Therapeutic Class Overview
Ophthalmic Steroids

Therapeutic Class

- **Overview/Summary:** Ophthalmic steroids are used in managing postoperative inflammation following various ocular surgeries, anterior uveitis, ocular allergies, external eye inflammatory diseases associated with infections, corneal injury from chemical, radiation or thermal burns and penetration of foreign bodies.[1-17] Ocular inflammation is a manifestation of cellular and vascular response of the host tissue to injury.[18,19] Prostaglandins cause vasodilation and increase vascular permeability resulting in increased aqueous humor protein concentration and ocular inflammation. They also act on intraocular pressure (IOP) and iris smooth muscle causing miosis. Topical administration of anti-inflammatory agents for ocular conditions is preferred over systemic administration due to higher ocular drug concentrations with minimal systemic adverse events.[18-20] Steroids inhibit edema, cellular infiltration, fibrin deposition, capillary dilation, leukocyte migration, capillary and fibroblast proliferation, collagen deposition and scar formation associated with inflammation.[21,22] There is no generally accepted mechanism of action for ocular steroids; however, they are thought to exert their anti-inflammatory activity by inhibiting phospholipase A_2 and subsequently inhibiting both cyclooxygenase and lipoxygenase pathways. Most agents in this class are indicated to treat various steroid-responsive inflammatory ocular conditions of the palpebral and bulbar conjunctiva, cornea, and anterior segment of the globe such as allergic conjunctivitis, acne rosacea, superficial punctuate keratitis, herpes zoster keratitis, iritis and cyclitis.[1-17] Currently, dexamethasone, fluorometholone, prednisolone acetate and prednisolone sodium phosphate are available generically in at least one ophthalmic dosage form or strength.[23] The use of ophthalmic steroids in some individuals may elevate IOP.[24] The ability of a specific ophthalmic steroid to induce elevation of IOP is based on several factors including dosage, anti-inflammatory potency and duration of treatment. Increases in IOP have been observed with ophthalmic fluorometholone, loteprednol etabonate, and rimexolone in clinical trials.

Table 1. Current Medications Available in the Class[1-17]

Generic (Trade Name)	Food and Drug Administration Approved Indications	Dosage Form/Strength	Generic Availability
Dexamethasone ophthalmic* (Maxidex®)	Corneal injury from chemical, radiation or thermal burns; penetration of foreign bodies; steroid-responsive inflammatory ocular conditions†	Ophthalmic solution: 0.1% (5 mL) Ophthalmic suspension: 0.1% (5 mL)	a
Difluprednate ophthalmic (Durezol®)	Anterior uveitis, endogenous; postoperative inflammation and pain following ocular surgery	Ophthalmic emulsion: 0.05% (5 mL)	-
Fluorometholone ophthalmic (Flarex®, FML®, FML Liquifilm®*, FML Forte®)	Steroid-responsive inflammatory ocular conditions†	Ophthalmic ointment: 0.1% (3.5 g) Ophthalmic suspension: 0.1% (5, 10, 15 mL) 0.25% (5, 10 mL)	a
Loteprednol etabonate ophthalmic (Alrex®, Lotemax®)	Postoperative inflammation and pain following ocular surgery (gel, ointment); postoperative inflammation following ocular surgery (0.5% suspension); temporary relief of the signs and symptoms of seasonal allergic conjunctivitis (0.2% suspension); steroid-responsive inflammatory	Ophthalmic gel: 0.5% (5 g) Ophthalmic ointment: 0.5% (3.5 g) Ophthalmic suspension: 0.2% (5, 10 mL) 0.5% (2.5, 5, 10, 15 mL)	-

Generic (Trade Name)	Food and Drug Administration Approved Indications	Dosage Form/Strength	Generic Availability
	ocular conditions (0.5% suspension)†		
Prednisolone acetate ophthalmic (Omnipred®*, Pred Forte®*, Pred Mild®)	Corneal injury from chemical, radiation or thermal burns; penetration of foreign bodies; steroid-responsive inflammatory ocular conditions†	Ophthalmic solution: 1% (10 mL) Ophthalmic suspension: 0.12% (5, 10 mL) 1% (1, 5, 10, 15 mL)	a
Prednisolone sodium phosphate ophthalmic	Corneal injury from chemical, radiation or thermal burns; penetration of foreign bodies; steroid-responsive inflammatory ocular conditions†	Ophthalmic solution: 1% (10 mL)	a
Rimexolone ophthalmic (Vexol®)	Anterior uveitis; postoperative inflammation following ocular surgery	Ophthalmic suspension: 1% (5, 10 mL)	-

*Generic available in at least one dosage form or strength.
†Indicated for the treatment of steroid-responsive inflammatory ocular conditions of the palpebral and bulbar conjunctiva, cornea and anterior segment of the globe, such as allergic conjunctivitis, acne rosacea, superficial punctuate keratitis, herpes zoster keratitis, iritis, cyclitis and selected infective conjunctivitides when the inherent risk of steroid use is accepted to obtain a diminution in edema and inflammation.

Evidence-based Medicine

- In patients who underwent cataract surgery (N=438), significantly more patients had an anterior chamber cell grade of zero on days eight, 15 and 29 in the ophthalmic difluprednate group compared to the placebo group (*P*<0.0001 for all). No serious adverse events were reported.[25]
- In two, six-week trials in patients with seasonal allergic conjunctivitis, ophthalmic loteprednol 0.2% was significant more effective for treatment of the symptoms of seasonal allergic conjunctivitis compared to placebo.[26,27] There was a greater reduction in bulbar conjunctival injection and itching in the ophthalmic loteprednol 0.2% group than the placebo group, beginning approximately two hours after instillation and throughout the first 14 days of treatment (*P*<0.001).[26]
- In patients who underwent cataract removal surgery, ophthalmic loteprednol 0.5% was significantly more effective than placebo for the treatment of anterior chamber inflammation (grade of zero).[28]
- The safety and efficacy of ophthalmic rimexolone 1% was compared to ophthalmic prednisolone acetate 1% in patients with acute or chronic uveitis or recurrent iridocyclitis in three randomized-controlled trials.[29,30] There were no significant differences in anterior chamber cell and flare scores between the two treatment groups and the overall clinical efficacy was similar at the end of treatment (four weeks). More patients in the ophthalmic prednisolone acetate 1% group had an increase in intraocular pressure (IOP) ≥10 mm Hg compared to patients in the ophthalmic rimexolone 1% group (*P* value not reported).[31] The results of a study by Biswas et al (N=78) did not demonstrate any difference in IOP elevation between the two ophthalmic steroids.[32]
- Ophthalmic rimexolone 1% was compared to ophthalmic prednisolone acetate 1% in two randomized-controlled trials in patients who underwent cataract extraction surgery.[33,34] Both treatments were administered for 15 days. There were no significant differences between the two treatment groups in terms of anterior chamber cells and flare or conjunctival hyperemia on days seven and 15 (*P*>0.05). The IOP measurements were similar between the two treatment groups in both studies.
- In children four to eight years of age undergoing bilateral strabismus surgery, the change in IOP was greater with ophthalmic rimexolone 1% compared to ophthalmic fluorometholone 0.1% (*P*<0.001). There was no difference between groups in the number of eyes that experienced an IOP >21 mm Hg (*P*=0.53). There was a greater improvement in conjunctival inflammation on days 13 and 20 in the ophthalmic rimexolone 1% group compared to the ophthalmic fluorometholone 0.1% group (*P*=0.03).[35]
- Two ophthalmic prednisolone acetate 1% formulations, Omnipred® and Pred Forte®, were compared in adult patients who underwent cataract surgery.[42] There were no statistically significant differences

in clinical efficacy between the ophthalmic prednisolone acetate treatment groups in terms of postoperative ocular pain, keratitis, aqueous cell counts or aqueous flare on days one, 12 and 28.[36]

Key Points within the Medication Class

- According to Current Clinical Guidelines:
  - In patients undergoing cataract surgery, topical anti-inflammatory agents are used postoperatively to reduce the inflammatory response and to treat established cystoid macular edema. Topically applied nonsteroidal anti-inflammatory drugs alone or in combination with corticosteroids are more effective than topical corticosteroids alone in preventing and treating cystoid macular edema.[37]
  - A short course (less than two weeks) of a low-potency topical corticosteroid may be added to the allergic conjunctivitis treatment regimen if symptoms are not controlled despite treatment with an ophthalmic antihistamine with mast-cell stabilizing properties. Topical corticosteroids are effective in relieving allergy symptoms ; however, their use should be limited to the acute suppression of symptoms due to the potential for adverse side effects with prolonged use (e.g., cataract formation and elevated intraocular pressure [IOP]).[38,39]
  - Low dose topical corticosteroids may be used for short-term (two-week) suppression of irritation secondary to inflammation in moderate dry eye syndrome. Patients should be monitored for adverse side effects.[40]
  - There is insufficient evidence to make definitive recommendations for the treatment of blepharitis, and cure is not possible in most cases. Treatments include:
    - Warm compresses.
    - Eyelid hygiene.
    - Antibiotics (topical and/or systemic).
    - Ophthalmic anti-inflammatory agents (e.g., topical corticosteroids, cyclosporine).[41]
  - Topical corticosteroids are typically applied several times daily to the eyelids or ocular surface. Once the inflammation is controlled, treatment should be tapered and discontinued and then used intermittently to maintain patient comfort. [41]
  - Ophthalmic corticosteroid therapy may have a beneficial role in treating some cases of infectious keratitis; however, there is no conclusive evidence that ophthalmic corticosteroids alter clinical outcomes. Potential disadvantages of ophthalmic corticosteroid use include infection reoccurrence, local immunosuppression, inhibition of collagen synthesis predisposing to corneal melting and increased IOP.[42]
- Other Key Facts:
  - Dexamethasone, fluorometholone, prednisolone acetate and prednisolone sodium phosphate are available generically in at least one ophthalmic dosage form or strength.[23]
  - The ability of a specific ophthalmic steroid to induce elevation of IOP is based on several factors including dosage, anti-inflammatory potency and duration of treatment.[24]

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Therapeutic Class Review
Ophthalmic Steroids

Overview/Summary

Ophthalmic steroids are used in managing postoperative inflammation following various ocular surgeries, anterior uveitis, ocular allergies, external eye inflammatory diseases associated with infections, corneal injury from chemical, radiation or thermal burns and penetration of foreign bodies.[1-17] Ocular inflammation is a manifestation of cellular and vascular response of the host tissue to injury.[18,19] Tissue injury activates phospholipase A_2, breaking down cell membrane phospholipids to arachidonic acid.[20] Arachidonic acid enters the cyclooxygenase pathway resulting in the formation of prostaglandins and thromboxanes, or enters the lipoxygenase pathway resulting in the formation of eicosanoids.[18,20] Prostaglandins are implicated in the pathogenesis of ocular inflammation. Prostaglandins cause vasodilation and increase vascular permeability resulting in increased aqueous humor protein concentration. They also act on intraocular pressure (IOP) and iris smooth muscle causing miosis.

The pharmacological management of ocular inflammation involves the administration of anti-inflammatory medications.[18] Topical administration of anti-inflammatory agents for ocular conditions is preferred over systemic administration due to higher ocular drug concentrations with minimal systemic adverse events.[18-20] Ophthalmic steroids and ophthalmic nonsteroidal anti-inflammatory drugs (NSAIDs) are two medication classes used in the management of ocular inflammation. Ophthalmic steroids have been widely used in ophthalmic clinical practice since the 1950s.[21] Steroids inhibit edema, cellular infiltration, fibrin deposition, capillary dilation, leukocyte migration, capillary and fibroblast proliferation, collagen deposition and scar formation associated with inflammation.[22,23] Moreover, steroids can enter the nucleus and interact with specific deoxyribonucleic acid sequences and alter the production of inhibitory proteins, the key enzymes and inflammatory cytokines responsible for inflammatory cell recruitment. There is no generally accepted mechanism of action for ocular steroids; however, they are thought to exert their anti-inflammatory activity by inhibiting phospholipase A_2 and subsequently inhibiting both cyclooxygenase and lipoxygenase pathways.

Most agents in this class are indicated for the treatment of various steroid-responsive inflammatory ocular conditions of the palpebral and bulbar conjunctiva, cornea, and anterior segment of the globe such as allergic conjunctivitis, acne rosacea, superficial punctuate keratitis, herpes zoster keratitis, iritis, and cyclitis. Ophthalmic steroids in combination with an ophthalmic anti-infective are indicated in ocular conditions, where the risk of infection is high, where the risk of steroid use in certain infective conjunctivitides is accepted to obtain a diminution in edema and inflammation, and where there is an expectation that potentially dangerous bacteria will be present in the eye.[1-17] Periocular steroid injections are used to treat some types of ocular inflammation, specifically when the posterior segment of the eye is involved, where topical administration would be ineffective. This review will focus on the single-entity ophthalmic steroid products.

Ophthalmic steroids are available in various formulations including emulsions, ointments, solutions and suspensions.[7-20] The steroids formulated for topical administration to the eye include ophthalmic dexamethasone (Maxidex®), difluprednate (Durezol®), fluorometholone (Flarex®, FML®, FML Liquifilm®, FML Forte®), loteprednol etabonate (Alrex®, Lotemax®), prednisolone acetate (Omnipred®, Pred Forte®, Pred Mild®), prednisolone sodium phosphate and rimexolone (Vexol®). Currently, dexamethasone, fluorometholone, prednisolone acetate and prednisolone sodium phosphate are available generically in at least one ophthalmic dosage form or strength.[24] The use of ophthalmic steroids in some individuals may elevate IOP. This is also known as steroid-induced ocular hypertension, and usually occurs within a few weeks or months of beginning treatment.[21] The ability of a specific ophthalmic steroid to induce elevation of IOP is based on several factors including dosage, anti-inflammatory potency and duration of treatment. Increases in IOP have been observed with ophthalmic fluorometholone, loteprednol etabonate, and rimexolone in clinical trials. Ophthalmic steroids are contraindicated in most viral diseases of the cornea

and conjunctiva including acute epithelial herpes simplex keratitis (dendritic keratitis), vaccinia, varicella and also in ocular mycobacterial infections and fungal disease of ocular structures.[1-17]

The American Optometric Association states that ophthalmic steroids may be used to suppress inflammation following cataract surgery. Specifically, ophthalmic steroids such as prednisolone acetate 1% may be used every two to four hours to control inflammation associated with anterior uveitis, depending on the degree of inflammation.[25] Topical anti-inflammatory agents are used postoperatively to reduce the inflammatory response to cataract surgery and to treat established cystoid macular edema, without preference given to on ophthalmic steroid over another. Topically applied NSAIDs alone or in combination with ophthalmic steroids are more effective than topical steroids alone in preventing and treating cystoid macular edema.[26] In addition, ophthalmic steroids are generally used immediately following refractive surgeries and tapered over a period of days to weeks, and sometimes months.[27] For the treatment of bacterial keratitis, there is no conclusive evidence that treatment with ophthalmic steroids alters clinical outcomes.[28]

Medications

Table 1. Medications Included Within Class Review[1-17]

Generic Name (Trade name)	Medication Class	Generic Availability
Dexamethasone ophthalmic* (Maxidex®)	Ophthalmic steroids	a
Difluprednate ophthalmic (Durezol®)	Ophthalmic steroids	-
Fluorometholone ophthalmic (Flarex®, FML®, FML Liquifilm®*, FML Forte®)	Ophthalmic steroids	a
Loteprednol etabonate ophthalmic (Alrex®, Lotemax®)	Ophthalmic steroids	-
Prednisolone acetate ophthalmic (Omnipred®*, Pred Forte®*, Pred Mild®)	Ophthalmic steroids	a
Prednisolone sodium phosphate ophthalmic	Ophthalmic steroids	a
Rimexolone ophthalmic (Vexol®)	Ophthalmic steroids	-

*Generic available in at least one dosage form or strength.

Indications

Table 2. Food and Drug Administration-Approved Indications[1-17]

Indication	Dexa-methasone	Diflu-prednate	Fluoro-metholone	Loteprednol Etabonate	Predni-solone Acetate	Prednisolone Sodium Phosphate	Rimex-olone
Anterior uveitis							a
Anterior uveitis, endogenous		a					
Corneal injury from chemical, radiation or thermal burns	a				a	a	
Penetration of foreign bodies	a				a	a	
Postoperative inflammation and pain following ocular surgery		a		a (gel, ointment)			
Postoperative inflammation following ocular surgery				a (0.5% suspension)			a
Temporary relief of the signs and symptoms of seasonal allergic conjunctivitis				a (0.2% suspension)			
Steroid-responsive inflammatory ocular conditions	a *		a *	a (0.5% suspension)*	a *	a *	

*Indicated for the treatment of steroid-responsive inflammatory ocular conditions of the palpebral and bulbar conjunctiva, cornea and anterior segment of the globe, such as allergic conjunctivitis, acne rosacea, superficial punctuate keratitis, herpes zoster keratitis, iritis, cyclitis and selected infective conjunctivitides when the inherent risk of steroid use is accepted to obtain a diminution in edema and inflammation.

Pharmacokinetics

Limited pharmacokinetic data is available for the ophthalmic steroids. Although there is the potential for systemic absorption with the administration of these agents, the true clinical significance of this is not known.[1-17]

Specifically, ophthalmic difluprednate undergoes deacetylation in vivo to 6α, 9-difluoroprednisolone 17-butyrate, an active metabolite.[9] The levels of the active metabolite of ophthalmic difluprednate were below the quantification limit at all time points for all subjects in clinical pharmacokinetic studies. Ophthalmic rimexolone is absorbed systemically, and when dosed bilaterally once every hour for one week, has demonstrated serum concentrations ranging from <80 to 470 pg/mL (mean serum concentrations of 130 pg/mL).[20] The half-life of this agent is short, estimated at approximately one to two hours based on the time required to reach steady-state. When studied for bioavailability in normal volunteers, plasma levels of ophthalmic loteprednol etabonate and its primary inactive metabolite were below the quantitation limit, <1 ng/mL at all sampling times.[14,15]

Clinical Trials

The clinical trials demonstrating the safety and efficacy of the ophthalmic steroids in their respective Food and Drug (FDA)-approved indications are described in Table 3.[29-58]

The FDA-approval of ophthalmic difluprednate was based on two randomized, double-blind, placebo-controlled trials (N=438) in patients who underwent cataract surgery.[35] One drop of ophthalmic difluprednate or vehicle was instilled either twice daily or four times daily for 14 days. There was a significantly greater proportion of patients who had an anterior chamber cell grade of zero on days eight, 15 and 29 in the ophthalmic difluprednate groups compared to the placebo group (P<0.0001 for all). There were no serious adverse events reported in either treatment group. Three patients in the ophthalmic difluprednate groups and two patients in the placebo groups had an increase in intraocular pressure (IOP) ≥21 mm Hg and ≥10 mm Hg from baseline (P values not reported).

In two six-week, double-blind, placebo-controlled trials (N=268) in patients with seasonal allergic conjunctivitis, ophthalmic loteprednol etabonate 0.2% dosed four times daily was significant more effective for the treatment of signs and symptoms of seasonal allergic conjunctivitis compared to placebo.[54,55] There was a greater reduction in bulbar conjunctival injection and itching in the ophthalmic loteprednol etabonate 0.2% group than the placebo group, beginning approximately two hours after instillation and throughout the first 14 days of treatment (P<0.001). In a double-blind, prospective, randomized-controlled trial (N=203) of patients who underwent cataract removal surgery, ophthalmic loteprednol etabonate 0.5% was significantly more effective than placebo for the treatment of anterior chamber inflammation (grade of zero).[40] In both trials, an increase in IOP >10 mm Hg was observed more frequently in the ophthalmic prednisolone acetate 1% group compared to the ophthalmic loteprednol etabonate 0.5% group (P value not reported).

The safety and efficacy of ophthalmic rimexolone 1% was compared to ophthalmic prednisolone acetate 1% in patients with acute or chronic uveitis or recurrent iridocyclitis in three randomized-controlled trials.[30,31] Medications were administered every hour initially with a gradual taper over four weeks. There were no significant differences in anterior chamber cell and flare scores between the two treatment groups and the overall clinical efficacy was similar at the end of treatment (four weeks). More patients in the ophthalmic prednisolone acetate 1% group had an increase in IOP ≥10 mm Hg compared to patients in ophthalmic rimexolone 1% group (P value not reported).[32] The results of a study by Biswas et al (N=78) did not demonstrate any difference in IOP elevation between the two ophthalmic steroids.[31] Ophthalmic rimexolone 1% was compared to ophthalmic prednisolone acetate 1% in two randomized- controlled trials in patients who underwent cataract extraction surgery.[34,35] Both treatments were administered four times daily for 15 days. There were no statistically significant differences between the two treatment groups in terms of anterior chamber cells and flare or conjunctival hyperemia on days seven and 15 (P>0.05). The IOP measurements were similar between the two treatment groups in both studies.

Ocular hypertensive and anti-inflammatory response of ophthalmic rimexolone 1% was compared to ophthalmic fluorometholone 0.1% in a randomized-controlled trial (N=54) in children four to eight years of age who underwent bilateral strabismus surgery.[38] The net change in IOP was greater with ophthalmic rimexolone 1% compared to ophthalmic fluorometholone 0.1% (P<0.001). Eighteen eyes in the ophthalmic rimexolone 1% group compared to fifteen eyes in the ophthalmic fluorometholone 0.1% group experienced an IOP >21 mm Hg (P=0.53). There was a greater improvement in conjunctival inflammation on days 13 and 20 in the ophthalmic rimexolone 1% group compared to the ophthalmic fluorometholone 0.1% group (P=0.03).

Two ophthalmic prednisolone acetate 1% formulations, Omnipred® and Pred Forte®, were compared in adult patients who underwent cataract surgery, in a double-blind, randomized-controlled trial (N=73).[42] There were no statistically significant differences in clinical efficacy outcomes between the two ophthalmic prednisolone acetate treatment groups in terms of postoperative ocular pain, keratitis, aqueous cell counts or aqueous flare on days one, 12 and 28.

Ophthalmic steroids have been compared to ophthalmic nonsteroidal anti-inflammatory drugs (NSAIDs) for the treatment of inflammation associated with cataract surgery. In three separate randomized-controlled trials, ophthalmic diclofenac 0.1% has been compared to ophthalmic prednisolone acetate 1% and ophthalmic dexamethasone 0.1%.[32,33,44] There were no significant differences between the treatment groups at any observation time in terms of postoperative inflammatory reaction. There was a statistically significant mean decrease from baseline in IOP at week one and month one in the ophthalmic diclofenac 0.1% group compared to the ophthalmic prednisolone acetate1% group (P=0.007).[44] At one month, the IOP was significantly higher in the ophthalmic dexamethasone 0.1% group compared to the ophthalmic diclofenac 0.1% group (P<0.05).[32] Ophthalmic ketorolac 0.5% has been compared to ophthalmic loteprednol 0.5%, ophthalmic rimexolone 1%, ophthalmic prednisolone acetate 1%, and ophthalmic fluorometholone in several clinical trials.[34,37,41,45,49,52] There were no reported differences between the treatment groups in measurements of postoperative inflammation or IOP. In a study by Hirneiss et al, there was a significant difference in overall aqueous flare of the anterior chamber between the treatment groups, lowest being in the ophthalmic ketorolac 0.5% group, followed by the ophthalmic prednisolone acetate1% group and then ophthalmic rimexolone 1% group (P=0.008).[43] The ophthalmic ketorolac 0.5% group had significantly higher IOP values followed by ophthalmic rimexolone 1%. Ophthalmic prednisolone acetate 1% was associated with the lowest IOP values of the three treatment groups (P=0.030 for overall group difference). Patients complained about stinging and itching more frequently with the application of ophthalmic ketorolac 0.5% compared to ophthalmic rimexolone 1%. Patient comfort was highest in the ophthalmic prednisolone acetate 1% group (P=0.041 for overall group difference).

None of the available ophthalmic NSAIDs have been FDA-approved for either the prevention or treatment of cystoid macular edema. There are number of ophthalmic steroid comparator studies evaluating the use of ophthalmic NSAIDs in cystoid macular edema.[39,46-48,54] Based upon available evidence, there are no substantive differences between the ophthalmic steroids in the prevention or treatment of cystoid macular edema.

Ophthalmic fluorometholone 0.1%, along with ophthalmic antihistamines were compared to placebo in a double-blind, prospective, randomized-controlled trial (N=100) in patients with a history of allergic conjunctivitis.[58] There was a greater improvement from baseline in itching, redness, tearing, eyelid swelling and chemosis at week two for patients in the ophthalmic olopatadine 0.1%, ophthalmic ketotifen 0.025%, ophthalmic epinastine 0.05%, ophthalmic emedastine 0.05%, and ophthalmic fluorometholone 0.1% groups compared to the placebo group (P<0.001, for all groups). There was smaller improvement in ocular itching and conjunctival redness in the ophthalmic fluorometholone group compared to the other treatment options (P value not reported). Ophthalmic loteprednol 0.2% was found to be less effective in reducing the acute signs and symptoms of seasonal allergic conjunctivitis during the early phase of ocular allergic reaction when compared to ophthalmic olopatadine 0.1%.[57]

Table 3. Clinical Trials

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Anterior Uveitis				
Foster et al[29] Difluprednate 0.05% one drop in affected eye(s) QID alternating with vehicle QID administered every two hours vs prednisolone acetate 1% one drop in affected eye(s) eight times daily The treatment period was 14 days, followed by a tapering period of 14 days, depending on the investigator's determination of treatment response.	AC, DB, MC, NI, RCT Patients ≥2 years of age with endogenous anterior uveitis in at least one eye and presenting with >10 anterior chamber cells and a flare score ≥2 in the same eye	N=90 4 weeks	Primary: Change from baseline in mean anterior chamber cell grade on day 14 Secondary: Anterior chamber cell clearing, anterior chamber flare, total symptom score (eye pain, photophobia, blurred vision, and lacrimation), QOL before and after treatment using the NEI VFQ-39 and WLQ, IOP, best-corrected visual acuity, slit lamp examination and adverse events	Primary: At day 14, treatment with difluprednate was NI to prednisolone acetate, with a mean anterior cell grade improvement of 2.1 and 1.9, respectively. The upper limit of the 95% CI was 0.22, within the NI margin of 0.50 grade units. Moreover, difluprednate was NI to prednisolone acetate at all time points assessed after day three of treatment. Secondary: The proportion of patients with anterior chamber cell clearing by day 14 was higher in the difluprednate group compared to the prednisolone acetate group (68.8 vs 61.5%; P value not reported); however, the difference was not statistically significant. The effect persisted at day 42. Difluprednate treatment cleared anterior chamber flare quicker than prednisolone acetate treatment; however, the differences were not statistically significant any time point evaluated. Difluprednate treatment reduced pain scores more than prednisolone acetate at all time points evaluated (P values not reported). The total symptom score (VAS) was improved with difluprednate treatment compared to prednisolone acetate treatment at all time points (P values not reported). Patients treated with difluprednate experienced a statistically significant improvement in best-corrected visual acuity compared to patients treated with prednisolone acetate on day three (P=0.02), day 21 (P=0.03), day 28 (P=0.03), and day 35 (P=0.04). The best-corrected visual acuity at days 14 (P=0.07) and 42 (P=0.08) were not significantly different between treatment groups. No clinically significant differences were observed between the treatment groups in the mean change from baseline in IOP at any time point.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				At day 42, patients receiving difluprednate improved on eight of 11 vision-related subscales of the NEI VFQ-39, and all subscales of the WLQ compared to prednisolone acetate. Adverse events were reported in 68% of patients in the difluprednate group and 70% of patients in the prednisolone acetate group. Most adverse events were ocular in nature and rated as mild or moderate in intensity. There was a higher incidence of moderate or severe adverse events in the prednisolone acetate group compared to the difluprednate group (40 vs 24%; P value not reported).
Foster et al (abstract)[30] Rimexolone 1% one or two drops every hour for one week, then every two hours for one week, then QID for one week, then QD for three days vs prednisolone acetate 1% one or two drops every hour for one week, then every two hours for one week, then QID for one week, then QD for three days	2 MC Patients with acute uveitis, recurrent iridocyclitis or chronic uveitis treatable with topical steroids	N=unknown 4 weeks	Primary: Anterior chamber cells and flare and IOP on days three, four, seven to 10, 14, 21 and 28 Secondary: Not reported	Primary: There were no differences between the two groups in terms of anterior chamber cells and flare. There were no statistically significant differences in cell scores in either of the two studies (P>0.05 for both). There were no statistically significant differences in flare scores on any of the days except on day 28 in study one (P=0.04). More patients in the prednisolone acetate group had experienced an increase in IOP ≥10 mm Hg compared to patients in the rimexolone group (P value not reported). Secondary: Not reported
Biswas et al (abstract)[31] Rimexolone 1% one drop every hour for one week, then one drop every two hours for one week, then QID for one week, then BID for four days and then	AC, PG, RCT, TB Patients >10 years of age diagnosed as having acute uveitis, recurrent iridocyclitis or chronic uveitis	N=78 4 weeks	Primary: Anterior chamber aqueous cells and aqueous flare Secondary: Ciliary flush, keratic precipitates,	Primary: The reduction in aqueous cells was not significantly different between the prednisolone acetate and rimexolone groups on days one, three to four, seven, 14, 28 and hour 32 respectively (P=0.927, P=0.628, P=0.657, P=0.979, P=0.903 and P=0.540, respectively). On day 21, there was a 20% reduction in aqueous cells in the rimexolone group compared to the prednisolone acetate group (P=0.016).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
QD for three days vs prednisolone acetate 1% one drop every hour for one week, then one drop every two hours for one week, then QID for one week, then BID for four days and then QD for three days			photophobia, discomfort and IOP	There was no statistically significant difference in the reduction of aqueous flare between the rimexolone and prednisolone acetate groups on days one (P=0.307), three to four (P=0.108), seven (P=0.353), 14 (P=0.235), 21 (P=0.350), 28 (P=0.410) and hour 32 (P=0.279). Secondary: No statistical or clinical differences were observed for ciliary flush, keratic precipitates, photophobia and discomfort between the rimexolone and prednisolone acetate groups (P value not reported). There were no significant differences in IOP elevations between the rimexolone and prednisolone acetate groups (P value not reported). An elevation in IOP occurred throughout the study and was more frequent in the prednisolone acetate group compared to the rimexolone group (P>0.05 for all days).
Postoperative Inflammation Following Ocular Surgery				
Laurell et al[32] Diclofenac 0.1% one drop in the affected eye(s) QID for one week following surgery, then one drop in the affected eye(s) BID for three weeks vs dexamethasone 0.1% one drop in the affected eye(s) QID for one week following surgery, then one drop in the affected eye(s) BID for three weeks vs	AC, DB, PRO, RCT, SC Patients 64 to 85 years of age scheduled to undergo cataract surgery by phacoemulsification and IOL implantation	N=180 4 years	Primary: Inflammatory reaction in the anterior chamber measured with laser flare photometry preoperatively and at one, three and eight days, two and four weeks, two and six months, and one, two and four years postoperatively and inflammatory symptoms Secondary: Visual acuity, rate of striate keratopathy, IOP and capsulotomy rate	Primary: There were no statistically significant differences in inflammation between the three treatment groups on first postoperative day (P=0.830). The flare values at three and eight days, two weeks and one month following surgery were significantly lower in the diclofenac and dexamethasone groups compared to the placebo group (P≤0.05 for all). There were no significant differences between diclofenac and dexamethasone at any observation time (P values not reported). Inflammatory symptoms were reported in 11 of 60 patients (18.3%) on day three and in 18 of 59 patients (30.5%) at day eight in the placebo group. The rate of patients with inflammatory symptoms was greater in the placebo group at day three (P<0.001) and day eight (P<0.001) but not at two weeks and thereafter. There were no significant differences between diclofenac and dexamethasone treatment groups at any observation time. Secondary: With regard to visual acuity, the only significant difference between the treatment groups was at day eight when visual acuity was better in the

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vehicle one drop in the affected eye(s) QID for one week following surgery, then one drop in the affected eye(s) BID for three weeks				dexamethasone group compared to the placebo group (81.7 vs 62.7%; P<0.05). At day eight, striate keratopathy was more frequent in the placebo group compared to the other two treatment groups (P=0.01). There were no subsequent corneal reactions. There were no epithelial complications found in any of the three treatment groups. The median IOP was significantly higher in the dexamethasone group than in the placebo group after eight days (16 vs 13 mm Hg; P<0.05). At one month IOP was slightly higher in dexamethasone group compared to the diclofenac group (15 vs 14 mm Hg; P<0.05). No significant IOP differences were reported at other observation times. The rate of Nd:YAG laser posterior capsulotomies were equal in the three treatment groups after two years. It was significantly lower in the placebo group than in the diclofenac group after four years (P<0.05).
Reddy et al[33] Diclofenac 0.1% one drop in the affected eye(s) six times a day vs dexamethasone 0.1% one drop in the affected eye(s) six times a day Each patient also received tropicamide 1% for preoperative dilation and it was also included in the postoperative regimen.	AC, DB, PRO, RCT Patients >25 years of age who underwent uncomplicated extracapsular cataract extraction with posterior chamber IOL implantation	N=60 21 days	Primary: Aqueous flare and cells in anterior chamber, conjunctival congestion and corneal edema on days one, three, seven, 14 and 21 following surgery and severity of inflammation graded on a four-point scale Secondary: Not reported	Primary: There was no significant difference in anti-inflammatory activity between the two treatment groups on days three, seven, 14 or 21 following surgery for signs of flare, cells in the anterior chamber, conjunctival congestion and corneal edema (P values not reported). The time to achieve anti-inflammatory activity was significant (P<0.0001). The rate of improvement did not differ significantly between the two treatment groups (P values not reported). In terms of response of cells in the anterior chamber, the trend for improvement appeared to be faster and greater in magnitude with dexamethasone compared to diclofenac (P values not reported). Best corrected visual acuity did not differ statistically between treatment groups (P values not reported). Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Ostrov et al[34] Ketorolac 0.5% one drop in the affected eye(s) TID starting one day before surgery and for four weeks following surgery vs dexamethasone 0.1% one drop in the affected eye(s) TID starting one day before surgery and for four weeks following surgery vs prednisolone acetate 1% one drop in the affected eye(s) TID starting one day before surgery and for four weeks following surgery Seventy-nine percent of patients also received perioperative subconjunctival injections of a glucocorticoid (e.g., betamethasone or equivalent) and 82% of patients received an antibiotic.	AC, MC, RCT, SB Patients who underwent routine extracapsular cataract extraction or phaco-emulsification and posterior chamber IOL implantation	N=157 6 weeks	Primary: Signs of anterior-segment inflammation-primarily cells and flare in the anterior chamber observed by slit-lamp biomicroscopy, fluorescein leakage across blood-aqueous barrier measured by fluorophotometry, rating of efficacy by investigator, IOP, visual acuity and adverse events Secondary: Other clinical signs of inflammation (lid edema and hyperemia)	Primary: There were no statistically significant differences between the three groups in terms of infiltration of cells into the anterior chamber on days one to two, day five, week two, week four or week six (P=0.59, P=0.51, P=0.08, P=0.32 and P=0.37, respectively). There were no statistically significant differences between the three groups in terms of anterior chamber flare on days one to two, day five, week two, week four or week six (P=0.40, P=0.09, P=0.45, P=0.09 and P=0.70, respectively). The postoperative elevation in fluorescein concentration was significantly lower in the ketorolac group than the two corticosteroid groups at day five and week two (P≤0.001 and P=0.016, respectively). There were no differences between the prednisolone acetate and dexamethasone groups at day five (P=0.53) or week two (P=0.77). Ketorolac, prednisolone acetate and dexamethasone groups had mean scores ranging from 86 to 91 for overall effectiveness (P=0.32) and 87 to 91 for overall acceptability (P=0.46). There were no significant differences between the three groups at any visit with respect to IOPs and visual acuity tests (P≥0.33 for both). Two of the six adverse events were treatment-related. One patient in the dexamethasone group had a moderate allergic reaction at weeks two and four and one patient in the ketorolac group developed severe uveitis (P values not reported). Secondary: The ketorolac group had higher conjunctival hyperemia scores compared to the prednisolone acetate group at week two (P=0.04 among groups).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Korenfeld et al[35] Difluprednate 0.05% one drop in the affected eye(s) BID for 29 days vs difluprednate 0.05% one drop in the affected eye(s) QID for 29 days vs vehicle one drop in the affected eye(s) BID for 29 days vs vehicle one drop in the affected eye(s) QID for 29 days Patients received study drug on the day after surgery and patients that had an anterior chamber cell grade of zero or who had responded satisfactorily to treatment as judged by the investigator began tapering the study drug.	DB, MC, PC, PG, RCT Patients >2 years of age who had unilateral ocular surgery on the day before study enrollment with an anterior chamber cell grade of two or higher on day one	N=438 36 days	Primary: Anterior chamber cell count and grade, anterior chamber flare, chemosis, bulbar conjunctival injection, corneal edema, keratic precipitates, pain/discomfort and photophobia Secondary: Best corrected visual acuity, IOP and adverse events	Primary: A significantly greater proportion of patients had an anterior chamber cell grade of zero on days eight, 15 and 29, in the difluprednate BID and QID groups compared to placebo (P<0.0001 for both). There was a significantly greater proportion of patients who achieved a clinical response in both the difluprednate BID and QID groups compared to the placebo group (P<0.05, on days three and four and P<0.0001 for days eight, 15 and 29, respectively). There was significantly greater improvement from baseline in postoperative inflammation in terms of anterior chamber cell grade in both difluprednate treatment groups compared to the placebo group (P<0.0001 on days three, four, eight, 15 and 29). There was a greater decrease from baseline in anterior chamber cell count in both difluprednate groups compared to the placebo group (87 vs 30%; P value not reported). The difluprednate BID group experienced a significantly greater reduction in pain/discomfort on days three, four, eight, 15 and 29 compared to the placebo group (P<0.05, for all). The difluprednate QID group also experienced a statistically significant reduction in pain on days three to four, eight, 15 and 29 compared to the placebo group (P<0.0001 for all). There was a statistically significant improvement in photophobia from baseline on days three and four in the difluprednate BID (-4.7; P=0.0041), and difluprednate QID groups (-9.6; P<0.0001) but not in the placebo group (+1.1; P value not reported). A significantly greater proportion of patients had no photophobia on days eight and 15 in the difluprednate BID group compared to the placebo group (36.4 vs 19.7%; P=0.0009 and 42.7 vs 25.7%; P=0.0013, respectively). A greater proportion of patients in the difluprednate QID group experienced no photophobia on days eight and 15 compared to the placebo group (40.2 vs 19.7%; P=0.0001 and 54.2 vs 25.7%; P<0.0001, respectively).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				On day eight, there was a significantly greater improvement in corneal edema score from baseline in the difluprednate BID group (-0.3 vs -0.1; P=0.0003) and difluprednate QID group compared to the placebo group (-0.5 vs -0.1; P<0.0001). On days three and four, there was a significantly greater improvement from baseline in chemosis in the difluprednate BID and QID groups compared to the placebo group (P=0.0039 and P=0.0023, respectively). This difference persisted through day 29 (P value not reported). Secondary: Three patients in both difluprednate groups and two patients in the placebo group experienced an IOP increase ≥21 and ≥10 mm Hg from baseline. These patients did not discontinue the study (P value not reported). The incidence of most ocular adverse events was lower in the difluprednate BID and QID groups compared to the placebo group. Conjunctival hyperemia was lower in both difluprednate BID and QID groups compared to the placebo group (5.6 and 4.5 vs 19.5%), as was ciliary hyperemia (4.7 and 4.5 vs 17.3%) and visual acuity reduction (0.9 vs 4.5 vs 8.6%). No serious adverse events were reported in either of the treatment groups.
Donnenfeld et al[36] Difluprednate 0.05% in the eye undergoing surgery vs prednisolone acetate 1% in the other eye undergoing surgery One drop was instilled in the eye scheduled for surgery every 15 minutes for the hour before arrival	AC, DB, MC, PRO, RCT, XO Patients ≥21 years of age who were scheduled to undergo standard cataract surgery in both eyes with six to 25 days between surgeries and a best-corrected visual acuity better than 20/100 in both eyes	N=52 2 weeks	Primary: Change from baseline in corneal thickness at day one Secondary: Corneal thickness at days 15 and 30, uncorrected visual acuity, best-corrected visual acuity, corneal edema (epithelial and stromal) and IOP at all time points, endothelial cell counts at day 30	Primary: On day one, the mean central corneal thickness was significantly lower with difluprednate treatment compared to prednisolone acetate treatment (28 vs 57 µm; P=0.026). Secondary: There was no statistically significant difference in corneal thickness between the treatments at days 15 (P=0.26) or 30 (P=0.74). On day one, uncorrected visual acuity was significantly improved in patients treated with difluprednate compared to prednisolone acetate (0.643 vs 0.566 logMAR; P=0.0416). There was no significant difference in uncorrected visual acuity between the difluprednate and prednisolone acetate treatment groups by day 15 (P=0.84) or 30 (P=0.35).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
at the surgery center (four drops total). On arrival, one drop was instilled every 15 minutes (three drops total). A single drop was instilled immediately following surgery, while in surgical recovery and when leaving surgical recovery. After discharge, one drop was instilled every two hours for the remainder of the surgery day. On the day after surgery, patients administered one drop QID for one week and then BID for the second week following surgery. Moxifloxacin 0.5% or gatifloxacin 0.3% were administered QID starting three days before surgery and for 10 days after surgery. An NSAID (nepafenac 0.1% or ketorolac tromethamine 0.4%) was used beginning three days			and OCT-CRT at days 15 and 30	On day one following cataract surgery, the change from baseline in best-corrected visual acuity was significantly greater with difluprednate treatment compared to prednisolone acetate treatment (0.279 vs 0.114 logMAR; P=0.0003). There was no statistically significant difference in best-corrected visual acuity between the treatments at day 15 (P=0.6655); however, significant improvements were reported with difluprednate compared to prednisolone acetate by day 30 (P=0.03). The proportion of eyes in which no stromal corneal edema was observed on day one was significantly higher for patients treated with difluprednate compared to patients receiving prednisolone acetate (62 vs 38%; P=0.019). At days 15 and 30, stromal and epithelial edema had resolved in all cases, and there were no differences between treatment groups. A rise in IOP was seen on day one following surgery in both the difluprednate and prednisolone acetate treatment groups (3.52 vs 2.92 mm Hg; P=0.467). The rise in IOP was resolved in both groups by day 15 following surgery. No significant difference in IOP was observed between treatment groups at any time. The mean density of endothelial cells was higher by 195.52 cells/mm^2 in the eyes treated with difluprednate compared to eyes treated with prednisolone acetate (P<0.001). At day 15, the eyes treated with difluprednate had a mean retinal thickness that was 7.74 µm less than that of eyes treated with prednisolone acetate (P=0.011). There was no difference in retinal thickness between the treatment groups by day 30 (P=0.21).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
before surgery and for four weeks after surgery.				
Trinavarat et al (abstract)[37] Ketorolac one drop in the affected eye(s) QID vs fluorometholone one drop in the affected eye(s) QID vs prednisolone acetate one drop in the affected eye(s) QID	AC, PRO, RCT, SB Patients undergoing phacoemulsification	N=120 28 days	Primary: Visual acuity, IOP, slit-lamp biomicroscopy, grading of cells and flare in anterior chamber and ocular symptoms Secondary: Not reported	Primary: The number of eyes with a minimal amount of cells in the anterior chamber was significantly lower with prednisolone acetate compared to ketorolac on days seven (11 vs 20; P=0.008) and 14 (23 vs 31; P=0.015). Similarly, more patients treated with fluorometholone had a minimal amount of cells in the anterior chamber on day seven compared to patients receiving ketorolac (11 vs 21; P=0.011). The IOP was significantly higher in the prednisolone acetate group compared to the ketorolac group on day 21 (14.6 vs 12.2 mm Hg; P=0.016). One eye in the prednisolone group had an IOP of 32 mm Hg. Burning sensation was reported frequently in the ketorolac group (P values not reported). Secondary: Not reported
Fan et al[38] Fluorometholone 0.1% one drop one eye QID for four weeks vs rimexolone 1% one drop in other eye QID for four weeks Patients received both study drugs in the contralateral eye from the other study drug during the	AC, DB, RCT Patients four to eight years of age who underwent bilateral symmetric strabismus surgery with a preoperative IOP ≤21 mm Hg and a cup-disc ratio ≤0.3 with no other systemic or ocular disease	N=54 55 days	Primary: IOP, ocular discomfort, conjunctival hyperemia and conjunctival discharge Secondary: Not reported	Primary: The peak IOP in the rimexolone group was significantly higher compared to the fluorometholone (19.7 vs 17.6 mm Hg; P<0.001). The net change in IOP was also significantly greater in the rimexolone group compared to the fluorometholone group (5.9 vs 3.9 mm Hg; P<0.001). Eighteen eyes in the rimexolone group compared to fifteen eyes in the fluorometholone group had an IOP >21 mm Hg (P=0.53). There was a greater proportion of eyes with IOP >20 mm Hg at days six (14.8 vs9.3%), 13 (33.3 vs 11.1%), 20 (42.6 vs 22.2%) and 27 (46.3 vs 24.2%), respectively, with rimexolone treatment compared to fluorometholone treatment (P=0.82). There was a greater rise in IOP >10 mm Hg in the rimexolone group compared to the fluorometholone group (P value not reported).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
full course of therapy; patients also received chloramphenicol 0.25% one drop in both eyes QID for four weeks.				There was a greater proportion of patients who were judged as being intermediate or high responders in terms of ocular hypertensive response in the rimexolone group compared to the fluorometholone group (P=0.02). There was a greater proportion of patients who were judged as being intermediate responders in terms of ocular hypertensive response using the Becker classification in the rimexolone group compared to the fluorometholone group (P=0.003). There was a greater improvement in conjunctival inflammation on days 13 and 20 in the rimexolone group compared to the fluorometholone group (P=0.03). There was no difference in the proportion of patients who had no ocular discomfort between the treatment groups (P=0.08). Secondary: Not reported
Miyake et al[39] Diclofenac 0.1% one drop in the affected eye(s) three hours, two hours, one hour and 30 minutes prior to surgery and TID for eight weeks following surgery vs fluorometholone 0.1% one drop in the affected eye(s) three hours, two hours, one hour and 30 minutes prior to surgery and TID for eight weeks following	AC, MC, OL, PRO Patients between 60 and 70 years of age with an indication for unilateral cataract surgery	N=106 8 weeks	Primary: Visual acuity, IOP, amount of anterior chamber flare and cells measured by laser flare-cell photometry and severity of cystoid macular edema determined by fluorescein fundus angiography Secondary: Not reported	Primary: There was no significant difference between the two groups in the change in visual acuity at any time point. Both groups experienced significantly lower IOPs at three days, and one, two, five and eight weeks following surgery compared to preoperative values (P<0.05 for all time points). Treatment with diclofenac was associated with a significantly lower flare in the anterior chamber at three days, and one, two, five and eight weeks following surgery compared to treatment with fluorometholone (P<0.01 for all). Both treatment groups experienced a statistically significant increase in flare in eyes with cystoid macular edema at three days, and one, two, five and eight weeks following surgery compared to eyes without cystoid macular edema (P<0.001).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
surgery Each patient was also receiving oral and topical antimicrobial medications.				There was a statistically significant increase in flare in eyes with and without cystoid macular edema in the fluorometholone group compared to the diclofenac group (P<0.05 to P<0.01). More patients in the fluorometholone group developed cystoid macular edema compared to the diclofenac group over eight weeks of treatment (54.7 vs 5.7%; P<0.001). Secondary: Not reported
Beehler et al[40] Loteprednol 0.5% one drop in the affected eye(s) QID for 14 days vs vehicle one drop in the affected eye(s) QID for 14 days Each patient also received one drop of tobramycin (or respective anti-infective agent) in the affected eye(s) QID for one week postoperatively.	DB, MC, PC, PG, PRO, RCT Patients 25 to 99 years of age undergoing cataract removal (extracapsular and phacoemulsification cataract extraction) and IOL implantation performed in a single uncomplicated procedure, with minimum anterior chamber inflammation	N=203 42 days	Primary: Resolution of anterior chamber inflammation Secondary: Anterior chamber cells and flare, treatment failures (patients who discontinued early for inadequate control or who had an increase of three or more in their anterior chamber inflammation score), investigator's global assessment and safety	Primary: A greater proportion of patients in the loteprednol group achieved resolution of anterior chamber inflammation (anterior chamber inflammation score of zero) by visit five compared to the patients in the placebo group (55 vs 28%; P<0.001). Secondary: There was a statistically significant resolution of anterior chamber cells with loteprednol compared to placebo (60 vs 31%; P<0.001). There was a statistically significant resolution of anterior chamber flare with loteprednol compared to and placebo (67 vs 36%; P<0.001). A significantly greater proportion of patients treated with loteprednol experienced a treatment response as determined by investigator's global assessment compared to patients treated with placebo (89 vs 49%; P<0.001). Five patients in the loteprednol group compared to 25 patients in the placebo group discontinued treatment due to inadequate anti-inflammatory efficacy. There was no statistically significant difference between the loteprednol group and the placebo group in mean change from baseline in IOP (P>0.206). The mean IOPs in the loteprednol and placebo groups were

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				16.4 and 16.3 mm Hg, respectively (P=0.847). No patient within the loteprednol group experienced an IOP increase >10 mm Hg. One patient in the placebo group experienced an increase in IOP from 19 mm Hg at baseline to 48 mm Hg at day 11. Significantly fewer patients treated with loteprednol experienced at least one treatment-emergent medical event compared to patients receiving placebo (54 vs 75%; P=0.002). Adverse events reported in placebo group included tearing, blurred vision, pain, photophobia, toxic keratitis, corneal edema and elevated IOP. One patient in the loteprednol group had itching of body areas which was determined to be unrelated to study medication.
Holzer et al[41] Ketorolac 0.5% one drop in the affected eye(s) QID starting 24 hours following surgery for one week, then one drop in the affected eye(s) BID for three weeks vs loteprednol 0.5% one drop in the affected eye(s) QID starting 24 hours following surgery for one week, then one drop in the affected eye(s) BID for three weeks Each patient also received ofloxacin 0.3% one drop in the affected eye(s) QID starting three days before surgery, one drop	DB, PRO, RCT Patients >18 years of age scheduled to have cataract extraction with posterior chamber IOL implantation	N=60 30 days	Primary: Signs and symptoms of inflammation documented by external slit-lamp examination, IOP, Kowa cell and flare measurements on days one, four, seven and 30 Secondary: Not reported	Primary: There was no statistically significant difference between the two groups in any of the ocular symptoms including deep eye pain, photophobia, itching, foreign-body sensation, stinging and burning (P values not reported). There were no statistically significant differences between the ketorolac and loteprednol groups in terms of preoperative laser cell and flare meter evaluation of cells and flare (P=0.83 and P=0.92, respectively). The mean cell and flare values evaluated by laser cell and flare meter at day one was higher in the ketorolac group compared to the loteprednol group (P=0.72 and P=0.67, respectively). The mean cell measurement by laser cell and flare meter at week one, was 3.96 in the ketorolac group and 4.89 in the loteprednol group (P=0.16). The mean flare measurement at week one was 1.43 in the ketorolac group and 0.94 in the loteprednol group (P=0.61). The mean IOP in both groups ranged from 12 to 16 mm Hg. Two patients in the loteprednol group had IOPs of 23 and 24 mm Hg one month postoperatively. These two patients had elevated preoperative IOPs of 25 and 24 mm Hg, respectively (P values not reported).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
perioperatively, at completion of surgery and one drop in the affected eye(s) QID immediately following surgery.				Secondary: Not reported
Raizman et al[42] Prednisolone acetate 1% (Omnipred®) one drop in the affected eye(s) QID starting one day prior to surgery, on the day of surgery, continuing postoperatively for 14 days and then one drop in the affected eye(s) BID until 10 mL bottle was empty vs prednisolone acetate 1% (Pred Forte®) one drop in the affected eye(s) QID starting one day prior to surgery, on the day of surgery, continuing postoperatively for 14 days and then one drop in the affected eye(s) BID until 10 mL bottle was empty Each patient also received moxifloxacin 0.5% one drop in the affected eye(s) QID for seven days, nepafenac 0.1% one drop	DB, MC, RCT Patients ≥18 years of age scheduled to undergo planned phacoemulsification surgery with IOL implantation	N=73 4 weeks	Primary: Signs of inflammation, pain, aqueous cell counts, aqueous flare, keratitis, safety obtained postoperatively on day one, two weeks and four weeks Secondary: Not reported	Primary: There were no significant differences in clinical outcomes between the two prednisolone acetate groups in terms of postoperative ocular pain, keratitis, aqueous cell counts or aqueous flare (ocular pain; P=0.6129, P=0.3466, P=0.3466 on day one, 12 and 28, respectively; keratitis; P=0.6872, P=0.8846, P=0.3466 on day one, 12 and 28, respectively; aqueous cell counts; P=0.6587, P=0.8851, P=0.7877 on day one, 12 and 28, respectively; aqueous flare; P=0.6346, P=0.1798, P=0.3466 on day one, 12 and 28, respectively). There were no statistically significant differences between the proportions of patients with none/trace aqueous cell counts, no aqueous flare, and no keratitis postoperatively on day one, 12 and 28 between the two groups. There was no difference in pain between the two groups (P=0.61, P=0.35 and P=0.35 on day one, 12 and 28, respectively). No severe adverse events were reported in either of the two groups. Five adverse events in the Pred Forte® group (steroid responder in terms of IOP, dense punctate epithelial keratitis and iritis in the operated eye) compared to one adverse event (rebounded scleritis in the operated eye) in the Omnipred® group occurred. Of these adverse events, iritis was not resolved by the end of the study period (P values not reported). Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
in the affected eye(s) QID for 14 days and artificial tear (Systane®) one drop in the affected eye(s) QID for seven days postoperatively.				
Hirneiss et al[43] Ketorolac 0.5% in the affected eye(s) per taper schedule as follows: six drops on days one to three, five drops on days four to 10, four drops on days 11 to 14, three drops on days 15 to 18, two drops on days 19 to 21 and then one drop on days 22 to 28 vs prednisolone acetate 1% in the affected eye(s) per taper schedule as follows: six drops on days one to three, five drops on days four to 10, four drops on days 11 to 14, three drops on days 15 to 18, two drops on days 19 to 21 and then one drop on days 22 to 28 vs	DB, PRO, RCT, SC Patients ≥18 years of age who underwent elective, unilateral extracapsular cataract extraction using phacoemulsification and implantation of a posterior chamber IOL	N=45 28 days	Primary: Conjunctival hyperemia, corneal edema, best-corrected visual acuity, measurement of IOP, standardized slit-lamp examination of the anterior segment of the eye and cells and flare, stereoscopic dilated retinal examination with the biomicroscope and report of patient comfort or discomfort on postoperative days one, three, five, 14 and 28 Secondary: Not reported	Primary: Overall aqueous flare in the anterior chamber was significantly lower in the ketorolac group followed by the prednisolone acetate and rimexolone groups (P=0.008). Regarding conjunctival hyperemia, most hyperemia was observed in the ketorolac group, followed by rimexolone and prednisolone acetate groups. Prednisolone acetate treatment was associated with the lowest occurrence conjunctival hyperemia followed by rimexolone and ketorolac treatments (P=0.002 for overall group difference). Aqueous cells and corneal edema did not differ among the three groups (P=0.165 and P=0.311, respectively). There were no significant differences in pre- and postoperative visual acuity measurements between the groups (P=0.183). The ketorolac group had a significantly higher mean IOP followed by the rimexolone group. Prednisolone acetate had the lowest IOP values of the three groups (P=0.030 for overall group difference). More patients complained of stinging and itching in the ketorolac group compared to the rimexolone group. Patient comfort was highest with the prednisolone acetate group (P=0.041 for overall group difference). Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
rimexolone 1% in the affected eye(s) per taper schedule as follows: six drops on days one to three, then five drops on days four to 10, then four drops on days 11 to 14, then three drops on days 15 to 18, then two drops on days 19 to 21 and then one drop on days 22 to 28 Patients received antibiotic eye drops containing polymyxin-B, neomycin and gramicidin one drop in the affected eye(s) QID for first three days following surgery.				
Roberts et al[44] Diclofenac 0.1% one drop in the affected eye(s) QID for one week then one drop in the affected eye(s) BID for three weeks vs prednisolone acetate 1% one drop in the affected eye(s) QID for one week then one drop in the affected eye(s) BID for three weeks	AC, DB, RCT Patients who underwent phacoemulsification with posterior chamber IOL implantation	N=52 1 month	Primary: Subjective postoperative inflammation evaluation by slit-lamp assessment of cell and flare and objective evaluation by measurement of cell and flare with a laser of cell and flare meter on one day, one week and one month following surgery Secondary: IOP	Primary: Diclofenac treatment was associated with lower inflammation scores compared to prednisolone acetate treatment at one week and one month following surgery; however, the results were not statistically significant (flare; P=0.138 and P=0.196, cell; P=0.588 and P=0.218, slit-lamp score; P=0.139 and P=0.521, respectively). Secondary: Both treatment groups experienced a reduction from baseline in IOP at one week and one month. The mean decrease was significantly greater with diclofenac compared to prednisolone acetate (4.7 vs 0.9 mm Hg; P=0.007). The difference between the two groups, after adjusting for the baseline difference in the analysis, was not statistically significant (P=0.074).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Each patient also received gentamicin sulfate eye drops.				
Simone et al[45] Ketorolac 0.5% one to two drops in the affected eye(s) QID on week one, TID on week two, BID on week three and QD on week four vs prednisolone acetate 1% one to two drops in the affected eye(s) QID on week one, TID on week two, BID on week three and QD on week four Each patient also received ofloxacin one drop in the affected eye(s) QID for one week.	DB, RCT, SC Patients who underwent extracapsular cataract extraction and posterior chamber IOL implantation	N=59 4 weeks	Primary: Intraocular anti-inflammatory efficacy (assessed by lid edema, lid injection, conjunctival injection, corneal edema, ciliary flush, and anterior chamber cells) and analgesic efficacy (assessed by patient reported pain severity, pain frequency, total symptom sum and overall global improvement) Secondary: Not reported	Primary: There were no statistically significant differences between the two groups in any measure of anti-inflammatory efficacy, with the exception of anterior chamber cells. The prednisolone acetate group had fewer cells in the anterior chamber compared to the ketorolac group at seven days (P=0.0073). At 28 days, there was no significant difference between the treatments (P=0.23). The ketorolac group had less frequent and severe pain symptoms at day 28 compared to the prednisolone group; however, the difference was not statistically significant (P value not reported). There were no statistically significant differences between the two treatment groups in terms of sum of symptoms, overall global improvement and IOP (P values not reported). There were no serious adverse events during the course of the study in either of the two treatment groups and no adverse event was considered to be treatment related (P values not reported). Secondary: Not reported
Wittpenn et al[46] Ketorolac 0.4% plus prednisolone acetate 1% one drop in the affected eye(s) QID for four weeks postoperatively (patients in this group also received ketorolac 0.4% one drop in the affected eye(s) QID for three days preoperatively)	AC, MC, PRO, RCT, SB Patients scheduled to undergo phaco-emulsification with no recognized cystoid macular edema risks (diabetic retinopathy, retinal	N=546 6 weeks	Primary: Cystoid macular edema incidence measured by slit-lamp biomicroscopy and OCT Secondary: Retinal thickness as measured by OCT, Snellen best-corrected visual acuity, contrast	Primary: Five patients in the prednisolone acetate group had clinically apparent cystoid macular edema compared to zero patients in the combination group based on slit-lamp biomicroscopy (P=0.032). Based on OCT analysis, no patients in the combination group and six patients in the prednisolone acetate group developed definite or probable cystoid macular edema (P=0.018). Significantly fewer patients in the combination treatment group were identified with possible cystoid macular edema based on OCT compared to

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs prednisolone acetate 1% one drop in the affected eye(s) QID for four weeks Each patient also received ketorolac 0.4% one drop in the affected eye(s) every 15 minutes for a total of four doses, one hour before surgery.	vascular disease, or macular abnormality)		sensitivity and adverse events	the prednisolone acetate group (2.2 vs 6.0%; P=0.037). Secondary: Mean retinal thickening in the combined treatment group was lower than in the prednisolone acetate group (3.9 vs 9.6 µm; P=0.003). Significantly more patients in the prednisolone acetate group than in the combination group had a >10 µm of retinal thickening on OCT (49.0 vs 26.4%; P<0.001). The prednisolone acetate group had a significantly higher incidence of retinal thickening of ≥15 µm compared to the group receiving combination treatment (P<0.001). The incidence of thickening of ≥25 µm and ≥40 µm was higher in the prednisolone acetate group than in the combination treatment group; however, the difference was not statistically significant (P=0.056 and P=0.069, respectively). In the combination group, 1.3% of patients had best-corrected visual acuity worse than 20/40 at week four compared to 2.5% of patients in the prednisolone acetate group (P=0.360). The difference in contrast sensitivity between the two treatment groups was not statistically significant (P≥0.581). Burning/stinging/tearing was the most commonly reported adverse event in the combination group, whereas, transient elevations in IOP were the most commonly reported adverse event in the prednisolone acetate group. There were two serious adverse events, both in the prednisolone acetate group. One patient developed endophthalmitis and one patient died due to a cause unrelated to study medication.
Singal et al (abstract)[47] Ketorolac 0.5% plus	DB, PRO, RCT Patients with	N=10 90 days	Primary: Improvement in Early Treatment Diabetic	Primary: There were no statistically significant differences between the two treatment groups in the outcomes measures at any visit (P values not reported).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vehicle vs ketorolac 0.5% plus prednisolone acetate 1% Dosing regimens were not reported.	clinical cystoid macular edema occurring at least six weeks following cataract extraction		Retinopathy Study Snellen equivalent vision and resolution of cysts on clinical examination Secondary: Not reported	There were no significant differences between the two treatment groups in the subgroup analysis of patients with chronic cystoid macular edema (P values not reported). Secondary: Not reported
Heier et al[48] Ketorolac 0.5% one drop in the affected eye(s) QID vs prednisolone acetate 1% one drop in the affected eye(s) QID vs ketorolac 0.5% plus prednisolone acetate 1% one drop in the affected eye(s) QID Study medications were tapered at the rate of one drop per week when cystoid macular edema was resolved or for three months, whichever occurred first.	AC, DB, PRO, RCT Patients diagnosed with acute clinical cystoid macular edema occurring after phaco-emulsification and posterior chamber IOL implantation	N=28 4 months	Primary: Snellen visual acuity, contrast sensitivity, Amsler grid, slit-lamp examination, dilated fundus examination and fluorescein angiography Secondary: Not reported	Primary: There was a significant improvement in Snellen visual acuity with combination therapy compared to prednisolone acetate at all visits (P<0.05 for all time points). In addition, combination therapy significantly improved visual acuity compared to ketorolac alone at visits four (P=0.006) and five (P=0.042). There was no significant difference in the number of patients receiving ketorolac or prednisolone acetate who experienced a two-line or greater change from baseline in visual acuity during the study (P values not reported). There was a significant difference for the combination therapy group compared to the prednisolone acetate group at visits two, three, four and five (P≤0.05 for all) and compared to the ketorolac group at visits four and five (P=0.017 and P=0.012 respectively). Fifty percent of patients in the prednisolone acetate group, 67% of patients in the ketorolac group and 89% of patients in the combination therapy group achieved a two-line or greater improvement in Snellen acuity. Sixty five percent of patients experienced an improvement in contrast sensitivity at final visit compared to baseline (50, 55 and 89% in the prednisolone acetate, ketorolac, and combination therapy groups, respectively; P values not reported). Most patients experienced an improvement in fluorescein angiography compared to baseline (50, 55 and 77% in the prednisolone acetate, ketorolac and combination groups, respectively; P values not reported).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				Recurrence of cystoid macular edema was noted in one patient from the ketorolac group and one patient from the combination therapy group, after an initial two-line improvement in visual acuity. Secondary: Not reported
El-Harazi et al (abstract)[49] Diclofenac 0.1% one drop in the affected eye(s) QID for one week, then BID for next three weeks vs ketorolac 0.5% one drop in the affected eye(s) QID for one week, then BID for next three weeks vs prednisolone acetate 1% one drop in the affected eye(s) QID for one week, then BID for next three weeks	AC, DB, RCT Patients undergoing phacoemulsification with posterior chamber IOL implantation	N=58 28 days	Primary: Flare, cells and IOP on postoperative days one, seven and 28 Secondary: Medication-related complications	Primary: There were no statistically significant differences in flare or cell counts or change in flare or cell counts from baseline between the treatment groups (P values not reported). There were no statistically significant differences in IOP or in change in IOP from baseline between the three treatment groups (P values not reported). Secondary: There were no medication-related complications observed at any time during the course of study (P values not reported).
Yaylali et al[50] Rimexolone 1% one drop in the affected eye(s) QID vs prednisolone acetate 1%	AC, DB, PRO, RCT Patients underwent uncomplicated cataract extraction with phaco-emulsification followed by	N=48 15 days	Primary: Anterior chamber cells, anterior chamber flare and conjunctival hyperemia Secondary: IOP and adverse	Primary: There was no statistically significant difference in the reduction of anterior chamber cells between the rimexolone and the prednisolone acetate groups, except on day three, in which more cells were observed in the rimexolone group (P=0.01). Inflammation scores on days one, three, seven and 15 were similar between the rimexolone group and the prednisolone acetate group in

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
one drop in the affected eye(s) QID Each patient also received ofloxacin 0.3% one drop in the affected eye(s) QID 10 minutes after topical steroid for 15 days.	posterior chamber IOL implantation		events	lowering aqueous flare (P>0.05 for all). There was no statistical difference between the rimexolone and prednisolone acetate treatment groups on days one, three, seven and 15 in terms of conjunctival hyperemia (P>0.05 for all). Secondary: There was no significant difference in IOP value between the rimexolone and prednisolone acetate groups on days one, seven and 15 (P>0.05). On day three, IOP was significantly lower in the rimexolone group compared to the prednisolone acetate group (P=0.038). Other than mild ocular itching that occurred at a similar frequency in both the rimexolone and prednisolone acetate groups during instillation, no other adverse events were reported (P value not reported).
Kavuncu et al[51] Rimexolone 1% one drop in the affected eye(s) QID for 15 days vs prednisolone acetate 1% one drop in the affected eye(s) QID for 15 days Each patient also received gentamicin 0.3% one drop in affected eye(s) QID ≥5 minutes after topical steroid for 14 days.	PRO, RCT, SB Patients 17 to 87 years of age undergoing cataract extraction either by extracapsular cataract extraction or phaco-emulsification surgery with IOL implantation	N=80 18 days	Primary: Anterior chamber cell count, flare, visual acuity, pain, corneal edema, conjunctival hyperemia and ciliary injection and IOP evaluated postoperatively on days one, three, eight, 15 and 18 Secondary: Not reported	Primary: There was no statistically significant difference between the rimexolone and prednisolone acetate groups at any postoperative visit with regard to anterior chamber cells and flare (P>0.05, for all). Corneal edema was significantly reduced in the rimexolone group on day eight compared to the prednisolone acetate group (P<0.05). There was no significant difference in corneal edema between the rimexolone and prednisolone acetate groups on days one, three, 15 or 18, respectively (P value not reported). There was no statistically significant difference between the rimexolone and prednisolone acetate treatment group in terms of visual acuity, ciliary injection or pain scores (P value not reported). No statistically significant differences in IOP were observed between the rimexolone and the prednisolone acetate groups on days one, three, eight, 15 and 18 (P>0.05 for all visits). Two patients discontinued treatment due to the IOP being >30 mm Hg during follow up. During the postoperative visits on days one and three, there was a

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				statistically significant reduction in conjunctival hyperemia in the prednisolone acetate group compared to the rimexolone group (P<0.05). On days eight, 15 and 18, there were no statistically significant differences between the two treatment groups in reduction of conjunctival hyperemia (P value not reported). Secondary: Not reported
Solomon et al[52] Ketorolac 0.5% one drop in the affected eye(s) QID starting 24 hours following surgery for one week and then BID for remainder of study vs rimexolone 1% one drop in the affected eye(s) QID starting 24 hours following surgery for one week and then BID for remainder of study Each patient also received ofloxacin QID (duration not reported).	AC, DB, PRO, RCT Patients >18 years of age scheduled to undergo cataract extraction with posterior chamber IOL implantation	N=36 30 days	Primary: Signs and symptoms of inflammation, IOP, visual acuity, slit-lamp cell and flare, and Kowa cell and flare measurements evaluated at one, four, seven and 30 days postoperatively Secondary: Not reported	Primary: Subjective measurement of inflammation by slit-lamp measurements of cell and flare were not significantly different between the two groups (P=0.17 and P=0.48, respectively). Objective measurement of cell and flare using Kowa cell and flare meter did not significantly differ between the two groups (P=0.17 and P=0.48, respectively). The cell measurements at visit two (postoperative day one) in the ketorolac and rimexolone groups were 17.5 and 8.3, respectively (P=0.28). The flare measurements at visit two in the ketorolac and rimexolone groups were 18.3 and 4.7, respectively (P=0.17). There were no differences in IOP reported between treatment groups (P values not reported). Visual acuity measurements at each visit and the overall improvement in visual acuity were similar in both groups (P values not reported). No significant difference was reported between the two groups in terms of ocular symptoms (P values not reported). Secondary: Not reported
Guzey et al (abstract)[53] Ketorolac/tobramycin vs	AC, PRO, RCT, SC Patients undergoing phacoemulsification	N=60 2 weeks	Primary: Burning/stinging sensation, blurred vision, ocular discomfort, conjunctival	Primary: There was no statistically significant difference between the two treatment groups in terms of ocular inflammation at any of the postoperative visits (P values not reported).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
fluorometholone/ tobramycin	cataract extract with sclera tunnel incision		hyperemia, anterior chamber flare, and anterior chamber cells assessed preoperatively and postoperatively on days one (baseline), two, three, seven and 14 Secondary: Not reported	Both treatment regimens were well tolerated by patients (P values not reported). Secondary: Not reported
Sivaprasad et al[54] Diclofenac 0.1% vs fenoprofen 1% vs flurbiprofen 0.03% vs indomethacin 25 mg (oral) vs ketorolac 0.5% vs prednisolone acetate 1% vs	SR Seven trials; three studied acute cystoid macular edema and four trials compared NSAIDs to placebo in chronic cystoid macular edema	N=266 4 to 12 weeks	Primary: Two-line or greater improvement in Snellen visual acuity, persistence of improvement of vision one month following discontinuation of treatment Secondary: Proportion of patients with improvement in leakage on fundus fluorescein angiography, proportion of participants with improved contrast sensitivity and quality of life	Primary: The mean time for a two-line improvement in Snellen visual acuity and resolution of cystoid macular edema was similar between the diclofenac and ketorolac groups. There was minimal evidence of any difference between ketorolac and placebo in achieving a two-line improvement in Snellen visual acuity at the end of crossover period for treatment of acute cystoid macular edema. There was a statistically significant benefit in using ophthalmic NSAIDs for chronic cystoid macular edema in two of the three studies for the improvement of visual acuity at the end of treatment (RR, 8.00; 95% CI, 1.16 to 55.20 and RR, 2.34; 95% CI, 1.25 to 4.40). There was a statistically significant benefit in using ophthalmic NSAIDs for chronic cystoid macular edema in one of the three studies for the improvement of visual acuity one month after treatment (RR, 3.37; 95% CI, 1.60 to 7.09). Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vehicle				
Allergic Conjunctivitis				
Shulman et al[55] Loteprednol 0.2% one drop in both eyes QID vs vehicle one drop in both eyes QID Nasal rescue medications were used as needed for control of excessive allergic symptoms including phenylephrine hydrochloride, and cromolyn solution.	DB, MC, PC, PG, RCT Patients 19 to 74 years of age with signs and symptoms of seasonal allergic conjunctivitis presenting with moderate to severe signs and symptoms of cedar mountain pollen	N=135 42 days	Primary: Bulbar conjunctival injection and ocular itching scores Secondary: Discharge, photophobia, palpebral conjunctival injection, investigator global assessment, palpebral conjunctival injection, chemosis, erythema, discomfort, foreign body sensation, burning/stinging, photophobia, epiphora, discharge and IOP	Primary: At hour two (P<0.001) and days two to three (P=0.001), seven (P<0.001), 14 (P<0.001) and 28 (P=0.010) respectively, there was a statistically significant improvement in bulbar conjunctival injection in the loteprednol group compared to the placebo group, but not at one hour (P=0.054) and day 42 (P=0.087). There was no statistically significant improvement in itching between the loteprednol and placebo groups from hours one and two and on days two to three, 28 and 42 (P>0.05 for all). On days seven and 14, there was a greater reduction in itching in the loteprednol group compared to the placebo group (P=0.014 and P=0.004, respectively). Secondary: A significantly greater proportion of patients treated with loteprednol were judged as having “mostly” to “fully” controlled signs and symptoms using the investigators global assessment compared to placebo (80 vs 44%; P<0.001). There was a significant reduction in severity of palpebral conjunctival injection, erythema, discomfort and epiphora in the loteprednol group compared to the placebo group (P values not reported). Both the loteprednol and placebo groups had one patient that had an increase in IOP >10 mm Hg (right eye/left eye). On day 14, one patient in the placebo group had an IOP 30/35 mm Hg from baseline of 18/17 mm Hg. On day 42, one patient in the loteprednol group had an IOP 36/32 mm Hg from baseline 14/14 mm Hg. There was no statistically significant difference in terms of visual acuity between the two groups (P value not reported). The proportion of patients continuing to experience at least one allergy

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				symptom was significantly lower in the loteprednol group compared to the placebo group (64 vs 81%; P=0.035). Criteria for statistical significance for adverse events was determined to be P≤0.15 instead of P<0.05. Loteprednol compared to placebo was associated with a significantly higher incidence of infection, digestive events and rhinitis (P=0.119, P=0.115 and P=0.126, respectively). The placebo group had a higher incidence of special events, burning and stinging, injection and sticky eye (P=0.005, P=0.115, P=0.004 and P=0.058, respectively). Three patients discontinued treatment. Two patients in the placebo group discontinued due to an increase IOP and spasm on instillation of a drop and one patient from the loteprednol etabonate group due to hospitalization from a motor vehicle accident.
Dell et al[56] Loteprednol 0.2% one drop in both eyes QID vs vehicle one drop in both eyes QID	DB, MC, PC, PG, PRO, RCT Patients with a history of positive skin prick or radioallergosorbent test and at time of enrollment had moderate to severe signs and symptoms of seasonal allergic conjunctivitis caused by mountain cedar pollen	N=133 6 weeks	Primary: Bulbar conjunctival injection, ocular itching and investigators global assessment Secondary: Visual acuity, IOP and medical events	Primary: In the first two weeks, there was a significantly greater improvement from baseline in bulbar injection with loteprednol treatment compared to placebo treatment (-1.32 vs -0.79; P<0.001).There was greater proportion of patients that experienced resolution of bulbar injection at day 14 in the loteprednol group compared to the placebo group (31 vs 9%; P value not reported). There was a significant improvement in bulbar injection at hour two and days two to three, seven, 14 and 28 in the loteprednol group compared to the placebo group (P<0.05 for all). There was no significant difference between the two groups at hour one or day 42 (P=0.274 and P=0.135, respectively). Over the first two weeks, the loteprednol group experienced a significantly greater itch relief compared to the placebo group (-3.36 vs -2.75; P<0.001). There was a greater proportion of patients that experienced resolution from itching at day 14 in the loteprednol group compared to the placebo group (54 vs 38%; P value not reported). During hour one and two and days 28 and 42 respectively, there was no

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				significant difference in itching relief between the loteprednol group and the placebo group (P=0.590, P=0.304, P=1.000 and P=0.134, respectively). There was a significant improvement between the two treatment groups in itching on days two to three, seven and 14 respectively (P<0.05 for all). After the first two weeks, there was a greater proportion of patients in the loteprednol group compared to the placebo group who were judged as having "mostly" to "fully" controlled signs and symptoms using the investigators global assessment (79 vs 47%; P<0.001). Secondary: No patients in the loteprednol or placebo groups had an IOP elevation ≥10 mm Hg. There was a greater proportion of patients with at least one allergy symptom in the placebo group compared to the loteprednol group (90 vs 68%; P=0.002). Flu symptoms were greater in the placebo group compared to the loteprednol group (P value not reported). Two patients in the placebo group discontinued treatment due to severe itching and viral conjunctivitis and two in the loteprednol group discontinued for acute pharyngeal reactions with headache and IOP 9 mm Hg.
Berdy et al[57] Olopatadine 0.1% one drop in both eyes QID for 14 days, then one drop in both eyes at evaluation visit vs loteprednol 0.2% one drop in both eyes QID for 14 days, then one drop in both eyes at evaluation	AC, DB, PG, RCT, SC Patients >18 years of age with a history of seasonal allergic conjunctivitis or perennial allergic conjunctivitis with no severe atopic, vernal or giant papillary conjunctivitis	N=50 21 days	Primary: Scores for itching and redness and IOP Secondary: Not reported	Primary: Greater itching relief was achieved following treatment with olopatadine compared to loteprednol at three, five and 10 minutes following CAC test (P=0.001, P<0.001 and P<0.001, respectively). Loteprednol significantly decreased itching scores compared to placebo at three and five minutes following CAC test (P<0.05 for both). No statistically significant difference between these two groups was reported at 10 minutes (P value not reported). Olopatadine provided a significant improvement in itching relief compared to placebo (P<0.001 at three, five and 10 minutes). Olopatadine was significantly more effective for the prevention of ocular

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
visit vs vehicle one drop in both eyes QID for 14 days, then one drop in both eyes at evaluation visit				redness compared to loteprednol at minutes 10, 15 and 20 (P=0.003, P=0.011 and P=0.034, respectively). No statistically significant difference in the prevention of ocular redness was reported at minutes 10, 15 and 20 for loteprednol compared to placebo (P value not reported). Olopatadine was significantly more effective for preventing ocular redness at 10, 15 and 20 minutes compared to placebo (P<0.001, P=0.012 and P=0.027, respectively). There was a statistically significant increase in IOP during the third visit with loteprednol compared to both olopatadine and placebo (P<0.001 for both). There were no adverse events reported during the course of study. Secondary: Not reported
Borazan et al[58] Ketotifen 0.025% one drop in one eye BID vs olopatadine 0.1% one drop in one eye BID vs emedastine 0.05% one drop in one eye BID vs epinastine 0.05% one drop	AC, DB, PC, PRO, RCT Patients with seasonal allergic conjunctivitis	N=100 2 weeks	Primary: Scores for itching, redness, tearing, chemosis and eyelid swelling assessed after one and two weeks of treatment and conjunctival impression cytology at baseline and after treatment Secondary: Not reported	Primary: After one and two weeks of treatment, all agents were significantly more effective in alleviating itching, redness, tearing, chemosis and eyelid swelling compared to placebo (P<0.001 for all). Fluorometholone was significantly less effective in reducing itching and redness at all visits compared to the other agents (P values not reported). Although scores for tearing, chemosis and eyelid swelling showed a clinical improvement in all groups, there were no statistically significant differences between treatment groups (P values not reported). At the end of treatment, conjunctival impression cytology scores were significantly lower for all active treatments compared to placebo (P<0.01). There were no statistically significant differences between treatment groups (P values not reported). Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
in one BID vs fluorometholone 0.1% one drop in one eye BID vs vehicle one drop in one eye BID One eye of each patient was treated with the study drug and the other eye was treated with placebo.				
Oner et al[59] Loteprednol 0.5% one drop in the affected eye(s) QID vs fluorometholone 0.1% one drop in the affected eye(s) QID vs prednisolone acetate 1% one drop in the affected eye(s) QID	AC, DB, PRO, RCT Patients with active vernal keratoconjunctivitis	N=60 4 weeks	Primary: Mean scores for itching, redness, burning, tearing, foreign body sensation, conjunctival hyperemia, papillary hypertrophy, Trantas' dots, chemosis, pannus and incidence of adverse events Secondary: Not reported	Primary: Over four weeks, symptom scores improved in all treatment groups compared to baseline values (P<0.001 for all, excluding Trantas' dots in the fluorometholone group), except for pannus formation in the fluorometholone group (P>0.05). In addition, loteprednol or prednisolone acetate significantly improved all symptom scores compared to fluorometholone, with the exception of chemosis (P<0.01 for all). There were no significant differences between the loteprednol and prednisolone acetate groups regarding any of the signs and symptoms at any time point. The loteprednol and prednisolone acetate groups had similar final mean visual acuity scores, and both groups had higher mean scores compared to the fluorometholone group (P=0.02 for both). The mean IOP values were similar among all groups at baseline and day three. There was a significant IOP elevation in the prednisolone acetate group only after the day three (P<0.001). Three patients in the prednisolone acetate group were excluded from the study in the second week because of the IOP elevation; however, the mean IOP remained significantly elevated in this group (P<0.001). There were no other adverse events in any of the

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				groups. Secondary: Not reported
External Ocular Infections				
Shulman et al[60] Neomycin/polymyxin B/ dexamethasone 3,500 units/mL/6,000 units/mL/0.1% vs dexamethasone 0.1%	DB Patients with bacterial blepharitis or conjunctivitis	N=111 Duration not specified	Primary: Bacterial count, bacterial eradication and reduction in symptoms Secondary: Not reported	Primary: Neomycin/polymyxin B/dexamethasone showed a significantly greater decrease in bacterial counts and bacterial eradication when compared to dexamethasone (90 vs 50% and 34 vs 17%, respectively; P values not reported). Neomycin/polymyxin B/dexamethasone was shown to significantly reduce conjunctival discharge when compared to dexamethasone (P value not reported). Both groups were equally efficacious in alleviating other ocular signs and symptoms (P value not reported). Secondary: Not reported

*Agent not available in the United States.
Drug regimen abbreviations: BID=twice daily, QD=once daily, QID=four times daily, TID=three times daily
Study abbreviations: AC=active control, DB=double-blind, CI=confidence interval, MC=multicenter, NI=noninferiority, OL=open-label, PC=placebo-controlled, PG=parallel-group, PRO=prospective, RCT=randomized controlled trial, RR=relative risk, SB=single-blind, SC=single center, SR=systematic review, TB=triple blind, XO=crossover
Miscellaneous abbreviations: CAC=conjunctival allergen challenge, CRT=central retinal thickness, IOL=intraocular lens, IOP=intraocular pressure, logMAR= logarithm of the minimum angle of resolution, Nd:YAG: neodymium-doped yttrium aluminum garnet, NEI VFQ-39= 39-question National Eye Institute Visual Function Questionnaire, NSAID=nonsteroidal anti-inflammatory drug, OCT=ocular coherence tomography, QOL=quality of life, VAS=visual analog scale, WLQ=work limitations questionnaire

Special Populations

Table 4. Special Populations[1-17]

Generic Name	Population and Precaution				
	Elderly/ Children	Renal Dysfunction	Hepatic Dysfunction	Pregnancy Category	Excreted in Breast Milk
Dexamethasone	No evidence of overall differences in safety or efficacy observed between elderly and younger adult patients. Safety and efficacy in children have not been established.	Not reported	Not reported	C	Unknown
Difluprednate	No evidence of overall differences in safety or efficacy observed between elderly and younger adult patients. Safety and efficacy in children have not been established.	Not reported	Not reported	C	Unknown
Fluorometholone	No evidence of overall differences in safety or efficacy observed between elderly and younger adult patients. Safety and efficacy in children <2 years of age have not been established.	Not reported	Not reported	C	Unknown
Loteprednol etabonate	No evidence of overall differences in safety or efficacy observed between elderly and younger adult patients. Safety and efficacy in children have not been established.	Not reported	Not reported	C	Unknown
Prednisolone acetate	No evidence of overall differences in safety or efficacy observed between elderly and younger adult patients.	Not reported	Not reported	C	Unknown

Generic Name	Population and Precaution				
	Elderly/ Children	Renal Dysfunction	Hepatic Dysfunction	Pregnancy Category	Excreted in Breast Milk
	Safety and efficacy in children have not been established.				
Prednisolone sodium phosphate	No evidence of overall differences in safety or efficacy observed between elderly and younger adult patients. Safety and efficacy in children have not been established.	Not reported	Not reported	C	Unknown
Rimexolone	No evidence of overall differences in safety or efficacy observed between elderly and younger adult patients. Safety and efficacy in children have not been established.	Not reported	Not reported	C	Unknown

Adverse Drug Events

Table 5. Adverse Drug Events (%)[1-17]

Adverse Event	Dexa-methasone	Diflu-prednate	Fluoro-metholone	Lote-prednol Etabonate	Predni-solone	Rime-xolone
Cardiovascular						
Hypotension	-	-	-	-	-	<2
Central Nervous System						
Headache	-	-	-	<15.0[§]; 1.5[‡]	-	<2
Ocular						
Anterior chamber cells	-	5 to 15	-	-	-	-
Anterior chamber flare	-	5 to 15	-	-	-	-
Anterior chamber inflammation	-	-	-	5[†]; 25[‡]	-	-
Bleb formation increased	a	-	a	-	a *	-
Blepharitis	-	5 to 15	-	-	-	-
Blurred vision	-	-	a	5 to 15[§]	-	1 to 5
Burning	a	-	a	5 to 15[§]	a *	-
Chemosis	-	-	-	5 to 15[§]	-	-
Ciliary hyperemia	-	5 to 15	-	-	-	-
Conjunctival edema	-	5 to 15	-	-	-	<1
Conjunctival hyperemia	-	5 to 15	a	4 to 5[‡]	a	1 to 5
Conjunctivitis	-	-	a	<5[§]	a	-

Adverse Event	Dexa-methasone	Diflu-prednate	Fluoro-metholone	Lote-prednol Etabonate	Predni-solone	Rime-xolone
Corneal abnormalities	-	-	-	<5[§]	-	-
Corneal edema	-	5 to 15	-	4 to 5[‡]	-	<1
Corneal erosion	-	-	-	-	-	<1
Corneal or sclera thinning	-	-	-	a	-	-
Corneal staining	-	<1	-	-	-	<1
Corneal striae	-	<1	-	-	-	-
Corneal ulcer	-	-	a	-	a	<1
Delayed wound healing	-	-	a	a	a	-
Discharge	-	-	-	5 to 15	-	1 to 5
Discomfort	-	<1	-	<5	-	1 to 5
Dry eye	-	-	-	5 to 15[§]	-	<1
Edema	-	-	-	-	-	<1
Elevation in intraocular pressure	-	a	a	2[§]	a	1 to 5
Epiphora	-	-	-	5 to 15[§]	-	-
Eye inflammation	-	1 to 5	-	-	-	-
Eye irritation	-	-	a	<5[§]	-	-
Eye pain	-	5 to 15	-	≤5	-	1 to 5
Eye pruritus	-	<1	-	5 to 15[§]	-	1 to 5
Eyelid crusting	-	<1	-	-	-	-
Eyelid erythema	-	-	-	<5[§]	-	-
Eyelid irritation	-	<1	-	-	-	-
Foreign body sensation	-	<1	-	5 to 15[§]; 2[†]	-	1 to 5
Glaucoma with optic nerve damage	a	-	-	-	a	-
Increased fibrin	-	-	-	-	-	<1
Infiltrate	-	-	-	-	-	<1
Injection	-	-	-	5 to 15[§]	-	-
Iritis	-	1 to 5	-	-	-	-
Irritation upon instillation	-	<1	a	-	-	<1
Keratitis	-	-	a	-	a	<1
Keratoconjunctivitis	-	-	-	<5[§]	-	-
Lacrimation disorder	-	<1	-	-	-	-
Lid margin crusting	-	-	-	-	-	<1
Loss of accommodation	-	-	-	-	a	-
Macular edema	-	<1	-	-	-	-
Mydriasis	-	-	a	-	a	-
Papillae	-	-	-	<5[§]	-	-
Perforation of the globe	a	a	a	a	a	-
Photophobia	-	5 to 15	-	5 to 15[§]	-	<1
Posterior capsule opacification	-	5 to 15	-	-	-	-
Posterior subcapsular cataract formation	a	a	a	a	a	-
Ptosis	-	-	a	-	a	-
Secondary ocular infection	a	a	a	a	a	-
Sticky sensation	-	-	-	-	-	<1

Adverse Event	Dexa-methasone	Diflu-prednate	Fluoro-metholone	Lote-prednol Etabonate	Predni-solone	Rime-xolone
Stinging	a	-	a	-	a *	-
Superficial punctuate keratitis	-	1 to 5	-	-	-	-
Tearing	-	-	-	-	-	<1
Visual acuity and field defects	a	1 to 5	a	a	a	-
Uveitis	-	<1	a	<5§	a	-
Other						
Allergic reactions	-	-	a	-	-	-
Pharyngitis	-	-	-	<15§	-	<2
Rhinitis	-	-	-	<15§	-	<2
Systemic hypercorticoidism (rare)	-	-	a	-	a	-
Taste perversion	-	-	a	-	-	<2

a Percent not specified.
- Event not reported or incidence <1%.
*Prednisolone sodium phosphate only.
† Gel.
‡ Ointment.
§ Suspension.

Contraindications

Table 6. Contraindications[1-17]

Contraindication	Dexa-methasone	Diflu-prednate	Fluoro-metholone	Lote-prednol Etabonate	Predni-solone	Rime-xolone
Acute purulent untreated infections	-	-	a *	-	a †	a
Epithelial herpes simplex keratitis (dendritic keratitis), vaccinia, varicella and many other active viral diseases of the cornea and conjunctiva	a	a	a	a	a	a
Fungal diseases of ocular or auricular structures	a	a	a	a	a	a
Hypersensitivity to any component of the product	a	-	a	a	a	a
Mycobacterial infection of the eye	a	a	a	a	a	a
Uncomplicated removal of a superficial corneal foreign body	-	-	-	-	a ‡	-

*Flarex® only.
†0.12% suspension only.
‡Prednisolone sodium phosphate only.

Warnings/Precautions

Table 7. Warnings and Precautions[1-17]

Warning/Precaution	Dexa-methasone	Diflu-prednate	Fluoro-metholone	Lote-prednol Etabonate	Predni-solone	Rime-xolone
Amblyopia treatment; do not use in children following ocular surgery	-	-	-	a *	-	-
Cataract formation; use with caution	a	a	a	a	a	a
Contact lens use; do not wear contact lenses during course of therapy with ophthalmic steroids	-	a	-	a	-	-
Corneal and sclera thinning and perforation; use with caution in diseases know to thin corneal or sclera tissue	a	-	a	a	a	a
Corticosteroid use may mask or enhance acute purulent infections of the eye; use with caution	a	-	a	a	a	a
Delayed healing after cataract surgery; use with caution	-	a	a †	a	a	-
Fungal infection of the cornea; consider taking fungal cultures in any persistent corneal ulceration	a	a	a	a	a	a
Intraocular pressure increase; use with caution in the presence of glaucoma and monitor intraocular pressure if used beyond 10 days	a	a	a	a	a	a
Mustard gas keratitis and Sjögren's keratoconjunctivitis; avoid in these conditions	-	-	a *†	-	a	-
Ophthalmic ointments may slow corneal healing and cause blurred vision; use with caution	-	-	a *	-	-	-
Secondary bacterial infection; reevaluate if	a	a	a	a	a	-

Warning/Precaution	Dexa-methasone	Diflu-prednate	Fluoro-metholone	Lote-prednol Etabonate	Predni-solone	Rime-xolone
signs and symptoms fail to improve after two days of treatment						
Sodium bisulfate; use with caution in patients with sulfite sensitivity	-	-	-	-	a ‡	-
Topical ophthalmic use only; not for injection or intraocular administration	a	a	a	a	a	a

*Ointment only.
†0.1% suspension only.
‡Prednisolone acetate only.

Drug Interactions

Since ophthalmic medications have minimal systemic absorption, studies have not been conducted to assess drug interactions associated with these medications.[1-17]

Dosage and Administration

Table 8. Dosing and Administration[1-17]

Generic Name	Adult Dose	Pediatric Dose	Availability
Dexamethasone	Corneal injury from chemical, radiation or thermal burns, penetration of foreign bodies and steroid-responsive inflammatory ocular conditions Ophthalmic solution: initial, instill one or two drops into the conjunctival sac(s) every hour during the day and every two hours during the night; reduce dose to one drop every three or four hours when favorable response is observed; may further reduce dose to three or four times daily later in the course of therapy Ophthalmic suspension: instill one or two drops into the conjunctival sac(s); in severe disease, may be dosed hourly then taper based on response; in mild disease, may be dosed four to six times daily	Safety and efficacy in children have not been established.	Ophthalmic solution: 0.1% (5 mL) Ophthalmic suspension: 0.1% (5 mL)
Difluprednate	Anterior uveitis, endogenous Ophthalmic emulsion: instill one drop into the conjunctival sac(s) four times daily for 14 days followed by tapering as clinically indicated Postoperative inflammation following ocular surgery Ophthalmic emulsion: instill one drop	Safety and efficacy in children have not been established.	Ophthalmic emulsion: 0.05% (5 mL)

Generic Name	Adult Dose	Pediatric Dose	Availability
	into the conjunctival sac(s) four times daily beginning 24 hours after surgery and continuing throughout the first two weeks of the postoperative period, followed by two times daily for one week and then taper based on response		
Fluorometholone	Steroid-responsive inflammatory ocular conditions Ophthalmic ointment: apply a small amount (approximately a ½ inch ribbon) into the conjunctival sac(s) one to three times daily; during the initial 24 to 48 hours, dosage may be increased to one application every four hours Ophthalmic suspension (Flarex®): instill one or two drops into the conjunctival sac(s) four times daily; during the initial 24 to 48 hours, dosage may be increased to two drops every two hours Ophthalmic suspension (FML®, FML Forte®): instill one drop into the conjunctival sac(s) two to four times daily; during the initial 24 to 48 hours, dosage may be increased to one drop every four hours	Safety and efficacy in children <2 years of age have not been established.	Ophthalmic ointment: 0.1% (3.5 g) Ophthalmic suspension: 0.1% (5, 10, 15 mL) 0.25% (5, 10 mL)
Loteprednol etabonate	Postoperative inflammation and pain following ocular surgery: Ophthalmic gel: instill one to two drops into the conjunctival sac(s) four times daily beginning the day after surgery and continuing throughout the first two weeks of the postoperative period Ophthalmic ointment: apply a small amount (approximately a ½ inch ribbon) into the conjunctival sac(s) four times daily beginning the day after surgery and continuing throughout the first two weeks of the postoperative period Postoperative inflammation following ocular surgery: Ophthalmic suspension (0.5%): instill one to two drops into the conjunctival sac(s) four times daily beginning 24 hours after surgery and continuing	Safety and efficacy in children have not been established.	Ophthalmic gel: 0.5% (5 g) Ophthalmic ointment: 0.5% (3.5 g) Ophthalmic suspension: 0.2% (5, 10 mL) 0.5% (2.5, 5, 10, 15 mL)

Generic Name	Adult Dose	Pediatric Dose	Availability
	throughout the first two weeks of the postoperative period Temporary relief of the signs and symptoms of seasonal allergic conjunctivitis: Ophthalmic suspension (0.2%): instill one drop into the affected eye(s) four times daily Steroid responsive inflammatory ocular conditions: Ophthalmic suspension (0.5%): instill one to two drops into the conjunctival sac(s) four times daily; during the initial first week, dosage may be increased up to one drop every hour if needed		
Prednisolone acetate	Corneal injury from chemical, radiation or thermal burns, penetration of foreign bodies and steroid-responsive inflammatory ocular conditions Ophthalmic solution: initial, instill one to two drops into the conjunctival sac(s) up to every hour during the day and every two hours during the night as necessary; reduce dose to one drop every four hours when favorable response is observed; may further reduce dose to one drop three to four times daily later in the course of therapy Ophthalmic suspension (Omnipred®): instill two drops in the affected eye(s) four times daily Ophthalmic suspension (Pred Forte® and Pred Mild®): instill one to two drops into the conjunctival sac(s) two to four times daily; during the initial 24 to 48 hours, dosing frequency may be increased if necessary	Safety and efficacy in children have not been established.	Ophthalmic solution: 1% (10 mL) Ophthalmic suspension: 0.12% (5, 10 mL) 1% (1, 5, 10, 15 mL)
Prednisolone sodium phosphate	Corneal injury from chemical, radiation or thermal burns, penetration of foreign bodies and steroid-responsive inflammatory ocular conditions Ophthalmic solution: initial, instill one to two drops into the conjunctival sac(s) up to every hour during the day and every two hours during the night as necessary; reduce dose to one drop every four hours when favorable	Safety and efficacy in children have not been established.	Ophthalmic solution: 1% (10 mL)

Generic Name	Adult Dose	Pediatric Dose	Availability
	response is observed; may further reduce dose to one drop three to four times daily later in the course of therapy		
Rimexolone	Anterior uveitis: Ophthalmic suspension: instill one to two drops into the conjunctival sac(s) every hour during waking hours for the first week, then one drop every two hours during waking hours of second week and then taper until uveitis is resolved Postoperative inflammation following ocular surgery: Ophthalmic suspension: instill one to two drops into the conjunctival sac(s) four times daily beginning 24 hours after surgery and continuing throughout the first two weeks of the postoperative period	Safety and efficacy in children have not been established.	Ophthalmic suspension: 1% (5, 10 mL)

Clinical Guidelines

Table 9. Clinical Guidelines

Clinical Guideline	Recommendation(s)
American Academy of Ophthalmology: **Preferred Practice Pattern: Cataract in the Adult Eye (2011)**[26]	Infection prophylaxis · Two emerging concerns are the increasing resistance of *Staphylococcus* species (the most common cause of endophthalmitis) to a broad spectrum of antibiotics, including the latest generation fluoroquinolones, and the increased occurrence of acute endophthalmitis more than a week after surgery. · Prophylactic strategies that have been used include applying topical antibiotic eye drops before surgery, applying 5% povidone iodine to the conjunctival cul de sac, preparing the periocular skin with 10% povidone iodine, careful sterile draping of the eyelid margins and eyelashes, adding antibiotics to the irrigating solution, instilling intracameral antibiotics at the close of surgery, injecting subconjunctival antibiotics and applying topical antibiotic eye drops after surgery. · Because of the lack of and impracticality of sufficiently large prospective clinical trials, there is insufficient evidence to recommend a specific antibiotic drug or method of delivery for endophthalmitis prophylaxis. · Systemic antibiotics are rarely used; however, it has been shown that certain oral fluoroquinolone antibiotics penetrate the blood/ocular barrier adequately to reach levels above the minimum inhibitory concentrations for many organisms inside the eye, and oral antibiotics that penetrate well into the eye may be beneficial. Postoperative follow-up · Postoperative regimens of topically applied antibiotics, corticosteroids and nonsteroidal anti-inflammatory drugs (NSAIDs) vary among practitioners. · No controlled investigations establish optimal regimens for the use of

Clinical Guideline	Recommendation(s)
	topical agents. · The operating surgeon is responsible for making the decision whether to use any or all of the topical products singly or in combination. · Complications of postoperative medications include elevated intraocular pressure with corticosteroids and allergic reactions to antibiotics. Significant corneal reactions, including epithelial defects and stromal ulceration and melting, have rarely been reported with topical NSAIDs. Cystoid macular edema · Topical anti-inflammatory agents are used in an attempt to reduce the inflammatory response to cataract surgery and to treat established cystoid macular edema. · There is evidence that topically applied NSAIDs alone or in combination with corticosteroids is more effective than topical corticosteroids alone in preventing and treating cystoid macular edema.
American Optometric Association: **Care of the Adult Patient with Cataract (2004)**[25]	· A combination of topical and oral anti-glaucoma, antibiotic and anti-inflammatory medications may be administered to the patient before, during and after an operation. · Topical corticosteroids may be used to suppress inflammation associated with cataract surgery. · To control inflammation associated with anterior uveitis, topical corticosteroids such as prednisolone acetate 1% may be used every two to four hours depending on the degree of inflammation.
American Academy of Ophthalmology: **Preferred Practice Pattern: Refractive Errors and Refractive Surgery (2012)**[27]	Surface ablation techniques · Topical antibiotics are administered to minimize the risk of postoperative infection. · Topical corticosteroids are generally started immediately after surgery and tapered over a period of days to weeks, and sometimes months. If corticosteroid treatment is prolonged, the intraocular pressure should be monitored. · Although postoperative pain may be reduced by the use of a bandage, contact lens and NSAID drops, patients may still require prescription oral analgesics. · Since NSAID drops may delay corneal epithelialization, they should be applied judiciously. · Sterile corneal infiltrates associated with the use of NSAID drops without the concomitant use of topical corticosteroids have been described. · Periodic examinations are necessary to monitor ocular status and to check for corticosteroid-related side effects such as elevated intraocular pressure. Laser in situ keratomileusis · Topical antibiotics are administered to minimize the risk of postoperative infection. · Corticosteroids are generally used for a short time postoperatively. · Frequent lubrication is recommended in the postoperative period. · Symptoms of post-laser in situ keratomileusis epitheliopathy (reduced best corrected visual acuity, fluctuating vision, foreign-body sensation and discomfort) typically improve with time, but in certain cases they may persist for months or years. Supplemental lubrication, topical cyclosporine eye drops and punctal occlusion may be helpful in such cases. · Diffuse lamellar keratitis is a noninfectious aggregation of inflammatory

Clinical Guideline	Recommendation(s)
	cells, and treatment is commonly guided by the severity of the inflammation. Increasing the frequency of topical corticosteroid administration with a closer follow-up is practiced by most surgeons.
American Academy of Ophthalmology: **Preferred Practice Pattern: Conjunctivitis (2013)**[61]	Seasonal allergic conjunctivitis · Treatment of conjunctivitis is ideally directed at the root cause. Indiscriminate use of topical antibiotics or corticosteroids should be avoided because antibiotics can induce toxicity, and corticosteroids can potentially prolong adenoviral infections and worsen herpes simplex virus infections. · Treat mild allergic conjunctivitis with an over-the-counter (OTC) antihistamine/vasoconstrictor or second-generation topical histamine H_1-receptor antagonist. The guideline does not give preference to one OTC antihistamine/vasoconstrictor or antihistamine vs another. The guideline does not address the role of prescription vasoconstrictors in the management of allergic conjunctivitis. · If the condition is frequently recurrent or persistent, use mast-cell stabilizers. The guideline does not give preference to one mast-cell stabilizer vs another. · Medications with antihistamine and mast-cell stabilizing properties may be utilized for either acute or chronic disease. The guideline does not give preference to one antihistamine/mast-cell stabilizer vs another. · If the symptoms are not adequately controlled, a brief course (one to two weeks) of low-potency topical corticosteroid may be added to the regimen. The lowest potency and frequency of corticosteroid administration that relieves the patient's symptoms should be used. · Ketorolac, an NSAID, is also Food and Drug Administration (FDA)-approved for the treatment of allergic conjunctivitis. · Additional measures include allergen avoidance and using cool compresses, oral antihistamines and artificial tears, which dilute allergens and treat coexisting tear deficiency. Frequent clothes washing and bathing before bedtime may also be helpful. · Consultation with an allergist or dermatologist may be helpful for patients with disease that cannot be adequately controlled with topical medications and oral antihistamines. Vernal/atopic conjunctivitis · General treatment measures include: o Modifying the environment to minimize exposure to allergens or irritants o Using cool compresses and ocular lubricants. o Topical and oral antihistamines and topical mast-cell stabilizers can be useful to maintain comfort. · For acute exacerbations of vernal/atopic conjunctivitis: o Topical corticosteroids are usually necessary to control severe signs and symptoms o The minimal amount of corticosteroid should be used based on patient response and tolerance. o Topical cyclosporine 2% is effective as adjunctive therapy to reduce the amount of topical corticosteroid used to treat severe atopic keratoconjunctivitis. o Commercially available topical cyclosporine 0.05% may be a useful adjunct in the treatment of vernal/atopic conjunctivitis.

Clinical Guideline	Recommendation(s)
	o For entities such as vernal keratoconjunctivitis, which may require repeat short-term therapy with topical corticosteroids, patients should be informed about potential complications of corticosteroid therapy, and general strategies to minimize corticosteroid use should be discussed. · For severe sight-threatening atopic keratoconjunctivitis that is not responsive to topical therapy, supratarsal injection of corticosteroid can be considered. · Systemic immunosuppression is rarely warranted. o In patients 2 years old or older, eyelid involvement can be treated with pimecrolimus cream 1% or topical tacrolimus ointment applied to the affected eyelid skin. o Tacrolimus ointment 0.03% is used for children 2 years to 15 years old; either 0.03% or 0.1% is used for patients 16 years and older. o A randomized, placebo-controlled clinical trial of topical tacrolimus 0.1% showed efficacy in patients who had failed therapy with topical corticosteroids and topical antiallergy medications. o Tacrolimus or pimecrolimus are rarely associated with development of skin cancer or lymphoma. · Frequency of follow-up visits is based on the severity of disease presentation, etiology, and treatment. · Consultation with a dermatologist is often helpful. · A follow-up visit should include an interval history, measurement of visual acuity, and slit-lamp biomicroscopy. · If corticosteroids are prescribed, baseline and periodic measurement of intra-ocular pressure and pupillary dilation should be performed to evaluate for glaucoma and cataract. · Discussion of treatment of complications such as corneal plaques and ulceration is beyond the scope of this document. <u>Mild bacterial conjunctivitis</u> · Mild bacterial conjunctivitis may be self-limited and resolve spontaneously without treatment in immunocompetent adults. · Ophthalmic antibacterial therapy is associated with earlier clinical and microbiological remission compared to placebo at days two to five of treatment. The advantages persist over six to 10 days, but the benefit over placebo lessens over time. · The choice of ophthalmic antibiotic is usually empirical. · A five to seven day course of ophthalmic broad-spectrum antibiotic is usually effective. · The most convenient or least expensive option can be selected. <u>Severe bacterial conjunctivitis</u> · Severe bacterial conjunctivitis is characterized by copious purulent discharge, pain and marked inflammation of the eye. · The choice of ophthalmic antibiotic is guided by the results of laboratory tests. · Methicillin-resistant *Staphylococcus aureus* (MRSA) has been isolated with increasing frequency from patients with bacterial conjunctivitis. Many MRSA organisms are resistant to commercially available ophthalmic

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	antibiotics. · Systemic antibiotic therapy is necessary to treat conjunctivitis due to *Neisseria gonorrhoeae* and *Chlamydia trachomatis*. · If corneal involvement is present, the patient should also be treated topically for bacterial keratitis. Herpes simplex virus conjunctivitis · Topical and/or oral antiviral treatment is recommended for herpes simplex virus conjunctivitis to prevent corneal infection. · Possible options include topical ganciclovir 0.15% gel applied three to five times per day, trifluridine 1% solution applied five to eight times per day, or oral acyclovir 200 to 400 mg administered five times per day. · Oral valacyclovir and famciclovir also can be used. · Topical antiviral agents may cause toxicity if used for more than two weeks. · Topical corticosteroids potentiate herpes simplex virus infection and should be avoided. · Follow-up care management within one week of treatment is advised and should include an interval history, visual acuity measurement, and slit-lamp biomicroscopy. · Neonates require prompt consultation with the pediatrician or primary care physician, because systemic herpes simplex virus infection is a life-threatening condition.
American Optometric Association: **Optometric Clinical Practice Guideline: Care of the Patient With Conjunctivitis (2007)**[62]	Allergic conjunctivitis (includes atopic keratoconjunctivitis, simple allergic conjunctivitis, seasonal or perennial conjunctivitis and vernal conjunctivitis) · The treatment of allergic conjunctivitis is based upon identification of specific antigens and elimination of specific pathogens, when practical, and upon the use of medications that decrease or mediate the immune response. The use of supportive treatment, including unpreserved lubricants and cold compresses, may provide symptomatic relief. · The following agents are useful in treating allergic conjunctivitis: topical corticosteroids (numerous products listed), vasoconstrictors/antihistamines (specific products not listed), antihistamines (azelastine, emedastine and levocabastine*), NSAIDs (ketorolac), mast cell stabilizers (cromolyn, lodoxamide, nedocromil and pemirolast), antihistamines/mast cell stabilizers (ketotifen and olopatadine) and immunosuppressants; and systemic immunosuppressants and antihistamines. · Topical corticosteroids are effective in relieving the acute symptoms of allergy; however, their use should be limited to the acute suppression of symptoms because of the potential for adverse side effects with prolonged use (e.g., cataract formation and elevated intraocular pressure). · Topical vasoconstrictors/antihistamines cause vascular constriction, decrease vascular permeability and reduce ocular itching by blocking histamine H_1 receptors. The guideline does not address the role of prescription vasoconstrictors in the management of allergic conjunctivitis. · Topical antihistamines competitively bind with histamine receptor sites and reduce itching and vasodilation. Azelastine, emedastine and levocabastine* are effective in reducing the symptoms of allergic conjunctivitis, and emedastine may be more efficacious than levocabastine*. · Topical diclofenac and ketorolac, which are both NSAIDS, are effective in

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	reducing the signs and symptoms associated with allergic conjunctivitis, although only ketorolac is FDA approved for this indication. · Nedocromil, an effective treatment for seasonal allergic conjunctivitis, is more effective than cromolyn (2%†) in treating vernal conjunctivitis. Nedocromil was less effective than fluorometholone in treating severe vernal keratoconjunctivitis but has fewer side effects. Lodoxamide has demonstrated a greater improvement in the signs and symptoms of allergic eye disease, including vernal keratoconjunctivitis, than cromolyn (2† or 4%). Pemirolast has FDA-approval as a treatment to relieve (to prevent) itching associated with allergic conjunctivitis. · Ketotifen and olopatadine are selective histamine H_1-receptor antagonists that also have mast cell stabilizing properties. Olopatadine may be more effective than other mast cell stabilizing agents in targeting the subtype of mast cell found in the conjunctiva. Compared to ketorolac or ketotifen, olopatadine is more effective in relieving the itching and redness associated with acute allergic conjunctivitis. · Systemically administered cyclosporine may be an effective treatment for patients with severe atopic keratoconjunctivitis. Topical cyclosporine is an alternative to topical corticosteroids for treatment of patients with severe atopic keratoconjunctivitis. Topical cyclosporine may also be beneficial in patients with vernal keratoconjunctivitis who have failed conventional therapy. · Systemic antihistamines are useful when the allergic response is associated with lid edema, dermatitis, rhinitis or sinusitis. They should be used with caution because of the sedating and anticholinergic effects of some first-generation antihistamines. Newer antihistamines are much less likely to cause sedation, but their use may result in increased ocular surface dryness. <u>Viral conjunctivitis</u> · Most viral conjunctivitis is related to adenoviral infection; however, no antiviral agent has been demonstrated to be effective in treating these infections. · Topical NSAID therapies have shown no benefit in reducing viral replication, decreasing the incidence of sub-epithelial infiltrates, or alleviating symptoms. · Topical antibiotics are not routinely used to treat viral conjunctivitis, unless there is evidence of secondary bacterial infection. · The treatment of herpes simplex conjunctivitis may include the use of antiviral agents such as trifluridine, although there is no evidence that this therapy results in a lower incidence of recurrent disease or keratitis. · Supportive therapy, including lubricants and cold compresses, which may be as effective as antiviral drugs, eliminates the potential for toxic side effects. · Topical steroids are specifically contraindicated for treating herpes simplex conjunctivitis.
American Academy of Ophthalmology Cornea/External Disease Panel, Preferred Practice Patterns Committee:	· Dry eye can be stratified by severity level into three categories based on the signs and symptoms of disease, with treatment recommendations specific for disease severity. · The sequence and combination of therapies should be determined on the basis of the patient's needs and preferences, as well as the treating physician's medical judgment.

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Dry Eye Syndrome (2013)[63]	· Specific therapies may be chosen from any category regardless of the level of disease severity, depending on physician experience and patient preference. · Tear replacement is frequently unsuccessful when used as the sole treatment if additional causative factors are not concomitantly addressed. · Recommended treatment options that are particularly effective for evaporative tear deficiency include environmental modifications, eyelid therapy for conditions such as blepharitis or meibomianitis, artificial tear substitutes, moisture chamber spectacles, and/or surgery such as tarsorrhaphy. <u>Treatment for mild dry eye syndrome</u> · Treatment options listed for patients with mild dry eye syndrome include: o Education and environmental modifications. o Discontinuation of any offending topical or systemic medications. o Aqueous enhancement using artificial tear substitutes, gels or ointments. o Eyelid therapy (warm compresses and eyelid hygiene). o Treatment of contributing ocular factors such as blepharitis or meibomianitis, if present. · Patients with suggestive symptoms of dry eye syndrome without signs should be placed on trial treatments with artificial tears when other potential causes of ocular irritation have been eliminated. · Potentially exacerbating exogenous factors (i.e. antihistamine or diuretic use) should be addressed. · Education and environmental modifications include: avoidance of smoking or second hand smoke, humidifying ambient air, avoiding air drafts, adjusting computer screen height to change lid aperture and increasing blink frequency may decrease computer and reading-related discomfort. · As the severity increases, aqueous enhancement with topical agents such as emulsions, gels, and ointments can be used. Artificial tear use may be increased, but the practicality of frequent installation depends on patient lifestyle and dexterity. · Preservative-free tear substitutes are generally preferable. Tear substitutes with preservatives may be sufficient for mild dry eye and an otherwise healthy ocular surface. When tear substitutes are used more than four times a day, preservative-free tears are generally recommended. <u>Treatment of moderate dry eye syndrome (in addition to treatments for mild dry eye)</u> · In addition to the treatments listed for mild disease, treatments for moderate disease include: o Anti-inflammatory agents (e.g., topical corticosteroids and cyclosporine 0.05%), systemic omega-3 fatty acid supplements. o Punctal plugs. o Spectacle side shields and moisture chambers. · Anti-inflammatory therapies may be considered in addition to aqueous enhancement therapies. · Low dose topical corticosteroids can be used at infrequent intervals for short-term (two-week) suppression of irritation secondary to inflammation. Patients should be monitored for adverse effects such as increased intraocular pressure, corneal melting, and cataract formation. Loteprednol

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	etabonate 0.5% has demonstrated benefit in patients with keratoconjunctivitis sicca with at least a moderate inflammatory component. · Systemic omega-3 fatty acids may be beneficial; however, only a small amount of literature that supports its use is available. · Punctal occlusion should be considered for patients with aqueous tear deficiency when the medical means of aqueous enhancement are ineffective or impractical. · Punctal occlusion may be accomplished surgically with silicone or thermal labile polymer plugs. Silicone plugs placed in the punctum and both silicone and collagen plugs placed in the canaliculus may improve dry eye signs and symptoms. · An advantage of punctal plugs are their ability to be removed and they may be retained for years without complications, when appropriately sized. · Spectacle side shields and moisture chambers are noninvasive therapies that can be used; although they may not be well tolerated due to negative cosmetic effect. · Moisture inserts (e.g., hydroxypropyl cellulose) may be helpful for patients who are unable to use frequent artificial tears. <u>Treatment of severe dry eye syndromes (in addition to treatments for mild and moderate dry eye)</u> · In addition to the treatments listed for mild and moderate severity disease, treatments for severe disease include: o Systemic anti-inflammatory agents. o Systemic cholinergic agonists (cevimeline and pilocarpine). o Mucolytic agents. o Autologous serum tears. o Contact lenses. o Correction of eyelid abnormalities. o Permanent punctal occlusion. o Tarsorrhaphy. · Oral medications are available for patients with combined dry eye and dry mouth (Sjögren syndrome). · Cevimeline may have less adverse systemic effects than oral pilocarpine. · For patients with systemic disease, such as rheumatoid arthritis, systemic anti-inflammatory/immunosuppressive therapy may be appropriate.
American Academy of Ophthalmology: **Preferred Practice Pattern: Blepharitis (2013)**[64]	· There is insufficient evidence to make definitive recommendations for the treatment of blepharitis, and cure is not possible in most cases. · Treatments that are helpful include the following: o Warm compresses. o Eyelid hygiene. o Antibiotics (topical and/or systemic). o Ophthalmic anti-inflammatory agents (e.g., corticosteroids, cyclosporine). · These treatment options are often used in combination. · Eyelid hygiene is especially useful for anterior blepharitis, and warm compresses are especially helpful for posterior blepharitis. · Optimal treatment regimens often require a trial and error approach. · An ophthalmic antibiotic ointment such as ophthalmic bacitracin or ophthalmic erythromycin can be prescribed and applied on the eyelid margins one or more times daily or at bedtime for one or more weeks. The

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	frequency and duration of treatment should be guided by the severity of the blepharitis and response to treatment. In severe cases or for patients who do not tolerate ointment, metronidazole gel applied to the eyelid skin is an alternative treatment, although it has not been approved by the FDA for this indication. · The combination of tobramycin/dexamethasone ophthalmic suspension and azithromycin in a sustained-release system has been evaluated and appears to reduce some of the symptoms of blepharitis, but its use for this indication has not been approved by the FDA. · For patients with meibomian gland dysfunction, whose chronic signs and symptoms are not adequately controlled with eyelid hygiene, an oral tetracycline can be prescribed. Macrolide antibiotics also have anti-inflammatory activity. · Treatments can be intermittently discontinued and reinstated, based on the severity of the patient's blepharitis and tolerance for the medication, and to allow re-colonization of normal flora. · Ophthalmic corticosteroid eye drops or ointments are typically applied several times daily to the eyelids or ocular surface. · Once the inflammation is controlled, the ophthalmic corticosteroid can be tapered and discontinued and then used intermittently to maintain patient comfort. · The minimal effective dose of ophthalmic corticosteroid should be utilized, and long-term ophthalmic corticosteroid therapy should be avoided if possible. · Potential adverse effects of ophthalmic corticosteroid use, including the risk for developing increased intraocular pressure and cataracts may be minimized by using a site-specific ophthalmic corticosteroid such as ophthalmic loteprednol etabonate and ophthalmic corticosteroids with limited ocular penetration, such as ophthalmic fluorometholone. · Topical cyclosporine may be helpful in some patients with posterior blepharitis. · Artificial tears may improve symptoms when used as an adjunct to eyelid hygiene and medications. If used more than four times per day, non-preserved tears should be used to avoid preservative toxicity.
American Academy of Ophthalmology: **Preferred Practice Pattern: Bacterial Keratitis (2013)**[28]	Initial treatment · Ophthalmic antibiotic eye drops are the preferred method of treatment in most cases of bacterial keratitis. · Ophthalmic ointments may be useful at bedtime in less severe cases and may be useful for adjunctive therapy. · Ophthalmic broad-spectrum antibiotics are used initially in the empiric treatment of bacterial keratitis. · The recommended ophthalmic empiric treatments include: o No organism identified or multiple types of organisms: ophthalmic cefazolin sodium (with gentamicin sulfate or tobramycin) or ophthalmic fluoroquinolones (fewer gram-positive cocci are resistant to gatifloxacin and moxifloxacin hydrochloride than other fluoroquinolones). o Gram-positive cocci: ophthalmic cefazolin sodium, vancomycin (for resistant Enterococcus and Staphylococcus species and penicillin allergy), ophthalmic bacitracin (for resistant Enterococcus and Staphylococcus species and penicillin allergy) or ophthalmic fluoroquinolones (fewer gram-positive cocci are resistant to

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	gatifloxacin and moxifloxacin hydrochloride than other fluoroquinolones). o Gram-negative rods: ophthalmic formulations of tobramycin or gentamicin sulfate, ceftazidime or fluoroquinolones. o Gram-negative cocci: ophthalmic ceftazidime, ceftriaxone sodium or fluoroquinolones (systemic therapy is necessary for suspected gonococcal infection). o Nontuberculous mycobacteria: ophthalmic amikacin sulfate, azithromycin, clarithromycin or fluoroquinolones. o Nocardia: ophthalmic amikacin sulfate, sulfacetamide sodium or trimethoprim/sulfamethoxazole. · Single-drug therapy using an ophthalmic fluoroquinolone has been shown to be as effective as combination therapy with ophthalmic antibiotics that are fortified by increasing their concentration over commercially available topical antibiotics. Ciprofloxacin 0.3%, ofloxacin 0.3% and levofloxacin 1.5% are FDA-approved for this indication. The fourth generation fluoroquinolones have not been approved for the treatment of bacteria keratitis; however, both agents have performed at least as well as standard therapy, fortified cefazolin/tobramycin combination therapy and potentially better than ciprofloxacin. · Some pathogens (e.g., Streptococci, anaerobes) reportedly have variable susceptibility to ophthalmic fluoroquinolones, and the prevalence of resistance to fluoroquinolones appears to be increasing. · Combination fortified-antibiotic therapy is an alternative to consider for severe infection and for eyes unresponsive to initial treatment. · Treatment with more than one agent may be necessary for nontuberculous mycobacteria; infection with this pathogen has been reported in association with laser in situ keratomileusis. · MRSA has been isolated with increasing frequency from patients with bacterial keratitis and has been reported following kerato-refractive surgery. Ophthalmic fluoroquinolones are generally poorly effective against MRSA ocular isolates. MRSA isolates are generally sensitive to ophthalmic vancomycin. · Systemic antibiotics are rarely needed, but they may be considered in severe cases where the infectious process has extended to adjacent tissues (e.g., the sclera) or when there is impending or frank perforation of the cornea. · Systemic therapy is necessary in cases of gonococcal keratitis. Modification of therapy · Efficacy of the regimen is judged primarily by clinical response. The results of cultures and sensitivity testing may have an impact on therapeutic decision making, especially if the patient is not responding to initial therapy. · Dual antibiotic treatment designed to achieve broad-spectrum coverage may become unnecessary once the causative organism has been isolated. · The initial therapeutic regimen should be modified (change in type, concentration or frequency of antibiotic) when the eye shows a lack of improvement or stabilization within 48 hours. · Most antibiotic eye drops should not be tapered below three to four times a day, because low doses are sub-therapeutic and may increase the risk

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	of developing antibiotic resistance. Corticosteroid therapy · Ophthalmic corticosteroid therapy may have a beneficial role in treating some cases of infectious keratitis due to the probable suppression of inflammation, which may reduce subsequent corneal scarring and associated visual loss. · Potential disadvantages of ophthalmic corticosteroid use include infection reoccurrence, local immunosuppression, inhibition of collagen synthesis predisposing to corneal melting and increased intraocular pressure. · There is no conclusive evidence that ophthalmic corticosteroids alter clinical outcome. · Despite risks involved, it is believed that sensible use of ophthalmic corticosteroids can reduce morbidity. · Patients being treated with ophthalmic corticosteroids at the time of presentation of suspected bacterial keratitis should have their ophthalmic corticosteroid regimen reduced or eliminated until the infection has been controlled. · Inflammation may temporarily increase as ophthalmic corticosteroids are reduced. · The minimum amount of ophthalmic corticosteroid required should be used to achieve control of inflammation. · Ophthalmic corticosteroids should not be part of initial treatment of presumed bacterial ulcers, and ideally, they should not be used until the organism has been determined by cultures. · The use of ophthalmic corticosteroids in the initial treatment of corneal ulcers has been determined to be a risk factor for requiring a penetrating keratoplasty. · Ophthalmic antibiotics, which are generally administered more frequently than ophthalmic corticosteroids during treatment of active infection, are continued at high levels and tapered gradually. · Patient compliance is essential; intraocular pressure must be monitored frequently, and the patient should be examined within one to two days after initiation of ophthalmic corticosteroid therapy.

*Product is not available in the United States.
†Cromolyn 4% but not 2% is available in the United States. The concentrations of cromolyn that were used in the original clinical studies are noted in this table.

Conclusions

Ophthalmic steroids have been utilized as first-line therapy in clinical practice since the 1950s for the treatment of ophthalmic inflammatory conditions. They are used in managing postoperative inflammation following various ocular surgeries, anterior uveitis, ocular allergies, external eye inflammatory diseases associated with some infections, corneal injury from chemical, radiation or thermal burns and penetration of foreign bodies.[1-17] Ophthalmic steroids are available in various formulations including emulsions, ointments, solutions and suspensions. Currently, the steroids formulated for ophthalmic administration include dexamethasone (Maxidex®), difluprednate (Durezol®), fluorometholone (Flarex®, Fluor-Op®, FML®, FML Liquifilm®, FML Forte®), loteprednol etabonate (Alrex®, Lotemax®), prednisolone acetate (Omnipred®, Pred Forte®, Pred Mild®) prednisolone sodium phosphate, and rimexolone (Vexol®). Ophthalmic steroids are also available in combination with ophthalmic anti-infectives including bacitracin zinc, gentamicin sulfate, neomycin sulfate, polymyxin B sulfate, sulfacetamide and tobramycin. Currently, dexamethasone, fluorometholone, prednisolone acetate and prednisolone sodium phosphate are available generically in at least one dosage form or strength.[24]

The use of ophthalmic steroids can elevate intraocular pressure; however, in clinical trials comparing ophthalmic steroids and ophthalmic nonsteroidal anti-inflammatory drugs (NSAIDs), there is lack of clinical differences between the two ophthalmic anti-inflammatory medication classes when used according to their Food and Drug Administration-approved labeling. Increases in intraocular pressure have been reported with ophthalmic fluorometholone, ophthalmic loteprednol etabonate and ophthalmic rimexolone in clinical trials. The American Optometric Association suggest that topical steroids be used to suppress inflammation following cataract surgery, specifically, prednisolone acetate 1% may be used every two to four hours to control inflammation associated with anterior uveitis, depending on the degree of inflammation.[25] Topical anti-inflammatory agents are used postoperatively to reduce the inflammatory response to cataract surgery and to treat established cystoid macular edema without preference given to on topical steroid over another. The American Academy of Ophthalmology recommends that ophthalmic NSAIDs alone or in combination with ophthalmic steroids are more effective than ophthalmic steroids alone in preventing and treating cystoid macular edema.[26] In addition, ophthalmic steroids are generally used immediately following refractive surgeries and tapered over a period of days to weeks, and sometimes months.[27]

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