits (Study No. I07U0101)

0.5% Azithromycin Eye Drop. Ocular Distribution after Multiple Instillations into the Conjunctival Sac of Albino Rabbits (Study No. I07U1000)

0.5% and 1.0% Azithromycin Eye Drop. Comparison of Plasma Distribution after a Single Instillation into the Conjunctival Sac of Albino Rabbits (Study No. I07U0301)

This study was reviewed under IND 62,873-007:

1-Month Ocular Toxicity Study of 1.0% ISV-401 in Dutch-Belted Rabbits with a 1- and 2-Month Recovery Period (Study No. 6435-107)

This study was reviewed under IND 62,873-046:

AzaSite™: A 30-Day Ocular Toxicity Study in Dutch-Belted Rabbits Followed by a 60-Day Recovery Period (Study No. 1004-2864)

2.6.2 PHARMACOLOGY

2.6.2.1 Brief summary

Azithromycin exerts its antimicrobial activity by binding to the 50S ribosomal subunit, thus inhibiting protein synthesis in susceptible bacteria. It is known to concentrate in phagocytes and fibroblasts.

Age: 14 weeks
Weight: 2.3-3.1 kg (females), 2.5-3.0 (males)
Sampling times for TK: Not done
Unique study design or methodology: The first daily dose was omitted on days when ophthalmoscopic examinations were conducted.

Results:

Mortality: Animals were observed for mortality and moribundity twice daily. There were no treatment-related deaths.

All Group 1 animals survived until scheduled sacrifice. The cause of death for one Group 3 female found dead during Week 8 was not apparent. A Group 2 female sacrificed in moribund condition during Week 21 had lymphocytic leukemia. The deaths of 3 additional rabbits between Weeks 39 and 48 (Group 2 female, Group 3 female, Group 3 male) appeared related to gastrointestinal hairballs, though the report also notes the presence of "systemic infectious processes" in these animals.

A Group 3 male was discarded at Week 20. The animal should not have been placed on study due to an ophthalmic lesion (not specified in the study report) identified at the pretreatment examination; this lesion was still present at the Week 13 ophthalmic examination.

Clinical signs: Cageside observations were conducted once daily prior to the first daily dose. Eyes were observed for conjunctival irritation weekly. Neither clinical signs nor ocular changes related to the test articles were seen. Slight conjunctival congestion was observed occasionally in treated eyes from all groups and ocular discharge was also seen periodically. The left (untreated) eye of one Group 1 female was cloudy and enlarged beginning around Week 36. Anorexia, thin appearance, lethargy, and ataxia were seen in the rabbits that died early.

Body weights: Measured before the initiation of dosing, weekly for the first 16 weeks of dosing, every fourth week for Weeks 16-48, at Weeks 51 and 52, and after fasting at the time of sacrifice. No treatment-related changes in body weight were seen. Body weight reductions were observed in animals that died early.

Food consumption: Recorded weekly for the first 16 weeks of dosing, every fourth week for Weeks 16-48, and at Week 51. No treatment-related effects on food consumption were observed. Reduced food consumption was seen in rabbits that died early.

Electrocardiogram: Not done.

Ophthalmoscopy: Macroscopic ocular examinations were conducted weekly during the treatment period before the first daily dose of test article. Biomicroscopy (slit lamp examinations) and indirect ophthalmoscopy were performed before the initiation of treatment and at 3 month intervals thereafter. No drug-related ophthalmic findings were observed. Buphthalmia was observed at Weeks 41 and 52 in the swollen, cloudy untreated eye of the Group 1 female discussed above (see Clinical signs).

Hematology/Clinical chemistry: Blood samples for hematology and clinical chemistry were drawn from fasted rabbits prior to the initiation of dosing, during Week 13, and prior to sacrifice. There were no drug-related changes in hematology or clinical chemistry parameters. The female rabbit diagnosed with lymphocytic leukemia exhibited anemia, thrombocytopenia, lymphocytosis, hypoglycemia, uremia, elevated liver enzymes (AST, ALT, alkaline phosphatase, GGT) and hypoproteinemia (both albumin and globulin).

Urinalysis: Urine samples were obtained via bladder puncture at the time of necropsy. No drug-related changes in urinalysis parameters were observed. The female rabbit with lymphocytic leukemia had increased occult blood in the urine and the male with the GI hairball sacrificed at Week 40 had increased protein and occult blood in the urine.

Gross pathology: Gross necropsy did not reveal any findings that appeared drug-related. Animals that were found dead or sacrificed in moribund condition had gross changes consistent with the deterioration of their health or agonal changes.

Organ weights: Adrenals, liver, kidneys, brain (with brainstem), testes with epididymides, and ovaries. There were no differences in mean absolute or relative organ weights between the treatment groups.

Histopathology: Adequate Battery: A standard list of tissues was preserved, but microscopic evaluation was performed only on lens, cornea, retina, lacrimal glands, and optic nerves. Examination of only ocular tissues was acceptable for this study.
Peer review: yes ( ), no (x)

The ocular tissues listed above were examined in the control and high dose ([redacted] polycarbophil) rabbits and any animals that died during the dosing period or were sacrificed in moribund condition. Gross lesion identified at necropsy were also examined microscopically. There were no microscopic changes in the ocular tissues that appeared treatment-related. b(4)

Toxicokinetics: Not done.

2.6.6.4 Genetic toxicology

The label for oral azithromycin products states that the compound was not mutagenic and/or clastogenic in mouse lymphoma cells, human lymphocytes, or mouse bone marrow cells.

2.6.6.5 Carcinogenicity

The label for oral azithromycin products states that carcinogenicity studies have not been performed with the compound.

2.6.6.6 Reproductive and developmental toxicology

Pregnancy Category B has been assigned to azithromycin. The label for oral azithromycin products states that the compound was not associated with impairment of fertility or fetal harm at maternal doses of up to 200 mg/kg/day given to rats and mice.

2.6.6.7 Local tolerance

Repeat-dose ocular toxicity studies conducted with AzaSite™ demonstrated that it is not an ocular irritant.

2.6.6.8 Special toxicology studies

No special toxicology studies were conducted with AzaSite™.

2.6.6.9 Discussion and Conclusions

Both AzaSite™ and its vehicle, DuraSite®, were well tolerated by rabbits when applied to eyes several times daily for 30 days or 52 weeks, respectively. Neither of these products caused ocular irritation or toxicity. The microvacuolation in the corneal epithelium and corneal stromal cells associated with application of azithromycin is likely a manifestation of phospholipidosis. This finding was not associated with inflammation or tissue damage, and it was reversible after the application of AzaSite™ was discontinued.

AzaSite™ appears reasonably safe to use as directed in the proposed product label.

2.6.6.10 Tables and Figures

All tables and figures relevant to this NDA have been included in other sections of this review.

2.6.7 TOXICOLOGY TABULATED SUMMARY

As provided in the NDA:

Type of Study	Species/ Strain	Gender and No. per group	Route of Administration	Duration of Dosing	Doses	GLP	Noteworthy Findings	Study Reference	Location
Repeat-Dose Toxicity	New Zealand white rabbits	3/sex/group	Ocular Topical	14 days	one drop 0.2% AzaSite qid, one drop 0.5% AzaSite qid, one drop 1.0% AzaSite qid, one drop vehicle qid	Yes	None except microvacuolation in corneal epithelium and stroma.	6435-106	Section 4.2.3.2.1
Repeat Dose Toxicity	Dutch Belted rabbits	7/sex/group	Ocular Topical	1-month dosing with a 1- and 2-month recovery	one drop 1.0% AzaSite bid, one drop vehicle bid	Yes	No adverse effects and no ocular findings were observed. Minimal to mild, reversible multifocal cytoplasmic microvacuolation in the ocular corneal epithelium was noted.	6435-107	Section 4.2.3.2.1
Repeat Dose Toxicity	Dutch Belted rabbits	12 males/group	Ocular Topical	1-month dosing with a 2-month recovery	one drop 1.0% AzaSite bid, one drop degraded AzaSite formulation bid, one drop vehicle bid	Yes	No adverse effects and no ocular findings were observed. Minimal to mild, reversible multifocal cytoplasmic microvacuolation in the ocular corneal epithelium was noted.	1004-2864	Section 4.2.3.2.1

Type of Study	Species/ Strain	Gender and No. per group	Route of Administration	Duration of Dosing	Doses	GLP	Noteworthy Findings	Study Reference	Location
Repeat Dose Toxicity	New Zealand white rabbits	10/sex/group	Ocular Topical	52 weeks	one drop of 0.6% DuraSite (Carbopol 976, or Noveon AA-1, or polycarbophil) formulation tid, one drop of 1.3% DuraSite formulation tid, One drop of Optisoft, a vehicle control, tid	Yes	Ocular administration of DuraSite with concentrations ranging from 0.6% to 1.3% to New Zealand White rabbits three times daily for at least 52 weeks elicited no evidence of ocular or systemic toxicity.	2584-100	Section 4.2.3.7

OVERALL CONCLUSIONS AND RECOMMENDATIONS

Conclusions: AzaSite™ appears reasonably safe to use as directed in the proposed product label. This product caused neither ocular irritation nor toxicity when applied to rabbit eyes for up to 30 days.

Unresolved toxicology issues: None.

Recommendations: The pharmacologist has no objection to the approval of this NDA.

Suggested labeling: The sponsor's proposed labeling for the *Pregnancy* and *Nonclinical Toxicology* sections is below. The sponsor has based the AzaSite™ label on that for systemic azithromycin products, which was mostly appropriate. Additions recommended by the reviewer are in **bold** font and suggested deletions are in ~~strikethrough~~.

Pregnancy:
Pregnancy Category B. Reproduction studies have been performed in rats and mice at doses up to **200 mg/kg/day. The highest dose was associated with moderate maternal toxicity**.

[redacted] In the animal studies, no evidence of harm to the fetus due to azithromycin was found. [redacted] b(4)

There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, azithromycin should be used during pregnancy only if clearly needed.

NONCLINICAL TOXICOLOGY

Carcinogenesis, Mutagenesis, Impairment of Fertility:
Long term studies in animals have not been performed to evaluate carcinogenic potential. [redacted] Azithromycin has shown no mutagenic potential in standard laboratory tests: mouse lymphoma assay, human lymphocyte clastogenic assay, and mouse bone marrow clastogenic assay. No evidence of impaired fertility due to azithromycin was found **in mice or rats that received oral doses of up to 200 mg/kg/day**. b(4)

Animal Toxicology and/or Pharmacology:
Phospholipidosis (intracellular phospholipid accumulation) has been observed in some tissues of mice, rats, and dogs given multiple systemic doses of azithromycin. Cytoplasmic microvacuolation, which is **likely a manifestation of** [redacted] phospholipidosis, has been observed in the corneas of rabbits given multiple ocular doses of AzaSite™. This effect was reversible upon cessation of AzaSite™ treatment. The significance of this toxicological finding for animals and for humans is unknown. b(4)

Signatures:

Reviewer Signature _____

Team Leader Signature_____ Concurrence Yes ___ No ___

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 Ellis
2/5/2007 02:41:56 PM
PHARMACOLOGIST

The pharmacologist has no objection to the approval of this NDA. Labeling recommendations should be conveyed to the sponsor.

Terry- You signed the paper copy of this review on 2/5/07.

Terry Peters
2/5/2007 02:53:03 PM
PHARMACOLOGIST