CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

50-810

PROPRIETARY NAME REVIEW(S)

CONSULTATION RESPONSE
DIVISION OF MEDICATION ERRORS AND TECHNICAL SUPPORT
OFFICE OF SURVEILLANCE AND EPIDEMIOLOGY
(DMETS; WO 22, STOP: 4447)

DATE RECEIVED: July 3, 2006 **DATE OF DOCUMENT:** June 28, 2006	**DESIRED COMPLETION DATE:** January 25, 2007 **PDUFA DATE:** April 28, 2007	**OSE REVIEW #:** 06-0202

TO: Janice Soreth, MD
Director, Division of Anti-Infective and Ophthalmology Products, HFD-520

THROUGH: Alina Mahmud, RPh, MS, Team Leader
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Division of Medication Errors and Technical Support, HFD-420

FROM: Deveonne Hamilton-Stokes, RN, Safety Evaluator
Division of Medication Errors and Technical Support, HFD-420

PRODUCT NAME:	**NDA SPONSOR: InSite Vision, Inc**
AzaSite (Azithromycin Ophthalmic Solution) 1% **NDA#: 50-810**	

RECOMMENDATIONS:

1. DMETS does not recommend the use of the proprietary name, AzaSite.

2. DMETS recommends implementation of the label and labeling revisions outlined in section III of this review to minimize potential errors with the use of this product.

3. DDMAC finds the proprietary name, AzaSite, acceptable from a promotional perspective.

DMETS would appreciate feedback of the final outcome of this consult. We would be willing to meet with the Division for further discussion, if needed. If you have further questions or need clarifications, please contact Cherye Milburn, Project Manager, at 301-796-2084.

Division of Medication Errors and Technical Support (DMETS)
Office of Surveillance and Epidemiology
WO 22, STOP: 4447
Center for Drug Evaluation and Research

PROPRIETARY NAME, LABEL AND LABELING REVIEW

DATE OF REVIEW: August 7, 2006

NDA#: 50-810 (IND 62,873)

NAME OF DRUG: AzaSite
(Azithromycin Ophthalmic Solution)
1%

NDA HOLDER: InSite Vision

I. INTRODUCTION:

This consult was written in response to a request from the Division of Anti-Infective and Ophthalmology Products (HFD-520), for assessment of the proprietary name, "AzaSite", regarding potential name confusion with other proprietary or established drug names. Container label, carton and insert labeling were provided for review and comment.

PRODUCT INFORMATION

AzaSite (azithromycin ophthalmic solution 1%) is a topical ophthalmic preparation of an azalide anti-infective indicated for the treatment of bacterial conjunctivitis. The recommended dose and dosing interval is on days 1 and 2: instill 1 drop in the affected eye(s) 2 times per day and on days 3-7: instill 1 drop in the affected eye(s) once per day. AzaSite is supplied as a 2.5 mL bottle containing a total of 25 mg of azithromycin.

II. RISK ASSESSMENT:

The medication error staff of DMETS conducted a search of several standard published drug product reference texts[1,2] as well as several FDA databases[3,4] for existing drug names which sound-alike or look-alike to AzaSite to a degree where potential confusion between drug names could occur under the usual clinical practice settings. A search of the electronic online version of the U.S. Patent and Trademark Office's Text and Image Database was also conducted[5]. The Saegis[6] Pharma-In-Use database was searched for drug names with potential for confusion. An expert panel discussion was conducted to review all findings from the searches. In addition, DMETS conducted three prescription analysis studies

[1] MICROMEDEX Integrated Index, 2006, MICROMEDEX, Inc., 6200 South Syracuse Way, Suite 300, Englewood, Colorado 80111-4740, which includes all products/databases within ChemKnowledge, DrugKnowledge, and RegsKnowledge Systems.
[2] Facts and Comparisons, online version, Facts and Comparisons, St. Louis, MO.
[3] AMF Decision Support System [DSS], Drugs@FDA, the Division of Medication Errors and Technical Support [DMETS] database of Proprietary name consultation requests, and the electronic online version of the FDA Orange Book.
[4] Phonetic and Orthographic Computer Analysis (POCA)
[5] WWW location http://www.uspto.gov/tmdb/index.html.
[6] Data provided by Thomson & Thomson's SAEGIS ™ Online Service, available at www.thomson-thomson.com

consisting of two written prescription studies (inpatient and outpatient) and one verbal prescription study, involving health care practitioners within FDA. This exercise was conducted to simulate the prescription ordering process in order to evaluate potential errors in handwriting and verbal communication of the name.

A. EXPERT PANEL DISCUSSION (EPD)

An Expert Panel discussion was held by DMETS to gather professional opinions on the safety of the proprietary name AzaSite. Potential concerns regarding drug marketing and promotion related to the proposed name were also discussed. This group is composed of DMETS Medication Errors Prevention Staff and representation from the Division of Drug Marketing, Advertising, and Communications (DDMAC). The group relies on their clinical and other professional experiences and a number of standard references when making a decision on the acceptability of a proprietary name.

1. DDMAC finds the proposed proprietary name, AzaSite, acceptable from a promotional perspective.

2. The Expert Panel identified five proprietary names that were thought to have the potential for confusion with AzaSite. These products are listed in Table 1 (see below), along with the dosage form available and usual dosage.

Table 1: Potential Sound-Alike/Look-Alike Names Identified by DMETS Expert Panel

Product Name	Dosage form(s), Established name	Usual adult dose*	Other**
AzaSite	Azithromycin Ophthalmic Drops 1%	Days 1 and 2: Instill 1 drop in the affected eye(s) two times per day Days 3-7: Instill 1 drop in the affected eye(s) once per day	NA
AquaSite (Same manufacter: Insite Vision)	Artificial tears Solutions or ointments	Solution: Instill 1 to 2 drops into eye(s) 3 or 4 times daily, as needed Ointments: Apply one-fourth of an inch to the inside of the eyelid	LA/SA
Aquavit-E	Vitamin E Solution (oral drops-butterscotch) 15 IU/0.3 mL	0.6 mL once daily	LA
Avalide	Hydrochlorothiazide and Irbesartan Tablets: 12.5 mg/150 mg; 12.5 mg/300 mg; 25 mg/300 mg	One tablet daily	LA
Accusite	Fluororacil;Epinephrine;Bovine Collagen Intralesional Injection	0.5mL/lesion injection once weekly for 6 weeks	SA
Azasan	Azathioprine Tablets: 75 mg, 100 mg	Renal Hemotransplantation: 1-5 mg/kg daily; Rheumatoid Arthritis: 1-2.5 mg/kg daily;	SA

*Frequently used, not all-inclusive.
**LA (look-alike) SA (sound-alike)

B. PRESCRIPTION ANALYSIS STUDIES

1. Methodology:

Three separate studies were conducted within the Centers of the FDA for the proposed proprietary name to determine the degree of confusion of AzaSite with marketed U.S. drug names (proprietary and established) due to similarity in visual appearance with handwritten prescriptions or verbal pronunciation of the drug name. These studies employed a total of 124 health care professionals (pharmacists, physicians, and nurses). This exercise was conducted in an attempt to simulate the prescription ordering process. An inpatient order and outpatient prescriptions were written, each consisting of a combination of marketed and unapproved drug products and a prescription for AzaSite (see below). These prescriptions were optically scanned and one prescription was delivered to a random sample of the participating health professionals via e-mail. In addition, the outpatient orders were recorded on voice mail. The voice mail messages were then sent to a random sample of the participating health professionals for their interpretations and review. After receiving either the written or verbal prescription orders, the participants sent their interpretations of the orders via e-mail to the medication error staff.

HANDWRITTEN PRESCRIPTION	VERBAL PRESCRIPTION
Outpatient RX: AzaSite #1 Instill 1 drop into affected eye(s) BID x 2 days. then 1 drop qd x 5 days	AzaSite 1 bottle Instill 1 drop in affected eye twice daily for 2 days, then 1 drop once daily for 5 days.
Inpatient Rx:	

2. Results:

None of the interpretations of the proposed name overlap, sound similar, or look similar to any currently marketed U.S. product. See Appendix A for the complete listing of interpretations from the verbal and written studies.

C. SAFETY EVALUATOR RISK ASSESSMENT

In reviewing the proprietary name, AzaSite, the primary concerns relating to look-alike and sound alike confusion with AzaSite are Aquasite, Aquavit-E, Avalide, Accusite and Azasan.

DMETS also conducted prescription studies to simulate the prescription ordering process. In this case, there was no confirmation that the proposed name could be confused with any of the aforementioned names. However, negative findings are not predicative as to what may occur once the drug is widely prescribed, as these studies have limitations primarily due to a small

sample size. The majority of misinterpretations were misspelled/phonetic variations of the proposed name, AzaSite.

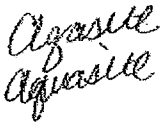
Upon further review of the name Accusite, it was not considered a safety risk because it is an investigational drug in the United Kingdom which has numerous differentiating product characteristics such as the product strength, indication for use, frequency of administration, route of administration and dosage form.

The remaining names of concern are discussed below.

1) Look Alike/Sound Alike Names

a) AquaSite was found to have look-alike and sound-alike similarities with AzaSite. AquaSite contains artificial tears and is indicated in the symptomatic treatment of dry eye. The dose of AquaSite solution is 1-2 drops instilled into affected eye(s) 3 or 4 times daily, as needed.

Both names begin with letter "A", end in the same five letters (aSite) and have the same number of syllables (three), which contribute to their orthographic (see sample below) and phonetic similarities. Both have a downstoke at the second letter.

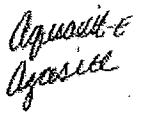


The two products differ in frequency of administration (1-2 times daily vs. 3-4 times daily), and prescription status (over-the-counter products vs. prescription products). However, Aquasite and AzaSite have multiple overlapping characteristics, such as dosage form (solution), route of administration (ophthalmic), and dosage (1-2 drops), which increase the risk of confusion.

Additionally, the products share the same sponsor, InSite Vision, Inc. Although Aquasite has been discontinued, as of 2004, it still appears in many online references, such as Google, Rxlist.com, Clinical Pharmacology, and Epinions.com. Furthermore, it still remains on the sponsor's website, Insitevision.com. Also, since generic versions of Aquasite exist, DMETS is concerned that if a prescription for AzaSite is misinterpreted as Aquasite, the pharmacist may dispense a generic equivalent artificial tears product. The consequences of this mistake are very concerning since the patient will be without the antibiotic therapy of Azasite. This can happen if the prescription for Azasite is misinterpreted as Aquasite due to their familiarity with Aquasite. Because the brand name would not be available a generic equivalent would be dispensed. Thus, the strong look-alike similarities with the two product names coupled with multiple overlapping product characteristics increase the potential for name confusion resulting in medication errors involving Aquasite and AsaSite.

b) Aquavit-E was found to have look-alike similarities with AzaSite, when the modifier "E" is omitted from the name. Aquavit-E is a nutritional supplement used to treat Vitamin E deficiency.

The visual similarity of this name pair can be attributed to the fact both names begin with the letter "A" and contain the same trailing letters (-IT). Additionally, the letter "q" in Aquavit-E and the letter "z" in AzaSite can look alike when scripted (see example top of next page) since both are downstroke letters.



The products differ in dose (0.6 mL vs. 1 drop), strength (15 IU/0.3 mL vs. 1%), route of administration (oral vs. ophthalmic), prescription status (over-the-counter vs. prescription) and indication for use (Vitamin E deficiency vs. bacterial conjunctivitis). However, Aquavit-E and Azasite share a similar dosage form (oral drops vs. ophthalmic drops) and a similar frequency of administration (once daily vs. once daily on days 3-7). In addition, both products are available in only one strength, which allows the prescriber to order either product without specifying a strength. Also, despite Aquavit-E's OTC status, it would not be unusual to see a prescription written for Aquavit-E as prescribers oftentimes write prescriptions for OTC medications for Medicaid, VA and Military Hospital patients or as reminders on prescription blanks. A prescription written for "Azasite –use as directed #1" may be misinterpreted for "Aquavit-E -use as directed #1" due to some pharmacist's familiarity with Aquavit-E. Aquavit-E's sponsor, Cypress Pharmaceutical, indicated that their product is kept behind the pharmacy counter or it must be special ordered if the pharmacy does not carry it. Additionally, we have concerns about the varying routes of administration, especially if the patient is anticipating an oral product but receives an ophthalmic product and vise versa. If the wrong product is dispensed, this may result in the inadvertent administration of the oral medication, since it comes with a dropper, in the eye. Therefore, DMETS believes the likelihood for confusion between Aquavit-E and AzaSite exists.

c) Azasan was found to have sound-alike similarities with AzaSite. Azasan (azathioprine) is an adjunct for the prevention of rejection in renal hemotransplantation. It is also indicated for the management of severe, active rheumatoid arthritis. Azasan can be administered intravenously or orally. The ususal dose is 1-5 mg/kg daily.

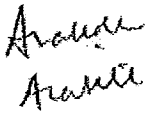
Azasan and AzaSite have the same number of syllables (three) and contain the same four initial letters (AZAS), which contributes to their similar sound. Additionally the first two syllables in both names sound similar.

However the two products have differing product characteristics such as dosage form (tablet vs. solution), route of administration (oral vs. ophthalmic), and dose (1-5 mg/kg/day vs. 1 drop). Although an AzaSite prescription may be written as "AzaSite-use as directed #1", a prescription for Azasan will include a strength (either 75 mg or 100 mg) and dose, which does not overlap with AzaSite. This will further distinguish the name pair. Therefore, despite the phonetic similarities, DMETS believes the likelihood for confusion between Azasan and AzaSite is minimal due to the numerous product differences.

d) Avalide was found to have look-alike similarities with AzaSite. Avalide is indicated for the treatment of hypertension. Avalide and AzaSite have the same number of letters (seven). All but three letters in the names are identical, which contributes to their

orthographic similarities (see sample top next page). In addition, both have an upstroke next to the last letter, "d" in Avalide and "t" in AzaSite.

AVALIDE
AZASITE



Although the products have a similar dosing frequency (once daily), the two products have numerous differing product characteristics such as dosage form (tablets vs. ophthalmic solution), route of administration (oral vs. ophthalmic), dosage strength (12.5 mg/150 mg, 12.5/300 mg and 25 mg/300 mg vs. 1%), and indication for use (hypertension vs. bacterial conjunctivitis). Therefore, due to the product differences, DMETS believes the likelihood for confusion between Avalide and AzaSite is minimal.

2) Concerns with Proliferation of Sponsor's Name

DMETS questions if there may be a trend regarding the use of the suffix "site" which stems from the sponsor's name. In addition to the proposed name Azasite, we note that the sponosor, "Insite", also utilized the suffix "site" for their discontinued product containing artificial tears (Aquasite). DMETS questions whether the sponsor intends to utilize the suffix "site" in conjunction with other names with subsequent applications. Post-marketing experience has shown confusion and resulting medication errors due to proliferation of names with a common prefix or suffix. One example of such confusion has been seen with products having the prefix "APO", manufactured in Canada by Apotex (see Appendix B for list of names with prefix "APO"). Consequently, DMETS objected to the inclusion of the prefix "APO" for proprietary names proposed in this country since this practice may result in the introduction of numerous sound-alike/look-alike names. DMETS continues to object to proposals which would lead to proliferation of products with commonalities in nomenclature. DMETS believes that the entrance in the marketplace of different products which include common lettering, "site", would lead to confusion and result in additional look alike and/or sound alike medication errors. Therefore, subsequent names proposed for varying applications from this sponosor including the suffix "site" should take into consideration the potential for this type of confusion.

III. COMMENTS TO THE SPONSOR

DMETS does not recommend the use of the name AzaSite. In reviewing the proprietary name, the primary concerns were relating to look-alike confusion with AzaSite are AquaSite and Aquavit-E. In addition, DMETS questions the sponsor's trend with using the suffix "site".

A) Look-Alike/Sound-Alike Names

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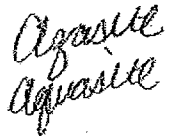

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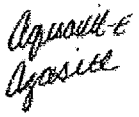

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In addition, DMETS reviewed the container labels, carton and insert labeling of Azasite and identified the following areas of improvement that may minimize potential user error.

C) CONTAINER LABEL

1. Revise the established name appearing immediately after the proprietary name to include the dosage form and to read: Azithromycin Ophthalmic Solution
1%

   Additionally, the established name should be at least ½ the size of the proprietary name per 21 CFR 201.10 (g)(2).

2. Revise the proprietary name so that it is the same font and color. As currently presented the different colors bring more attention to one portion of the name.

3. If space permits, include the route of administration on the principle display panel.

4. Include a net quantity statement on the principle display panel. Ensure it is not in close proximity to the presentation of the strength.

D) CARTON LABELING

1. See comments A1 and A2.

2. Increase the prominence and the legibility of the route of administration on the principle display panel. Although it appears in the green panel in the middle of the carton, this statement is difficult to see.

3. The illustration of the eye competes with the proprietary name, please decrease the size of the eye illustration.

4. Decrease the prominence of the manufacture's name on the principal display panel, it is currently more prominent than the established name and route of administration.

5. The "KEEP OUT OF REACH OF CHILDREN" statement appearing prominently and immediately above the storage statements minimizes the prominence of the storage requirements. Since there is a difference in the storage conditions (i.e., pharmacy vs. patient) this information is important. Therefore, increase the prominence of the storage statements and separate the storage statements from the "KEEP OUT OF REACH OF CHILDREN" statement.

6. Revise the statement 'see package insert' to read "Usual Dose: See package insert." Additionally relocate this statement to appear at the top of this panel as it is difficult to find in its current position.

7. On the 2nd panel of the carton labeling, delete the trailing zero from the established name. The use of terminal zeroes may result in error as decimals are often overlooked. As evidence by our post-marketing surveillance, the use of terminal zeroes could potentially result in a ten-fold medication dose error. The use of terminal zeroes in the expression of strength or volume is not in accordance with the General Notices (page 10) of 2004 USP, which states, "...to help minimize the possibility of error in the dispensing and administration of the drugs...the quantity of active ingredient when expressed in whole numbers shall be shown WITHOUT a decimal point that is followed by a terminal zero." In addition, the use of trailing zeroes is specifically listed as a dangerous abbreviation, acronym or symbol in the 2006 National Patient Safety Goals of The Joint Commission for the Accreditation of Hospitals (JCAHO). Safety groups such as ISMP also list terminal zeroes on their dangerous abbreviations and dose designations list. Moreover, FDA launched a campaign in June 2006, warning health care providers and consumers not to use error-prone abbreviations and terminal zeroes. Thus, we request that the OND Divisions not approve or use abbreviations or terminal zeroes in their labels and labeling as they can be misinterpreted and contribute to error.

E) PACKAGE INSERT LABELING

1. Revise the established name from "azithromycin 1% ophthalmic solution" to "azithromycin ophthalmic solution 1%" throughout insert labeling to be consistent.

2. Please delete the use of trailing zeroes throughout the insert labeling (see comment D-7 above regarding trailing zeros).

3. In the How Supplied/Storage and Handling section, delete the size of the bottle. The 5 mL bottle size may be confused with the amount/volume of actual medication in the bottle.

Appendix A:

Inpatient Written	Outpatient Written	Verbal
Azasite	Arasite	Asasite
Azasite	Arasite	Azacyt
Azasite	Arasite	Azacyte
AzaSite	Arasite	Azacyte
AzaSite	Asacite	Azacyte
AzaSite	Asasite	Azasite
AzaSite	Aza Site	Azasite
AzaSite	AzaSite	Azocyte
AzaSite	Cira Site	Azosite
AzaSite	Cirasite	
AzaSite	Cirasite	
Azasite	Cizasite	
Azasite	Cizasite	
Azasite	Coza site	
AzaSite	Coza Site	
Azasitl	Cozasite	

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