



Ophthalmic Antibiotic–Steroid Combinations Therapeutic Class Review (TCR)

March 8, 2020

No part of this publication may be reproduced or transmitted in any form or by any means, electronic or mechanical, including photocopying, recording, digital scanning, or via any information storage or retrieval system without the express written consent of Magellan Rx Management.

All requests for permission should be mailed to:

Magellan Rx Management
Attention: Legal Department
6950 Columbia Gateway Drive
Columbia, Maryland 21046

The materials contained herein represent the opinions of the collective authors and editors and should not be construed to be the official representation of any professional organization or group, any state Pharmacy and Therapeutics committee, any state Medicaid Agency, or any other clinical committee. This material is not intended to be relied upon as medical advice for specific medical cases and nothing contained herein should be relied upon by any patient, medical professional or layperson seeking information about a specific course of treatment for a specific medical condition. All readers of this material are responsible for independently obtaining medical advice and guidance from their own physician and/or other medical professional in regard to the best course of treatment for their specific medical condition. This publication, inclusive of all forms contained herein, is intended to be educational in nature and is intended to be used for informational purposes only. Send comments and suggestions to PSTCReDitor@magellanhealth.com.

March 2020

Proprietary Information. Restricted Access – Do not disseminate or copy without approval.
© 2004-2020 Magellan Rx Management. All Rights Reserved.

MagellanRx
MANAGEMENTSM

FDA-APPROVED INDICATIONS

All 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.

Drug	Strength	Manufacturer
dexamethasone / neomycin sulfate / polymyxin B sulfate (Maxitrol®) ¹	0.1%; EQ 3.5 mg base/mL; 10,000 units/mL	generic, Alcon/Novartis (suspension, ointment)
dexamethasone / tobramycin (TobraDex®) ²	0.1%; 0.3%	generic, Alcon/Novartis (suspension), Alcon/Novartis (ointment)
dexamethasone / tobramycin (TobraDex® ST) ³	0.05%; 0.3%	Alcon/Eyevance (suspension)
hydrocortisone / neomycin sulfate / polymyxin B sulfate ⁴	1%; EQ 3.5 mg base/mL; 10,000 units/mL	Sandoz (suspension)
hydrocortisone / neomycin sulfate / bacitracin zinc / polymyxin B sulfates ⁵	1%; EQ 3.5 mg base/gm; 400 units/gm; 10,000 units/gm	generic (ointment)
loteprednol / tobramycin (Zylet™) ⁶	0.5%; 0.3%	Valeant (suspension)
prednisolone acetate / gentamicin sulfate (Pred-G®) ⁷	1%; EQ 0.3% base	Allergan (suspension)
prednisolone acetate / gentamicin sulfate (Pred-G® S.O.P.) ⁸	0.6%; EQ 0.3% base	Allergan (ointment)
prednisolone acetate / sulfacetamide sodium (Blephamide®, Blephamide® S.O.P.) ⁹	0.2%; 10%	generic, Allergan (suspension, ointment)
prednisolone sodium phosphate / sulfacetamide sodium ¹⁰	EQ 0.23% phosphate; 10%	Valeant/Bausch

OVERVIEW¹¹

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, which may be associated with the inflammation. The agents within this class are indicated for corticosteroid-responsive inflammatory ocular conditions (e.g., bacterial conjunctivitis, corneal abrasion, uveitis) for which a corticosteroid is indicated and where bacterial infection or a risk of bacterial infection exists.

PHARMACOLOGY^{12,13}

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.

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 the addition of cell wall subunits 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.

PHARMACOKINETICS¹⁴

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 to decrease the loss of drug by tears. Compared to solutions, ophthalmic suspensions mix with tears less rapidly and remain in the cul-de-sac longer. Systemic absorption of these products is minimal.

CONTRAINDICATIONS/WARNINGS^{15,16,17,18,19,20,21,22,23}

These combination agents are contraindicated in most viral diseases of the cornea and conjunctiva, 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 10 days or longer, IOP should be monitored even though it may be difficult in children and uncooperative patients.

Neomycin has been associated with hypersensitivity reactions and cross-sensitization to other aminoglycosides can occur.

DRUG INTERACTIONS

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

ADVERSE EFFECTS^{24,25,26,27,28,29,30,31,32,33,34}

Most effects are related to local irritation on instillation. Occasionally, allergic sensitization (e.g., itching, swelling, and conjunctival erythema) may occur. Serious hypersensitivity reactions (e.g., 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. Studies in healthy volunteers showed loteprednol/tobramycin (Zylet) to cause less increase in IOP and better tolerability compared to dexamethasone/tobramycin (TobraDex). Elevations in intraocular pressure should not be clinically significant with short-term use.

Ulcerative keratitis, headache, and Stevens-Johnson syndrome have been reported with neomycin/polymyxin B/dexamethasone (Maxitrol) post-marketing.

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^{35,36,37,38,39,40,41,42,43,44}

Pediatrics

Safety and effectiveness of these agents in pediatrics have not been established, apart from tobramycin/dexamethasone (TobraDex, TobraDex ST) and neomycin/polymyxin B/dexamethasone (Maxitrol), which are indicated in patients 2 years and older. Data are available for patients older than 2 months for prednisolone/sulfacetamide (Blephamide).

In clinical trials, loteprednol/tobramycin (Zylet) did not show efficacy for lid inflammation or blepharoconjunctivitis in pediatric patients aged 0 to 6 years.

Pregnancy

Neomycin/polymyxin B/dexamethasone (Maxitrol) and prednisolone acetate/gentamicin sulfate (Pred-G) were previously Pregnancy Category C agents, but the drug labeling has been updated to comply with the Pregnancy and Lactation Labeling Rule (PLLR). The current labeling state that there are no adequate studies in pregnant women; neomycin/polymyxin B/dexamethasone label also states that prolonged or repeated use of a corticosteroid during pregnancy has been associated with intra-uterine growth retardation. The remaining products in this class are Pregnancy Category C.

DOSAGES^{45,46,47,48,49}

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 3 to 4 hours	1 to 2 drops every 3 to 4 hours	5 mL suspension; 3.5 g ointment
0.1% dexamethasone / 0.3% tobramycin (TobraDex)	½ inch up to 3 or 4 times daily	1 to 2 drops every 4 to 6 hours; During the first 24 to 48 hours, the dosage may be increased to 1 to 2 drops every 2 hours	2.5 mL, 5 mL, and 10 mL suspension; 3.5 g ointment
0.05% dexamethasone / 0.3% tobramycin (TobraDex ST)	--	1 drop every 4 to 6 hours; During the initial 24 to 48 hours, dosage may be increased to 1 drop every 2 hours	5 mL suspension
1% hydrocortisone / 0.35% neomycin sulfate / 10,000 units polymyxin B suspension	--	1 to 2 drops every 3 to 4 hours	7.5 mL suspension
1% hydrocortisone / 0.35% neomycin base / 400 units bacitracin zinc / 10,000 units polymyxin B ointment	Apply every 3 to 4 hours	--	3.5 g ointment
0.5% loteprednol / 0.3% tobramycin suspension (Zylet)	--	1 to 2 drops every 4 to 6 hours; during the first 24 to 48 hours, may increase to 1 to 2 drops every 2 hours	5 mL 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 1 to 3 times daily	1 drop 2 to 4 times daily; May increase to 1 drop every hour during first 24 to 48 hours	5 mL suspension; 3.5 g ointment
0.2% prednisolone / 10% sulfacetamide suspension (Blephamide) 0.2% prednisolone / 10% sulfacetamide ointment (Blephamide S.O.P.)	½ inch up to 3 or 4 times daily	1 to 3 drops every 1 to 4 hours	5 mL and 10 mL suspension; 3.5 g ointment
0.23% prednisolone / 10% sulfacetamide solution	--	1 to 3 drops every 1 to 4 hours	5 mL solution

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% 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 and/or 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.⁵⁰ 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 3 (extensive) to 0 (minimum) for each component. Patients with a total score of greater than 6 were included in the trial. After 3 to 5 days, the ocular surface was re-evaluated 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 trials to distinguish any of the available products from the others.

REFERENCES

- 1 Maxitrol [package insert]. Fort Worth, TX; Alcon; May 2018.
- 2 TobraDex suspension [package insert]. Ft. Worth, TX; Alcon; May 2018.
- 3 TobraDex ST [package insert]. Ft. Worth, TX; Alcon; February 2009.
- 4 Available at: <http://clinicalpharmacology.com>. Accessed March 8, 2020.
- 5 Available at: <http://clinicalpharmacology.com>. Accessed March 8, 2020.
- 6 Zylet [package insert]. Tampa, FL; Bausch and Lomb; September 2019.
- 7 Pred-G [package insert]. Irvine, CA; Allergan; July 2018.
- 8 Available at: <http://clinicalpharmacology.com>. Accessed March 8, 2020.
- 9 Available at: <http://clinicalpharmacology.com>. Accessed March 8, 2020.
- 10 Available at: <http://clinicalpharmacology.com>. Accessed March 8, 2020.
- 11 Available at: <http://clinicalpharmacology.com>. Accessed March 15, 2019.
- 12 Available at: <http://clinicalpharmacology.com>. Accessed March 8, 2020.
- 13 Lotemax [package insert]. Bridgewater, NJ; Bausch and Lomb; September 2016.
- 14 Available at: <http://clinicalpharmacology.com>. Accessed March 8, 2020.
- 15 Cortisporin ointment [package insert]. Bristol, TN; Monarch; August 2003.
- 16 Cortisporin suspension [package insert]. Bristol, TN; Monarch; July 2003.
- 17 TobraDex ointment [package insert]. Ft. Worth, TX; Alcon; October 2003.
- 18 TobraDex suspension [package insert]. Ft. Worth, TX; Alcon; May 2018.
- 19 Zylet [package insert]. Tampa, FL; Bausch and Lomb; September 2019.
- 20 Maxitrol [package insert]. Fort Worth, TX; Alcon; May 2018.
- 21 Pred-G [package insert]. Irvine, CA; Allergan; July 2018.
- 22 Available at: <http://clinicalpharmacology.com>. Accessed March 8, 2020.
- 23 TobraDex ST [package insert]. Ft. Worth, TX; Alcon; February 2009.
- 24 Cortisporin ointment [package insert]. Bristol, TN; Monarch; August 2003.
- 25 Cortisporin suspension [package insert]. Bristol, TN; Monarch; July 2003.
- 26 TobraDex ointment [package insert]. Ft. Worth, TX; Alcon; October 2003.
- 27 TobraDex suspension [package insert]. Ft. Worth, TX; Alcon; May 2018.
- 28 Zylet [package insert]. Tampa, FL; Bausch and Lomb; September 2019.
- 29 Maxitrol [package insert]. Fort Worth, TX; Alcon; May 2018.
- 30 Pred-G [package insert]. Irvine, CA; Allergan; July 2018.
- 31 Available at: <http://clinicalpharmacology.com>. Accessed March 8, 2020.
- 32 TobraDex ST [package insert]. Ft. Worth, TX; Alcon; February 2009.
- 33 Holland EJ, Bartlett JD, Paterno MR, et al. Effects of loteprednol/tobramycin versus dexamethasone/tobramycin on intraocular pressure in healthy volunteers. *Cornea*. 2008; 27(1):50-5.
- 34 Bartlett JD, Holland EJ, Usner DW, et al. Tolerability of loteprednol/tobramycin versus dexamethasone/tobramycin in healthy volunteers: results of a 4-week, randomized, double-masked, parallel-group study. *Curr Med Res Opin*. 2008; 24(8):2219-27.
- 35 Cortisporin ointment [package insert]. Bristol, TN; Monarch; August 2003.
- 36 Cortisporin suspension [package insert]. Bristol, TN; Monarch; July 2003.
- 37 TobraDex ointment [package insert]. Ft. Worth, TX; Alcon; October 2003.
- 38 TobraDex suspension [package insert]. Ft. Worth, TX; Alcon; May 2018.
- 39 Zylet [package insert]. Tampa, FL; Bausch and Lomb; September 2019.
- 40 Maxitrol [package insert]. Fort Worth, TX; Alcon; May 2018.
- 41 Pred-G [package insert]. Irvine, CA; Allergan; July 2018.
- 42 Available at: <http://clinicalpharmacology.com>. Accessed March 8, 2020.
- 43 TobraDex ST [package insert]. Ft. Worth, TX; Alcon; February 2009.
- 44 Zylet [package insert]. Tampa, FL; Bausch and Lomb; September 2019.
- 45 Available at: <http://clinicalpharmacology.com>. Accessed March 8, 2020.
- 46 TobraDex suspension [package insert]. Ft. Worth, TX; Alcon; May 2018.
- 47 Zylet [package insert]. Tampa, FL; Bausch and Lomb; September 2019.
- 48 Pred-G [package insert]. Irvine, CA; Allergan; July 2018.
- 49 TobraDex ST [package insert]. Ft. Worth, TX; Alcon; February 2009.
- 50 Rhee SS, Mah FS. Comparison of tobramycin 0.3%/dexamethasone 0.1% and tobramycin 0.3%/loteprednol 0.5% in the management of blepharokeratoconjunctivitis. *Adv Ther*. 2007; 24(1):60-7.