CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

50-810/S012

Trade Name: AzaSite

Generic Name: AZITHROMYCIN

Sponsor: Inspire Pharmaceuticals, Inc.

Approval Date: 10/16/2012

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

50-810/S012

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Reviews / Information Included in this NDA Review.

Approval Letter	✓
Other Action Letters	✓
Labeling	✓
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Summary Review	
Officer/Employee List	
Office Director Memo	
Cross Discipline Team Leader Review	
Medical Review(s)	✓
Chemistry Review(s)	✓
Environmental Assessment	
Pharmacology Review(s)	
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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

50-810/S012

APPROVAL LETTER

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 50-810/S-012

SUPPLEMENT APPROVAL

Merck Sharp & Dohme Corp.
Attention: Scott Grossman, Ph.D.
Director, Worldwide Regulatory Affairs
P.O. Box 1000
Mail Drop: UG2CD48
Upper Gwynedd, PA 19454-2505

Dear Dr. Grossman:

Please refer to your Supplemental New Drug Application (sNDA) dated October 14, 2010, received October 15, 2010, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for AzaSite (azithromycin ophthalmic solution) 1%.

We acknowledge receipt of your amendments dated December 19, 2011, June 18, July 19, September 5, and September 25, 2012.

The December 19, 2011, submission constituted a complete response to our February 15, 2011, action letter.

This "Prior Approval" supplemental new drug application requests approval of a comparability protocol, *"Comparability Protocol: Plan for Assessing the Impact Changes to the Container Closure System for Azasite (azithromycin ophthalmic solution) 1%,"* to demonstrate the suitability of the drug product in a new container/closure system as a result of a change in shape and size of the bottle and to demonstrate the suitability of the drug product filled at a fill size of 1mL. This supplement also provides for associated changes to the labeling.

We have completed our review of this supplemental application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed, agreed-upon labeling text.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Content of labeling must be identical to the enclosed labeling (text for the package insert, Patient

Information and Instructions for Use), with the addition of any labeling changes in pending "Changes Being Effected" (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling.

Information on submitting SPL files using eLIST may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As" at http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf.

The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications for this NDA, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in MS Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes and annotate each change. To facilitate review of your submission, provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

CARTON AND IMMEDIATE CONTAINER LABELS

Submit final printed carton and container labels that are identical to the enclosed carton and immediate container labels as soon as they are available, but no more than 30 days after they are printed.

Please submit these labels electronically according to the guidance for industry titled "Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (June 2008)." Alternatively, you may submit 12 paper copies, with 6 of the copies individually mounted on heavy-weight paper or similar material. For administrative purposes, designate this submission "**Product Correspondence – Final Printed Carton and Container Labels for approved NDA 50-810/S-012**." Approval of this submission by FDA is not required before the labeling is used.

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, please call Ms. Althea Cuff, Regulatory Health Project Manager, at (301) 796-4061.

Sincerely,

{See appended electronic signature page}

Wiley A. Chambers, M.D.
Deputy Director
Division of Transplant and Ophthalmology Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

ENCLOSURES:
Content of Labeling
Carton and Container Labeling

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

/s/

WILEY A CHAMBERS
10/16/2012

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

50-810/S012

OTHER ACTION LETTER(s)

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 50810/S-012 **COMPLETE RESPONSE**

Inspire Pharmaceuticals, Inc.
Attention: Kimberly A. Davis
Director, Post-Marketing Regulatory Affairs
4222 Emperor Boulevard, Suite 200
Durham, NC 27703-8466

Dear Ms. Davis:

Please refer to your Supplemental New Drug Application (sNDA) dated October 14, 2010, received October 15, 2010, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Azasite (azithromycin ophthalmic solution) 1%.

This "Prior Approval" supplemental new drug application requests approval of a comparability protocol, *"Comparability Protocol: Plan for Assessing the Impact Changes to the Container Closure System for Azasite (azithromycin ophthalmic solution) 1%,"* to demonstrate the suitability of the drug product in a new container/closure system as a result of a change in shape and size of the bottle and to demonstrate the suitability of the drug product filled at a fill size of 1mL.

We have completed the review of your application and have determined that we cannot approve this application in its present form. To change an ophthalmic container/closure system or fill size, a supplement must include data to support the comparability of the container/closure system, a clinical justification for the new fill size, and the proposed labeling. This type of supplement must be approved by the Agency prior to implementation.

In addition, the comparability protocol itself as submitted is inadequate. Specifically:

1) The proposed acceptance criteria for the drug product impurity test are not justified. Justification should be provided.

2) The proposal does not adequately evaluate potential leachables with the new container/closure system. You should conduct a leachable study under accelerated conditions for 6 months and long term storage conditions through expiry using a screening method (e.g., (b) (4) GC and/or (b) (4) HPLC) on the new container closure system in the final market package. A minimum of 3 months data should be provided for review with any submitted supplement. In addition please include particulate matter testing at month 3 for the accelerated storage condition, if only 3 month data will be available at the time of a supplement submission.

3) The proposal does not adequately evaluate the type of stability data that will be needed. You should provide the stability data from the final market package with upright, inverted, and horizontal orientations. Future stability studies may be conducted using only the worst case orientation.

Within one year after the date of this letter, you are required to resubmit or take other actions available under 21 CFR 314.110. If you do not take one of these actions, we may consider your lack of response a request to withdraw the application under 21 CFR 314.65. You may also request an extension of time in which to resubmit the supplemental application. A resubmission must fully address all the deficiencies listed. A partial response to this letter will not be processed as a resubmission and will not start a new review cycle.

Under 21 CFR 314.102(d), you may request a meeting or telephone conference with us to discuss what steps you need to take before the application may be approved. If you wish to have such a meeting, submit your meeting request as described in the FDA's "Guidance for Industry - Formal Meetings Between the FDA and Sponsors or Applicants", May 2009 at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM153222.pdf.

This product may be considered to be misbranded under the Federal Food, Drug, and Cosmetic Act if it is marketed with this change before approval of this supplemental application.

If you have any questions, call Raphael R. Rodriguez, Regulatory Project Manager, at (301) 796-0798.

Sincerely,

{See appended electronic signature page}

Wiley A. Chambers, M.D.
Acting Director
Division of Anti-Infective and Ophthalmology Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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

/s/

WILEY A CHAMBERS
02/15/2011

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

50-810/S012

LABELING

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use AzaSite safely and effectively. See full prescribing information for AzaSite.

AzaSite® (azithromycin ophthalmic solution) 1%
Sterile topical ophthalmic drops
Initial U.S. Approval: 2007

---------- RECENT MAJOR CHANGES----------
Contraindications (4) 07/2012

----------INDICATIONS AND USAGE ----------
AzaSite is a macrolide antibiotic indicated for the treatment of bacterial conjunctivitis caused by susceptible isolates of the following microorganisms: CDC coryneform group G, *Haemophilus influenzae*, *Staphylococcus aureus*, *Streptococcus mitis* group, and *Streptococcus pneumoniae.* (1)

---------- 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. (2)

----------DOSAGE FORMS AND STRENGTHS ----------
2.5 mL of 1% sterile topical ophthalmic solution. (3)

---------- CONTRAINDICATIONS ----------
Hypersensitivity (4)

---------- WARNING AND PRECAUTIONS ----------
- For topical ophthalmic use only. (5.1)
- Anaphylaxis and hypersensitivity have been reported with systemic use of azithromycin. (5.2)
- Growth of resistant organisms may occur with prolonged use. (5.3)
- Patients should not wear contact lenses if they have signs or symptoms of bacterial conjunctivitis. (5.4)

---------- ADVERSE REACTIONS ----------
Most common adverse reaction reported in patients was eye irritation (1-2% of patients). (6)

To report SUSPECTED ADVERSE REACTIONS, contact Inspire Pharmaceuticals, Inc., a subsidiary of Merck & Co., Inc., at 1-800-672-6372 or FDA at 1-800-FDA-1088 or www fda.gov/medwatch.

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 10/2012

FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

AzaSite® is indicated for the treatment of bacterial conjunctivitis caused by susceptible isolates of the following microorganisms:

CDC coryneform group G*
Haemophilus influenzae
Staphylococcus aureus
Streptococcus mitis group
Streptococcus pneumoniae

**Efficacy for this organism was studied in fewer than 10 infections.*

2 DOSAGE AND ADMINISTRATION

The recommended dosage regimen for the treatment of bacterial conjunctivitis is:

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.

3 DOSAGE FORMS AND STRENGTHS

2.5 mL of a 1% sterile topical ophthalmic solution.

4 CONTRAINDICATIONS

Hypersensitivity to any component of this product.

5 WARNINGS AND PRECAUTIONS

5.1 Topical Ophthalmic Use Only

NOT FOR INJECTION. AzaSite is indicated for topical ophthalmic use only, and should not be administered systemically, injected subconjunctivally, or introduced directly into the anterior chamber of the eye.

5.2 Anaphylaxis and Hypersensitivity with Systemic Use of Azithromycin

In patients receiving systemically administered azithromycin, serious allergic reactions, including angioedema, anaphylaxis, and dermatologic reactions including Stevens-Johnson syndrome and toxic epidermal necrolysis have been reported rarely in patients on azithromycin therapy. Although rare, fatalities have been reported. The potential for anaphylaxis or other hypersensitivity reactions should be considered based on known hypersensitivity to azithromycin when administered systemically.

5.3 Growth of Resistant Organisms with Prolonged Use

As with other anti-infectives, prolonged use may result in overgrowth of non-susceptible organisms, including fungi. If super-infection occurs, discontinue use and institute alternative therapy. Whenever clinical judgment dictates, the patient should be examined with the aid of magnification, such as slit-lamp biomicroscopy, and where appropriate, fluorescein staining.

5.4 Avoidance of Contact Lenses

Patients should be advised not to wear contact lenses if they have signs or symptoms of bacterial conjunctivitis.

6 ADVERSE REACTIONS

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in one clinical trial of a drug cannot be directly compared with the rates in the clinical trials of the same or another drug and may not reflect the rates observed in practice.

The data described below reflect exposure to AzaSite in 698 patients. The population was between 1 and 87 years old with clinical signs and symptoms of bacterial conjunctivitis. The most frequently reported ocular adverse reaction reported in patients receiving AzaSite was eye irritation. This reaction occurred in approximately 1-2% of patients. Other adverse reactions associated with the use of AzaSite were reported in less than 1% of patients and included ocular reactions (blurred vision, burning, stinging and irritation upon instillation, contact dermatitis, corneal erosion, dry eye, eye pain, itching, ocular discharge, punctate keratitis, visual acuity reduction) and non-ocular reactions (dysgeusia, facial swelling, hives, nasal congestion, periocular swelling, rash, sinusitis, urticaria).

8 USE IN SPECIFIC POPULATIONS

8.1 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. These doses are estimated to be approximately 5,000 times the maximum human ocular daily dose of 2 mg. In the animal studies, no evidence of harm to the fetus due to azithromycin was found. 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.

8.3 Nursing Mothers

It is not known whether azithromycin is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when azithromycin is administered to a nursing woman.

8.4 Pediatric Use

The safety and effectiveness of AzaSite solution in pediatric patients below 1 year of age have not been established. The efficacy of AzaSite in treating bacterial conjunctivitis in pediatric patients one year or older has been demonstrated in controlled clinical trials *[see Clinical Studies (14)]*.

8.5 Geriatric Use

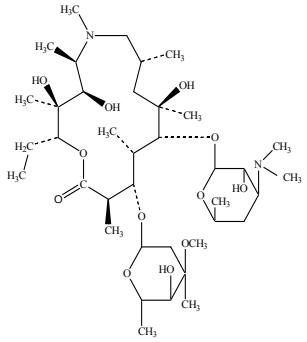
No overall differences in safety or effectiveness have been observed between elderly and younger patients.

11 DESCRIPTION

AzaSite (azithromycin ophthalmic solution) is a 1% sterile aqueous topical ophthalmic solution of azithromycin formulated in DuraSite® (polycarbophil, edetate disodium, sodium chloride). AzaSite is an off-white, viscous liquid with an osmolality of approximately 290 mOsm/kg.

Preservative: 0.003% benzalkonium chloride. **Inactives:** mannitol, citric acid, sodium citrate, poloxamer 407, polycarbophil, edetate disodium (EDTA), sodium chloride, water for injection, and sodium hydroxide to adjust pH to 6.3.

Azithromycin is a macrolide antibiotic with a 15-membered ring. Its chemical name is (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-aza-cyclopentadecan-15-one, and the structural formula is:



Azithromycin has a molecular weight of 749, and its empirical formula is $C_{38}H_{72}N_2O_{12}$.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Azithromycin is a macrolide antibiotic *[see Clinical Pharmacology (12.4)]*.

12.3 Pharmacokinetics

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

12.4 Microbiology

Azithromycin acts by binding to the 50S ribosomal subunit of susceptible microorganisms and interfering with microbial protein synthesis.

Azithromycin has been shown to be active against most isolates of the following microorganisms, both *in vitro* and clinically in conjunctival infections *[see Indications and Usage (1)]*.

CDC coryneform group G*
Haemophilus influenzae
Staphylococcus aureus
Streptococcus mitis group
Streptococcus pneumoniae

**Efficacy for this organism was studied in fewer than 10 infections.*

The following *in vitro* data are also available, **but their clinical significance in ophthalmic infections is unknown.** The safety and effectiveness of AzaSite in treating ophthalmological infections due to these microorganisms have not been established.

The following microorganisms are considered susceptible when evaluated using systemic breakpoints. However, a correlation between the *in vitro* systemic breakpoint and ophthalmological efficacy has not been established. This list of microorganisms is provided as an aid only in assessing the potential treatment of conjunctival infections. Azithromycin exhibits *in vitro* minimal inhibitory concentrations (MICs) of equal or less (systemic susceptible breakpoint) against most (≥90%) of isolates of the following ocular pathogens:

Chlamydia pneumoniae
Chlamydia trachomatis
Legionella pneumophila
Moraxella catarrhalis
Mycoplasma hominis
Mycoplasma pneumoniae
Neisseria gonorrhoeae
Peptostreptococcus species
Streptococci (Groups C, F, G)
Streptococcus pyogenes
Streptococcus agalactiae
Ureaplasma urealyticum
Viridans group streptococci

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term studies in animals have not been performed to evaluate carcinogenic potential. 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.

13.2 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 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.

14 CLINICAL STUDIES

In a randomized, vehicle-controlled, double-blind, multicenter clinical study in which patients were dosed twice daily for the first two days, then once daily on days 3, 4, and 5, AzaSite solution was superior to vehicle on days 6-7 in patients who had a confirmed clinical diagnosis of bacterial conjunctivitis. Clinical resolution was achieved in 63% (82/130) of patients treated with AzaSite versus 50% (74/149) of patients treated with vehicle. The p-value for the comparison was 0.03 and the 95% confidence interval around the 13% (63%-50%) difference was 2% to 25%. The microbiological success rate for the eradication of the baseline pathogens was approximately 88% compared to 66% of patients treated with vehicle ($p<0.001$, confidence interval around the 22% difference was 13% to 31%). Microbiologic eradication does not always correlate with clinical outcome in anti-infective trials.

16 HOW SUPPLIED/STORAGE AND HANDLING

AzaSite is a sterile aqueous topical ophthalmic formulation of 1% azithromycin.

NDC 31357-040-25: 2.5 mL in 5 mL bottle containing a total of 25 mg of azithromycin in a white, round, low-density polyethylene (LDPE) bottle, with a clear LDPE dropper tip, and a tan colored high density polyethylene (HDPE) eyedropper cap. A white tamper evident over-cap is provided.

NDC 31357-040-03: 2.5 mL in 4 mL bottle containing a total of 25 mg azithromycin in a white, round, low-density polyethylene (LDPE) bottle, with a clear LDPE dropper tip, and a tan colored high density polyethylene (HDPE) eyedropper cap. A white tamper evident over-cap is provided.

Storage and Handling:

Store unopened bottle under refrigeration at 2°C to 8°C (36°F to 46°F). Once the bottle is opened, store at 2°C to 25°C (36°F to 77°F) for up to 14 days. Discard after the 14 days.

17 PATIENT COUNSELING INFORMATION

See FDA-Approved Patient Labeling (Patient Information).

Patients should be advised to avoid contaminating the applicator tip by allowing it to touch the eye, fingers or other sources.

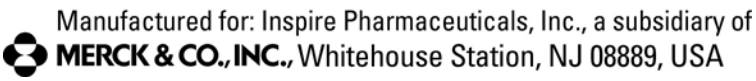
Patients should be directed to discontinue use and contact a physician if any signs of an allergic reaction occur.

Patients should be told that although it is common to feel better early in the course of the therapy, the medication should be taken exactly as directed. Skipping doses or not completing the full course of therapy may (1) decrease the effectiveness of the immediate treatment and (2) increase the likelihood that bacteria will develop resistance and will not be treatable by AzaSite (azithromycin ophthalmic solution) or other antibacterial drugs in the future.

Patients should be advised not to wear contact lenses if they have signs or symptoms of bacterial conjunctivitis.

Patients should be advised to thoroughly wash hands prior to using AzaSite.

Patients should be advised to invert the closed bottle (upside down) and shake once before each use. Remove cap with bottle still in the inverted position. Tilt head back, and with bottle inverted, gently squeeze bottle to instill one drop into the affected eye(s).



Manufactured by:
Catalent Pharma Solutions, LLC
Woodstock, IL 60098

U.S. PAT NO. 6,159,458; 6,239,113; 6,569,443; 6,861,411; 7,056,893; and Patents Pending

AzaSite is a registered trademark of InSite Vision Inc.

Revised: 10/2012

XXXX-XX-XXXXXXXXXXXX

PATIENT INFORMATION
AzaSite® (A-zuh-site)
(azithromycin ophthalmic solution) 1%

Read this Patient Information before you start using AzaSite® and each time you get a refill. There may be new information. This information does not take the place of talking to your doctor about your medical condition or treatment.

What is AzaSite?

AzaSite is a prescription sterile eye drop solution. AzaSite is used to treat bacterial conjunctivitis which is an infection of the eye caused by certain bacteria.

It is not known if AzaSite is safe and effective in children less than 1 year of age.

Information about bacterial conjunctivitis.

Bacterial conjunctivitis is a bacterial infection of the mucous membranes which line the inside of the eyelids. Symptoms may include redness of the eye and discharge. The infection can be spread to other people and to both eyes.

Who should not use AzaSite?

Do not use AzaSite if you are allergic to azithromycin or any of the ingredients in AzaSite. See the end of this Patient Information leaflet for a complete list of the ingredients in AzaSite.

What should I tell my doctor before using AzaSite?

Before you use AzaSite, tell your doctor if you:

- wear contact lenses. Do not wear contact lenses if you have signs or symptoms of bacterial conjunctivitis.
- are pregnant or plan to become pregnant. It is not known if AzaSite will harm your unborn baby. Talk to your doctor if you are pregnant or plan to become pregnant.
- are breast-feeding or plan to breast-feed. It is not known if AzaSite passes into your breast milk. Talk to your doctor about the best way to feed your baby if you are using AzaSite.

Tell your doctor about all the medicines you take, including prescription and non-prescription medicines, vitamins, and herbal supplements.

Know the medicines you take. Keep a list of them to show your doctors and pharmacist when you get a new medicine.

How should I use AzaSite?

- **Read the Instructions for Use at the end of this Patient Information** leaflet for the right way to use AzaSite.
- Use AzaSite exactly as your doctor tells you to use it.

- For the first 2 days place 1 drop of AzaSite in your eye (or eyes) each morning and 1 drop in your eye (or eyes) each evening. Wait 8 to 12 hours after placing your morning drops before you place evening drops in your eye (or eyes).
- For the next 5 days place 1 drop of AzaSite in your eye (or eyes) 1 time each day.
- Make sure you continue to use AzaSite as directed by your doctor even if you feel better after you start using it. Skipping drops can increase the chances that:
    - your medicine will not work well
    - Bacteria can develop resistance, which means in the future your bacterial conjunctivitis may not improve from AzaSite or other drugs that treat infections from bacteria.

What should I be aware of while using AzaSite?

Do not wear contact lenses if you have signs or symptoms of bacterial conjunctivitis and until you have finished your prescribed course of treatment. The symptoms of bacterial conjunctivitis may include:

- discharge coming from the eye
- eye redness
- eye irritation

Only your doctor can tell you if you have bacterial conjunctivitis.

Severe allergic reactions have been reported rarely when azithromycin has been taken by mouth.

- Serious rash or serious allergic reactions may occur. Azithromycin, the active ingredient in AzaSite, may cause a serious rash or a serious allergic reaction. Both of these reactions may need to be treated in a hospital and may be life-threatening.
- Stop taking AzaSite and call your doctor right away or get emergency help if you have any of these symptoms:
    - skin rash, hives, sores in your mouth, or your skin blisters and peels
    - swelling of your face, eyes, lips, tongue, or throat
    - trouble swallowing or breathing

Increased risk of other infections caused by bacteria or fungi.

- Using AzaSite for a long time may cause other bacteria or fungi to grow. If this happens you may get a new infection. Tell your doctor right away if your symptoms do not get better.

What are the possible side effects of AzaSite?

The most common side effect of AzaSite is eye irritation.
Other side effects seen with AzaSite include:

- eye burning, stinging and irritation when the drop hits your eye
- irritation on your eyelid and the skin around your eye
- a feeling of discomfort and irritation or that something is in your eye
- dry eye
- eye pain
- eye itching
- discharge coming from your eye

- changes to the surface of your eye
- blurred vision
- changes in your taste
- hives and rash on your skin
- stuffy nose and sinus infection
- swelling around your eye or of your face

Tell your doctor about any side effect that bothers you or that does not go away.

These are not all of the possible side effects of AzaSite. For more information, ask your doctor or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store AzaSite?

- Before you open your AzaSite, store it in the refrigerator between 36°F to 46°F (2°C to 8°C).
- After you open your AzaSite, store it at room temperature or the refrigerator between 36°F to 77°F (2°C to 25°C).
- **AzaSite should not be stored for more than 14 days after opening. After 14 days, throw the AzaSite bottle away.**
- Safely throw away medicine that is out of date or no longer needed.

Keep AzaSite and all medicines out of reach of children.

General information about the safe and effective use of AzaSite

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. Do not use AzaSite for a condition for which it was not prescribed. Do not give AzaSite to other people, even if they have the same symptoms that you have. It may harm them.

This Patient Information summarizes the most important information about AzaSite. If you would like more information, talk with your doctor. You can ask your pharmacist or doctor for information about AzaSite that is written for health professionals.

For more information, go to www.azasite.com or call 1-800-622-4477.

What are the ingredients in AzaSite?

Active ingredient: azithromycin

Inactive ingredients: 0.003% benzalkonium chloride, mannitol, citric acid, sodium citrate, poloxamer 407, polycarbophil, edetate disodium (EDTA), sodium chloride, water, and sodium hydroxide.

Instructions for Use

AzaSite® (A-zuh-site)

(azithromycin ophthalmic solution) 1%

Read this Instructions for Use for AzaSite before you start using it and each time you get a refill. There may be new information. This leaflet does not take the place of talking to your doctor about your medical condition or treatment.

Important:

- **AzaSite is for use as an eye drop only.**

The checklist below tells you when to use your medicine for each eye that has bacterial conjunctivitis:

□ □	Day 1: _____	1 drop in the morning and 1 drop in the evening
□ □	Day 2: _____	1 drop in the morning and 1 drop in the evening
□	Day 3: _____	1 drop anytime during the day
□	Day 4: _____	1 drop anytime during the day
□	Day 5: _____	1 drop anytime during the day
□	Day 6: _____	1 drop anytime during the day
□	Day 7: _____	1 drop anytime during the day

This is a total of 9 drops of AzaSite for each infected eye.

- Avoid letting the applicator tip touch your eye, your fingers, or other objects.
- If a drop misses your eye, try again.
- Follow the steps below to use AzaSite correctly.

Before using a new bottle of AzaSite:

Figure A

- Turn the white cap clockwise until it comes off. Throw away the white cap. **See Figure A**

Figure B

- Hold the bottle straight, turn the tan cap counterclockwise until it comes off. Put the tan cap back on the bottle and close tightly. (This lets out the air.) **See Figure B**

Wash your hands each time you use AzaSite.

To use AzaSite:

Figure C

Step 1. Turn the closed bottle upside down. **See Figure C**

Figure D

Step 2. Shake your hand firmly. This helps move the medicine into the tip of the bottle. **See Figure D**

Figure E

Step 3. Hold the bottle upside down and take off the tan cap. **See Figure E**

Figure F

Step 4. Tilt your head back. Hold the bottle over your eye and gently squeeze the bottle to let 1 drop into each eye that has bacterial conjunctivitis. Put the tan cap back on the bottle and close tightly. **See Figure F**

If a drop does not come out of the bottle, repeat steps one to four.

This Patient Information and Instructions for Use have been approved by the U.S. Food and Drug Administration.

Manufactured for: Inspire Pharmaceuticals, Inc., a subsidiary of
MERCK & CO., INC., Whitehouse Station, NJ 08889, USA

Manufactured by:
Catalent Pharma Solutions, LLC
Woodstock, IL 60098

AzaSite is a registered trademark of InSite Vision Inc.

Revised: 10/2012

XXXXXXX

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

50-810/S012

MEDICAL REVIEW(S)

Clinical Review of NDA 50-810
Prior Approval Labeling Supplement

NDA 50-810/S-012

SDN-204	**Submission Date:**	December 19, 2011
	Receipt Date:	December 20, 2011
SDN-218	**Submission Date:**	June 18, 2012
	Receipt Date:	June 18, 2012
SDN-225	**Submission Date:**	July 19, 2012
	Receipt Date:	July 19, 2012
SDN-233	**Submission Date:**	September 5, 2012
	Receipt Date:	September 5, 2012
SDN-237	**Submission Date:**	September 25, 2012
	Receipt Date:	September 25, 2012
	Review Date:	September 26, 2012

Applicant: Merck Sharp & Dohme Corp.
P.O. Box 1000
Mail drop: UG2CD48
Upper Gwynedd, PA 19454-2505

Applicant's Representative: Scott Grossman, Ph.D.
Director, Worldwide Regulatory Affairs
267-305-6679

Drug: AzaSite (azithromycin ophthalmic solution) 1%

Pharmacologic Category: macrolide antibiotic

Submitted:

The applicant has submitted a Complete Response to the February 15, 2011, CR Letter for Supplement-012. S-012 proposed a new bottle shape and size, new fill size for professional samples, and alternate resin supplies for the bottle and tip.

On September 2, 2011, the applicant submitted S-013 for the use of resins, from new suppliers, in the manufacture of the current bottle and tip. As a result, this resubmission to S-012 will only address the new bottle shape and size and fill change for professional samples.

On June 15, 2012, Althea Cuff, Regulatory Health Project Manager (ONDQA), informed the applicant that the figures in section 3.2.P.8.1 of the Stability Summary and Conclusion section

did not clearly indicate which line and/or symbol was associated with each batch/configuration. The applicant submitted an amendment (SDN-218) on June 18, 2012, which provides an updated Section 3.2.P.8.1, and includes the figures in color.

On July 5, 2012, Supplement-014 was approved for AzaSite. This sNDA provided for a new contraindication of hypersensitivity and a Patient Package Insert (PPI). In the Approval Letter for S-014, the applicant was instructed to amend all pending supplemental applications with the changes approved in S-014. The applicant submitted an amendment (SDN-225) on July 19, 2012, which provides a revised Package Insert (PI), the current approved PPI, and revised carton labels, consistent with the labeling approved in S-014. Carton labels were revised to remove the storage statement, (b) (4) from the sample carton for professional samples, and updated the legal entity to "Inspire Pharmaceuticals, Inc., a subsidiary of Merck & Co. Inc." on both sample and trade cartons.

On May 15, 2012, Judit Milstein, Chief, Project Management Staff (DTOP), held a discussion with the applicant where she was informed that S-012 was part of a corrective and preventative action plan resulting from a field alert report (FAR), which was issued following the applicant's receipt of reports of the lot number and expiry date, printed on the bottle label, becoming illegible. Similar discussions were held with Dr. William Boyd, Clinical Team Leader (DTOP), on May 15 and 17, 2012.

On August 27, 2012, a telephone discussion was held between the applicant and Althea Cuff and Dr. Li, Chemistry Reviewer (ONDQA), where the Agency requested the addition of the expiry date and lot number to the container label for the proposed new bottle for AzaSite. The Agency also requested that the storage conditions be added to the container label, if the label size permits. If the addition of the storage conditions is not feasible, the applicant was requested to provide rationale explaining why this cannot be done.

The applicant submitted an amendment (SDN-233) on September 5, 2012, in response to the information requested in the August 27, 2012, telephone discussion.

A CMC Review completed September 25, 2012, recommends approval of S-012. Per the CMC Review, the applicant has appropriately addressed the deficiencies outlined in the February 15, 2011, CR Letter.

Following is the current approved Package Insert (PI).

Applicant proposed changes from SDN-225 are shown in track-changes. Applicant proposed additions are noted by underline and deletions by within the review. **Deleted:** strikethrough

Reviewer proposed changes are noted by underline and deletions by within the review. **Deleted:** strikethrough

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use AzaSite safely and effectively. See full prescribing information for AzaSite.

AzaSite® (azithromycin ophthalmic solution) 1%
Sterile topical ophthalmic drops
Initial U.S. Approval: 2007

---------- RECENT MAJOR CHANGES ----------
Contraindications (4) 07/2012

---------- INDICATIONS AND USAGE ----------
AzaSite is a macrolide antibiotic indicated for the treatment of bacterial conjunctivitis caused by susceptible isolates of the following microorganisms: CDC coryneform group G, *Haemophilus influenzae, Staphylococcus aureus, Streptococcus mitis* group, and *Streptococcus pneumoniae.* (1)

---------- 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. (2)

---------- DOSAGE FORMS AND STRENGTHS ----------
2.5 mL of 1% sterile topical ophthalmic solution. (3)

---------- CONTRAINDICATIONS ----------
Hypersensitivity (4)

---------- WARNING AND PRECAUTIONS ----------
- For topical ophthalmic use only. (5.1)
- Anaphylaxis and hypersensitivity have been reported with systemic use of azithromycin. (5.2)
- Growth of resistant organisms may occur with prolonged use. (5.3)
- Patients should not wear contact lenses if they have signs or symptoms of bacterial conjunctivitis. (5.4)

---------- ADVERSE REACTIONS ----------
Most common adverse reaction reported in patients was eye irritation (1-2% of patients). (6)

To report SUSPECTED ADVERSE REACTIONS, contact Inspire Pharmaceuticals, Inc., a subsidiary of Merck & Co., Inc., at 1-800-672-6372 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 10/2012

Deleted: 07/2012
Deleted: XX
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Deleted: 5 mL size bottle filled with

FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

AzaSite® is indicated for the treatment of bacterial conjunctivitis caused by susceptible isolates of the following microorganisms:

CDC coryneform group G*
Haemophilus influenzae
Staphylococcus aureus
Streptococcus mitis group
Streptococcus pneumoniae

**Efficacy for this organism was studied in fewer than 10 infections.*

2 DOSAGE AND ADMINISTRATION

The recommended dosage regimen for the treatment of bacterial conjunctivitis is:

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.

3 DOSAGE FORMS AND STRENGTHS

2.5 mL of a 1% sterile topical ophthalmic solution.

Deleted: 5 mL bottle containing

Reviewer's Comment: *The applicant has proposed a revision to Section 3 Dosage Forms and Strengths in both the Highlights and the Full Prescribing Information. This is acceptable.*

4 CONTRAINDICATIONS

Hypersensitivity to any component of this product.

5 WARNINGS AND PRECAUTIONS

5.1 Topical Ophthalmic Use Only

NOT FOR INJECTION. AzaSite is indicated for topical ophthalmic use only, and should not be administered systemically, injected subconjunctivally, or introduced directly into the anterior chamber of the eye.

5.2 Anaphylaxis and Hypersensitivity with Systemic Use of Azithromycin

In patients receiving systemically administered azithromycin, serious allergic reactions, including angioedema, anaphylaxis, and dermatologic reactions including Stevens-Johnson syndrome and toxic epidermal necrolysis have been reported rarely in patients on azithromycin therapy. Although rare, fatalities have been reported. The potential for anaphylaxis or other hypersensitivity reactions should be considered based on known hypersensitivity to azithromycin when administered systemically.

5.3 Growth of Resistant Organisms with Prolonged Use

As with other anti-infectives, prolonged use may result in overgrowth of non-susceptible organisms, including fungi. If super-infection occurs, discontinue use and institute alternative therapy. Whenever clinical judgment dictates, the patient should be examined with the aid of magnification, such as slit-lamp biomicroscopy, and where appropriate, fluorescein staining.

5.4 Avoidance of Contact Lenses

Patients should be advised not to wear contact lenses if they have signs or symptoms of bacterial conjunctivitis.

6 ADVERSE REACTIONS

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in one clinical trial of a drug cannot be directly compared with the rates in the clinical trials of the same or another drug and may not reflect the rates observed in practice.

The data described below reflect exposure to AzaSite in 698 patients. The population was between 1 and 87 years old with clinical signs and symptoms of bacterial conjunctivitis. The most frequently reported ocular adverse reaction reported in patients receiving AzaSite was eye irritation. This reaction occurred in approximately 1-2% of patients. Other adverse reactions associated with the use of AzaSite were reported in less than 1% of patients and included ocular reactions (blurred vision, burning, stinging and irritation upon instillation, contact dermatitis, corneal erosion, dry eye, eye pain, itching, ocular discharge, punctate keratitis, visual acuity reduction) and non-ocular reactions (dysgeusia, facial swelling, hives, nasal congestion, periocular swelling, rash, sinusitis, urticaria).

8 USE IN SPECIFIC POPULATIONS

8.1 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. These doses are estimated to be approximately 5,000 times the maximum human ocular daily dose of 2 mg. In the animal studies, no evidence of harm to the fetus due to azithromycin was found. 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.

8.3 Nursing Mothers

It is not known whether azithromycin is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when azithromycin is administered to a nursing woman.

8.4 Pediatric Use

The safety and effectiveness of AzaSite solution in pediatric patients below 1 year of age have not been established. The efficacy of AzaSite in treating bacterial conjunctivitis in pediatric

patients one year or older has been demonstrated in controlled clinical trials *[see Clinical Studies (14)]*.

8.5 Geriatric Use

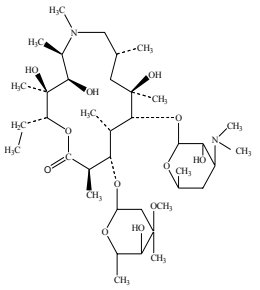
No overall differences in safety or effectiveness have been observed between elderly and younger patients.

11 DESCRIPTION

AzaSite (azithromycin ophthalmic solution) is a 1% sterile aqueous topical ophthalmic solution of azithromycin formulated in DuraSite® (polycarbophil, edetate disodium, sodium chloride). AzaSite is an off-white, viscous liquid with an osmolality of approximately 290 mOsm/kg.

Preservative: 0.003% benzalkonium chloride. **Inactives:** mannitol, citric acid, sodium citrate, poloxamer 407, polycarbophil, edetate disodium (EDTA), sodium chloride, water for injection, and sodium hydroxide to adjust pH to 6.3.

Azithromycin is a macrolide antibiotic with a 15-membered ring. Its chemical name is (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-aza-cyclopentadecan-15-one, and the structural formula is:



Azithromycin has a molecular weight of 749, and its empirical formula is $C_{38}H_{72}N_2O_{12}$.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Azithromycin is a macrolide antibiotic *[see Clinical Pharmacology (12.4)]*.

12.3 Pharmacokinetics

The plasma concentration of azithromycin following ocular administration of AzaSite (azithromycin ophthalmic solution) in humans is unknown. Based on the proposed dose of one drop to each eye (total dose of 100 mcL or 1 mg) and exposure information from systemic administration, the systemic concentration of azithromycin following ocular administration is

estimated to be below quantifiable limits (≤10 ng/mL) at steady-state in humans, assuming 100% systemic availability.

12.4 Microbiology

Azithromycin acts by binding to the 50S ribosomal subunit of susceptible microorganisms and interfering with microbial protein synthesis.

Azithromycin has been shown to be active against most isolates of the following microorganisms, both *in vitro* and clinically in conjunctival infections *[see Indications and Usage (1)]*.

CDC coryneform group G*
Haemophilus influenzae
Staphylococcus aureus
Streptococcus mitis group
Streptococcus pneumoniae

**Efficacy for this organism was studied in fewer than 10 infections.*

The following *in vitro* data are also available, **but their clinical significance in ophthalmic infections is unknown.** The safety and effectiveness of AzaSite in treating ophthalmological infections due to these microorganisms have not been established.

The following microorganisms are considered susceptible when evaluated using systemic breakpoints. However, a correlation between the *in vitro* systemic breakpoint and ophthalmological efficacy has not been established. This list of microorganisms is provided as an aid only in assessing the potential treatment of conjunctival infections. Azithromycin exhibits *in vitro* minimal inhibitory concentrations (MICs) of equal or less (systemic susceptible breakpoint) against most (≥90%) of isolates of the following ocular pathogens:

Chlamydia pneumoniae
Chlamydia trachomatis
Legionella pneumophila
Moraxella catarrhalis
Mycoplasma hominis
Mycoplasma pneumoniae
Neisseria gonorrhoeae
Peptostreptococcus species
Streptococci (Groups C, F, G)
Streptococcus pyogenes
Streptococcus agalactiae
Ureaplasma urealyticum
Viridans group streptococci

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term studies in animals have not been performed to evaluate carcinogenic potential. 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.

13.2 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 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.

14 CLINICAL STUDIES

In a randomized, vehicle-controlled, double-blind, multicenter clinical study in which patients were dosed twice daily for the first two days, then once daily on days 3, 4, and 5, AzaSite solution was superior to vehicle on days 6-7 in patients who had a confirmed clinical diagnosis of bacterial conjunctivitis. Clinical resolution was achieved in 63% (82/130) of patients treated with AzaSite versus 50% (74/149) of patients treated with vehicle. The p-value for the comparison was 0.03 and the 95% confidence interval around the 13% (63%-50%) difference was 2% to 25%. The microbiological success rate for the eradication of the baseline pathogens was approximately 88% compared to 66% of patients treated with vehicle ($p<0.001$, confidence interval around the 22% difference was 13% to 31%). Microbiologic eradication does not always correlate with clinical outcome in anti-infective trials.

16 HOW SUPPLIED/STORAGE AND HANDLING

AzaSite is a sterile aqueous topical ophthalmic formulation of 1% azithromycin.

NDC 31357-040-25: 2.5 mL in 5 mL bottle containing a total of 25 mg of azithromycin in a white, round, low-density polyethylene (LDPE) bottle, with a clear LDPE dropper tip, and a tan colored high density polyethylene (HDPE) eyedropper cap. A white tamper evident over-cap is provided.

NDC 31357-040-03: 2.5 mL in 4 mL bottle containing a total of 25 mg azithromycin in a white, round, low-density polyethylene (LDPE) bottle, with a clear LDPE dropper tip, and a tan colored high density polyethylene (HDPE) eyedropper cap. A white tamper evident over-cap is provided.

Deleted: in a white, round, low-density polyethylene (LDPE) bottle, with a natural LDPE dropper tip, and a tan colored high density polyethylene (HDPE) eyedropper cap A white tamper evident overcap is provided

Reviewer's Comment: *The applicant has revised the language in Section 16 How Supplied/Storage and Handling to reflect its proposal to add a new bottle shape and size.*

Deleted: 2 5 mL in 5 mL bottle containing a total of 25 mg of azithromycin (NDC 31357-040-25)¶

From a Clinical perspective, the new 4 mL bottle is acceptable. CMC provided concurrence in the September 25, 2012, CMC Review; refer to the CMC Review for further details.

Storage and Handling:

Store unopened bottle under refrigeration at 2°C to 8°C (36°F to 46°F). Once the bottle is opened, store at 2°C to 25°C (36°F to 77°F) for up to 14 days. Discard after the 14 days.

17 PATIENT COUNSELING INFORMATION

See FDA-Approved Patient Labeling (Patient Information).

Patients should be advised to avoid contaminating the applicator tip by allowing it to touch the eye, fingers or other sources.

Patients should be directed to discontinue use and contact a physician if any signs of an allergic reaction occur.

Patients should be told that although it is common to feel better early in the course of the therapy, the medication should be taken exactly as directed. Skipping doses or not completing the full course of therapy may (1) decrease the effectiveness of the immediate treatment and (2) increase the likelihood that bacteria will develop resistance and will not be treatable by AzaSite (azithromycin ophthalmic solution) or other antibacterial drugs in the future.

Patients should be advised not to wear contact lenses if they have signs or symptoms of bacterial conjunctivitis.

Patients should be advised to thoroughly wash hands prior to using AzaSite.

Patients should be advised to invert the closed bottle (upside down) and shake once before each use. Remove cap with bottle still in the inverted position. Tilt head back, and with bottle inverted, gently squeeze bottle to instill one drop into the affected eye(s).

Manufactured for: Inspire Pharmaceuticals, Inc., a subsidiary of
MERCK & CO., INC., Whitehouse Station, NJ 08889, USA

Manufactured by:
Catalent Pharma Solutions, LLC
Woodstock, IL 60098

U.S. PAT NO. 6,159,458; 6,239,113; 6,569,443; 6,861,411; 7,056,893; and Patents Pending

AzaSite is a registered trademark of InSite Vision Inc.

Revised: XX/XXXX

Deleted: 07/2012

XXXX-XX-XXXXXXXXXXXX

PATIENT INFORMATION
AzaSite® (A-zuh-site)
(azithromycin ophthalmic solution) 1%

Read this Patient Information before you start using AzaSite® and each time you get a refill. There may be new information. This information does not take the place of talking to your doctor about your medical condition or treatment.

What is AzaSite?

AzaSite is a prescription sterile eye drop solution. AzaSite is used to treat bacterial conjunctivitis which is an infection of the eye caused by certain bacteria.

It is not known if AzaSite is safe and effective in children less than 1 year of age.

Information about bacterial conjunctivitis.

Bacterial conjunctivitis is a bacterial infection of the mucous membranes which line the inside of the eyelids. Symptoms may include redness of the eye and discharge. The infection can be spread to other people and to both eyes.

Who should not use AzaSite?

Do not use AzaSite if you are allergic to azithromycin or any of the ingredients in AzaSite. See the end of this Patient Information leaflet for a complete list of the ingredients in AzaSite.

What should I tell my doctor before using AzaSite?

Before you use AzaSite, tell your doctor if you:

- wear contact lenses. Do not wear contact lenses if you have signs or symptoms of bacterial conjunctivitis.
- are pregnant or plan to become pregnant. It is not known if AzaSite will harm your unborn baby. Talk to your doctor if you are pregnant or plan to become pregnant.
- are breast-feeding or plan to breast-feed. It is not known if AzaSite passes into your breast mi k. Talk to your doctor about the best way to feed your baby if you are using AzaSite.

Tell your doctor about all the medicines you take, including prescription and non-prescription medicines, vitamins, and herbal supplements.

Know the medicines you take. Keep a list of them to show your doctors and pharmacist when you get a new medicine.

How should I use AzaSite?

- **Read the Instructions for Use at the end of this Patient Information** leaflet for the right way to use AzaSite.
- Use AzaSite exactly as your doctor tells you to use it.

- For the first 2 days place 1 drop of AzaSite in your eye (or eyes) each morning and 1 drop in your eye (or eyes) each evening. Wait 8 to 12 hours after placing your morning drops before you place evening drops in your eye (or eyes).
- For the next 5 days place 1 drop of AzaSite in your eye (or eyes) 1 time each day.
- Make sure you continue to use AzaSite as directed by your doctor even if you feel better after you start using it. Skipping drops can increase the chances that:
    - your medicine will not work well
    - Bacteria can develop resistance, which means in the future your bacterial conjunctivitis may not improve from AzaSite or other drugs that treat infections from bacteria.

What should I be aware of while using AzaSite?

Do not wear contact lenses if you have signs or symptoms of bacterial conjunctivitis and until you have finished your prescribed course of treatment. The symptoms of bacterial conjunctivitis may include:

- discharge coming from the eye
- eye redness
- eye irritation

Only your doctor can tell you if you have bacterial conjunctivitis.

Severe allergic reactions have been reported rarely when azithromycin has been taken by mouth.

- Serious rash or serious allergic reactions may occur. Azithromycin, the active ingredient in AzaSite, may cause a serious rash or a serious allergic reaction. Both of these reactions may need to be treated in a hospital and may be life-threatening.
- Stop taking AzaSite and call your doctor right away or get emergency help if you have any of these symptoms:
    - skin rash, hives, sores in your mouth, or your skin blisters and peels
    - swelling of your face, eyes, lips, tongue, or throat
    - trouble swallowing or breathing

Increased risk of other infections caused by bacteria or fungi.

- Using AzaSite for a long time may cause other bacteria or fungi to grow. If this happens you may get a new infection. Tell your doctor right away if your symptoms do not get better.

What are the possible side effects of AzaSite?

The most common side effect of AzaSite is eye irritation.
Other side effects seen with AzaSite include:

- eye burning, stinging and irritation when the drop hits your eye
- irritation on your eyelid and the skin around your eye
- a feeling of discomfort and irritation or that something is in your eye
- dry eye
- eye pain
- eye itching
- discharge coming from your eye

- changes to the surface of your eye
- blurred vision
- changes in your taste
- hives and rash on your skin
- stuffy nose and sinus infection
- swelling around your eye or of your face

Tell your doctor about any side effect that bothers you or that does not go away.

These are not all of the possible side effects of AzaSite. For more information, ask your doctor or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store AzaSite?

- Before you open your AzaSite, store it in the refrigerator between 36°F to 46°F (2°C to 8°C).
- After you open your AzaSite, store it at room temperature or the refrigerator between 36°F to 77°F (2°C to 25°C).
- **AzaSite should not be stored for more than 14 days after opening. After 14 days, throw the AzaSite bottle away.**
- Safely throw away medicine that is out of date or no longer needed.

Keep AzaSite and all medicines out of reach of children.

General information about the safe and effective use of AzaSite

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. Do not use AzaSite for a condition for which it was not prescribed. Do not give AzaSite to other people, even if they have the same symptoms that you have. It may harm them.

This Patient Information summarizes the most important information about AzaSite. If you would like more information, talk with your doctor. You can ask your pharmacist or doctor for information about AzaSite that is written for health professionals.

For more information, go to www.azasite.com or call 1-800-622-4477.

What are the ingredients in AzaSite?

Active ingredient: azithromycin

Inactive ingredients: 0.003% benzalkonium chloride, mannitol, citric acid, sodium citrate, poloxamer 407, polycarbophil, edetate disodium (EDTA), sodium chloride, water, and sodium hydroxide.

Instructions for Use

AzaSite® (A-zuh-site)

(azithromycin ophthalmic solution) 1%

Read this Instructions for Use for AzaSite before you start using it and each time you get a refill. There may be new information. This leaflet does not take the place of talking to your doctor about your medical condition or treatment.

Important:

- **AzaSite is for use as an eye drop only.**

The checklist below tells you when to use your medicine for each eye that has bacterial conjunctivitis:

□ □	Day 1: _____	1 drop in the morning and 1 drop in the evening
□ □	Day 2: _____	1 drop in the morning and 1 drop in the evening
□	Day 3: _____	1 drop anytime during the day
□	Day 4: _____	1 drop anytime during the day
□	Day 5: _____	1 drop anytime during the day
□	Day 6: _____	1 drop anytime during the day
□	Day 7: _____	1 drop anytime during the day

This is a total of 9 drops of AzaSite for each infected eye.

- Avoid letting the applicator tip touch your eye, your fingers, or other objects.
- If a drop misses your eye, try again.
- Follow the steps below to use AzaSite correctly.

Before using a new bottle of AzaSite:

Figure A

- Turn the white cap clockwise until it comes off. Throw away the white cap. **See Figure A**

Figure B

- Hold the bottle straight, turn the tan cap counterclockwise until it comes off. Put the tan cap back on the bottle and close tightly. (This lets out the air.) **See Figure B**

Wash your hands each time you use AzaSite.

To use AzaSite:

Figure C

Figure D

Step 1. Turn the closed bottle upside down. **See Figure C**

Step 2. Shake your hand firmly. This helps move the medicine into the tip of the bottle. **See Figure D**

Figure E

Figure F

Step 3. Hold the bottle upside down and take off the tan cap. **See Figure E**

Step 4. Tilt your head back. Hold the bottle over your eye and gently squeeze the bottle to let 1 drop into each eye that has bacterial conjunctivitis. Put the tan cap back on the bottle and close tightly. **See Figure F**

If a drop does not come out of the bottle, repeat steps one to four.

This Patient Information and Instructions for Use have been approved by the U.S. Food and Drug Administration.

Manufactured for: Inspire Pharmaceuticals, Inc., a subsidiary of
MERCK & CO., INC., Whitehouse Station, NJ 08889, USA

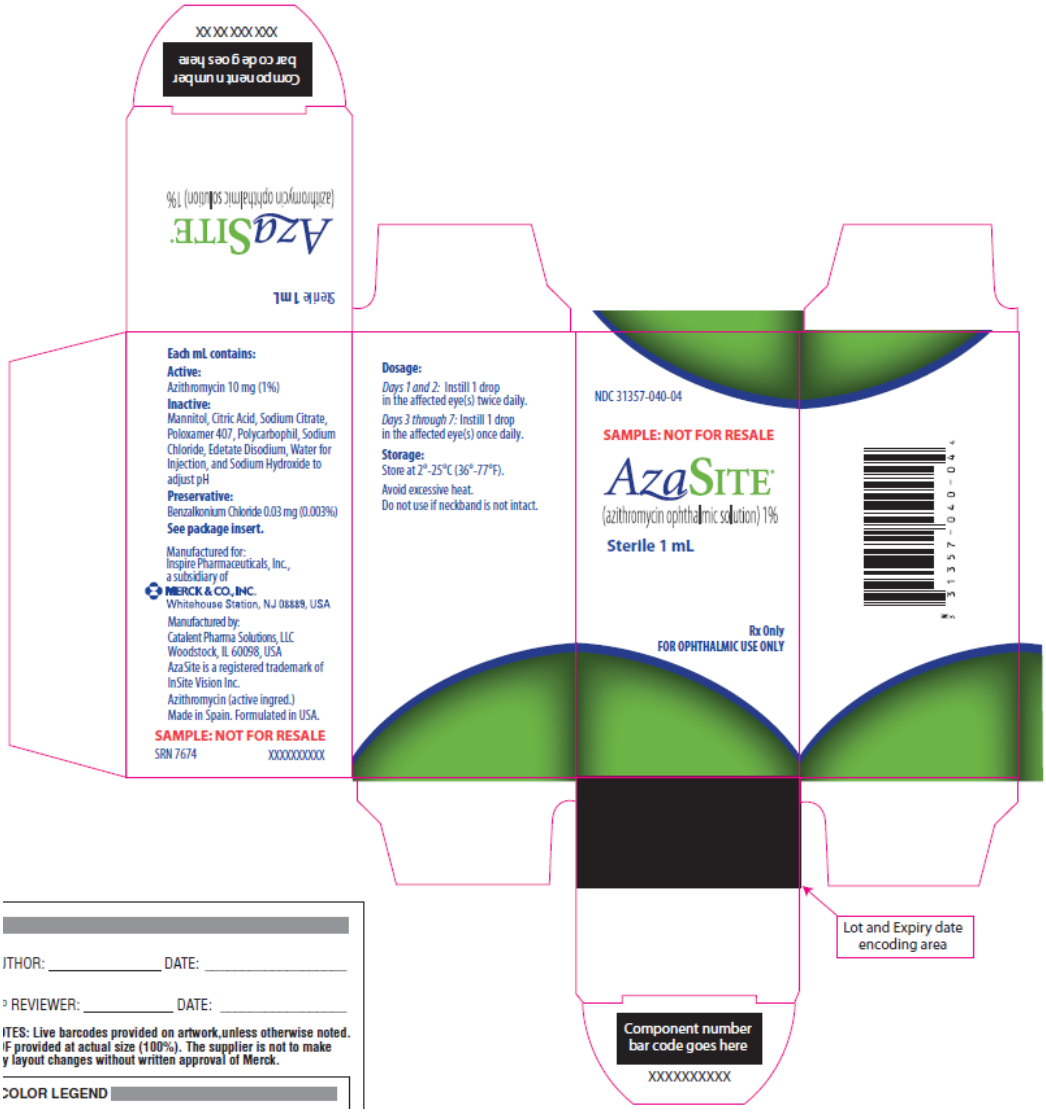
Manufactured by:
Catalent Pharma Solutions, LLC
Woodstock, IL 60098

AzaSite is a registered trademark of InSite Vision Inc.

Revised: XX/XXXX

XXXXXXX

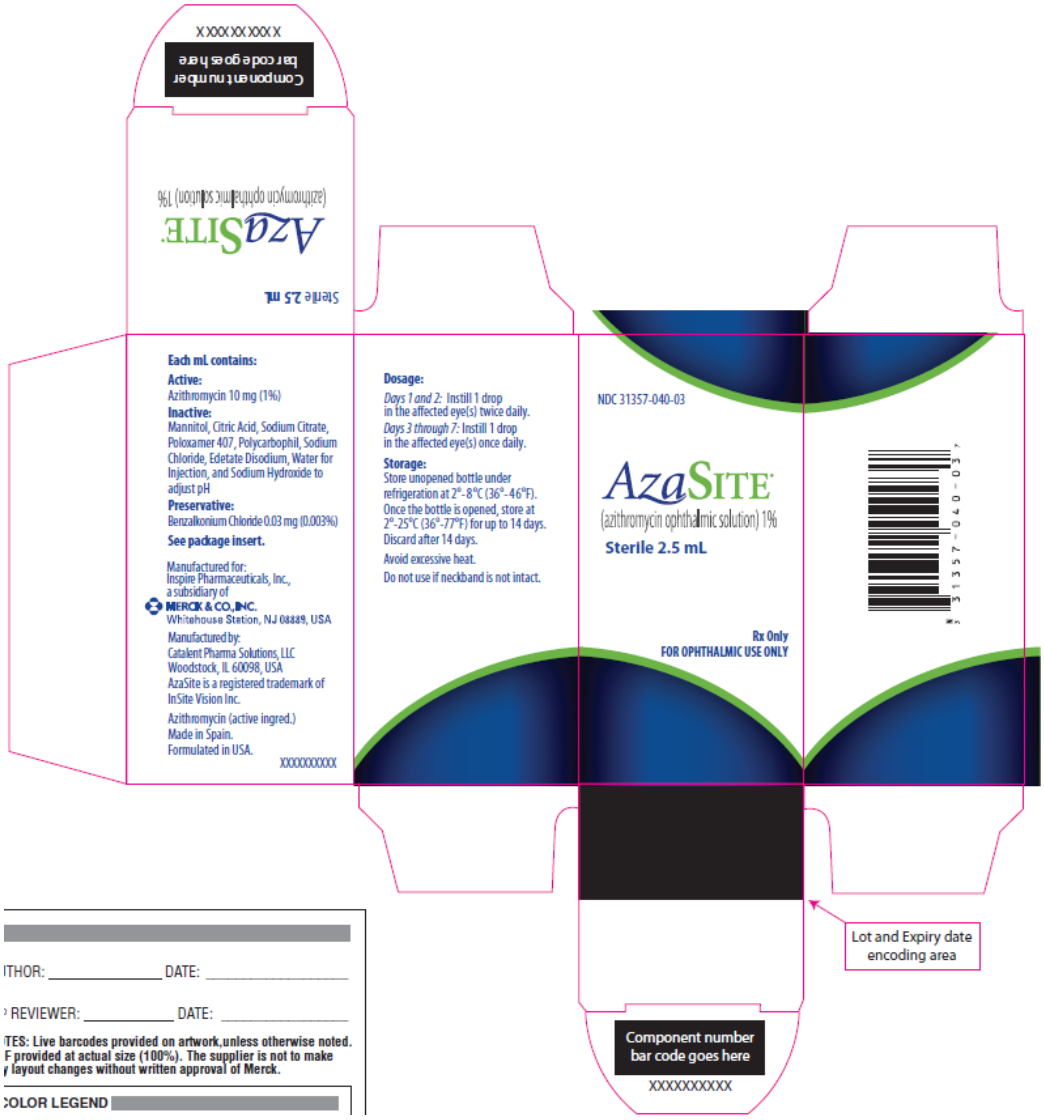
Proposed 1 mL Sample Carton from the July 19, 2012, submission:



Reviewer's Comment:

The proposed 1 mL Sample Carton from the July 19, 2012, submission is acceptable.

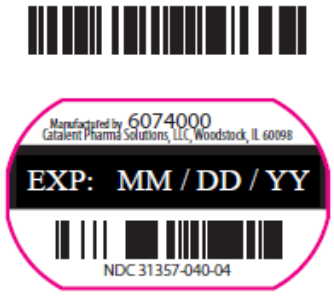
Proposed 2.5 mL in the 4 mL bottle Trade Carton from the July 19, 2012, submission:



Reviewer's Comments:

The proposed 2.5 mL Trade Carton from the July 19, 2012, submission is acceptable.

Proposed Back Label for the 1 mL Sample Container Label submitted September 5, 2012:



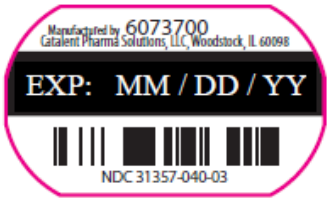
Reviewer's Comment:
The proposed Back Label for the 1 mL Sample Container Label submitted September 5, 2012, has been revised to include the expiry date and lot number. This is acceptable.

Due to space limitations, the applicant has proposed to not add the storage statement to the container label as was originally requested by ONDQA in the August 27, 2012, telephone discussion. The September 25, 2012, CMC Review provides concurrence; this is acceptable.

Proposed Front Label for the 1 mL Sample Container Label submitted September 5, 2012:

Reviewer's Comment:
The proposed Front Label for the 1 mL Sample Container Label submitted September 5, 2012, is acceptable.

Proposed Back Label for the 2.5 mL in a 4 mL bottle Trade Container Label submitted September 5, 2012:



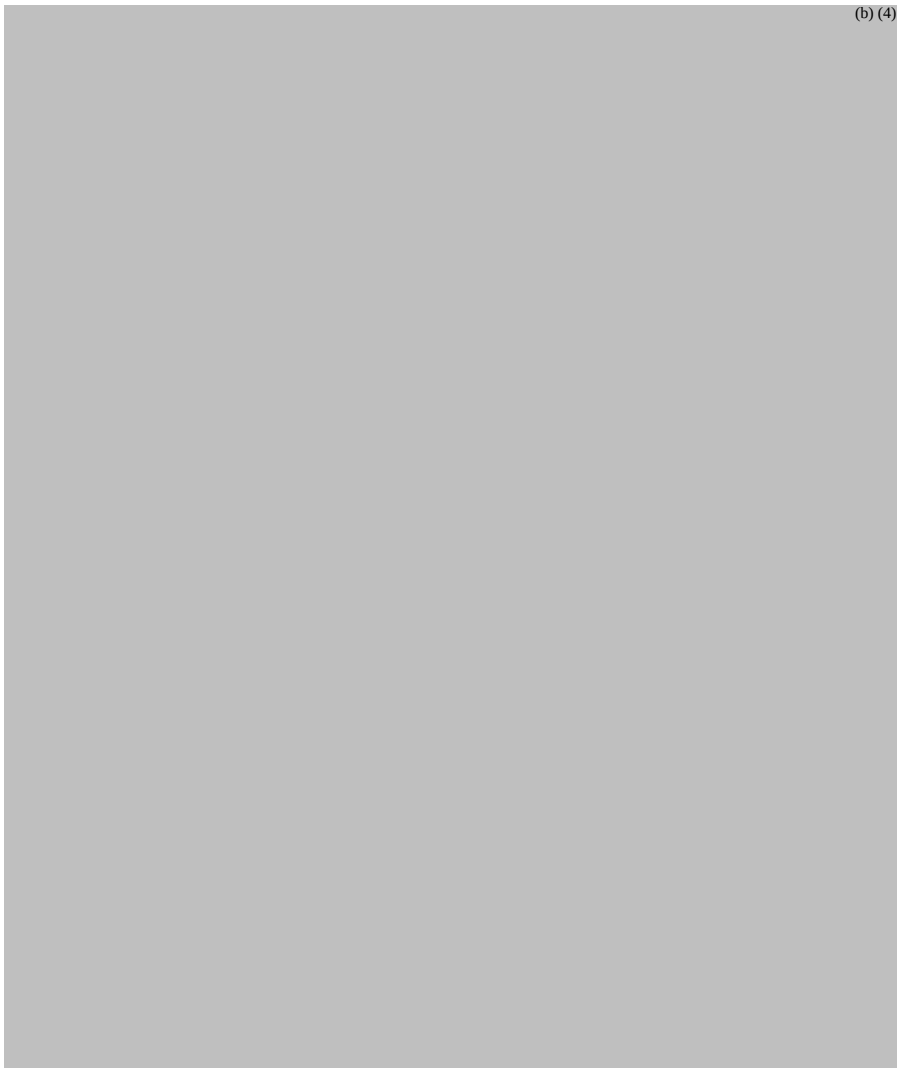
Reviewer's Comment:
The proposed Back Label for the 2.5 mL Trade Container Label submitted September 5, 2012, has been revised to include the expiry date and lot number. This is acceptable.

Due to space limitations, the applicant has proposed to not add the storage statement to the container label as was originally requested by ONDQA in the August 27, 2012, telephone discussion. The September 25, 2012, CMC Review provides concurrence; this is acceptable.

Proposed Front Label for the 2.5 mL in a 4 mL bottle Trade Container Label submitted September 5, 2012:

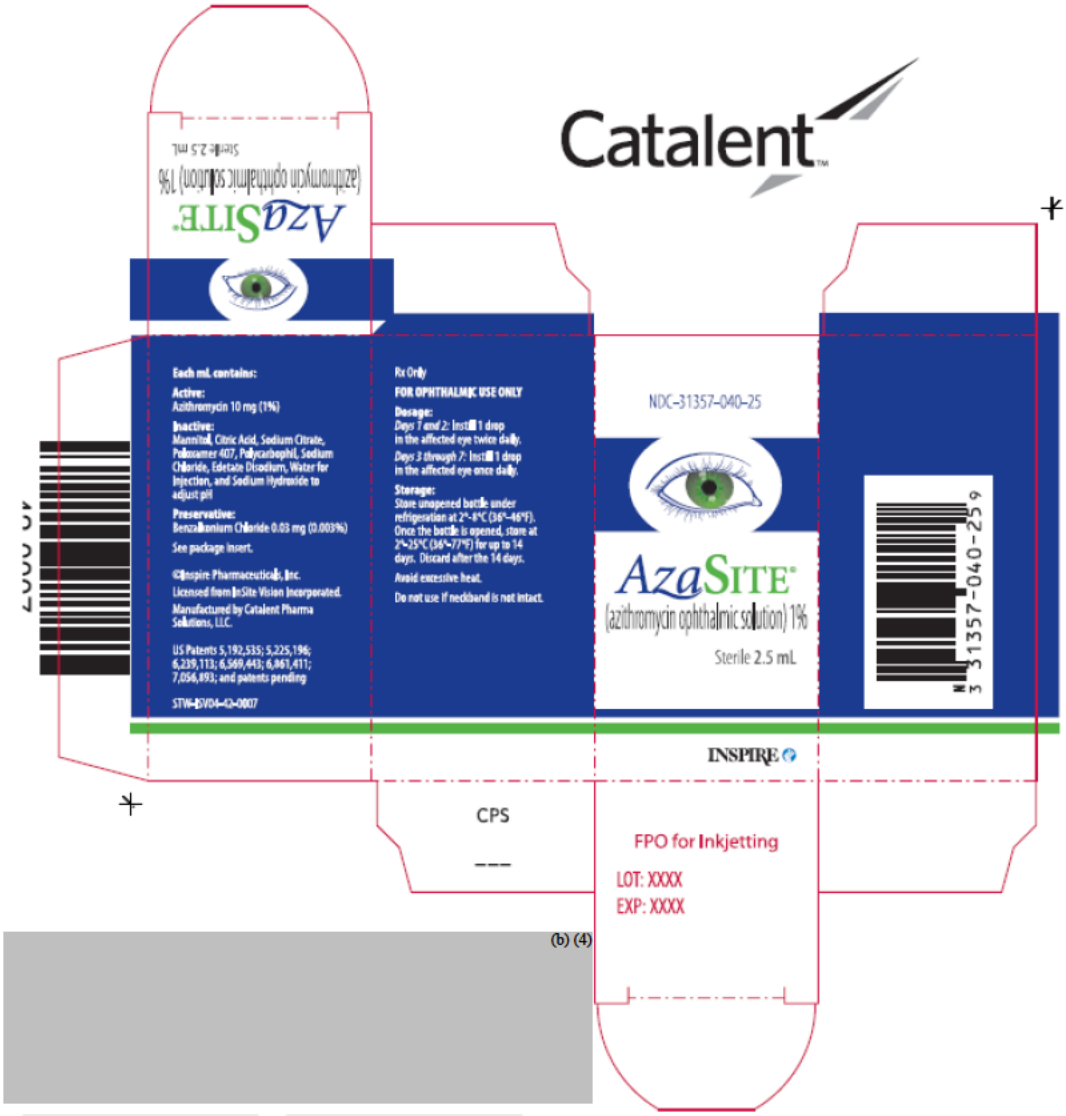
Reviewer's Comment:
The proposed Front Label for the 2.5 mL Trade Container Label submitted September 5, 2012, is acceptable.

Proposed Bottle showing an embossed lot number submitted September 5, 2012:



Reviewer's Comment:
The CMC Review had no objection to the proposed bottle with the embossed lot number. This is acceptable.

Current Trade Carton for the 2.5 mL in a 5 mL bottle presentation:



Reviewer's Comments:

The applicant submitted an amendment, SDN-237, on September 25, 2012, which provides the carton and container labels for the 5 mL bottle presentation. The carton label for the Trade presentation of 2.5 mL in a 5 mL bottle is acceptable.

Current Container Label for the 2.5 mL in a 5 mL bottle presentation:

Reviewer's Comments:

The applicant submitted an amendment, SDN-237, on September 25, 2012, which provides the carton and container labels for the 5 mL bottle presentation. The container label for the Trade presentation of 2.5 mL in a 5 mL bottle is acceptable.

Recommendations:
This supplement is recommended for approval.

Leanna M. Kelly
Consumer Safety Officer

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/s/

LEANNA M KELLY
10/05/2012

WILLIAM M BOYD
10/09/2012

Clinical Review of NDA 50-810
Prior Approval Supplement

NDA 50-810/S-012
SDN-75

Submission Date: October 14, 2010
Receipt Date: October 15, 2010
Review Date: February 3, 2011

Applicant: Inspire Pharmaceuticals, Inc.
4222 Emperor Blvd, Suite 200
Durham, NC 27703

Applicant's Representative: Kimberly A. Davis
919-941-9777

Drug: Azasite (azithromycin ophthalmic solution) 1%

Pharmacologic Category: macrolide antibiotic

Submitted:

From the cover letter:

> In accordance with 21 CRF § 314.70 (e), Inspire is submitting this Prior Approval Supplement (PAS) to seek approval of the enclosed comparability protocol to demonstrate the suitability of the drug product in the new container/closure system as a result of the change in shape and size of the bottle and suitability of the drug product filled at a fill size of 1mL in this new container/closure system.
>
> Inspire is submitting this PAS to seek approval of the enclosed *Comparability Protocol: Plan for Assessing the Impact of Changes to the Container Closure System for AzaSite (azithromycin ophthalmic solution),* 1% *Drug Product.* The Comparability Protocol provides a full description of the planned changes, proposed assessments and studies, stability plan and evaluation, test data and post-approval stability protocol and commitment. Upon approval of the PAS by the Agency, Inspire will submit the data collected and required container labeling changes as a Changes Being Effected in 30 Days (CBE-30) Supplement.
>
> This comparability protocol has been drafted in accordance with the February 2003 Draft Guidance for Industry: *'Comparability Protocols - Chemistry, Manufacturing and Controls.'* This comparability protocol is being submitted pursuant to Inspire Pharmaceuticals, Inc. discussion with the Agency. Inspire has incorporated the Division's requests in the attached PAS.

Reviewer's Comments:

This supplement requests approval of a comparability protocol to assess a change in the container/closure system including fill size of Azasite.

This is not the proper method for seeking approval of a new container/closure system (and thus a new fill size).

A Prior Approval Supplement should be submitted to the New Drug Application when there is a change in the container/closure system or fill size for an ophthalmic product because it may affect the handling of the product and the ability of patients to properly dose the product. The supplement should include a justification for the new fill size, and proposed labeling.

Recommendation:

This supplement is not recommended for approval.

The Complete Response letter should state that a prior approval supplement is needed for any change to an ophthalmic container/closure system or fill size. The supplement should include data to support the comparability of the container/closure system, a clinical justification for the new fill size, and the proposed labeling.

William M. Boyd, M.D.
Clinical Team Leader

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/s/

WILLIAM M BOYD
02/03/2011

WILEY A CHAMBERS
02/07/2011

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

50-810/S012

CHEMISTRY REVIEW(S)

810Chemistry Review: #1	**a. Division:** HFD-520	**b. NDA Number:** **50-810**

c. Name and Address of Applicant:
Inspire Pharmaceuticals, Inc.
4222 Emperor Boulevard, Suite 200
Durham, NC 27703-8466

4. Supplement(s): PA
Number: 012 resubmission
Date(s): 19 Dec 2011 (Letter Date)
20 Dec 2011 (CDER received)
15 May 2012 (Reviewer received)
20 Apr 2012 (PDUFA)

5. Name of Drug:
AzaSite® (azithromycin ophthalmic solution) 1%

6. Nonproprietary name:
Azithromycin, Azithromycin monohydrate

7.Supplement Provides for
a comparability protocol to demonstrate the suitability of the drug product in the new container/closure system as a result of the change in shape/size of the bottle and suitability of the DP filled at a fill size of 1 mL in this new container closure

8. Amendment(s):
Quality/Quality info submitted on 06/18/2012
Labeling/Package insert submitted on 07/25/2012

9. Pharmacological Category:
Antibiotic

10. How Dispensed:
R_x

11. Related Documents:
S011 resubmission review
S013 review

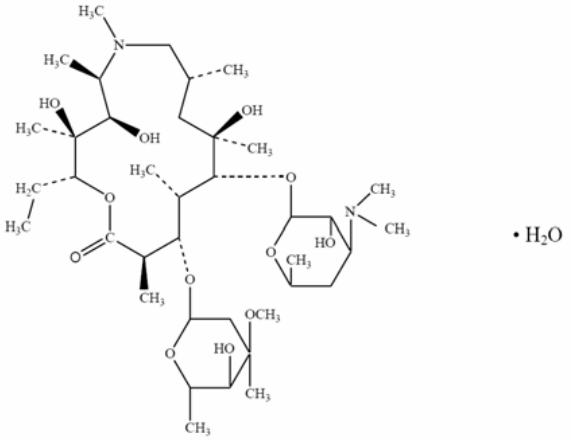
12. Dosage Form:
Ophthalmic solution

13. Potency:
1%

14. Chemical Name and Structure:
(2R,3S,4R,5R,8R,10R,11R,12S,13S,14R)-13-[(2,6-dideoxy-3-C-methyl-3-O-methyl-a- Lribo-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-azacyclopentadecan-15-one. monohydrate

Molecular Formula
$C_{38}H_{72}N_2O_{12}•H_2O$

Molecular Weight
azithromycin monohydrate: 767
azithromycin: 749



15. Comments
This is a resubmission in response to CR letter to S-012 issued on 15 Feb 2011. The information provided in this resubmission appropriately addressed the deficiencies outline S-012 CR letter.

16. Conclusion:
This resubmission is recommended for Approval from CMC perspective.

17. Name: **Signature:** **Date:**
Xuhong Li, Ph.D., Chemist

18. Concurrence: **Signature:** **Date:**
Thomas F. Oliver, Ph.D., Branch Chief, Branch VI, ONDQA

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/s/

XUHONG LI
09/24/2012

THOMAS F OLIVER
09/25/2012

Chemistry Review: #1	**a. Division:** HFD-520	**b. NDA Number:** 50-810

c. Name and Address of Applicant:
Inspire Pharmaceuticals, Inc.
4222 Emperor Boulevard, Suite 200
Durham, NC 27703-8466

4. Supplement(s): PA
Number: 012
Date(s): 15 Oct 2010 (CDER received)
22 Nov 2010 (Reviewer received)
15 Feb 2011 (PDUFA)

5. Name of Drug:
AzaSite® (azithromycin ophthalmic solution) 1%

6. Nonproprietary name:
Azithromycin, Azithromycin monohydrate

7.Supplement Provides for
To seek approval a comparability protocol to demonstrate the suitability of the drug product in the new container/closure system in two fill configuration: 2.5 mL for commercial and 1 mL for professional samples.

8. Amendment(s):
NA

9. Pharmacological Category:
Antibiotic

10. How Dispensed:
R_x

11. Related Documents:
Quality Micro review
DMF (b) (4) review
DMF (b) (4) review

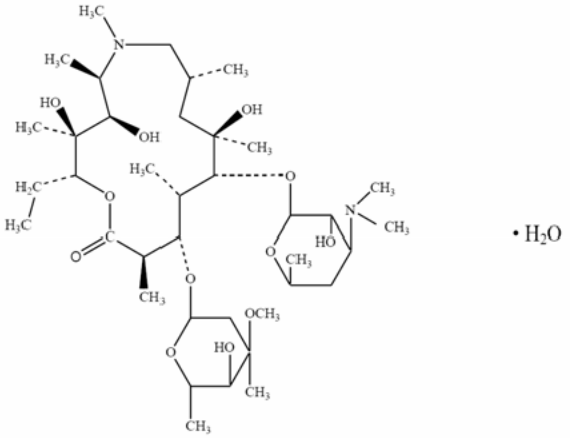
12. Dosage Form:
Ophthalmic solution

13. Potency:
1%

14. Chemical Name and Structure:
(2R,3S,4R,5R,8R,10R,11R,12S,13S,14R)-13-[(2,6-dideoxy-3-C-methyl-3-O-methyl-a- Lribo-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-azacyclopentadecan-15-one. monohydrate

Molecular Formula
$C_{38}H_{72}N_2O_{12}•H_2O$

Molecular Weight
azithromycin monohydrate: 767,
azithromycin: 749



15. Comments
This Prior Approval Supplement (PAS) seeks for approval of a comparability protocol to demonstrate the suitability of the drug product in the new container/closure system in two fill configuration: 2.5 mL for commercial and 1 mL for professional samples. Micro consult found information submitted in this supplement acceptable from microbiological perspective. The following CMC deficiencies and/or comments needs to be communicated to the applicant:

1. The proposed acceptance criteria for the drug product impurity test are not justified (refer to FDA Complete Response letter for NDA 50-810/S011).

2. Conduct a leachable study with accelerated for 6 months, and long term storage conditions through expiry using a screening method (e.g., (b) (4) GC and/or (b) (4) HPLC) on the new container closure system in the final market package (i.e., the primary and secondary package components). A minimum of 3 months data should be provided for review in the next submission.
3. Provide the stability data from the final market package with both upright and sideway orientations as a part of stability. Future stability studies may be conducted using only the worst case orientation.
4. Include particulate matter testing at month 3 for the accelerated storage condition, if only 3 month data will be available for evaluation in the next submission.

Clinical division recommended a Complete Response to this supplement (DARRTs date 02/07/2011).

16. Conclusion:

This supplement is recommended for Complete Response from CMC perspective. The above mentioned deficiencies and/or comments should be conveyed to the applicant in the Complete Response letter to be issued by OND.

17. Name:	**Signature:**	**Date:**
Xuhong Li, Ph.D., Chemist		
18. Concurrence:	**Signature:**	**Date:**
Thomas F. Oliver, Ph.D., Branch Chief, Branch VI, ONDQA		

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/s/

XUHONG LI
02/15/2011

THOMAS F OLIVER
02/15/2011

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

50-810/S012

MICROBIOLOGY REVIEW(S)

Product Quality Microbiology Review

08 FEB 2011

NDA: 50-810/S-012

Drug Product Name
Proprietary: AzaSite
Non-proprietary: Azithromycin Ophthalmic Solution 1%

Review Number: 1

Dates of Submission(s) Covered by this Review

Submit	Received	Review Request	Assigned to Reviewer
14 OCT 2010	15 OCT 2010	15 NOV 2010	18 NOV 2010
1 FEB 2011	1 FEB 2011	N/A	N/A

Applicant/Sponsor
Name: Inspire
Address: 4222 Emperor Boulevard, Suite 200
Durham, NC 27703
Representative: Kimberly A. Davis
Telephone: 919-941-9777

Name of Reviewer: Jessica G. Cole, Ph.D.

Conclusion: Recommend approval.

Product Quality Microbiology Data Sheet

A. 1. TYPE OF SUBMISSION: Prior Approval Supplement for a 505(b)(2) drug product.

2. SUBMISSION PROVIDES FOR: A comparability protocol for a change to the container-closure system.

3. MANUFACTURING SITE: Catalent Pharma Solutions, LLC
2200 Lake Shore Drive
Woodstock, IL 60098

4. DOSAGE FORM, ROUTE OF ADMINISTRATION AND STRENGTH/POTENCY:

- Ophthalmic solution
- Topical administration
- 1% Azithromycin

5. METHOD(S) OF STERILIZATION: [redacted] (b) (4) followed by [redacted] (b) (4) processing.

6. PHARMACOLOGICAL CATEGORY: Antibiotic.

B. SUPPORTING/RELATED DOCUMENTS: Microbiology review of NDA 50-810 dated 17 April 2007.

C. REMARKS: This is a paper submission not in the CTD format. The applicant was asked to clarify the container-closure test method on 19 January 2011. A response was received on 1 February 2011.

filename: N050810S012R1.doc

Executive Summary

I. Recommendations

A. Recommendation on Approvability – Recommended for approval on the basis of product quality microbiology.

B. Recommendations on Phase 4 Commitments and/or Agreements, if Approvable – Not applicable.

II. Summary of Microbiology Assessments

A. Brief Description of the Manufacturing Processes that relate to Product Quality Microbiology – A portion of the bulk solution is (b) (4) sterilized but the final drug product is (b) (4) processed. The container is formed with (b) (4) technology.

B. Brief Description of Microbiology Deficiencies – Not applicable.

C. Assessment of Risk Due to Microbiology Deficiencies – Not applicable.

III. Administrative

A. Reviewer's Signature _____
Jessica G. Cole, Ph.D.

B. Endorsement Block _____
Stephen Langille, Ph.D.
Senior Microbiology Reviewer

C. CC Block
N/A

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/s/

JESSICA COLE
02/08/2011

STEPHEN E LANGILLE
02/08/2011

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

50-810/S012

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

Memo to the Division File

NDA 50810/S012

AzaSite ophthalmic solution 1%

Material reviewed: DMF [redacted], 6/10/05

From: Wendelyn Schmidt, Pharmacology/Toxicology Supervisor, DAIOP

To: Xuhong Li, Chemist, ONDQA

Background:
In the new formulation of AzaSite Ophthalmic solution 1%, a [redacted] resin will be used in the container closure system that will be in direct contact with the solution. This resin, [redacted], is a low-density polyethylene. Extracts were made with [redacted] L of the vehicle at 70° C for 24 hours. The extract was then injected intracutaneously or intramuscularly into rabbits (n=4 or 2), or intravenously/ intraperionteally in mice (n=5). Rabbits were observed macroscopically for 24 hours, while mice were observed for up to 72 hours post-dose and body weight was also monitored. There were no remarkable changes with any extraction in either species by either route.

Conclusions:
Using a crude extraction of the resin, and gross observations in the rabbit and mouse, there were no apparent toxic extractables. Given that minimal systemic toxicity would result from absorption of the extractables, and that any local toxicity would be observed clinically, there should be no major issues with the [redacted] resin.

Recommendation: There are no pharmacology/toxicology objections to the new container system.

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/s/

WENDELYN J SCHMIDT
01/24/2011

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 50-810/S-012

INFORMATION REQUEST

Inspire Pharmaceuticals, Inc.
Attention: Kimberly A. Davis
Director, Post-Marketing Regulatory Affairs
4222 Emperor Blvd, Suite 200
Durham, NC 27703-8466

Dear Ms. Durham:

Please refer to your supplemental new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for AzaSite® (azithromycin ophthalmic solution).

We also refer to your submission dated October 15, 2010.

We are reviewing the Chemistry Manufacturing and Controls section of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your supplemental application.

Please provide the following information or a reference to its location in the subject submission.

Provide the test method and acceptance criteria for the container-closure integrity test to be performed on the new bottles. We note that at the teleconference held on 26 January 2010 you indicated that a microbial ingress test method would be employed. A dye immersion test method from (b) (4) Laboratories was provided in this submission and the relevance of this document is unclear. If container-closure testing will occur at (b) (4) Laboratories then add this information to the list of manufacturers and indicate that document STP0149 is the new container-closure test method for AzaSite.

If you have any questions, call Althea Cuff, Regulatory Health Project Manager, at (301) 796-4061.

Sincerely,

{See appended electronic signature page}

Thomas F. Oliver, Ph.D.
Branch Chief, Branch VI
Division of New Drug Quality Assessment II
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

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/s/

THOMAS F OLIVER
01/19/2011

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO *(Office/Division)*: Sylvia Gantt, HFD-003, Rm 3549

FROM (*Name, Office/Division, and Phone Number of Requestor)*: Althea Cuff, ONDQA, 301-796-4061

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
11/15/10		50-810	012	10/14/2010

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Azasite			1/15/2011

NAME OF FIRM: Inspire

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☒ MANUFACTURING CHANGE / ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE-NDA MEETING
- ☐ END-OF-PHASE 2a MEETING
- ☐ END-OF-PHASE 2 MEETING
- ☐ RESUBMISSION
- ☐ SAFETY / EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☐ OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

- ☐ PRIORITY P NDA REVIEW
- ☐ END-OF-PHASE 2 MEETING
- ☐ CONTROLLED STUDIES
- ☐ PROTOCOL REVIEW
- ☐ OTHER (SPECIFY BELOW):
- ☐ CHEMISTRY REVIEW
- ☐ PHARMACOLOGY
- ☐ BIOPHARMACEUTICS
- ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE 4 STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL - BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG SAFETY

- ☐ PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ NONCLINICAL

COMMENTS / SPECIAL INSTRUCTIONS: This supplement provides for use of a new container/closure system.

Please review.

PDUFA Date: 2/15/2011

SIGNATURE OF REQUESTOR
Althea Cuff

METHOD OF DELIVERY (Check one)
☐ DFS ☒ EMAIL ☐ MAIL ☐ HAND

PRINTED NAME AND SIGNATURE OF RECEIVER

PRINTED NAME AND SIGNATURE OF DELIVERER

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/s/

ALTHEA CUFF
11/15/2010

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO *(Office/Division)*: Francis Lasane and Wendy Schmidt	FROM (*Name, Office/Division, and Phone Number of Requestor)*: Althea Cuff, ONDQA, 301-796-4061

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
11/15/10		50-810	012	10/14/10

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
AzaSite			1/15/2011

NAME OF FIRM: Inspire

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE / ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE-NDA MEETING
- ☐ END-OF-PHASE 2a MEETING
- ☐ END-OF-PHASE 2 MEETING
- ☐ RESUBMISSION
- ☐ SAFETY / EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☐ OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

- ☐ PRIORITY P NDA REVIEW
- ☐ END-OF-PHASE 2 MEETING
- ☐ CONTROLLED STUDIES
- ☐ PROTOCOL REVIEW
- ☐ OTHER (SPECIFY BELOW):
- ☐ CHEMISTRY REVIEW
- ☒ PHARMACOLOGY
- ☐ BIOPHARMACEUTICS
- ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE 4 STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL - BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG SAFETY

- ☐ PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ NONCLINICAL

COMMENTS / SPECIAL INSTRUCTIONS: This supplement provides for new container/closure system

Please evaluate.

PDUFA date is supplement: 2/15/2011

SIGNATURE OF REQUESTOR	METHOD OF DELIVERY (Check one) ☒ DFS ☐ EMAIL ☐ MAIL ☐ HAND
PRINTED NAME AND SIGNATURE OF RECEIVER	PRINTED NAME AND SIGNATURE OF DELIVERER

Reference ID: 2864097

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/s/

ALTHEA CUFF
11/15/2010