



TRANSMITTED BY FACSIMILE

Kimberly A. Davis, RAC
Director, Post-Marketing Regulatory Affairs
Inspire Pharmaceuticals, Inc.
8081 Arco Corporate Dr., Suite 400
Raleigh, NC 27617

RE: NDA # 050810
AzaSite® (azithromycin ophthalmic solution) 1%
MACMIS #18525

Dear Ms. Davis:

The Division of Drug Marketing, Advertising, and Communications (DDMAC) has reviewed a professional "4-Page Journal Ad" (AZA-0384) (Journal Ad) for AzaSite® (azithromycin ophthalmic solution) 1% (AzaSite) submitted by Inspire Pharmaceuticals, Inc. (Inspire) under cover of Form FDA 2253. The Journal Ad is false or misleading because it broadens the indication, makes unsubstantiated claims, and omits and minimizes important risks associated with the use of AzaSite. Therefore, the Journal Ad misbrands AzaSite in violation of the Federal Food, Drug, and Cosmetic Act (the Act), 21 U.S.C. 352(n), 321(n), and FDA implementing regulations. 21 CFR 202.1(e)(5); (e)(6)(i); & (e)(7)(i) & (viii).

Background

According to the FDA-approved product labeling (PI),

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.*

The PI for AzaSite includes Warnings and Precautions regarding topical ophthalmic use only, anaphylaxis and hypersensitivity reactions with systemic use of azithromycin, growth of resistant organisms with prolonged use, and the need to avoid wearing contact lenses if patients have signs or symptoms of bacterial conjunctivitis.

The most frequently reported ocular adverse reaction in patients receiving AzaSite was eye irritation. Other adverse reactions associated with AzaSite included burning, stinging and irritation upon instillation, contact dermatitis, corneal erosion, dry eye, dysgeusia, nasal congestion, ocular discharge, punctate keratitis, and sinusitis.

Broadening of Indication

Promotional materials are misleading if they suggest that a drug is useful in a broader range of conditions or patients or is more effective than has been demonstrated by substantial evidence or substantial clinical experience.

The Journal Ad prominently presents the following claim and images (emphasis in original):

- **“An ocular surface condition causes damage ... AzaSite Can Restore a Healthy Ocular Surface”** (pages 1 and 3)
- Image of a partial face showing an eye with an ocular surface condition (the whites of the eye are pink with debris on the lower eyelid), furrowed brow and coarse skin on the nose, face, and eyelid (page 1)
- Image of the same partial face showing complete resolution of the ocular surface condition (the whites of the eye are clear with absence of debris on the lower eyelid), absence of a furrowed brow, and smooth facial skin (page 2)

The totality of this presentation broadens the indication for AzaSite because it suggests that AzaSite is indicated to treat any condition that causes ocular surface damage, which could include viral conjunctivitis (pinkeye), chemical injury, blepharitis, dry eye disease, and ocular rosacea, when such has not been demonstrated by substantial evidence or substantial clinical experience. As stated above, AzaSite is indicated only for the treatment of bacterial conjunctivitis caused by susceptible isolates to specific microorganisms. Azasite is also not indicated to treat ocular surface damage caused by bacterial conjunctivitis. We note that the indication is presented in very small font at the bottom of page three. However, this does not mitigate the overwhelming impression that Azasite is useful in a much broader range of conditions or patients than has been demonstrated.

Unsubstantiated Claims

The Journal Ad includes the claim, **“AzaSite[®] Can Restore a Healthy Ocular Surface By Delivering Significant Anti-Inflammatory and Antimicrobial Effects Directly to the Site of the Problem.”** (bolded emphasis in original; underlined emphasis added) This claim is misleading because it implies that AzaSite delivers anti-inflammatory effects, when this has not been demonstrated by substantial evidence or substantial clinical experience.

The Journal Ad cites Zhou, et al.¹, Sadrai, et al.², and Abelson, et.al.^{3, 4} to support this claim. The Zhou and the Sadrai references are poster presentations from the 2009 Association for Research in Vision and Ophthalmology Annual Meeting. These poster presentations do not provide adequate descriptions of the study materials, the study methods, or the study results. More importantly, the Zhou and the Sadrai references describe *in vitro* work on human corneal epithelial cells and pre-clinical animal work in mice, respectively. The clinical relevance of these findings is unknown. The two Abelson trials evaluated the efficacy of AzaSite in treating bacterial conjunctivitis only. The primary end points in the trials were clinical resolution of signs and symptoms (rating of zero on ocular discharge, bulbar and palpebral infection) at visit 3. Efficacy measures were clinical resolution and bacterial eradication as evaluated in the per-protocol population. As such, the Abelson trials do not constitute substantial evidence or substantial clinical experience to support claims that AzaSite is associated with anti-inflammatory effects. If you have evidence to support these claims, please submit it to FDA for review.

In addition, the Journal Ad claims, "AzaSite achieved therapeutic concentrations in ocular surface tissues and maintained them for at least five days after the *last* dose (Day 7)." (italicized emphasis in original) This presentation misleadingly implies that AzaSite has been shown to maintain therapeutic concentrations in ocular surface tissues for at least five days after the last dose (i.e., days 8-12) when this has not been demonstrated by substantial evidence or substantial clinical experience. We note that this claim is based on results found within a poster presented by Stewart et al⁵. This poster presentation does not provide an adequate description of the study materials, the study methods, or the study results. The Stewart reference describes assessments of pharmacokinetic parameters only, and did not assess clinical efficacy. Therefore, the clinical relevance of these findings is unknown. In addition, maintenance of therapeutic concentrations in ocular surface tissues for at least five days after the last dose was not a prespecified endpoint in the pivotal clinical trials. The primary efficacy variable in the clinical studies that served as the basis for approval was clinical resolution, defined as the complete resolution of ocular discharge and the microbiological resolution of the bacterial conjunctivitis (i.e., eliminating microorganisms cultured at baseline). The clinical resolution endpoint focused on the antimicrobial effect of the drug on bacterial conjunctivitis and not on the maintenance of therapeutic concentrations in ocular surface tissues.

¹ Zhou N, Ma P, Li D-Q, Pflugfelder SC. Azithromycin suppresses pro-inflammatory mediators stimulated by a TLR2 ligand zymosan in human corneal epithelial cells. Poster presented at: 2009 Association for Research in Vision and Ophthalmology Annual Meeting; May 3-7, 2009; Fort Lauderdale, FL.

² Sadrai Z, Hajrasouliha AR, Chauhan SK, Saban DR, Dastjerdi MH, Dana R. Effect of topical azithromycin on innate immune responses in experimental keratitis. Poster presented at: 2009 Association for Research in Vision and Ophthalmology Annual Meeting; May 3-7, 2009; Fort Lauderdale, FL.

³ Abelson M, Proizko E, Shapiro A, Garces-Soldana A, Bowman L. A randomized trial assessing the clinical efficacy and microbial eradication of 1% azithromycin ophthalmic solution vs tobramycin in adult and pediatric subjects with bacterial conjunctivitis. *Clin Ophthalmol.* 2007;1(2):177-182.

⁴ Abelson MB, Heller W, Shapiro AM, Si E, Hsu P, Bowman LM. Clinical cure of bacterial conjunctivitis with azithromycin 1%, vehicle-controlled. double-masked clinical trial. *Am J Ophthalmol.* 2008; 145:959-965.

⁵ Stewart WC, Crean CS, Zink RC, Haque R, Hwang DG. Pharmacokinetics of Azithromycin and Moxifloxacin in Human Conjunctiva and Aqueous Humor During and After the Approved Dosing Regimens. Poster presented at: 2009 Association for Research in Vision and Ophthalmology Annual Meeting; May 3-7, 2009; Fort Lauderdale, FL.

Omission and Minimization of Risk

Promotional materials are misleading if they fail to reveal facts that are material in light of the representations made or with respect to the consequences that may result from the use of the drug as recommended or suggested by the materials. The Journal Ad presents efficacy claims for AzaSite, but omits information about serious risks associated with the drug. Specifically, the Journal Ad omits the Warnings and Precautions regarding the risk of anaphylaxis and hypersensitivity with systemic use of azithromycin, including reports of fatalities, growth of resistant organisms with prolonged use, and avoidance of contact lenses. By failing to communicate information about these risks, the Journal Ad misleadingly suggests that AzaSite is safer than has been demonstrated.

Furthermore, the Journal Ad fails to present risk information with a prominence and readability reasonably comparable to the presentation of efficacy claims, taking into account all implementing factors such as typography, layout, contrast, headlines, paragraphing, white space, and any other techniques apt to achieve emphasis. Specifically, the Journal Ad prominently presents efficacy claims using large, bolded text, prominent images, and a significant amount of white space. However, the risk information is relegated to the bottom of the page and is presented in single-spaced block paragraph format, in small font size with poor contrast (i.e., black text on a gray background). The overall effect of this presentation undermines the communication of important risk information, thereby misleadingly suggesting that AzaSite is safer than has been demonstrated.

Conclusion and Requested Actions

For the reasons discussed above, the Journal Ad misbrands AzaSite in violation of the Act, 21 U.S.C. 352 (n); 321(n), and FDA implementing regulations. 21 CFR 202.1(e)(5); (e)(6)(i); & (e)(7)(i) & (viii).

DDMAC requests that Inspire immediately cease the dissemination of violative promotional materials for AzaSite that contain violations such as those described above. Please submit a written response to this letter on or before April 28, 2011, stating whether you intend to comply with this request, listing all promotional materials (with the 2253 submission date) for AzaSite that contain violations such as those described above, and explaining your plan for discontinuing use of such violative materials. Please direct your response to me at the Food and Drug Administration, Center for Drug Evaluation and Research, Division of Drug Marketing, Advertising, and Communications, 5901-B Ammendale Road, Beltsville, MD 20705-1266, facsimile at 301-847-8444. In all future correspondence regarding this matter, please refer to MACMIS # 18525 in addition to the NDA number. We remind you that only written communications are considered official.

The violations discussed in this letter do not necessarily constitute an exhaustive list. It is your responsibility to ensure that your promotional materials for AzaSite comply with each applicable requirement of the Act and FDA implementing regulations.

Sincerely,

{See appended electronic signature page}

Carole C. Broadnax, R.Ph., Pharm.D.
Regulatory Review Officer
Division of Drug Marketing,
Advertising, and Communications

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

/s/

CAROLE C BROADNAX
04/14/2011



**An ocular surface condition
causes damage...**



AzaSite[®] Can Restore a Healthy Ocular Surface

By Delivering Significant Anti-Inflammatory and
Antimicrobial Effects Directly to the Site of the Problem^{1,2,3,4}

AzaSite[®] achieved therapeutic concentrations in ocular surface tissues
and maintained them for at least five days after the *last* dose (day 7)⁵

AzaSite[®] (azithromycin ophthalmic solution) 1% is indicated for the treatment of bacterial conjunctivitis caused by the following organisms: CDC coryneform group G*, *Staphylococcus aureus*, *Streptococcus mitis* group, *Streptococcus pneumoniae*, and *Haemophilus influenzae*.


Important Safety Information: AzaSite[®] should not be injected subconjunctivally or introduced directly into the anterior chamber of the eye or otherwise administered systemically. In clinical trials, the most common ocular adverse event was eye irritation, which occurred in 1% to 2% of patients.

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

Please see the brief summary of Prescribing Information on the adjacent page.

For more information, visit www.azasite.com

AzaSITE[®]
(azithromycin ophthalmic solution) 1%

INSPIRE  ©2010 AZA-0384 March 2010 Inspire Pharmaceuticals, Inc.
AzaSite is a registered trademark of InSite Vision, Inc. All rights reserved.

References: 1. Zhou N, Ma P, Li D-Q, Pflugfelder SC. Azithromycin suppresses pro-inflammatory mediators stimulated by a TLR2 ligand zymosan in human corneal epithelial cells. Poster presented at: 2009 Association for Research in Vision and Ophthalmology Annual Meeting; May 3-7, 2009; Fort Lauderdale, FL. 2. Sadrai Z, Hajrasouliha AR, Chauhan SK, Saban DR, Dastjerdi MH, Dana R. Effect of topical azithromycin on innate immune responses in experimental keratitis. Poster presented at: 2009 Association for Research in Vision and Ophthalmology Annual Meeting; May 3-7, 2009; Fort Lauderdale, FL. 3. Abelson M, Protzko E, Shapiro A, Garces-Soldana A, Bowman L. A randomized trial assessing the clinical efficacy and microbial eradication of 1% azithromycin ophthalmic solution vs tobramycin in adult and pediatric subjects with bacterial conjunctivitis. *Clin Ophthalmol.* 2007;1(2):177-182. 4. Abelson MB, Heller W, Shapiro AM, Si E, Hsu P, Bowman LM. Clinical cure of bacterial conjunctivitis with azithromycin 1%: vehicle-controlled, double-masked clinical trial. *Am J Ophthalmol.* 2008;145:959-965. 5. Stewart WC, Crean CS, Zink RC, Haque R, Hwang DG. Pharmacokinetics of azithromycin and moxifloxacin in human conjunctiva and aqueous humor during and after the approved dosing regimens. Poster presented at: 2009 Association for Research in Vision and Ophthalmology Annual Meeting; May 3-7, 2009; Fort Lauderdale, FL.

AzaSITE[®]

(azithromycin ophthalmic solution) 1%

Sterile topical ophthalmic drops

Initial U.S. Approval: 2007

BRIEF SUMMARY

Before prescribing, please consult the full prescribing information.

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.

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.

CONTRAINDICATIONS

None

WARNINGS AND PRECAUTIONS

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.

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, since patients with a known hypersensitivity to azithromycin or erythromycin were excluded from study.

Growth of Resistant Organisms With Prolonged Use

As with other anti-infectives, prolonged use may result in overgrowth of nonsusceptible 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.

Avoidance of Contact Lenses

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

ADVERSE REACTIONS

The most frequently reported ocular adverse reaction in patients receiving AzaSite was eye irritation. This reaction occurred in approximately 1% to 2% of patients. Other adverse reactions associated with the use of AzaSite were reported in less than 1% of patients and included: burning, stinging and irritation upon instillation, contact dermatitis, corneal erosion, dry eye, dysgeusia, nasal congestion, ocular discharge, punctate keratitis, and sinusitis.

In addition to adverse events reported from clinical trials, the following events have been identified during post approval use of AzaSite. **Eye:** blurring, eyelid swelling, itching, pain, visual acuity reduction. **General:** allergic reactions including facial swelling, hives, periorcular swelling, rash, urticaria.

USE IN SPECIFIC POPULATIONS

Pregnancy

Pregnancy Category B. Reproduction studies have been performed in rats and mice at doses up to 200 mg/kg/d. The highest dose was associated with moderate maternal toxicity. These doses are estimated to be approximately 5000 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.

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.

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.

Geriatric Use

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

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.

PATIENT COUNSELING 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 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 are advised to thoroughly wash hands before using AzaSite.

Rx only

Inspire Pharmaceuticals Inc.
Licensee of InSite Vision Incorporated
Manufactured by Catalent Pharma Solutions, LLC
U.S. PAT NO. 5,192,535; 6,239,113; 6,569,443; 6,861,411; 7,056,893;
and Patents Pending
AZA-0301
Revised: 11/2008