

Azithromycin 1% Ophthalmic Solution for Treatment of Blepharitis

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ABSTRACT

Blepharitis is characterized by chronic inflammation of the lid margins, which may appear as simple hyperemia or as a true inflammation. It may occur in two forms anterior and posterior. The eyelid margins can become inflamed, irritated, and itchy when these glands produce abnormal secretions. Blepharitis is often seen in patients with acne rosacea, a generalized illness of oil glands. Anterior blepharitis is due to inflammation of the lid margin around the lashes. Seborrhoeic blepharitis is similar to dandruff of the scalp. Staphylococcal blepharitis is a result of bacterial infection of the lashes. Allergies due to reactions from mascara, contact lens solutions, and sprays, exposure to animals, environmental chemicals, or airborne allergens can also cause blepharitis.¹

The single most important treatment principle is a daily routine of good eyelid hygiene, this includes frequent scalp and face washing, using warm compresses to soak the eyelids, and doing eyelid scrubs but these treatments have very little efficacy in chronic and severe blepharitis. Antibiotic oral and ointment are also prescribed to decrease the bacterial load, other treatment modalities like artificial tear for dry eye and topical antibiotics are used in cases of severe inflammation. Topical antibiotics are recommended to decrease the bacterial load, and topical corticosteroids may help in cases of severe inflammation. Azithromycin ophthalmic solution 1% in Durasite has been proposed as a novel treatment for posterior blepharitis.¹

In this review I shall focus on Azithromycin 1% ophthalmic solution for the treatment of blepharitis based on its good anti-infective, anti-inflammatory and good tissue penetration.

Key words: Azithromycin, Blepharitis, Durasite, Topical

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INTRODUCTION

Blepharitis has a multi factorial etiology and the presenting signs and symptoms are variable. It may present alone or may often present in combination with other ocular surface diseases.²

Classification: It can be broadly classified according to anatomical location anterior and posterior blepharitis, anterior blepharitis affects the eyelid skin, base of the eyelashes and the eyelash follicles, and posterior blepharitis affects the meibomian glands and gland orifices. Blepharitis has traditionally been clinically subcategorized as staphylococcal, seborrheic, meibomian gland dysfunction (MGD), or a combination thereof. Staphylococcal and seborrheic blepharitis involve mainly the anterior eyelid and can each be referred to as anterior. Most cases of blepharitis are posterior blepharitis, due to inflammation of the meibomian glands of the lids. Blepharitis may also exacerbate symptoms of coexisting ocular surface disease, including allergy and aqueous tear deficiency. Compared with patients with anterior blepharitis, those with posterior blepharitis (MGD) tend to be older and may present with a longer history of symptoms. Although the disease typically first manifests in middle age, it can also present in childhood.³

Signs and symptoms: Includes redness, swelling, itching of the eyelid, crust and flecking of the eyelid margin, cyst in the eyelid (hordeolum), foreign body sensation in the eye, poor tear film which may sometimes lead to blurring of vision. Infectious blepharitis can cause hard crusts around the eyelashes which leave small ulcers that may bleed or ooze after cleaning, it may also cause matting or gluing of the eyelids in the morning. Allergic blepharitis usually occurs in the children, which causes dark eyelids also known as allergic shiners. Blepharitis that localizes in the skin of the eyelids may cause styes or chalazion, thickening of meibomian gland secretions and meibomian gland dysfunction.

Epidemiology: Interestingly, there is a lack of information on the epidemiology and prevalence rates of blepharitis.³ A survey done in United States in 2009 by Lemp et al indicated that blepharitis may be present in 37%–47% of all patients. Men older than 65 years and women aged between 46 and 65 years were most often predisposed to posterior blepharitis.⁴ Overall published prevalence rates range from 12% to 47%.^{5,6,7,8} A study by Macsai et al⁸ reported a significant overlap in symptoms between patients with dry eye disease and blepharitis; 68% of patients older than 60 years presented with signs and symptoms of both diseases. According to a study done by American Association of Ophthalmology in 2013 Prevalence of blepharitis is more common in Asian population than Caucasian population for clinically diagnosed MGD.⁴³

Most cases of chronic blepharitis, whether anterior or posterior, are associated with a bacterial component, usually consisting of gram-positive organisms such as staphylococcal species.³ However, due to the variety of associated bacteria,

the wide range of clinical signs and symptoms and the incidence of additional co-morbid ocular diseases, the current therapeutic goals are aimed at chronic disease management rather than a cure of the condition.¹

At present, there is no US Food and Drug Administration (FDA)-approved definitive therapy for either anterior or posterior blepharitis in the United States.^[2] Because both acute and chronic forms of the disease involve the presence of inflammation and bacteria, a comprehensive therapy that offers both antibiotic and anti-inflammatory properties coupled with good penetration into the lid tissue and convenient dosing may prove beneficial for this condition.^[1] Azithromycin ophthalmic solution 1% has been proposed as a novel treatment for blepharitis. Azithromycin, like erythromycin and doxycycline, has been historically shown to have anti-inflammatory properties,^{9,10} and to improve clinical signs and symptoms of blepharitis after oral administration.¹¹ An effective topical delivery system for Azithromycin could potentially deliver the same effects without the systemic side effects associated with oral administration. Topical delivery of ophthalmic preparations can be advantageous by delivering high drug concentrations directly to the ocular surface, yet challenges remain with this delivery system. Most notably, rapid clearance through the nasolacrimal duct, dilution through the production of reflex tearing, and protein binding are all concerns with topical ophthalmic delivery of antibiotic medications.^{12,13}

Furthermore, the Azithromycin molecule is extremely lipophilic, making a stable aqueous formulation of the drug. When Azithromycin is coupled with the Durasite drug delivery vehicle (which contains polycarbophil) developed by DuraSite® (AzaSite®; Inspire Pharmaceuticals, Durham, North Carolina, USA), Azithromycin can form a stable aqueous formulation, thus enhancing its stability and bioavailability on the ocular surface. When azithromycin is delivered via DuraSite, it binds to the mucin-coated surfaces of the eye (including the palpebral conjunctiva), resulting in the formation of a sustained-release gel that prolongs the release and availability of the drug on the ocular surface and enhances the penetration of the drug into the eyelids, conjunctiva, and cornea,^{14,15} thus increasing its potential as a treatment for blepharitis.¹

AZITHROMYCIN: DRUG DESCRIPTION:

Azithromycin is a semi-synthetic macrolide antibiotic of the azalide class. Azithromycin is derived from erythromycin; however, it differs chemically from erythromycin in that a methyl-substituted nitrogen atom is incorporated into the lactone ring.¹⁶

Molecular formula: C₃₈H₇₂N₂O₁₂•2H₂O¹⁶

Molecular weight: 785.¹⁶

Physical properties: Azithromycin, as the dihydrate, is a white crystalline powder.¹⁶

Solubility: practically insoluble in water, freely soluble in ethanol and in methylene chloride.¹⁶

STRUCTURAL FORMULA**PHARMACOLOGIC PROPERTIES**

Mechanism of action: Macrolides are protein synthesis inhibitors. The mechanism of action of macrolides is inhibition of bacterial protein biosynthesis, and they are thought to do this by preventing peptidyl transferase from adding the growing peptide attached to tRNA to the next amino acid, as well as inhibiting ribosomal translocation.³ Another potential mechanism is premature dissociation of the peptidyl-tRNA from the ribosome.⁵ Macrolide antibiotics do so by binding reversibly to the P site on the subunit 50S of the bacterial ribosome. This action is considered to be bacteriostatic. Macrolides tend to accumulate within leukocytes, and are, therefore, transported into the site of infection.

PHARMACOKINETICS

The plasma concentration of azithromycin following ocular administration of azithromycin ophthalmic solution in humans is unknown. Based on the proposed dose of one drop to each eye (total dose of 100 µL 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.²⁵

Absorption and bioavailability: Azithromycin is acid-stable, so it can be taken orally with no need of protection from gastric acids. It is readily absorbed, but its absorption is greater on an empty stomach. Bioavailability is 37% following oral administration. Absorption is not affected by food. Azithromycin is extensively distributed in tissues with tissue concentrations reaching up to 50 times greater than plasma concentrations. Drug becomes concentrated within macrophages and polymorphonucleocytes. Time to peak concentration in adults is 2.1 to 3.2 hours for oral dosage forms and one to two hours after a dose. Due to its high concentration in phagocytes, azithromycin is actively transported to the site of infection. During active phagocytosis, large concentrations are released.¹⁶

Volume of distribution: 31.1L/Kg, the concentration of azithromycin in the tissues can be over 50 times higher than in plasma; due to ion trapping and its high lipid solubility (volume of distribution is too high).¹⁶

Half life: The half-life of azithromycin allows a large single oral dose to be administered and yet maintain bacteriostatic levels in the infected tissue for several days up to 68 hrs. A single topical dose in healthy individuals found azithromycin to achieve significant tissue concentrations and maintain those levels for up to 24 hours.²⁴

Metabolism and elimination: Azithromycin undergoes hepatic metabolism. Biliary excretion of azithromycin, predominantly unchanged, is a major route of elimination. The administered dose is unchanged in urine.

Protein binding: Serum protein binding is variable in the concentration range approximating human exposure, decreasing from 51% at 0.02 µg /ml to 7% at 2 µg /ml.¹⁶

Plasma clearance: Apparent plasma clearance = 630 ml/min [following single 500 mg oral and i.v. doses.

PHARMACODYNAMICS

Azithromycin, a semisynthetic antibiotic belonging to the macrolide subgroup of azalides, is used to treat STDs due to chlamydia and gonorrhea, community-acquired pneumonia, pelvic inflammatory disease, pediatric otitis media and pharyngitis, and *Mycobacterium avium* complex (MAC) in patients with advanced HIV disease. Azithromycin reaches higher intracellular concentrations than erythromycin, increasing its efficacy and duration of action.¹⁶

CONTRAINDICATIONS

Azithromycin is contraindicated in patients with known hypersensitivity to azithromycin, erythromycin, any macrolide or ketolide antibiotic. Azithromycin is contraindicated in patients with a history of cholestatic jaundice/hepatic dysfunction associated with prior use of azithromycin. It is also not to be used in patients with Myasthenia Gravis, Hearing Problem, Very Rapid Heartbeat - Torsades de Pointes, Slow Heartbeat, Prolonged Q-T Interval on EKG, Abnormal EKG with QT changes from Birth, Clostridium Difficile Bacteria Related Colitis, Abnormal Liver Function Tests, Inflammation of the Liver with Stoppage of Bile Flow, Low Amount of Magnesium in the Blood, Low Amount of Potassium in the Blood.¹⁷

ADVERSE REACTIONS

Most common systemic side-effects are gastrointestinal: diarrhea (5%), nausea (3%), abdominal pain (3%), and vomiting. Nervousness, dermatologic reactions, and anaphylaxis have been reported. As with all antimicrobial agents, pseudo membranous colitis can occur during and up to several weeks after Azithromycin therapy.^{18,19}

In 2013, the FDA issued a warning saying that azithromycin "can cause abnormal changes in the electrical activity of the heart that may lead to a potentially fatal irregular heart rhythm." The FDA noted in the warning a 2012 study released by the New England Journal of Medicine that found the drug may increase the risk of death, especially in those with heart problems, compared with those on other antibiotics such as amoxicillin or no antibiotic. The warning indicated that people with preexistent conditions are at particular risk, such as those with QT interval prolongation, low blood levels of potassium or magnesium, a slower than normal heart rate, or those who use of certain drugs used to treat abnormal heart rhythms, or arrhythmias.²⁰⁻²⁴

The most frequently reported ocular adverse reaction reported was eye irritation, which occurred in 1% to 2% of patients. Other adverse reactions associated with the use of 1% ophthalmic solution are 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 nonocular reactions like

dysgeusia, facial swelling, hives, nasal congestion, periocular swelling, rash, sinusitis, urticaria.²⁵

OPHTHALMIC USE OF AZITHROMYCIN

In ophthalmology, oral azithromycin has been used to treat trachoma and adult inclusion conjunctivitis. The topical formulation is used for the treatment of bacterial conjunctivitis caused by susceptible isolates of CDC coryneform group G, *Haemophilus influenzae*, *Staphylococcus aureus*, *Streptococcus mitis* group, and *Streptococcus pneumoniae*.²⁵

In phase 3 studies, azithromycin in an ophthalmic formulation was shown to have a wide spectrum of coverage, as well as increased tissue penetration and persistence when compared with other common antibiotics.^[26] When compared with tobramycin for the treatment of bacterial conjunctivitis, azithromycin was shown to have equivalent outcomes with fewer doses.²⁷

AzaSite was also recommended by the Centers for Disease Control and Prevention as the treatment of choice for neonatal prophylaxis of chlamydia during the recent shortage of erythromycin ointment in the United States.¹

ANTI-INFLAMMATORY PROPERTIES OF AZITHROMYCIN

Studies have demonstrated the anti-inflammatory properties of azithromycin. They can inhibit the production of pro-inflammatory cytokines and the production of matrix metalloproteinases (MMPs).³² Although the specific anti-inflammatory mechanism of action remains unknown, the suppression of the nuclear transcription factor nuclear factor kappa B (NF-κB) has been shown to play a role.^{10,32-34}

Furthermore, the concentration of macrolide antibiotics such as azithromycin within polymorphonuclear leukocytes (PMNs) may also modulate their role in infection-mediated inflammation.³² With respect to ocular inflammatory diseases, an *in vitro* study found azithromycin in DuraSite as effective in suppressing MMPs in the corneal epithelium and endothelium as doxycycline in both human and bovine cells.¹⁰ MMPs have been implicated several ocular surface diseases, including blepharitis. Zymosan, a fungal toll-like receptor-2 ligand that stimulates production of inflammatory mediators in corneal epithelial cells, has been shown to be inhibited by treatment with azithromycin, suggesting another anti-inflammatory mechanism of action for azithromycin in ocular tissue.³⁵

RECENT STUDIES DONE ON TOPICAL 1% AZITHROMYCIN FOR THE TREATMENT OF BLEPHARITIS

Azithromycin 1% in DuraSite (AzaSite) is the only FDA-approved topical formulation of azithromycin available and marketed in the United States. It is indicated for the treatment of bacterial conjunctivitis.³⁶ In one study AzaSite was administered according to the FDA-indicated dosing regimen for bacterial conjunctivitis (twice daily [BID] for 2

days followed by once daily [QD] for 5 days), peak concentrations of azithromycin more than 200 µg/g of tissue were achieved in human eyelid tissue as the drug accumulated over the 7 days of therapy. Furthermore, 5 days after discontinuing the medication, tissue concentrations of azithromycin was more than 50 µg/g were still present in the eyelids.²⁶ The high levels of azithromycin, which can be achieved in ocular surface tissues, particularly eyelids, after topical administration when combined with the DuraSite delivery vehicle, and the degree to which these levels persist after discontinuing the drug, distinguish azithromycin in DuraSite from other commonly used topical antibiotics such as fluoroquinolones.

For example, another post marketing study compared AzaSite 1% and moxifloxacin 0.5% (an ocular antibiotic commonly prescribed for the treatment of bacterial conjunctivitis) to determine the pharmacokinetic parameters of the drops after a single instillation into healthy human conjunctiva (N = 48).³⁶ Azithromycin tissue concentrations peaked at 30 minutes after administration and remained high at therapeutic concentrations at 24 hours, whereas moxifloxacin concentrations peaked at 2 hours after administration and were undetectable at 24 hours, illustrating the differences in tissue absorption and clearance between topical azithromycin and fluoroquinolones.³⁶ The studies have demonstrated that concentrations of moxifloxacin in the aqueous humor are significantly higher than those of azithromycin after topical administration.³⁵ These results suggest that azithromycin tends to partition primarily within tissue, rather than in aqueous solution, whereas fluoroquinolones such as moxifloxacin partition readily in aqueous solution.³⁷ Since azithromycin has both antibacterial and anti-inflammatory properties that may make it a viable treatment option for chronic MGD.

A 2-week study comparing the efficacy of topical azithromycin 1% in the DuraSite drug delivery vehicle (AzaSite) combined with warm compresses to warm compresses alone for the treatment of posterior blepharitis was conducted by Jodi Luchs, Department of Ophthalmology and Visual Sciences, Albert Einstein College of Medicine, Bronx, NY, USA.¹ In this study (N = 21), 10 patients were randomized to the study drug and warm compresses; 11 received warm compresses alone. Patients in the azithromycin group showed a statistically significant improvement over baseline in the extent of lid margin redness, meibomian gland plugging, and quality of meibomian gland secretions, patients in the warm compress-only group did not show a statistically significant improvement in any of these parameters. 44% of the patients in the azithromycin group showed complete resolution of their plugging in at least 1 eye compared to none in the compress-only group; almost a quarter of those in the azithromycin group also showed a normalization of the meibomian gland secretions after 2 weeks of therapy. Further, there were only minor adverse

events (vision blur and eye irritation) in the azithromycin group.¹

A second multicenter pilot study³⁸ enrolled 76 patients with moderate to severe blepharitis, randomized to warm compresses alone or warm compresses and topical 1% azithromycin, for a 4-week treatment period. At week 1, investigators rated the efficacy of azithromycin as excellent or good in 44% of patients in the azithromycin group, compared with only 15% in the compress-only group. This improved to 70% in the azithromycin group after 4 weeks of therapy, compared to 48% in the compress-only group. The positive improvements achieved in the azithromycin group persisted as long as 2 weeks after therapy had concluded. Although the data did not reach statistical significance between the 2 groups, there was a trend toward improvement in the azithromycin group for eyelid swelling, quality of the meibomian gland secretions, and ocular pain or burning.¹

Another open-label study^[39,40] of 26 patients with moderate to severe blepharitis evaluated changes in the signs and symptoms of anterior and posterior blepharitis after a 4-week course of treatment with topical azithromycin 1% in DuraSite (AzaSite). Patients were prohibited from using warm compresses in this study. Patient-rated symptom scores for itching, foreign body sensation, ocular dryness, ocular burning, and swollen eyelids were all statistically significantly improved from baseline levels after 4 weeks of therapy, and the improvement persisted for 4 weeks after stopping therapy. This supported the investigator-rated assessment of the clinical signs of blepharitis, which demonstrated statistically significant improvements in lid margin and conjunctival hyperemia, meibomian gland plugging, and ocular discharge after 4 weeks of therapy, which also persisted for 4 weeks after stopping therapy.¹

CONCLUSION

At present there is no definitive FDA approved treatment of both anterior and posterior blepharitis.¹ Topical azithromycin has been listed as the first line prescription pharmaceutical therapy for the treatment of MGD International Workshop on MGD sponsored by the Tear Film Ocular Society.⁴¹ In addition to its anti microbial properties, it also has anti-inflammatory properties in several tissues of the body including ocular tissue.¹⁰ It is seen that orally administered macrolides have efficacy in reducing inflammation in sebaceous glands both in facial skin⁴² and lid margins³⁰ independent of their antibiotic effect. These studies suggest that topical azithromycin 1% in the DuraSite drug delivery vehicle may be effective as a standalone treatment for blepharitis as well as an adjunctive therapy with warm compress because the active drug reaches high sustained levels within eyelid tissue with topical administration.^{13,14} In addition it is a broad spectrum antibiotic which has a good efficacy against organisms associated with blepharitis along with its anti-inflammatory properties.^{15,25} The various studies also demonstrate that topical azithromycin is more successful in treating the signs

and symptoms of blepharitis than just mechanical therapy (warm compresses) alone.¹

REFERENCES

1. Luchs J. Azithromycin in DuraSite for the treatment of blepharitis. *Clin Ophthalmol* 2010;4:681-688.
2. American Optometric Association. Optometric clinical practice guideline: care of the patient with ocular surface disorders. 2002. Available from: <http://www.aoa.org/documents/CPG-10.pdf> Accessed Jan 14, 2010.
3. American Academy of Ophthalmology. Preferred practice patterns: blepharitis. 2008 Available from: <http://one.aao.org/CE/PracticeGuide-lines/PPP.aspx> Accessed Jan 20, 2010.
4. Lemp MA, Nichols KK. Blepharitis in the United States 2009: a survey-based perspective on prevalence and treatment. *Ocul Surf*. 2009;7(Suppl2):S1-S14.
5. Campbell Alliance Group. Patterns of practice and prevalence rates for lid margin disease. 2008 July-Aug.
6. Venturino G, Bricola G, Bagnis A, Traverso CE. Chronic blepharitis: treatment patterns and prevalence. *Invest Ophthalmol Vis Sci*. 2003. 44
7. Hom MM, Martinson JR, Knapp LL, Paugh JR. Prevalence of meibomian gland dysfunction. *Optom Vis Sci*. 1990;67:710-712.
8. Macsai MS. The role of omega-3 dietary supplementation in blepharitis and meibomian gland dysfunction (an AOS thesis) *Trans Am Ophthalmol Soc*. 2008;106:336-356.
9. Scaglione F, Rossoni G. Comparative anti-inflammatory effects of roxithromycin, azithromycin, and clarithromycin. *J Antimicrob Chemother*. 1998;41(Suppl B):47-50.
10. Jacot JL, Jacot TA, Sheppard JD, et al. Evaluation of MMP 2/9 modulation by AzaSite and DuraSite in human corneal epithelial cells and bovine corneal endothelial cells in vitro. Ft. Lauderdale, FL: Association for Research in Vision and Ophthalmology; 2008. Apr 28 Available from: <http://www.revoptom.com/content/c/27049/dnnprintmode/true/?skinsrc=%5B%5Dskins/ro2009/pageprint&containersrc=%5B%5Dcontainers/ro2009/simple>
11. Donaldson KE, Karp CL, Dunbar MT. Evaluation and treatment of children with ocular rosacea. *Cornea*. 2007;26(1):42-46.
12. Pecosky DA, Robinson JR. Bioadhesive polymers and drug delivery. In: Tarcha PJ, editor. *Polymers for Controlled Drug Delivery*. Boca Raton, FL: CRC Publications; 1991. pp. 100-122. DOI 10.1007/978-1-4419-6618-6
13. Lux A, Maier S, Dinslage S, et al. A comparative bioavailability study of three conventional eye drops versus a single lyophilisate. *Br J. Ophthalmol* 2003;87(4):436-440.
14. Protzko E, Bowman L, Abelson M, Shapiro A, for AzaSite Clinical Study Group Phase 3 safety comparisons for 1.0% azithromycin in polymeric mucoadhesive eye drops versus 0.3% tobramycin eye drops for bacterial conjunctivitis. *Invest Ophthalmol Vis Sci*. 2007;48(8):3425-3429.
15. Akpek EK, Vittitow J, Verhoeven RS, et al. Ocular surface distribution and pharmacokinetics of a novel ophthalmic 1% azithromycin formulation. *J Ocul Pharmacol Ther*. 2009;25(5):433-439

16. Tropical Azithromycin 1%. Available from: <http://www.drugbank.ca/drugs/DB00207>, Drug created on June 13, 2005 07:24 / Updated on February 08, 2013 16:19
17. Drugs & Medication- Oral Azithromycin, Available from: <http://www.webmd.com/drugs/mono-3223-AZITHROMYCIN+250%2F500MG+-+ORAL.aspx?drugid=1527&drugname=Azithromycin+Oral&pagenumber=5>
18. Tilelli, John A.; Smith, Kathleen M.; Pettignano, Robert (2006). "Life-Threatening Bradyarrhythmia After Massive Azithromycin Overdose". *Pharmacotherapy* 26 (1): 147–50.
19. Baselt, R. (2008). *Disposition of Toxic Drugs and Chemicals in Man* (8th ed.). Foster City, CA: Biomedical Publications. pp. 132–133.
20. Grady D (May 16, 2012). "Popular Antibiotic May Raise Risk of Sudden Death". *The New York Times*. Retrieved May 18, 2012.
21. Ray, Wayne A.; Murray, Katherine T.; Hall, Kathi; Arbogast, Patrick G.; Stein, C. Michael (2012). "Azithromycin and the Risk of Cardiovascular Death". *New England Journal of Medicine* 366(20): 1881–90.
22. FDA Statement regarding azithromycin (Zithromax, Azithrocin) and the risk of cardiovascular death. Available from: <http://www.fda.gov/Drugs/Drugsafety/ucm304372.htm>
23. Zithromax (azithromycin): FDA Statement on risk of cardiovascular death. Available from: <http://www.fda.gov/Drugs/Drugsafety/ucm304372.htm>
24. FDA Drug Safety Communication: Azithromycin (Zithromax or Zmax) and the risk of potentially fatal heart rhythms. Available from: <http://www.fda.gov/Drugs/Drugsafety/ucm304372.htm>
25. AzaSite [package insert] Durham, NC: Inspire Pharmaceuticals; 2008.
26. Friedlander MH, Protzko E. Clinical development of 1% azithromycin in DuraSite, a topical azalide anti-infective for ocular surface therapy. *Clin Ophthalmol*. 2007;1(1):3–10.
27. Kowalski RP, Yatea KA, Romanowski EG, Karenchak LM, Mah FS, Gordon YJ. An ophthalmologist's guide to understanding antibiotic susceptibility and minimum inhibitory concentration data. *Ophthalmology*. 2005;112:1987–1991
28. Abelson M, Protzko E, Shapiro A, Graces-Soldana A, Bowman L, for the 1% azithromycin in DuraSite Clinical Study Group 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.
29. Vigamox [package insert] Fort Worth, TX: Alcon Laboratories, Inc; 2008.
30. Zymar [package insert] Irvine, CA: Allergan, Inc; 2004.
31. Kowalski RP, Dhaliwal DK, Karenchak LM, et al. Gatifloxacin and moxifloxacin: an in vitro susceptibility comparison to levofloxacin, ciprofloxacin, and ofloxacin using bacterial keratitis isolates. *Am J Ophthalmol*. 2003;136:500–505.
32. Ianaro A, Ialenti A, Maffia P, et al. Anti-inflammatory activity of macrolide antibiotics. *J Pharmacol Exper Ther*. 2000;292(1):156–163.
33. Amsden GW. Anti-inflammatory effects of macrolides – an underappreciated benefit in the treatment of community-acquired respiratory tract infections and chronic inflammatory pulmonary conditions? *Review J Antimicrob Chemother* 2005. 55:10–21. Epub 2004 Dec 8.
34. Shinkai M, Rubin BK. Macrolides and airway inflammation in children. *Review. Paediatr Respir Rev*. 2005;6:227–235.
35. Zhou N, Ma P, Li D-Q, Pflugfelder SC. Ft. Lauderdale, FL: Association for Research in Vision and Ophthalmology; 2009. May 3–7, Azithromycin suppresses pro-inflammatory mediators stimulated by a TLR2 ligand zymosan in human corneal epithelial cells.
36. Torkildsen G, O'Brien TP. Conjunctival tissue pharmacokinetic properties of topical azithromycin 1% and moxifloxacin 0.5% ophthalmic solutions: a single-dose, randomized, open-label, active-controlled trial in healthy adult volunteers. *Clin Ther*. 2008;30(11):2005–2014.
37. Stewart WC, Crean CS, Zink RC, Haque R, Hwang DG. Ft. Lauderdale, FL: Association for Research in Vision and Ophthalmology; 2009. May 3–7, Pharmacokinetics of azithromycin and moxifloxacin in human conjunctiva and aqueous humor during and after the approved dosing regimens.
38. Trattler WB, Kuhn KL, Haque R, Zink RC, Sall KN, Luchs J. San Francisco, CA: American Society of Cataract and Refractive Surgery; 2009. Apr 3–8, Topical azithromycin improves blepharitis signs and symptoms.
39. Touhey D, Shapiro A, Torkildsen G, et al. Ft. Lauderdale, FL: Association for Research in Vision and Ophthalmology; 2009. May 3–7, Efficacy of topical azithromycin ophthalmic solution 1% in the treatment of chronic blepharitis patients.
40. Haque RM, Torkildsen GL, Brubaker K, et al. Multi-center, open-label study evaluating the efficacy of azithromycin ophthalmic solution 1% on the signs and symptoms of subjects with blepharitis. *Cornea*. In press. doi: 10.1097/ICO.0b013e3181ca38a0
41. Geerling G, Tauber J, Baudouin C, et al. The International Workshop on Meibomian Gland Dysfunction: report of the subcommittee on management and treatment of meibomian gland dysfunction. *Invest Ophthalmol Vis Sci*. 2011;52(4):2050–2064.
42. Sadrai Z, Hajrasouliha AR, Chauhan SK, et al. Effect of topical azithromycin on innate immune responses in experimental keratitis. *Invest Ophthalmol Vis Sci*. 2009;50:e-abstract5536 – Available at: <http://eyetubeod.com/2011/09/topical-azithromycin-for-the-treatment-of-blepharitis#sthash.064ks0jL.dpuf>.
43. Blepharitis PPP-2013, AAO Cornea/External Disease PPP Panel, Hogkins Centre for Quality Eye care, [HTTP://one.AAO.org/preffered-practice-pattern/blepharitis-PPP-2013](http://one.AAO.org/preffered-practice-pattern/blepharitis-PPP-2013)