INDIAN HEALTH SERVICE
National Pharmacy and Therapeutics Committee
Formulary Brief: *Ocular Treatment for Keratoconjunctivitis & Keratoconjunctivitis Sicca*

-February 2022-

Background:

The Indian Health Service (IHS) National Pharmacy and Therapeutics Committee (NPTC) provided a pharmacotherapeutic review of the ocular treatments for keratoconjunctivitis and keratoconjunctivitis sicca, which included in-depth analyses of ophthalmic antibiotics, artificial tear lubricants, and ophthalmic corticosteroid agents. This review is the first NPTC evaluation to address general, non-glaucoma, ophthalmic conditions routinely treated by IHS clinicians. As such, there are no ophthalmic medications for these conditions currently listed on the National Core Formulary. Following clinical review and pharmacoeconomic analysis, the NPTC voted to **ADD (1) ciprofloxacin ophthalmic solution, (2) polymyxin B/trimethoprim ophthalmic solution, (3) "Any" preservative-free artificial tear substitute, (4) "Any" low-potency ophthalmic corticosteroid suspension, and (5) prednisolone acetate ophthalmic suspension** to the National Core Formulary.

Discussion:

Fluoroquinolones, such as besifloxacin, ciprofloxacin, and moxifloxacin, are readily available as ophthalmic antibiotic agents. This drug class exhibits low bacterial resistance when used topically. Additionally, these broad-spectrum antibiotics are ideal first-line therapies for certain ocular conditions. Although not as bactericidal as its newer generation counterparts, ciprofloxacin exhibits substantial bactericidal and bacteriostatic properties.[1] In fact, ciprofloxacin demonstrates better minimum inhibitory concentration (MIC) values than most other fluoroquinolones for most strains of *Pseudomonas aeruginosa.*[1] In a recent study by Haas et al. in 2013, ciprofloxacin resulted in a MIC value of 2 ug/mL compared to the besifloxacin MIC of 8 ug/mL for strain B1181.[1] *P. aeruginosa* is a common bacterial pathogen associated with contact lens wear. This is significant since more than 90% of bacterial keratitis infections occur in contact lens wearers.[2] Additionally, ciprofloxacin exhibits good corneal stromal concentrations, second only to moxifloxacin.[3]

The antimicrobial combination solution of polymyxin B/trimethoprim provides broad-spectrum coverage as well and has the lowest approved age for use (≥2 months of age). Moreover, it is commonly regarded as the ophthalmic antimicrobial drug-of-choice for most pediatric patients.[4] It also exhibits very reliable coverage against both *Haemophilus influenzae* and *Staphylococcus pneumoniae*, which are common ocular pathogens in the pediatric population.

Preservative-free artificial tears are frequently used in the treatment of a number of acute keratoconjunctivitis and keratoconjunctivitis sicca conditions. In acute cases where artificial tears are needed, preservative-free options are favored over their preservative-containing counterparts due to the potential corneal toxicity of certain preservatives.[5] For example, one common ophthalmic preservative, benzalkonium chloride, has been shown to be toxic to the cornea and is found in over 70% of topical ophthalmics.[5] Despite being well documented in various topical glaucoma agents, the advantages of preservative-free artificial tears have been less clear.[6,7] Regardless, preservative-free artificial tear substitutes continue to be recommended for a variety of keratoconjunctivitis and keratoconjunctivitis sicca conditions[8].

Lower potency corticosteroids (**Table 1**) are also commonly indicated for a variety of keratoconjunctivitis and keratoconjunctivitis sicca conditions. A number of studies from refractive surgeries have demonstrated their safety and efficacy. Because higher potency corticosteroids are known to increase the risk of elevated intraocular pressure and posterior subcapsular cataracts, the selection of a "soft" or low-potency corticosteroid for certain ophthalmic conditions is paramount.[9]

Table 1. List of suggested low-potency "soft" corticosteroids
Fluorometholone 0.1%
Loteprednol etabonate 0.38-0.5%
Prednisolone acetate 0.12%

When a higher potency ophthalmic corticosteroid is needed, prednisolone acetate 1% is frequently used for inflammatory conditions such as uveitis, stromal keratitis, or post-operative cataract surgery. It is used in similar situations as difluprednate 0.05% where a number of head-to-head studies have yielded similar safety and efficacy profiles.[10,11] Of note, a recent study published in 2021 measured intraocular pressures in 181 patients before and after cataract surgery. The surgical outcomes were similar with both agents; authors reported that prednisolone acetate caused fewer intraocular pressure spikes but also noted that it was less effective at clearing inflammation at 1-week post-operative visits. Although minimal, the lower intraocular pressures in the prednisolone acetate 1% group at both 1 and 6 weeks appeared significant (p=0.0007 and 0.004 respectively) and is consistent with other studies.[12]

Findings:

The IHS National Core Formulary currently lists limited topical ophthalmic agents. The NPTC voted to add ciprofloxacin ophthalmic solution based on its safety, broad-spectrum efficacy and Agency utilization trends. Another ophthalmic antibiotic, polymyxin B/trimethoprim solution was added for its versatility and its approved use in younger patients, down to 2 months of age.

Additionally, a preservative-free artificial tear solution was added to the National Core Formulary based on well-documented toxicity concerns related to preservatives, such as benzalkonium chloride as well as their broad utility for acute and chronic ocular conditions. No particular preservative-free artificial tear substitute was specified because numerous studies, including a recent meta-analysis of 43 randomized controlled trials, have indicated their importance but have failed to show superiority of one artificial tear substitute over another.[13]

A low-potency ophthalmic corticosteroid was also added to the National Core Formulary. This addition provides for the ability to reduce superficial inflammation without significantly increasing the risk of raising intraocular pressures or causing cataracts. Suggested low-potency corticosteroid agents are listed in Table 1 of this Brief.

Lastly, a higher potency corticosteroid, prednisolone acetate 1% suspension was added to the National Core Formulary. This agent was preferred and selected over difluprednate 0.05% emulsion due to its ability to reach similar efficacy with less risk for increased intraocular pressure.[12]

If you have any questions regarding this document, please contact the NPTC at IHSNPTC1@ihs.gov . For more information about the NPTC, please visit the NPTC website.

References:

1. Haas W, Sanfilippo C, Morris T, et al. Contribution of the R8 substituent to the in vitro antibacterial potency of besifloxacin and comparator ophthalmic fluoroquinolones. Clinical Ophthalmology. 2013; (7):821.
2. Durand ML, Barshak MB, Chodosh J. Infectious keratitis in 2021. JAMA. 2021; 326(13):1319.
3. Tuft S, Somerville TF, Li J-PO, et al. Bacterial keratitis: Identifying the areas of clinical uncertainty. Progress in Retinal and Eye Research. 2021 Dec 13:101031.
4. Wagner RS. Pediatric ocular inflammation. Immunology and Allergy Clinics of North America. 2008 Feb;28(1):169-88.
5. Xiong C, Chen D, Liu J, et al. A rabbit dry eye model induced by topical medication of a preservative benzalkonium chloride. Investigative Ophthalmology & Visual Science. 2008 May;49(5):1850-6.
6. Goldstein MH, et al. Ocular benzalkonium chloride exposure: Problems and solutions. Eye. 2021 Feb;36(2):361–8.
7. Ribeiro MV, Barbosa FT, Ribeiro LE. Effectiveness of using preservative-free artificial tears versus preserved lubricants for the treatment of Dry eyes: A systematic review. Arquivos Brasileiros de Oftalmologia. 2019 Sep;82(5):436-445.
8. Gervasio KA, Peck TJ. The Wills Eye Manual: Office and emergency room diagnosis and treatment of eye disease, 8th edition. Philadelphia, PA: Lippincott, Williams & Wilkins; 2021. 478 p.
9. Kang C, Keam SJ, Shirley M, et al. Loteprednol Etabonate (submicron) ophthalmic gel 0.38%: A review in post-operative inflammation and pain following ocular surgery. Clinical Drug Investigation. 2020 April;40(4):387–94.
10. Sheppard JD, Foster CS, Toyos MM. Difluprednate 0.05% versus prednisolone acetate 1% for endogenous anterior uveitis: Pooled efficacy analysis of two phase 3 studies. Ocular Immunology and Inflammation. 2019;27(3):484–96.
11. Palacio-Pastrana C, et al. Difluprednate 0.05% Versus Prednisolone Acetate Post-phacoemulsification for Inflammation and Pain: An efficacy and safety clinical trial. Clinical Ophthalmology. 2020 June 12; 14:1581–9.
12. Panda BB, Nanda A, Swain SC. Therapeutic efficacy of difluprednate 0.05% versus prednisolone acetate 1% in controlling inflammation and macular oedema following phacoemulsification: An optical coherence tomography-based study. Cureus. 2021 Apr 25;13(4):14673.
13. Pucker AD, Ng SM, Nichols JJ. Over the counter (OTC) artificial tear drops for dry eye syndrome. February 2016 [Cited 2023 Feb 23] In: Cochrane Database of Systematic Reviews. [Internet]. Hoboken (NJ): John Wiley & Sons, Inc. c2016.