CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

50-810

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

OFFICE OF CLINICAL PHARMACOLOGY REVIEW

NDA:	50-810
Submission Date(s):	28JUN2006
Brand Name	AzaSite™
Generic Name	Azithromycin
Primary Reviewer	Kimberly L. Bergman, Pharm.D.
Acting Team Leader	Charles Bonapace, Pharm.D
OCP Division	DCP4
OND Division	DAIOP
Applicant	InSite Vision
Relevant IND(s)	IND 62,873
Submission Type; Code	505(b)(2) application
Formulation; Strength(s)	Azithromycin 1% ophthalmic solution
Indication	Treatment of bacterial conjunctivitis caused by susceptible strains of the following organisms: 1) Aerobes, Gram-positive: CDC coryneform group G, *Staphylococcus aureus*, [redacted] *Streptococcus mitis* group, *Streptococcus pneumoniae*, and 2) Aerobes, Gram-negative: *Haemophilus influenzae*. [redacted]

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1. EXECUTIVE SUMMARY

Azithromycin is an azalide antibiotic that acts by binding to the 50S ribosomal subunit of susceptible microorganisms, thus interfering with microbial protein synthesis. AzaSite

azithromycin ophthalmic solution 1% is proposed for use in the treatment of bacterial conjunctivitis caused by susceptible strains of Gram-positive aerobes, specifically CDC coryneform group G, *Staphylococcus aureus,* [redacted] , *Streptococcus mitis group, Streptococcus pneumoniae,* and Gram-negative aerobes, specifically *Haemophilus influenzae,* and [redacted] . The proposed dosage and route of administration for AzaSite is as follows: Days 1 and 2, instill one (1) drop in the affected eye(s) two (2) times per day; Days 3 through 7, instill one (1) drop in the affected eye(s) once per day. The active component of AzaSite, azithromycin, has been previously approved for systemic administration of doses ranging from 250 mg to 2 g (Zithromax® NDAs 50-670, 50-693, 50-710, 50-711, 50-730, 50-733, and 50-784). The current NDA for AzaSite 1% azithromycin ophthalmic solution included two Phase 3 studies designed to evaluate the clinical and microbial efficacy of AzaSite compared to vehicle and compared to active control (0.3% tobramycin ophthalmic solution) in the treatment of bacterial conjunctivitis. The Applicant did not perform any human pharmacokinetic assessments of AzaSite ophthalmic solution. The Applicant's request for waiver of the requirement for submission of evidence of in vivo bioavailability is acceptable based on the expected low systemic exposure of azithromycin following ophthalmic administration of AzaSite solution in comparison to exposures observed following systemically administered azithromycin (Zithromax®).

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1.1. Recommendation

The Clinical Pharmacology information provided by the Applicant is acceptable.

1.2. Phase IV Commitments

No phase IV commitments are recommended.

1.3. Summary of Important Clinical Pharmacology and Biopharmaceutics Findings

The active component of AzaSite, azithromycin, has been previously approved for systemic administration for the treatment of patients with mild to moderate infections caused by susceptible strains of designated microorganisms. The current NDA for AzaSite 1% azithromycin ophthalmic solution included two Phase 3 studies designed to evaluate the clinical and microbial efficacy of AzaSite compared to vehicle (Study C-01-401-003) and compared to active control (0.3% tobramycin ophthalmic solution; Study C-01-401-004) in the treatment of bacterial conjunctivitis. The Applicant did not perform any human pharmacokinetic assessments of AzaSite ophthalmic solution, and has requested a waiver of such requirement as the clinical pharmacology characteristics of azithromycin have been adequately established in previous NDA approvals for systemically administered azithromycin and the systemic availability following ophthalmic administration of AzaSite is expected to be far less than that observed with the FDA-approved oral and IV formulations of azithromycin.

The Applicant's proposed rationale that estimated plasma concentrations in humans upon ocular instillation are multiple orders of magnitude lower than those achieved by oral administration is justified. Assuming complete systemic availability of bilateral administration of a 25 to 50 µL drop of 1% azithromycin ophthalmic solution and an apparent volume of distribution of 30 L/kg for azithromycin, the highest possible plasma concentration is estimated to be approximately 0.48 ng/mL (or approximately 1/1000th the maximum concentration observed upon oral dosing). In addition, assuming complete systemic availability of bilateral administration of a 50 µL drop of 1% azithromycin ophthalmic solution (100 µL total dose), the total dose administered ophthalmically is at most 1/250th the recommended doses approved for orally administered

azithromycin (1 mg versus 250 mg to 2 g, respectively). Available safety data from the AzaSite Phase 3 development program are not indicative of significant systemic adverse events, in that there were no clinically significant differences among the treatment groups in the incidence of adverse events, specifically headache, or in the numbers of subjects discontinued in the AzaSite vs. comparator groups in the Phase 3 studies. In addition, assuming complete systemic availability of ophthalmically administered AzaSite, maximum plasma concentrations of azithromycin are expected to be well below the limit of quantification of currently available analytical methodology.

From a Clinical Pharmacology perspective, the requirement for submission of evidence of in vivo bioavailability can be waived based on the expected low systemic exposure of azithromycin following ophthalmic administration of AzaSite solution in comparison to exposures observed following systemically administered azithromycin (Zithromax®).

2. QUESTION BASED REVIEW

Since this submission is a 505(b)(2) NDA for a locally administered product relying upon conclusions drawn by the Agency for a previously approved systemically administered product, only relevant questions from the OCP question-based review (QBR) format are addressed below.

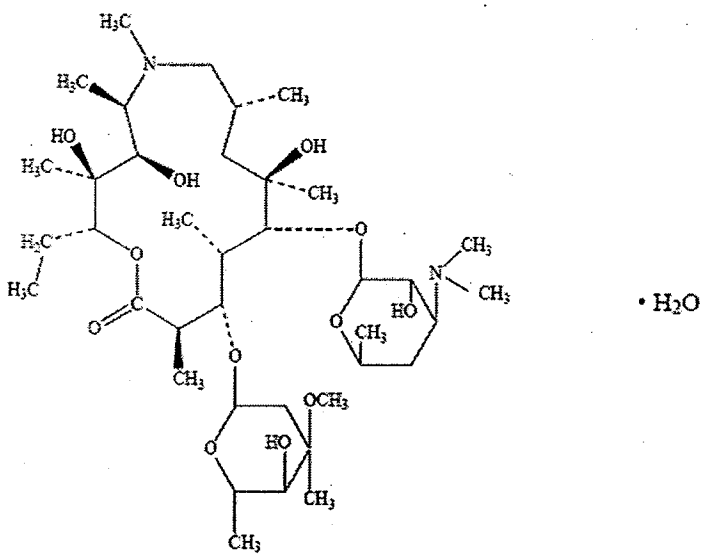
2.1. General Attributes of the Drug

2.1.1. What are the highlights of the chemistry and physical-chemical properties of the drug substance and the formulation of the drug product?

AzaSite™ (1% azithromycin ophthalmic solution) contains the active ingredient azithromycin, an azalide, a subclass of macrolide antibiotics, for ocular administration. The drug substance used to manufacture AzaSite is azithromycin monohydrate. The active ingredient, azithromycin, has been previously approved for systemic administration (Zithromax® NDAs 50-670, 50-693, 50-710, 50-711, 50-730, 50-733, and 50-784). The chemical structure and physical-chemical properties of azithromycin are shown below:

Structural Formula: $C_{38}H_{72}N_2O_{12}\cdot H_2O$

Chemical Structure:



Chemical Name: (*2R,3S,4R,5R,8R,10R,11R,12S,13S,14R*)-13-[(2,6-dideoxy-3-*C*-methyl-3-*O*-methyl-α-*L-ribo*-hexopyranosyl)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-azacyclo-pentadecan-15-one monohydrate

Approved Name: Azithromycin Monohydrate

USAN: Azithromycin

Molecular Weight: 767 (monohydrate)

Previously approved dosage forms of azithromycin indicated to treat bacterial infections include oral tablets, capsules, oral suspensions and IV injection. AzaSite is a topical, sterile aqueous ophthalmic formulation of 1% azithromycin solution in DuraSite® delivery vehicle and is intended for the treatment of bacterial conjunctivitis. The DuraSite® system is composed of polycarbophil USP [redacted] edetate disodium (EDTA), sodium chloride, [redacted] AzaSite contains 0.003% benzalkonium chloride (BAC) as preservative. b(4)

The quantitative composition of the proposed AzaSite drug product is shown in the following table (Table 2.2-1):

Table 2.2-1 Composition of AzaSite Ophthalmic Solution

Component	Percent W/W
Azithromycin Monohydrate, USP	1.0
Mannitol, USP	[redacted]
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]

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2.1.2. What is the proposed mechanism of drug action and therapeutic indication?

Azithromycin is an azalide antibiotic that acts by binding to the 50S ribosomal subunit of susceptible microorganisms, thus interfering with microbial protein synthesis. The proposed indication for AzaSite azithromycin ophthalmic solution 1% is for use in the treatment of bacterial conjunctivitis caused by susceptible strains of the following organisms:

- Aerobes, Gram-positive: CDC coryneform group G, *Staphylococcus aureus,* [redacted] *, Streptococcus mitis group, Streptococcus pneumoniae* b(4)
- Aerobes, Gram-negative: *Haemophilus influenzae,* [redacted]

2.1.3. What is the proposed dosage and route of administration?

The proposed dosage and route of administration for AzaSite is as follows: Days 1 and 2, instill one (1) drop in the affected eye(s) two (2) times per day; Days 3 through 7, instill one (1) drop in the affected eye(s) once per day.

2.2. General Clinical Pharmacology

2.2.1. What are the design features of the clinical pharmacology and clinical studies used to support dosing claims?

No clinical pharmacology studies were submitted in this NDA.

Two Phase 3 studies designed to evaluate the clinical and microbial efficacy of AzaSite compared to vehicle (Study C-01-401-003) and compared to active control (0.3% tobramycin ophthalmic solution; Study C-01-401-004) in the treatment of bacterial conjunctivitis have been submitted to support dosing claims. The primary endpoint in these studies was clinical resolution, defined as the complete resolution of clinical signs (conjunctival and/or bulbar injections) and symptoms (conjunctival discharge) of bacterial conjunctivitis to a score of 0. The approach to approval was to show superiority over vehicle in one trial and equivalence to tobramycin in the other trial.

2.2.2. What are the PK characteristics of the drug?

The Applicant has submitted a request for waiver of the requirement for submission of evidence of in vivo bioavailability for AzaSite, based on the following rationales:

1. the estimated plasma concentrations in humans upon ocular instillation is multiple orders of magnitude lower than those achieved by oral administration,
2. ocularly administered azithromycin (AzaSite) should be expected to cause little or no systemic side effect because of its significantly lower plasma concentrations, and
3. plasma concentrations in humans following ocular administration of AzaSite are expected to be so low that currently available analytical methods may not be able to detect them.

The Applicant's rationales in support of a waiver are addressed by the Clinical Pharmacology Reviewer, as follows:

Rationale #1: Estimated plasma levels in humans upon ocular instillation is multiple orders of magnitude lower than those achieved by oral administration.

The Applicant's proposed rationale that estimated plasma concentrations in humans upon ocular instillation is multiple orders of magnitude lower than those achieved by oral administration is justified. According to the FDA-approved product information for Zithromax®, following oral administration of a single 500 mg dose (two 250 mg tablets) of azithromycin (Zithromax®) to 36 fasted healthy male volunteers, the mean ± SD Cmax was 0.5 ± 0.2 μg/mL. With a regimen of 500 mg (two 250 mg capsules, bioequivalent to tablets in the fasted state) on day 1, followed by 250 mg daily (one 250 mg capsule) on days 2 through 5, maximum plasma concentrations of azithromycin in plasma in healthy young adults (18-40 years of age) were 0.41 and 0.24 μg/mL, respectively. In a two-way crossover study in which 12 adult healthy volunteers (6 males, 6 females) received 1500 mg of azithromycin administered in single daily doses over either 5 days (two 250 mg tablets on day 1, followed by one 250 mg tablet on days 2-5) or 3 days (500 mg per day for days 1-3), mean maximum plasma concentrations ranged between 0.24 and 0.54 μg/mL. Assuming complete systemic availability of bilateral administration of a 50 μL drop of 1% azithromycin ophthalmic solution and an apparent volume of distribution of 30 L/kg for azithromycin, the highest possible plasma concentration is estimated to be approximately 0.48 ng/mL (or approximately $1/1000^{th}$ the maximum concentration observed upon oral dosing). In addition, assuming complete systemic availability of bilateral administration of a 50 μL drop of 1% azithromycin ophthalmic solution (100 μL total dose), the total dose administered ophthalmically is at most $1/250^{th}$ the recommended doses approved for orally administered azithromycin (1 mg versus 250 mg to 2 g, respectively).

Rationale #2: Ocularly administered azithromycin (AzaSite) should be expected to cause little or no systemic side effect because of its significantly lower plasma concentrations.

Available safety data from the AzaSite Phase 3 development program support the Applicant's rationale that ocularly administered azithromycin should be expected to cause little or no systemic side effect because of its significantly lower plasma concentrations. There were no clinically significant differences among the treatment groups in the incidence of adverse events overall or those with an incidence >1%. Most of the common events were related to symptoms or worsening disease in the eye. Headache was reported by more Vehicle-treated subjects than in either active treatment group. Relatively few subjects discontinued the studies for adverse events. There was no clinically significant difference in the numbers of subjects discontinued in the AzaSite vs. Vehicle or tobramycin groups in the Phase 3 studies. Two serious adverse events were reported, both in Vehicle-treated subjects. There were no clinical chemistry, hematology, urinalysis, or vital signs assessments in the Phase 3 studies submitted in this NDA.

Rationale #3: Plasma concentrations in humans following ocular administration of AzaSite are expected to be so low that currently available analytical methods may not be able to detect them.

The Applicant's statement that plasma concentrations in humans following ocular administration of AzaSite are expected to be so low that currently available analytical methods may not be able to detect them is appropriate. Assuming complete systemic availability of ophthalmically administered AzaSite, maximum plasma concentrations of azithromycin are expected to be well below the limit of quantification of currently available analytical methodology, with a limit of quantification of 10 ng/mL.

In summary, from a Clinical Pharmacology perspective, the requirement for submission of evidence of in vivo bioavailability can be waived based on the expected low systemic exposure following ophthalmic administration of AzaSite solution in comparison to exposures observed following systemically administered azithromycin (Zithromax®).

3. LABELING RECOMMENDATIONS

The following changes reflect Clinical Pharmacology Reviewer recommendations to the proposed labeling (recommendations appear in ***bold italicized underlined type*** and deleted text in ~~strike-through~~ font).

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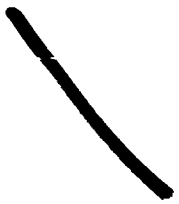
12.1 Mechanism of Action



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12.3 Pharmacokinetics

The plasma concentration of azithromycin following ocular administration of AzaSite (azithromycin 1% ophthalmic solution) in humans is unknown. Based on the maximum proposed dose of one drop to each eye (***total dose of 100 µL or*** 1 mg ***azithromycin***) and ~~PK~~ ***exposure*** information from ~~other routes of~~ ***systemic*** administration, the systemic concentration of azithromycin ***following ocular administration*** is estimated to be below ~~the limit of quantification~~ ***quantifiable limits*** (≤ 10 ng/mL) at steady-state in humans, ~~even assuming 100% absorption~~ ***assuming 100% systemic availability***.

APPEARS THIS WAY ON ORIGINAL

4. APPENDICES

4.1. Wavier Request for the Requirement for Submission of Evidence of In Vivo Bioavailability

The following request for waiver of the requirement for submission of evidence of in vivo bioavailability was submitted by the Applicant:

AzaSite™ is an ophthalmic formulation containing 1% azithromycin, a broad-spectrum antibiotic that is intended for the treatment of bacterial conjunctivitis. It is intended for dosing twice daily on the first and second day of treatment and once a day on subsequent treatment days.

We contend that it is unnecessary to perform a pharmacokinetics study in humans because, based on data from our own animal study and from the literature, the estimated blood plasma levels in humans upon ocular instillation are at least 3 orders of magnitude lower than those achieved by oral administration. Since there has been no significant systemic side effect reported during more than a decade of use of the orally administered drug in humans, the ocularly administered azithromycin (AzaSite) should be expected to cause little or no systemic side effect because of its significantly lower plasma concentrations. In addition, the plasma concentrations in humans are expected to be so low that the currently available analytical method may not be able to detect them. Based on these scenarios, a human pharmacokinetics study may not yield any meaningful information on the distribution or the systemic safety of the drug.

Azithromycin pharmacokinetics is characterized by rapid and extensive uptake into tissues resulting in a large volume of distribution (Vd). Both oral and intravenous administration of the drug have yielded similar Vd. Following intravenous administration of 1 and 2 g azithromycin in normal subjects, Vds were reported as 30.1 L/kg and 30.5 L/kg, respectively.[1] Azithromycin tablets and oral suspension package insert also reported the Vd to be 31.1 L/kg following oral administration.[2]

Based on the value of Vd from these studies, the Applicant calculated the maximum plasma concentration following ocular administration:

Volume of eyedrop = 25 µL
Concentration of azithromycin in the eyedrop = 1% = 10 mg/mL = 10 µg/uL
Assume bilateral administration;
The total amount of azithromycin administered to the eyes is
25 µL x 2 x 10 µg/uL = 500 µg

Volume of distribution = 30 L/kg
Weight of a normal male subject = 70 kg
Therefore, volume of distribution of a normal subject is:
30 L/kg x 70 kg = 2100 L

Assume 100% absorption, the maximum plasma concentration will be:
500 µg /2100 L = 0.24 µg/L = 0.24 ng/mL

Conversely, we could estimate the plasma concentration based on our rabbit studies.
In nonclinical Study 107U0301 (final report submitted November 1, 2001 as Serial No. 001 to this IND), following a single instillation of a 25 µL 1% AzaSite™ drop to both eyes of a rabbit, the peak plasma concentration (Cmax) was determined to be 4.4 ng/mL. Since the blood volume of a 2 kg rabbit is about 136 mL[3], and that of a 70 kg human is 5 L, the maximum plasma concentration in humans would be 4.4 ng/mL x 136 mL /5000 mL = 0.12 ng/mL. It is noted that this calculation does not take into account the much larger peripheral tissue compartment that

humans have as compared to rabbits. Since azithromycin is known to widely distribute in tissues, the realistic azithromycin plasma concentration in humans would be much lower than 0.12 ng/mL.

Both approaches yield approximately the same maximum plasma concentrations in the sub-ng/mL range. This concentration range has not been known to cause any pharmacologic or toxicologic effects in humans. Pharmacologically, this concentration range is sub-therapeutic in its action against target bacteria. The minimum inhibitory concentrations (MICs) of azithromycin were reported to range from 0.06 ug/mL (against *Streptococcus pneumoniae*) to 4 µg/mL (*Hemophilus influenza*)[2], which are substantially higher than the maximum attainable plasma concentrations following ocular administration. Toxicologically, this concentration range is expected to cause little, if any, systemic side effect. Oral administration of azithromycin at 500 mg/day for 3 days to healthy volunteers resulted in a peak plasma concentration of 0.42 ug/mL[4], which is three orders of magnitude higher than the estimated azithromycin concentration upon ocular instillation. Since oral administration of azithromycin with this and other similar dosing regimens has been known to be safe for more than a decade, ocular administration of azithromycin is expected to cause little, if any, systemic side effect.

Furthermore, the estimated human plasma levels following ocular administration would be too low to be detected by currently available analytical method. A recent paper by Bahrami et al. reported a fast and sensitive HPLC method for determination of azithromycin in human serum using fluorescence detection.[5] However, the limit of quantification of the assay was only 10 ng/mL, which is two orders of magnitude higher than the estimated blood concentrations.

In summary, based on the data from our animal pharmacokinetics studies and human systemic pharmacokinetics studies in the literature, we conclude that AzaSite™, an eyedrop formulation of azithromycin, is expected to have little systemic pharmacologic or toxicologic effects in humans. The estimated azithromycin plasma levels in humans may not be detected by the current assay methodology. Therefore, a human pharmacokinetics study employing AzaSite eyedrop formulation would be unnecessary.

References:

1. Luke DR, Foulds G, Cohen SF, Levy B. Safety, toleration, and pharmacokinetics of intravenous azithromycin. *Antimicrob Agents Chemother* 1996;40:2577-2581.
2. Zithromax® package insert.
3. Kaplan HM, Timmons EH. The rabbit, a model for the principles of mammalian physiology and surgery. Academic Press, New York, 1979, 84-89.
4. Wildfeuer A, Laufen H, Leitold M, Zimmermann T. Comparison of the pharmacokinetics of three-day and five-day regimens of azithromycin in plasma and urine. *Antimicrob Agents Chemother* 1993;31:Suppl E:51-56.
5. Bahrami G, Mirzaeei S, Kiani A. High performance liquid chromatographic determination of azithromycin in serum using fluorescence detection and its application in human pharmacokinetic studies. *J Chromatogr B* 2005;820:277-281.

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Kimberly Bergman
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