

# Ophthalmic Antibiotic–Steroid Combinations Review

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### **FDA-Approved Indications**<sup>1,2,3,4</sup>

All of the listed drugs are indicated for corticosteroid-responsive inflammatory ocular conditions for which a corticosteroid is indicated and where bacterial infection or a risk of bacterial infection exists.

<b>Drug</b>	<b>Manufacturer</b>
dexamethasone / neomycin / polymyxin B (Maxitrol <sup>®</sup> )	generic
dexamethasone / tobramycin (Tobradex <sup>®</sup> )	generic (suspension) Alcon (ointment)
hydrocortisone / neomycin / polymyxin B	generic
hydrocortisone / neomycin / bacitracin / polymyxin B	generic
loteprednol / tobramycin (Zylet <sup>™</sup> )	Bausch and Lomb
prednisolone / gentamicin (Pred-G <sup>®</sup> , Pred-G <sup>®</sup> S.O.P)	Allergan
prednisolone / neomycin / polymyxin B (Poly-Pred <sup>®</sup> )	Allergan
prednisolone / sulfacetamide (Blephamide <sup>®</sup> , Blephamide <sup>®</sup> S.O.P.)	generic (solution, suspension) Alcon (ointment)

### **Overview**

Infections of the eye can rapidly damage important functional structures and lead to permanent vision loss or blindness. A corticosteroid will reduce inflammation, and when combined with an antibiotic, the antibiotic treats or prevents an infection associated with the inflammation.

### **Pharmacology**

Corticosteroids provide local anti-inflammatory activity. Dexamethasone, hydrocortisone, loteprednol, and prednisolone provide local anti-inflammatory activity. Loteprednol is an analog of prednisolone and induces slightly less elevation of intraocular pressure (IOP) compared to prednisolone.<sup>5</sup>

Antibiotics provide local antibacterial activity in the respective spectrums. Selection of the antibiotic should depend on the known or suspected organisms involved in the potential or present infection.

Aminoglycosides, which include gentamicin, neomycin, and tobramycin, inhibit protein synthesis by binding to the 30S ribosomal subunit.

Polymyxin B is bactericidal for a variety of gram-negative organisms. It increases the permeability of the bacterial cell membrane by interacting with the phospholipid components of the membrane.

Bacitracin, which is bactericidal, inhibits bacterial growth through prevention of cell wall subunits being added to the peptidoglycan chain.

Sulfacetamide is a synthetic sulfonamide that inhibits bacterial dihydrofolate synthetase, a bacterial enzyme responsible for the conversion of *p*-aminobenzoic acid (PABA) into folic acid. Production of folic acid is an essential component of bacterial development.

### ***Pharmacokinetics***

Ophthalmic ointments have the longest contact time between the drug and the ocular tissues; however, ointments can impede delivery of other ophthalmic drugs by serving as a barrier. Ointments are useful in children so to decrease the loss of drugs by tears. Ophthalmic suspensions mix with tears less rapidly and remain in the cul-de-sac longer than solutions. Systemic absorption of these products is minimal.

### ***Contraindications/Warnings***<sup>6,7,8,9,10,11,12,13</sup>

These combination agents are contraindicated in most viral diseases of the cornea and conjunctiva, in mycobacterial infection of the eye, and fungal diseases of ocular structures.

Prolonged use of corticosteroids may result in glaucoma, as well as increase the hazard of secondary ocular infections. Corticosteroids should be used with caution in the presence of glaucoma. If corticosteroid-containing ophthalmic preparations are used for ten days or longer, IOP should be monitored even though it may be difficult in children and uncooperative patients.

### ***Drug Interactions***

Based on the minimal extent of absorption with these agents, interactions with systemically administered drugs are unlikely to occur.

### ***Adverse Effects***<sup>14,15,16,17,18,19,20,21</sup>

Most effects are related to local irritation on installation. Occasionally, allergic sensitization (itching, swelling, and conjunctival erythema) may occur. Serious hypersensitivity reactions (anaphylaxis) are rare.

Corticosteroids have been associated with elevated IOP with possible development of glaucoma, infrequent optic nerve damage, posterior subcapsular cataract formation, and delayed wound healing. Study of one patient population showed loteprednol/tobramycin (Zylet) to cause less IOP increases and less adverse event occurrence compared to dexamethasone/tobramycin (Tobradex).<sup>22,23</sup>

Secondary fungal and viral infections have been reported.

Adverse effects data are compiled from package inserts and cannot be considered comparative or all inclusive.

### ***Special Populations***<sup>24,25,26,27,28,29,30,31</sup>

#### *Pediatrics*

Safety and effectiveness of these agents in pediatrics have not been established with the exception of tobramycin/dexamethasone (Tobradex), which has been established in patients two years and older. Data are available for patients older than two months for prednisolone/sulfacetamide (Blephamide).

#### *Pregnancy*

All products in this class are Pregnancy Category C.

**Dosages**<sup>32,33,34,35</sup>

Apply to affected eye(s).

Drug	Ointment Dosage	Dropper Dosage	Availability
0.1% dexamethasone / 0.35% neomycin base / 10,000 units polymyxin B sulfate (Maxitrol)	Apply every three to four hours	One to two drops every three to four hours	5 mL suspension, 3.5 gm ointment
0.1% dexamethasone / 0.3% tobramycin (Tobradex)	½ inch up to three or four times daily	One to two drops every four to six hours. During the first 24-48 hours, the dosage may be increased to one to two drops every two hours.	2.5, 5, and 10 mL suspension, 3.5 gm ointment
1% hydrocortisone / 0.35% neomycin sulfate / 10,000 units polymyxin B suspension	--	One to two drops every three to four hours	7.5 mL suspension
1% hydrocortisone / 0.35% neomycin base / 400 units bacitracin zinc / 10,000 units polymyxin B ointment	Apply every three to four hours	--	3.5 gm ointment
0.5% loteprednol / 0.3% tobramycin suspension (Zylet)	--	One to two drops every four to six hours; during the first 24-48 hours, may increase to one to two drops every two hours	2.5, 5, and 10 mL suspension
1% prednisolone / 0.3% gentamicin base suspension (Pred-G) 0.6% prednisolone / 0.3% gentamicin base ointment (Pred-G S.O.P.)	½ inch once to three times daily	One drop two to four times daily; May increase to one drop every hour during first 24-48 hours	2, 5 mL suspension, 3.5 gm ointment
0.5% prednisolone / 0.35% neomycin base / 10,000 units polymyxin B sulfate suspension (Poly-Pred)	--	One to two drops every three to four hrs	5 mL suspension
0.25% prednisolone / 10% sulfacetamide solution 0.2% prednisolone / 10% sulfacetamide suspension (Blephamide) 0.2% prednisolone / 10% sulfacetamide ointment (Blephamide S.O.P.)	½ inch up to three or four times daily	One to three drops every one to four hours	5 and 10 mL solution, suspension, 3.5 gm ointment

## **Clinical Trials**

### Search strategy

Articles were identified through searches performed on PubMed and review of information sent by manufacturers. Search strategy included the FDA-approved use of all drugs in this class. Studies included for analysis in the review were published in English, performed with human participants, and randomly allocated participants to comparison groups. In addition, studies must contain clearly stated, predetermined outcome measure(s) of known or probable clinical importance, use data analysis techniques consistent with the study question, and include follow-up (endpoint assessment) of at least 80 percent of participants entering the investigation. Despite some inherent bias found in all studies, including those sponsored and/or funded by pharmaceutical manufacturers, the studies in this therapeutic class review were determined to have results or conclusions that do not suggest systematic error in their experimental study design. While the potential influence of manufacturer sponsorship/funding must be considered, the studies in this review have also been evaluated for validity and importance.

Very little good quality comparative data have been published for the products in this class.

### tobramycin/dexamethasone (Tobradex) and tobramycin/loteprednol (Zylet)

In a double-blind, randomized trial, tobramycin/dexamethasone and tobramycin/loteprednol were compared for effectiveness in controlling inflammation in 40 patients with blepharokeratoconjunctivitis.<sup>36</sup> Patients received tobramycin 0.3%/dexamethasone 0.1% or tobramycin 0.3%/loteprednol 0.5% twice daily in the test eye. Baseline evaluation recorded the severity of blepharitis, conjunctivitis, ocular discharge, and corneal punctate epithelial keratopathy on a scale of three (extensive) to zero (minimum) for each component. Patients with a total score of greater than six were included in the trial. After three to five days, the ocular surface was reevaluated for treatment response. No significant differences were noted between the groups at baseline. Mean post-treatment scores were as follows: total ocular surface scores, 1.8 and 3.4 ( $p=0.002$ ); blepharitis scores, 0.9 and 1.35 ( $p=0.017$ ); discharge scores, 0.2 and 0.6 ( $p=0.025$ ); and conjunctivitis scores, 0.15 and 0.6 ( $p=0.013$ ) for tobramycin/dexamethasone and tobramycin/loteprednol, respectively. Corneal punctate epithelial keratopathy scores were similar in both groups. Tobramycin 0.3%/dexamethasone 0.1% significantly decreased clinical signs of ocular inflammation and total ocular inflammation scores when compared with tobramycin 0.3%/loteprednol 0.5% in patients with moderate to severe blepharokeratoconjunctivitis.

## **Summary**

A wide variety of combinations of corticosteroids and antibiotics are available in this class. Several agents are available as ointments and suspensions. There are not enough published comparative data to distinguish any of the available products from the others.

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