CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

50-810

CHEMISTRY REVIEW(S)

NDA 50-810

AzaSite
(azithromycin ophthalmic solution 1%)

InSite Vision

Ko-Yu Lo, Ph.D.
Branch IV
Division of Pre-Marketing Assessment 2
Office of New Drug Quality Assessment

Table of Contents

Chemistry Review Data Sheet

1. NDA or ANDA 050-810

2. REVIEW #: 2

3. REVIEW DATE: 04/25/2007

4. REVIEWER: Ko-Yu Lo

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
NDA Review #1	2/27/2007

6. SUBMISSION(S) BEING REVIEWED:

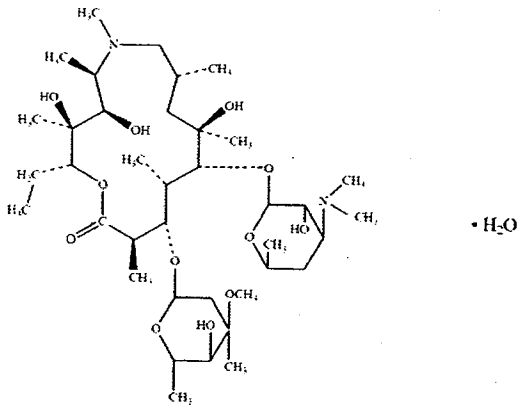
Submission(s) Reviewed	Document Date
Original	28/JUN/2006
Amendment BC	03/SEP/2006
Amendment BC	14/FEB/2007
Amendment BC	27/FEB/2007
Amendment BL	23/MAR/2007
Amendment BC	02/APR/2007
Amendment BL	17/APR/2007
Amendment BL	19/APR/2007

7. NAME & ADDRESS OF APPLICANT:

Name	InSite Vision
Address	965 Atlantic Ave., Alameda, CA 94501
Representative	Ronald Carlson, Ph.D., Vice President of Regulatory Affairs and Quality
Telephone	510-747-1228

8. DRUG PRODUCT NAME/CODE/TYPE:
   a) Proprietary Name:
   b) Non-Proprietary Name (USAN): Azithromycin monohydrate
   c) Code Name/# (ONDC only):
   d) Chem. Type/Submission Priority (ONDC only):
      - Chem. Type:
      - Submission Priority: S
9. LEGAL BASIS FOR SUBMISSION: N/A
10. PHARMACOL. CATEGORY: Antiinfective
11. DOSAGE FORM: Ophthalmic Solution
12. STRENGTH/POTENCY: 1%
13. ROUTE OF ADMINISTRATION: Eye drop
14. Rx/OTC DISPENSED: _X__Rx ___OTC
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
    _____SPOTS product – Form Completed
    __X___Not a SPOTS product
16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

INN	Azithromycin
USAN	Azithromycin
Approved Name	Azithromycin Monohydrate
Chemical Name	(2R,3S,4R,5R,8R,10R,11R,12S,13S,14R)-13-[(2,6-dideoxy-3-C-methyl-3-O-methyl-a-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)-ß-D-xylo-hexopyranosyl]oxy]-1-oxa-6-aza-cyclopentadecan-15-one. monohydrate
Molecular Formula	$C_{38}H_{72}N_2O_{12}\cdot H_2O$
Molecular Weight	azithromycin monohydrate: 767, azithromycin: 749
Structure Formula	



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

Chemistry Review Data Sheet

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
[redacted]	II	[redacted]	[redacted]	3	Adequate	9/05	[redacted]
[redacted]	IV	[redacted]	[redacted]	4	Adequate		

b(4)

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A		
EES	Acceptable	21/FEB/2007	
Pharm/Tox			
Biopharm	N/A		
LNC			
Methods Validation	Not needed		
OPDRA	Acceptable		
EA	Exclusion Acceptable	27/FEB/2007	Ko-Yu Lo
Microbiology	Acceptable		Stephen Langile

OGD:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology			
EES			
Methods Validation			
Labeling			
Bioequivalence			
EA			
Radiopharmaceutical			

19. ORDER OF REVIEW (OGD Only)

The application submission(s) covered by this review was taken in the date order of receipt. ____ Yes ____ No If no, explain reason(s) below:

APPEARS THIS WAY ON ORIGINAL

The Chemistry Review for NDA 50-810

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

From a chemistry, manufacturing, and controls standpoint, the NDA is recommended for approval.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

N/A

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

Drug Substance

Azithromycin is a broad spectrum macrolide antibiotic sold under the trade name of Zithromax®. Approved dosage forms indicated to treat bacterial infections include oral tablets, capsules, oral suspensions and IV injection. Azithromycin is available as azithromycin dehydrate and azithromycin monohydrate.

The active pharmaceutical ingredient for AzaSite formulation is azithromycin monohydrate supplied by [redacted]
Chemistry, manufacturing, and controls (CMC) for the drug substance is cross-referencing to Type II DMF [redacted] Manufacturing and controls for azithromycin monohydrate has been updated with a new DS specification (4/05) during the DMF review for ANDA [redacted] DMF [redacted] was found acceptable by the FDA in 9/05. b(4)

In the original NDA, InSite states that azithromycin monohydrate USP, has been used to prepare Phase 3 clinical materials, registration batches and toxicological supplies for a 30-day toxicology study, and will be used for future commercial production of AzaSite. Copies of 3 representative Certificates of Analysis (COA) are provided in the original submission (Section 3.2.S.1.) as support. However, the COAs reveal that these lots were not release with a USP specification. Per FDA request, 3 representative COAs for lots that were manufactured in 10/06 were amended (4/2/07). The COAs and available information for the drug product (analytical procedure as well as DP stability data) demonstrate that azithromycin monohydrate from [redacted] meets the USP requirements. In addition, the applicant has assured that USP grade drug substance will b(4)

be used for future commercial production of the drug product (3/29/07 teleconference). CMC information for the drug substance provided in the NDA/amendment is acceptable.

Drug Product

The drug product, AzaSite (azithromycin 1.0% ophthalmic solution) is an off-white, hazy viscous liquid with a pH of approximately 6.3 and an osmolality of approximately 290 mOsm/kg. AzaSite contains 0.003% benzakonium chloride (BAC) as preservative, and is formulated in a polycarbophil USP [redacted] vehicle [redacted] b(4)
[redacted] Extensive pharmaceutical development has been performed to address important parameters, including excipient compatibility and optimal concentration, toxicity profile, in-vivo performance, stability, ease of manufacturing, container/closure system (microbial integrity challenge, fill volume, adsorption/absorption, leaching, and dose reproducibility) and sterility.

AzaSite commercial product [redacted] will be manufactured by Cardinal Health, Woodstock, IL. Phase 3 and registration batches [redacted] were produced at the same facility. The commercial manufacturing process includes the following major steps: b(4)

[redacted] b(4)

InSite proposes a DP specification based on the stability data of the Phase 3 clinical samples that have been stored at room temperature for a period of up to 3 months after variable time storage at 5°C. The widened acceptance criteria (AC) is justified based on a 30-day ocular toxicology study. Since this worse-case scenario will not apply to commercial drug product that will be stored at 2-8°C and dispensed at 15-25°C for not more than 14 days, FDA has recommended tightening the AC for c [redacted] b(4)
[redacted]. However, during the 3/29/07 teleconference, InSite informs FDA that they just propose to add a physician sample in the NDA. The physician sample is identical to the commercial product but needs to be stored at room temperature for 6 months due to practical reasons (transportation and not all physician offices have refrigerators). This issue was subsequently discussed with the clinical division. Dr. Wiley Chambers (reviewing medical officer) considers a physician sample with 6 months room temperature reasonable. As a result, ONDQA agree that the AC for impurity will be established based on the 30-day ocular toxicity study (a risk base assessment). The AC proposed by InSite is acceptable.

Stability of the drug product has been evaluated on 3 stability batches [redacted] at b(4)
long-term conditions (5°C/AH) for 24 months and accelerated conditions (25°C/

20%RH) for 6 months. [redacted] is identified as the major degradant in the stability samples of the drug product. The [redacted] concentration increase during storage and is [redacted]

b(4)

[redacted] Statistical analysis (ANOVA) of the stability data has been performed with a prediction of greater than 48-month shelf-life. The submitted data support the proposed 24-months expiration dating period.

B. Description of How the Drug Product is Intended to be Used

AzaSite™ is a macrolide antibiotic indicated for the treatment of bacterial conjunctivitis caused by susceptible strains of gram-positive and gram-negative aerobes.

Dosage and Administration

Instill 1 drop in the affected eye(s) twice daily, eight to twelve hours apart for the first two days and then instill 1 drop in the affected eye(s) once daily for the next five days.

AzaSite is a sterile aqueous topical ophthalmic formulation of 1.0% azithromycin in a white, round low-density polyethylene bottle (LDPE) with a natural LDPE dropper tip and a tan colored high density polyethylene (HDPE) eyedropper cap. A white tamper evident overcap is provided. 2.5 mL in 5 mL bottle containing a total of 25 mg azithromycin.

C. Basis for Approvability or Not-Approval Recommendation

All manufacturing and testing facilities were found acceptable.

The NDA submission and amendments ultimately provided adequate information on the chemistry, manufacturing and controls for AzaSite (azithromycin ophthalmic solution) 1%

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

ChemistName/Date:
ChemistryTeamLeaderName/Date
ProjectManagerName/Date

C. CC Block

14 Page(s) Withheld

X Trade Secret / Confidential (b4)

_____ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

Withheld Track Number: Chemistry- 1

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/s/

Ko-yu Lo
4/26/2007 12:17:36 PM
CHEMIST

Stephen Paul Miller
4/26/2007 12:33:01 PM
CHEMIST
Acting Branch Chief

NDA 50-810

AzaSite
(azithromycin ophthalmic solution 1%)

Insite Vision

Ko-Yu Lo, Ph.D.
Branch IV
Division of Pre-Marketing Assessment 2
Office of New Drug Quality Assessment

Table of Contents

Chemistry Review Data Sheet

1. NDA or ANDA 050-810

2. REVIEW #: 1

3. REVIEW DATE: 02/27/2007

z4. REVIEWER: Ko-Yu Lo

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date

6. SUBMISSION(S) BEING REVIEWED:

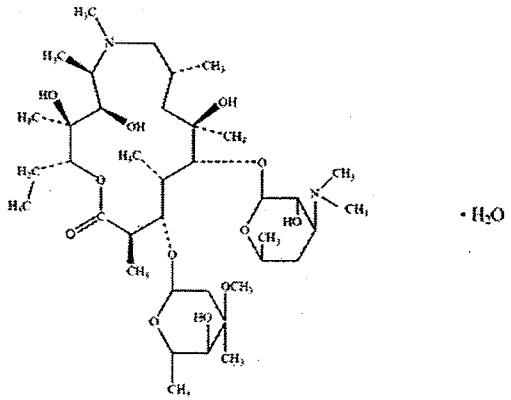
Submission(s) Reviewed	Document Date
Original	28/JUN/2006
Amendment BC	03/SEP/2006

7. NAME & ADDRESS OF APPLICANT:

Name	InSite Vision
Address	965 Atlantic Ave., Alameda, CA 94501
Representative	Ronald Carlson, Ph.D., Vice President of Regulatory Affairs and Quality
Telephone	510-747-1228

8. DRUG PRODUCT NAME/CODE/TYPE:
   a) Proprietary Name:
   b) Non-Proprietary Name (USAN): Azithromycin monohydrate
   c) Code Name/# (ONDC only):
   d) Chem. Type/Submission Priority (ONDC only):
      - Chem. Type:
      - Submission Priority: S
9. LEGAL BASIS FOR SUBMISSION: N/A
10. PHARMACOL. CATEGORY: Antiinfective
11. DOSAGE FORM: Ophthalmic Solution
12. STRENGTH/POTENCY: 1%
13. ROUTE OF ADMINISTRATION: Eye drop
14. Rx/OTC DISPENSED: _X__Rx ___OTC
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
    _____SPOTS product – Form Completed
    __X___Not a SPOTS product
16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

INN	Azithromycin
USAN	Azithromycin
Approved Name	Azithromycin Monohydrate
Chemical Name	(2R,3S,4R,5R,8R,10R,11R,12S,13S,14R)-13-[(2,6-dideoxy-3-C-methyl-3-O-methyl-a-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)-ß-D-xylo-hexopyranosyl]oxy]-1-oxa-6-aza-cyclopentadecan-15-one. monohydrate
Molecular Formula	$C_{38}H_{72}N_2O_{12}\cdot H_2O$
Molecular Weight	azithromycin monohydrate: 767, azithromycin: 749
Structure Formula	



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

Chemistry Review Data Sheet

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
[redacted]	II	[redacted]	[redacted]	3	Adequate	9/05	[redacted]
[redacted]	IV	[redacted]	[redacted]	4	Adequate		

b(4)

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[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND		

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A		
EES	Acceptable	21/FEB/2007	
Pharm/Tox			
Biopharm			
LNC			
Methods Validation	Not needed		
OPDRA	Acceptable		
EA	Exclusion Acceptable	27/FEB/2007	Ko-Yu Lo
Microbiology			

OGD:

Chemistry Review Data Sheet

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology			
EES			
Methods Validation			
Labeling			
Bioequivalence			
EA			
Radiopharmaceutical			

19. ORDER OF REVIEW (OGD Only)

The application submission(s) covered by this review was taken in the date order of receipt. ____ Yes ____ No If no, explain reason(s) below:

APPEARS THIS WAY ON ORIGINAL

The Chemistry Review for NDA 22-011

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The specification for the drug product has not been established at this time. However, the NDA is approvable from a chemistry, manufacturing, and controls standpoint.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

N/A

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

Drug Substance

Azithromycin is a broad spectrum macrolide antibiotic sold under the trade name of Zithromax®. Approved dosage forms indicated to treat bacterial infections include oral tablets, capsules, oral suspensions and IV injection. Azithromycin is available as azithromycin dehydrate and azithromycin monohydrate.

The active pharmaceutical ingredient for AzaSite formulation is azithromycin monohydrate supplied by [redacted]
Chemistry, manufacturing, and controls (CMC) for the drug substance is cross-referencing to Type II DMF [redacted] Manufacturing and controls for azithromycin monohydrate has been updated with a new DS specification (4/05) during the DMF review for ANDA [redacted] DMF [redacted] was found acceptable by the FDA in 9/05. b(4)

InSite states that azithromycin monohydrate USP, has been used to prepare Phase 3 clinical materials, registration batches and toxicological supplies for a 30-day toxicology study, and will be used for future commercial production of AzaSite. Copies of 3 representative Certificates of Analysis (COA) are provided (Section 3.2.S.1.) as support. However, the COAs reveal that these lots were not release with a USP specification. Because of this, it is recommended that the new DS specification be amended to the NDA, and drug substance lots released with the new DS specification be used for future commercial production of AzaSite. Aside from the above recommendation, CMC information for the drug substance provided in the NDA is acceptable.

Drug Product

The drug product, AzaSite (azithromycin 1.0% ophthalmic solution) is an off-white, hazy viscous liquid with a pH of approximately 6.3 and an osmolality of approximately 290 Osm/kg. AzaSite contains 0.003% benzakonium chloride (BAC) as preservative, and is formulated in a polycarbophil USP [redacted] vehicle t[redacted] Extensive pharmaceutical development has been performed to address important parameters, including excipient compatibility and optimal concentration, toxicity profile, in-vivo performance, stability, ease of manufacturing, container/closure system (microbial integrity challenge, fill volume, adsorption/absorption, leaching, and dose reproducibility) and sterility. b(4)

AzaSite commercial product [redacted] will be manufactured by Cardinal Health, Woodstock, IL. Phase 3 and registration batches [redacted] were produced at the same facility. The commercial manufacturing process includes the following major steps: b(4)

[redacted] b(4)

InSite proposes a DP specification based on the stability data of the Phase 3 clinical samples that have been stored at room temperature for a period of up to 3 months after variable time storage at 5°C. The widened acceptance criteria (AC) is justified based on a 30-day ocular toxicology study. However, this worse-case scenario will not apply to commercial drug product since the commercial product will be stored at 2-8°C and dispensed at 15-25°C for not more than 14 days. It is recommended that the AC for [redacted] be tightened to reflect real case scenario. The DP specification will be established following discussion with InSite.

Stability of the drug product has been evaluated on 3 stability batches [redacted] at long-term conditions (5°C/AH) for 18 months and accelerated conditions (25°C/ 20%RH) for 6 months. [redacted] is identified as the major degradant in the stability samples of the drug product. The [redacted] concentration increase during storage and [redacted] Statistical analysis (ANOVA) of the stability data has been performed with a prediction of greater than 48-month shelf-life. The submitted data would support the proposed 24-months expiration dating period. b(4)

A CMC amendment on stability (24-month stability report) and analytical procedures was submitted on 2/14/07. The data will be evaluated in a subsequent review.

B. Description of How the Drug Product is Intended to be Used

AzaSite™ is a topical ophthalmic preparation of an azalide anti-infective indicated for the treatment of bacterial conjunctivitis caused by susceptible strains of gram-positive and gram-negative aerobes.

Dosage and Administration

Day 1& 2:	Instill 1 drop in the affected eye(s) two times per day.
Day 3-7:	Instill 1 drop in the affected eye(s) once per day.

AzaSite is a topical sterile aqueous ophthalmic formulation of 1.0% azithromycin in a white, round low-density polyethylene bottle (LDPE) with a [redacted] dropper tip made with a natural low-density polyethylene (LDPE). 2.5 mL in 5 mL bottle containing a total of 25 mg azithromycin. b(4)

C. Basis for Approvability or Not-Approval Recommendation

All manufacturing and testing facilities were found acceptable.

The submitted CMC information is acceptable. Specification for the drug product will be established after discussion with the applicant.

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

ChemistName/Date:
ChemistryTeamLeaderName/Date
ProjectManagerName/Date

C. CC Block

40 Page(s) Withheld

X Trade Secret / Confidential (b4)

_____ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

Withheld Track Number: Chemistry- 2

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

/s/

Ko-yu Lo
2/27/2007 11:16:47 PM
CHEMIST

Norman Schmuff
3/1/2007 01:29:18 PM
CHEMIST