REPORT

Innovations in Topical Ocular Corticosteroid Therapy for the Management of Postoperative Ocular Inflammation and Pain

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ABSTRACT

Topical ophthalmic corticosteroids are of clinical benefit in the management of pain and inflammation after ocular surgery; however, their use can be associated with class-associated adverse events (AEs) and limited bioavailability. Selection of an appropriate topical corticosteroid depends on drug-specific variables such as AE profile, efficacy, potency, dosing, patient-specific administration needs, and formulation properties aimed at minimizing precorneal drug loss, increasing ocular surface drug residence time, and maximizing drug delivery to the anterior tissues. Recently, strategies for improving ocular penetration of ophthalmic formulations have included use of mucoadhesive formulations (ie, polycarbophil-containing gels) and drug particle size reduction, enabling faster drug dissolution and therefore increased bioavailability and penetration. Loteprednol etabonate (LE) is a carbon-20 ester corticosteroid developed through retrometabolic drug design with potent anti-inflammatory effects and a reduced propensity for eliciting corticosteroid class AEs. This drug has been formulated for topical ophthalmic use after surgery as 0.5% and 1% suspensions, a 0.5% ointment, and a 0.5% gel. Preclinical and clinical data for a new 0.38% LE gel will be reviewed demonstrating that reducing the drug particle size to the nanometer range in diameter provides effective ocular tissue penetration and resolution of pain and inflammation despite a reduced drug concentration (0.38%) and dosing frequency.

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For author information and disclosures, see end of text.

Several common ophthalmic conditions, including cataracts, glaucoma, late-onset Fuchs endothelial dystrophy, and uncorrected refractive errors, can result in visual impairment, including blindness.[1] Surgical intervention is a common treatment option for these and other ocular conditions. As the US population ages, these visually impairing ophthalmic conditions are expected to increase in prevalence (**Table 1**).[2-10] Given the substantial burden of ocular disease in the United States and the large number of ocular surgeries performed each year to address the condition, a need exists for therapies that effectively resolve postoperative inflammation with minimal adverse reactions, in addition to supporting patient needs for drop comfort and convenience of administration. Topical corticosteroids are routinely used as part of the postoperative treatment regimen after ocular surgery. Traditional topical ophthalmic corticosteroids are associated with varying degrees of class adverse events (AEs), whereas physiologic barriers to drug penetration (eg, tear clearance, corneal absorption) can result in limited ocular bioavailability.[11] Selection of an appropriate topical corticosteroid depends on drug-specific variables such as AE profile, efficacy, potency, dosing, patient-specific administration needs, and formulation properties aimed at minimizing precorneal drug loss, increasing drug residence time on the ocular surface, and maximizing bioavailability and the amount of drug delivered into the ocular tissues.

Loteprednol etabonate (LE) is a unique carbon-20 (C-20) ester corticosteroid designed to have potent anti-inflammatory effects after cataract, refractive, glaucoma, and corneal transplant surgeries, among others, with a lower propensity to elicit corticosteroid class-associated AEs.[12-15] Recently, strategies for improving ocular penetration of ophthalmic drug formulations, and LE formulations in particular, have included use of mucoadhesive polymers (ie, polycarbophil-containing gels) and drug particle size reduction, enabling faster drug dissolution and therefore increased penetration.[11,14-16] This article reviews the available topical ocular corticosteroids (suspensions, ointments, emulsions, and gels) indicated for the postoperative management of inflammation and pain after ocular surgery, with a brief review of LE drug design and focus

on formulation development of available LE products (Table 2).[17-21] An overview is provided for the newest ophthalmic formulation to enter the market, Lotemax® SM (loteprednol etabonate ophthalmic gel, 0.38%; Bausch + Lomb, Bridgewater, NJ). Preclinical and clinical data for this new submicron gel formulation are reviewed and demonstrate that reducing the drug particle size to the nanometer range in diameter provides effective ocular tissue penetration and resolution of pain and inflammation despite a reduced drug concentration (0.38%) and dosing frequency (3 times a day).[12-14,20]

Postoperative Management of Inflammation and Pain After Ocular Surgery

Mechanical trauma during ocular surgery (eg, membrane disruption and tissue injury) induces an inflammatory response. Inadequately controlled inflammation increases the risk of postoperative pain, edema, erythema, anterior chamber cells and flare, secondary glaucoma, posterior synechia, and, potentially, cystoid macular edema (CME).[22-26] There are no published consensus guidelines or sufficient evidence from randomized controlled studies to establish a preferred postoperative regimen for control of inflammation and pain after cataract surgery and other intraocular surgeries.[22,27] Treatment must be patient specific, and the cause of pain must be carefully identified and treated accordingly. In clinical practice, patients may be treated with combination therapy including both a topical ocular corticosteroid (eg, LE, difluprednate, fluorometholone, dexamethasone, or prednisolone) and a nonsteroidal anti-inflammatory drug (NSAID) (eg, ketorolac, diclofenac, bromfenac, or nepafenac) or with either class individually.[22,28] NSAIDs inhibit inflammation primarily through the cyclooxygenase (COX) pathway and are typically initiated 1 to 2 days before cataract surgery and continued for a minimum of 2 weeks after surgery.[26] Prolonged postoperative use of NSAIDs for 4 to 6 weeks or longer is often employed to prevent CME, especially in patients at high risk.[28,29] Recently, a prospective study in 914 nondiabetic patients demonstrated that a combination of a topical NSAID and a corticosteroid is more effective in the prevention of CME after cataract surgery than NSAID treatment alone.[30] Corneal melt—a rare, but serious, and potentially visually compromising AE—has been reported in association with the use of some topical ocular NSAIDs and should be considered when deciding to include a topical ocular NSAID in a patient's postoperative regimen, especially in patients with pre-existing ocular surface conditions.[26,31-35]

Topical ocular corticosteroids are a vital component of treatment for postoperative inflammation after ocular surgery to ameliorate inflammation-associated signs and symptoms, including photophobia, swelling, pain, and tenderness.[36] Corticosteroids, and more specifically glucocorticoids, are believed to modulate the inflammatory response through several independent mechanisms at cytosolic glucocorticoid receptors (GRs).[22,36-38] Corticosteroids bind to and activate GRs, allowing translocation into the nucleus, and directly and indirectly regulate the transcription of genes with anti-inflammatory effects (eg, regulating the expression of genes that encode inflammatory cytokines, chemokines, adhesion molecules, and other inflammatory mediators).[37,39-41] By inhibiting phospholipase A2-mediated arachidonic acid conversion from membrane phospholipids, corticosteroids block downstream COX and lipoxygenase pathways of the inflammatory cascade and prevent eicosanoid production (leukotrienes, prostaglandins, and thromboxanes).[23-26,36,40,42] At the tissue level, corticosteroids inhibit edema, fibrin deposition, capillary dilation, fibroblast production, leukocyte migration, and deposition of collagen, ultimately preventing scar formation.[19,36,43,44]

Topical ocular instillation delivers corticosteroids directly to the desired sites in the eye with negligible risk of systemic AEs.[16,45] Several ophthalmic formulations of corticosteroids are available (eg, suspension, emulsion, ointment, gel) and, where studied, have demonstrated safety and efficacy in resolving inflammation and pain after cataract, refractive, and corneal transplant surgeries.[15,19,38,44,46-50] Topical ocular corticosteroids are typically initiated after surgery, followed by a gradual taper.[24,36] The use of topical corticosteroids has been associated with local AEs, including delayed wound healing, exacerbation or reactivation of an existing infection (eg, reactivation of latent herpes simplex virus keratitis), and development of a secondary infection.[14,36,45,51] Ophthalmic use of ocular corticosteroids has also been associated with the formation of cataracts and clinically significant elevations in intraocular pressure (IOP) and subsequent potential for glaucoma, especially with longer-term use.[14,36,45,51]

TABLE 1. Estimates and Projections in the Prevalence of Vision Impairment in the United States, Adults Aged 40 Years and Older[2-10]

Condition	Cases in Total US Population Aged ≥40 years		Surgery Estimates (year)
	2010	2050	
Cataracts	24.4 million	50 million	3.4 million cataract surgeries were performed in the United States (2011)
Glaucoma	2.7 million	6.3 million	85,000 patients underwent surgery to correct glaucoma (2006)
Refractive errors			
Myopia (nearsightedness)	34.1 million	44.5 million	600,000 patients underwent LASIK surgery to correct a refractive error (2015)
Hyperopia (farsightedness)	14.2 million	23.4 million	

LASIK indicates laser-assisted in-situ keratomileusis.

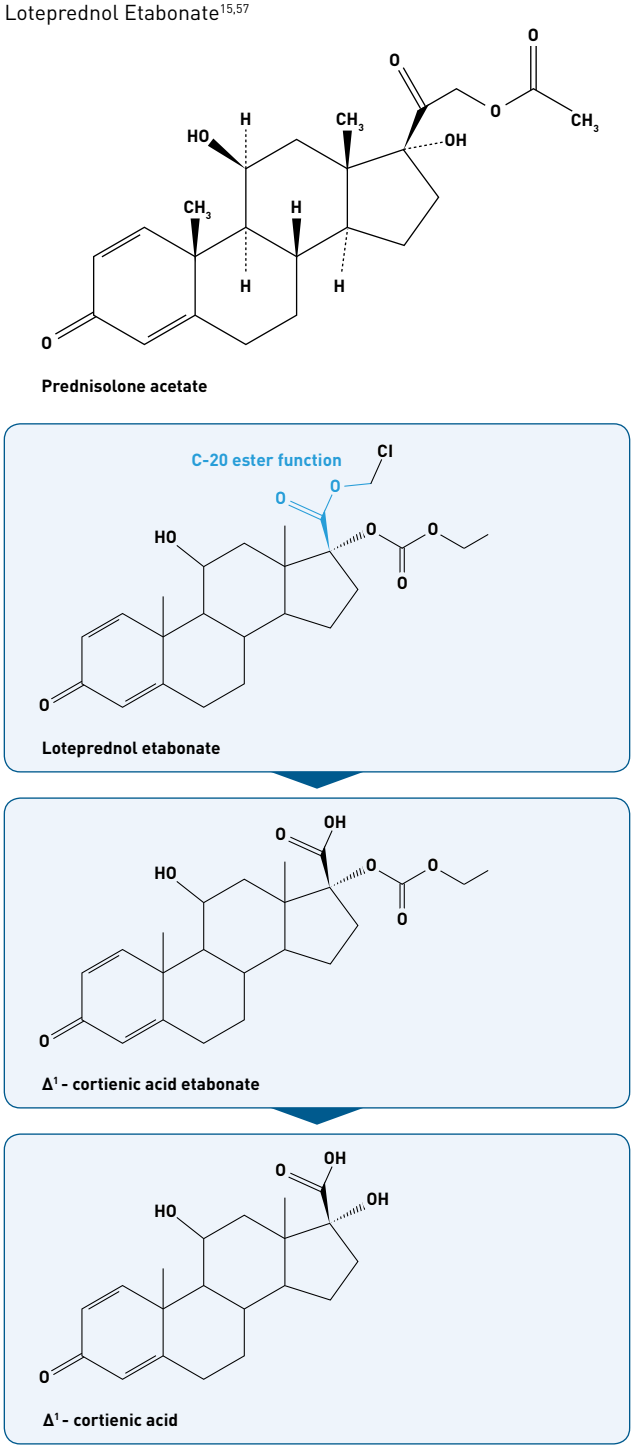
Although the precise mechanism is not fully understood, corticosteroid-induced elevations in IOP are believed to be the result of increased aqueous humor outflow resistance; if left untreated, elevations in IOP may lead to progressive optic nerve damage, vision loss, and corticosteroid-induced glaucoma.[36] The potential for a specific topical ocular corticosteroid to raise IOP may be influenced by the pharmacokinetics of the drug itself, such as differences between the tissue penetration and half-life of the drug, as well as dosage and treatment duration.[36,42] Moreover, an estimated 5% of the population are categorized as high steroid responders, meaning that they will experience clinically significant IOP elevations above 15 mm Hg after topical corticosteroid therapy.[42,45] Differences in the potency of particular ocular corticosteroids has also been suggested as a potential reason for differences in IOP-elevating potential, although there are not yet data to support this theory.[45] Several factors have made it difficult to quantify differences in the extent to which topical ocular corticosteroids, especially older agents (eg, dexamethasone and prednisolone), may cause elevations in IOP, including inconsistent IOP measures, lack of placebo-controlled trial data, and changes in stringency of regulatory approval requirements over time.[36]

The formation of cataracts, particularly posterior subcapsular cataracts, is a concerning AE with extended-duration corticosteroid therapy.[52] The presence of a C-20 ketone group in certain corticosteroids, including prednisolone, dexamethasone, fluorometholone, and difluprednate, is implicated in the formation of Schiff base intermediates with lens proteins, which is a common first step implicated in cataract formation with ketone steroids.[15,16,37,46-50,53] Another possible mechanism in the formation of posterior subcapsular cataracts may include aberrant migration of lens epithelial

TABLE 2. Available Formulations of Loteprednol Etabonate Indicated for Inflammation and Pain After Ocular Surgery[17-21]

Formulation	How Supplied	FDA Approval	Indication	Instructions For Use
Lotemax® ophthalmic suspension, 0.5%	5 mL 10 mL 15 mL	1998	Steroid responsive inflammatory conditions of the palpebral and bulbar conjunctiva, cornea and anterior segment of the globe such as allergic conjunctivitis, acne rosacea, superficial punctate keratitis, herpes zoster keratitis, iritis, cyclitis, selected infective conjunctivitides, when the inherent hazard of steroid use is accepted to obtain an advisable diminution in edema and inflammation	Shake vigorously before using. Apply 1-2 drops into the conjunctival sac of the affected eye 4 times daily; during the initial treatment within the first week, the dosing may be increased, up to 1 drop every hour, if necessary; care should be taken not to discontinue therapy prematurely; if signs and symptoms fail to improve after 2 days, patient should be re-evaluated.
			Post-operative inflammation following ocular surgery	Shake vigorously before using. Apply 1-2 drops into the conjunctival sac of the operated eye 4 times daily beginning 24 hours after surgery and continuing throughout the first 2 weeks of the post-operative period.
Lotemax® ophthalmic ointment, 0.5%	3.5 g	2011	Post-operative inflammation and pain following ocular surgery	Apply a small amount (approximately ½-inch ribbon) into the conjunctival sac of the operated eye 4 times daily beginning 24 hours after surgery and continuing throughout the first 2 weeks of the post-operative period.
Lotemax® ophthalmic gel, 0.5%	5 g in a 10-mL bottle	2012	Post-operative inflammation and pain following ocular surgery	Apply 1-2 drops into the conjunctival sac of the affected eye 4 times daily beginning the day after surgery and continuing throughout the first 2 weeks of the post-operative period.
Inveltys™ ophthalmic suspension, 1%	2.8 mL in a 5-mL bottle	2018	Post-operative inflammation and pain following ocular surgery	Shake for 1-2 seconds before using; instill 1-2 drops into the affected eye twice daily beginning the day after surgery and continuing throughout the first 2 weeks of the post-operative period.
Lotemax SM® ophthalmic gel, 0.38%	5 g in a 10-mL bottle	2019	Post-operative inflammation and pain following ocular surgery	Invert closed bottle and shake once to fill tip before instilling drops; apply 1 drop into the conjunctival sac of the affected eye 3 times a day beginning the day after surgery and continuing throughout the first 2 weeks of the post-operative period.

FIGURE 1. Retrometabolic Drug Design and Metabolism of Loteprednol Etabonate[15,57]



Loteprednol etabonate (LE) metabolism. The ketone group at the prednisolone carbon-20 position is replaced by a 17β-chloromethyl ester and a 17α-ethyl carbonate substitution of the 17α-hydroxyl group. This modification allows activity at the glucocorticoid receptor and subsequent predictable metabolism, after eliciting the anticipated pharmacologic activity. LE is metabolized by local esterases to Δ1-cortienic acid etabonate and hydrolyzed to the inactive carboxylic acid metabolite, Δ1-cortienic acid.

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cells, and there may be additional mechanisms of corticosteroid-induced cataractogenesis.[15,52]

Minimizing the Risk of Adverse Events Through Retrometabolic Drug Design

To minimize the risk of AEs associated with topical ocular corticosteroid use (eg, increased IOP and cataract formation) while maintaining or improving efficacy, several ocular corticosteroids were designed more than 20 years ago using retrometabolic design, a drug development process that takes into account structure-metabolism relationships and structure-activity relationships.[37,54] The goal of this strategy is to synthesize an analog of a reference compound from a known inactive metabolite of that reference compound. The inactive metabolite is converted into an analog of the reference compound with structural changes designed to elicit the targeted therapeutic effect before being metabolized to the original inactive metabolite.[15,37,55]

The C-20 chloromethyl ester corticosteroid LE was developed by retrometabolic drug design specifically to maintain steroid potency while lowering the risk of AEs.[56] LE is derived from the inactive metabolite of prednisolone acetate, Δ1-cortienic acid, with a 17β-chloromethyl ester replacing the ketone group at the C-20 position and a 17α-ethyl carbonate substitution of the 17α-hydroxyl group. This modification allows activity at the GR and subsequent predictable hydrolysis to the inactive carboxylic acid metabolite after eliciting the anticipated pharmacologic activity (**Figure 1**).[15,54,56,57] Studies confirmed that any LE not bound to GRs is quickly metabolized to Δ1-cortienic acid by local circulating esterases.[16,37] The cornea is the primary site of metabolism of LE to inactive metabolites, as exhibited by the highest overall concentration of LE and the highest ratio of metabolite (Δ1-cortienic acid) to LE.[58] Lower levels of LE were detected in the aqueous humor (100-fold less than levels found in the cornea) and underscore the probability that LE is less likely to cause elevations in IOP.[15] Data from preclinical research demonstrated that LE is able to penetrate into the ocular tissues, including the cornea, the aqueous humor, and the iris-ciliary body, with the latter tissue levels considered most relevant in the treatment of postoperative inflammation.[58] LE has a lipophilicity 10 times greater than that of dexamethasone, which enhances penetration into ocular tissue. LE has an increased binding affinity for GRs that is up to 4.3 times greater than that of dexamethasone and a therapeutic index (the ratio of drug activity to drug toxicity) that is up to 20-fold greater than other corticosteroids.[15,37,42,56] Collectively, these features allow LE to effectively penetrate ocular tissues, bind to GRs, and produce potent anti-inflammatory effects, with minimal potential for AEs.[42]

Across several head-to-head studies, LE demonstrated potent anti-inflammatory efficacy in reducing anterior chamber cells and flare after cataract surgery,[59,60] preventing immunologic transplant rejection episodes,[61] and preventing corneal haze after photorefractive

keratectomy surgery,[62] compared with either prednisolone acetate, difluprednate, or prednisolone acetate tapered to fluorometholone.[15,37] In addition, replacement of the ketone at the C-20 position in prednisolone with an ester is hypothesized to contribute to decreased potential for steroid-induced cataract development. The absence of a C-20 ketone precludes formation of Schiff base intermediates with lens proteins, which is a common first step implicated in cataract formation with ketone steroids.[15,16,53] Long-term use of LE suspension 0.2% for the treatment of seasonal allergic conjunctivitis did not reveal an increased propensity for cataract formation with follow-up of 12 to 36 months or more.[63] In alignment with this finding, review of AEs in association with the use of all marketed LE formulations (ophthalmic suspension [0.5% and 0.2%], gel [0.5%], and ointment [0.5%]) demonstrated a low incidence of cataracts; from launch of LE suspensions in 1998 to 2016, there were just 12 incidences of cataracts reported to the manufacturer's AE database.[64]

Pooled clinical evidence also confirmed that incidences of elevated IOP are low with short-term and long-term use of topical LE formulations.[15,42,65] Sheppard et al pooled data from studies that defined an IOP increase over baseline of at least 10 mm Hg as clinically significant and determined that 0.8% of patients (14/1725) given short-term LE treatment (less than 28 days) and 1.5% (21/1386) given long-term LE treatment (at least 28 days) experienced clinically relevant elevations in IOP.[42] Furthermore, studies have demonstrated that incidences of IOP elevations are lower with LE treatment relative to prednisolone acetate and dexamethasone.[42,59,61,66] In the review by Sheppard et al, pooled data indicated that the cumulative incidences of clinically significant IOP elevations were higher in patients given prednisolone acetate 1% (11.3% [33/292]) compared with those given LE (3.4% [10/291]) (P <.001) and in patients given dexamethasone 1%/tobramycin 0.3% (5.2% [25/485]) compared with those given LE/tobramycin 0.3% (1.8% [9/491]) (P = .008).[42] In known steroid responders, prednisolone acetate demonstrated greater mean IOP elevations compared with LE.[67] A comparison of the pivotal clinical trial data for each agent indicated that difluprednate, a derivative of prednisolone that is difluorinated at the C6 and C9 positions, demonstrated a higher propensity to raise IOP than LE.[13,23,68-71]

Addressing Drug Delivery Challenges Associated With Topical Ocular Corticosteroids

Delivery of corticosteroids to ocular tissues is challenging. Physiologic barriers may inhibit optimal drug delivery in the eye after topical administration. Local delivery of topical ocular corticosteroids is driven by the speed by which the drug dissolves in tears, or dissolution, which can be limited by a high rate of tear turnover, induced lacrimation (secretion of tears), loss of drug through nasolacrimal drainage, and the blinking process.[16,72] Any sensation of irritation causes patients to blink and tear, reducing retention and residence time on the ocular surface and diluting the drop. In addition, when a drug mixes with tear fluid, the physical properties of the combination, including pH and osmolality, may cause irritation or discomfort, leading to reflex tearing and blinking and further drug dilution.[16] As a result of these challenges, it is estimated that approximately 5% of a locally administered ophthalmic drug penetrates into and crosses the cornea to reach the intraocular tissues.[11,16,72,73] To overcome these barriers, developments in the formulation of topical ocular corticosteroids focus on improving corneal penetration, drug residence time, and bioavailability by the addition of viscosity and permeation enhancers.[11]

Most currently available topical ocular corticosteroids, including prednisolone, fluorometholone, dexamethasone, and LE, have often been formulated as suspensions because of their poor aqueous solubility.[37,46-50,74] Ophthalmic suspensions have poor viscosity; drug particles tend to settle out of solution and interact to form clumps, resulting in poor homogeneity, which may affect both efficacy and safety.[16,75-77] Typically, ophthalmic suspensions, including LE suspension 0.5%, require vigorous shaking before administration to resuspend drug particles, which has proven difficult for many patients, especially elderly patients, who are the main patient group eligible for cataract and other ophthalmic surgeries.[16,76,78,79] In particular, generic prednisolone suspension preparations may be associated with markedly more particle clumping than branded preparations and this clumping may not be easily remedied by vigorous shaking.[76]

Because corticosteroids have low aqueous solubility, ophthalmic ointments have been formulated to provide greater homogeneity.[80] Ophthalmic ointments create a drug reservoir when the ointment becomes trapped in the fornices of the eye, which may increase drug contact time with the ocular surfaces by up to 8 hours, thereby increasing drug absorption approximately 2-fold in blinking eyes and up to 4-fold in non-blinking eyes.[15,80,81] For these reasons, ophthalmic ointments may be ideal for nighttime dosing or for patients who have trouble instilling eye drops, such as those with tremors or arthritis.[15,81,82] Fluorometholone and LE are available as ophthalmic ointments.[18,49] The LE ointment formulation does not contain a preservative, and as a result, it is associated with better long-term tolerability and the potential for less epithelial toxicity than formulations that contain preservatives.[15,18,49,82] Inherent challenges with ophthalmic ointments include blurred vision, which can lead to poor adherence and dosing variability due to difficulty many patients experience when instilling a precise ribbon of ointment (eg, half inch) in the eye.[16,81]

A more recent development in the formulation of topical ocular corticosteroids is the oil-in-water lipid emulsion, which allows drugs with poor water solubility to be dissolved in an oil phase with surfactants to provide stability.[76] Difluprednate ophthalmic emulsion Durezol® (difluprednate ophthalmic emulsion, 0.05%; Alcon Laboratories, Fort Worth, TX) is the sole topical ocular corticosteroid available in this formulation; it received FDA approval in 2008

for the treatment of inflammation and pain associated with ocular surgery.[44,76] Compared with topical ocular corticosteroids formulated as suspensions, ophthalmic emulsions provide better dose uniformity without the need for vigorous shaking before administration and have the potential for improved ocular bioavailability.[76]

For most topical ocular corticosteroid formulations available (prednisolone, fluorometholone, dexamethasone, difluprednate, and most formulations of LE), frequent dosing—4 times per day—is required to achieve therapeutic levels of the active drug.[44,46-50] In general, dosing frequency has been identified as a major barrier to adherence, with more frequent dosing being associated with lower adherence.[83,84] Medication regimen complexity may further impede adherence, which is especially relevant because postoperative regimens after ocular surgery may include 2 or more drug classes.[27,83]

Formulation Advancements With Loteprednol Etabonate

LE Ophthalmic Gel, 0.5%

A novel LE gel 0.5% formulation, Lotemax® gel 0.5% (Bausch + Lomb, Bridgewater, NJ), indicated for postoperative inflammation and pain after ocular surgery, was approved by the FDA in 2012.[13,17] In general, an ophthalmic gel includes a mucoadhesive polymer to prolong drug contact time with ophthalmic tissues, thereby increasing bioavailability.[85] An important improvement in the design of nonsettling LE gel 0.5% is the addition of polycarbophil, a mucoadhesive polymer that functions as a suspending agent, imparting structure to the gel, inhibiting settling, and allowing the gel to remain in a semisolid state while in the bottle.[14,16] Provided no force is applied to the bottle, the gel remains homogenous and drug particles in the gel remain equally dispersed throughout the formulation, and therefore the bottle does not require shaking before administration. When the gel is dispensed from the bottle, shear stress generated by squeezing the bottle causes the gel to thin to a viscous liquid, which then fully transitions to a mucoadhesive fluid on the ocular surface on mixing with tears, thereby minimizing the potential for visual distortion often seen with other ophthalmic gels. Polycarbophil also extends ocular surface retention time and thus improves the potential absorption of the active drug into anterior segment tissues.[15,16] LE gel 0.5% strikes a balance in viscosity somewhere between that of LE suspension 0.5%, which has low viscosity, and LE ointment 0.5%, which has high viscosity; the result is a gel formulation expected to have the improved bioavailability associated with more viscous formulations, while at the same time minimizing the potential discomfort associated with high viscosity formulations.[16]

To enhance patient comfort and increase moisture retention on the ocular surface, LE gel 0.5% contains glycerin and propylene glycol, 2 ingredients commonly found in over-the-counter ophthalmic products that act as both lubricants (relieve irritation) and humectants (retain moisture).[16,17,86] In addition, the pH of LE gel 0.5% is approximately 6.5, which is higher than the pH of LE suspension 0.5% (5.5) and closer to that of normal tears (7.4), another feature expected to improve patient comfort.[16,17,82] To reduce the potential for toxicity and discomfort, a 70% lower concentration of the preservative benzalkonium chloride (BAK) was used in LE gel 0.5% (0.003% in the gel vs 0.01% in the suspension). To compensate for this lower concentration of BAK, boric acid and disodium edetate were added to enhance the antimicrobial activity of BAK.[16,17]

Unlike ophthalmic suspensions, which require vigorous shaking before administration to resuspend drug particles,[16,76] the nonsettling formulation LE gel 0.5% delivers consistent doses of the active drug without the need to shake the bottle, as demonstrated by the results of several studies. A 2014 study comparing LE gel 0.5% with prednisolone acetate suspension 1% demonstrated that LE gel 0.5% delivered a mean declared drug concentration of 102% regardless of whether the bottle was shaken.[77] As a result of settling, the concentration of the prednisolone acetate suspension drops was highly variable when not shaken, providing less than the declared drug concentration (71%-81%) in the first half of the 14-day dosing regimen and above the declared drug concentration (73%-132%) in the second half.[77] A similar study published in 2017 comparing LE gel 0.5% with fluorometholone acetate ophthalmic suspension 0.1% demonstrated that LE gel 0.5% delivered a dose that was 97% of the declared drug concentration when shaken and 99% of the declared drug concentration when not shaken; this difference was not significant ($P = .194$).[87] Fluorometholone acetate suspension delivered 94% of the declared drug concentration when shaken and 7.25% when not shaken; this difference was significant ($P = .0001$).[87] The results of these 2 studies demonstrated that LE gel 0.5% eliminates challenges of inconsistent dosing without the need to shake the bottle before administration.

LE Ophthalmic Suspension, 1%

An LE suspension with a drug concentration of 1% (Inveltys™, Kala Pharmaceuticals, Waltham, MA), twice that of the existing LE suspension 0.5%, was approved by the FDA in August 2018 for the treatment of postoperative inflammation and pain after ocular surgery.[21,88] LE suspension 1% uses proprietary technology to achieve enhanced delivery of the active drug through nanoparticle-based mucus-penetrating particles, which is thought to improve drug penetration into ocular tissues. Preclinical research with a prototype formulation (LE suspension 0.4%) indicated that mucus-penetrating particles facilitate higher ocular exposure and, in turn, higher peak concentrations of the active drug than LE suspension 0.5%.[88,89] LE suspension 1% is approved for twice-daily dosing[21] and thus has a wider dosing interval than other available formulations.[19,47,48] A drawback of any steroid suspension formulation, including the LE suspension 1% formulation, is the need to shake before dosing

to deliver a consistent dose of medication with each instillation. Compared with other topical ocular corticosteroid suspensions, LE suspension 1% requires only minimal shaking before administration, but this may still pose a continued challenge for patient adherence.[16,22] Potential other drawbacks associated with LE suspension 1% include a higher concentration of both the active drug and the preservative BAK. Like LE suspension 0.5%, LE suspension 1% contains BAK 0.01% as a preservative, which may be associated with toxicity in ocular tissues.[19,21,90]

Two randomized, double-masked, vehicle-controlled, parallel-group trials investigated the efficacy and safety of twice-daily LE suspension 1% compared with vehicle for 2 weeks in patients who experienced inflammation after routine, uncomplicated cataract surgery (**Table 3**).[88] The primary end points were complete resolution of anterior chamber cells and ocular pain at day 8 maintained through day 15 with no rescue medication before day 15 (defined as responders).[88] A significantly greater percentage of patients in the LE suspension 1% twice-daily group achieved complete resolution of anterior chamber cells at day 8 maintained through day 15 compared with the vehicle group. The between-group difference for percent responders in trial 1 was 16.1% (95% CI, 5.9–26.4; P = .0024) and in trial 2, 8.3% (95% CI, 2.0%-14.7%; P = .0105).[88] The between-group difference for percent of responders who achieved complete resolution of ocular pain at day 8 was 19.5% (95% CI, 7.4%-31.5%; P = .0019) and 20.0% (95% CI, 11.6-28.4; P <.0001) for trial 1 and trial 2, respectively.[88]

The LE 1% formulation is the highest concentration of LE available in the United States at the time of this publication.[17-21] Despite the increased concentration, the efficacy of LE suspension 1% in the resolution of anterior chamber cell inflammation and pain appears similar to that reported for LE suspension, ointment, and gel 0.5% in the treatment of postoperative cataract surgery.[70,71,81,91] and that reported for the newest marketed formulation, a novel LE (submicron) gel 0.38% formulation (Lotemax® SM).[13]

LE Ophthalmic Gel, 0.38%

In February 2019, a novel LE (submicron) gel 0.38% formulation (Lotemax® SM, Bausch + Lomb, Bridgewater, NJ) was approved by the FDA for the treatment of postoperative inflammation and pain after ocular surgery based on its demonstrated safety and efficacy in preclinical and clinical studies.[20] The key new feature of this formulation is that the drug particle size has been reduced to the submicron

TABLE 3. Primary Efficacy and Safety Outcomes with Loteprednol Etabonate 1% Suspension Twice Daily[88]

		Trial 1	Trial 2
ClinicalTrials.gov Identifier		NCT02163824	NCT02793817
Design		Randomized, double-masked, vehicle-controlled, parallel-group trials	
Patients		Adults (18 years and older) who had routine uncomplicated cataract surgery with posterior chamber intraocular lens implantation and ≥ grade 2 AC cells (≥ 6 cells)	
ITT population (n)			
LE suspension 1% twice daily		125	261
Vehicle		126	259
Primary efficacy outcomes[a]			
Proportion of patients with AC cell score = 0 (%)	LE suspension 1% twice daily	31.2[b]	20.7[c]
	Vehicle	15.1	12.4
Proportion of patients with pain score = 0 (%)	LE suspension 1% twice daily	53.6[d]	57.1[e]
	Vehicle	34.1	37.1
Selected safety outcomes[f]			
≥1 ocular AE in the study eye (%)	LE suspension 1% twice daily	7.3	
	Vehicle	12.9	
IOP elevation ≥10 mm Hg from baseline		0.8%	

AC indicates anterior chamber; AE, adverse event; IOP, intraocular pressure; ITT, intent to treat; LE, loteprednol etabonate.
[a]Primary efficacy outcomes included the proportion of patients with complete resolution of AC cells (cell score = 0) on postoperative day 8 (visit 5) and proportion of patients with no pain (pain score = 0) on postoperative day 8.
[b]P = .0024 (compared with vehicle).
[c]P = .0105 (compared with vehicle).
[d]P = .0019 (compared with vehicle).
[e]P <.0001 (compared with vehicle).
[f]Pooled safety population of LE suspension 1% twice daily (n = 386).

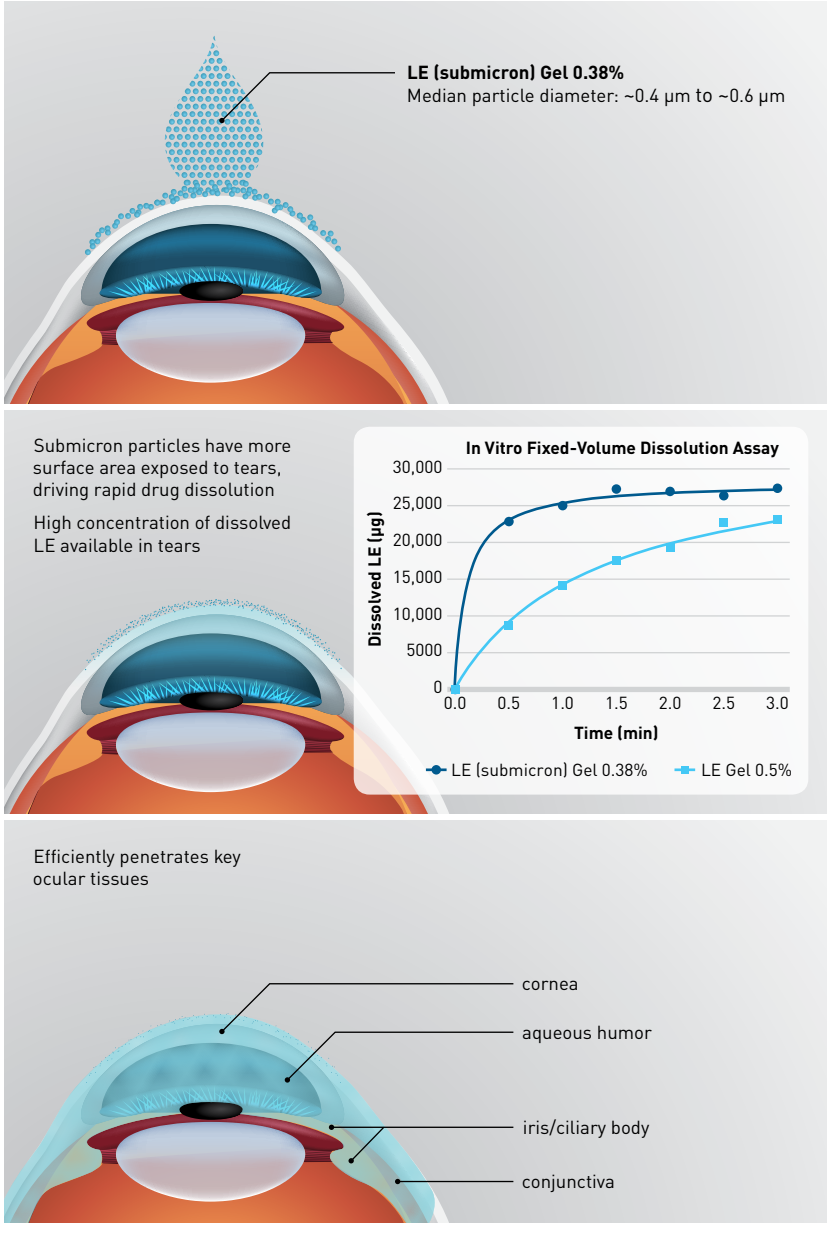
(nanometer) range in diameter using SM technology®, which allows for improved drug dissolution and thus more efficient ocular penetration. This, in turn, permits reductions in drug concentration in the formulation (from 0.5% to 0.38%) and dosing frequency (from 4 times daily to 3 times daily), with possible implications for both improved drug safety and patient adherence to the dosing regimen. LE (submicron) gel 0.38% retains the formulation attributes of LE gel 0.5%, such as a pH of approximately 6.5, which is close to that of normal tears (7.4), and a low concentration of BAK (0.003%), features that are expected to improve patient comfort.[13,14,17,20,82]

Preclinical Considerations

The new LE (submicron) gel 0.38% formulation is characterized by a median diameter particle size that has been reduced from the micrometer range to the submicron (nanometer) range by a proprietary milling process. All previous 0.5% LE formulations contain micronized drug particles with a median diameter of approximately 3 to 5 µm, whereas LE (submicron) gel 0.38% contains drug particles with a median diameter of approximately 0.4 to 0.6 µm, a roughly 80% reduction in median diameter (**Figure 2**).[14] The rationale for reducing the drug particle size into the nanometer diameter range was to decrease the volume of the drug particles and hence increase the total surface area of the LE particles by approximately 5- to 12.5-fold. The increase in total surface area, in turn, was expected to increase the rate of drug dissolution for increased absorption, penetration, and bioavailability.[13,14] In line with the current standards in pharmaceutical development, researchers also sought to identify the minimum effective concentration of LE needed to produce the desired therapeutic effect, thereby reducing overall drug exposure and further reducing the potential for AEs. The novel LE (submicron) gel 0.38% formulation achieves a 24% reduction in active drug concentration compared with the LE 0.5% suspension, ointment, and gel formulations and a 62% lower active drug concentration compared with the more recently approved LE suspension 1%, yet appears to provide similarly robust clinical anti-inflammatory activity.[14,17-21]

As with LE gel 0.5%, polycarbophil was used in the formulation of LE (submicron) gel 0.38%. Additional modifications to excipients, including the use of poloxamer and hypromellose, were added to stabilize drug particle size. Because hypromellose is a common ingredient in artificial tears and has known demulcent properties, it may also improve comfort.[14] Overall, these improvements to the LE formulation were expected to maximize the therapeutic

FIGURE 2. Loteprednol Etabonate (Submicron) Gel 0.38% Formulation: Reduction in Particle Size for Faster Drug Dissolution and Enhanced Penetration[14]



LE indicates loteprednol etabonate.

potential of LE and extend the dosing interval while reducing overall drug exposure and minimizing the potential for AEs.[14]

Preclinical studies were conducted to evaluate the in vitro rheologic properties and dissolution profile of LE (submicron) gel 0.38% (eg, viscosity and shear rate), as well as in vivo ocular pharmacokinetics in rabbits. The novel LE (submicron) gel 0.38% was compared with the FDA-approved LE gel 0.5% (with micron-sized drug particles).[14] Results of the in vitro rheologic assessments demonstrated nearly identical rheologic characteristics for LE (submicron) gel 0.38% compared with LE micronized gel 0.5%. In particular, the shear-thinning behavior of LE (submicron) gel 0.38% was nearly identical to that of LE micronized gel 0.5%; at low shear stress, both gels were semisolid, and viscosity could not be measured, whereas at high shear stress, both gels converted to a liquid, and viscosity was low.[14] Results of the in vitro dissolution assays confirmed that the LE particles in the submicron gel 0.38% were associated with a higher dissolution rate and higher peak concentration earlier in the dissolution time curve compared with particles in the micronized gel 0.5% (Figure 2).[14] Despite an overall decrease in LE concentration, results of the in vivo ocular pharmacokinetic assessments confirmed the hypothesis that the particles in the LE (submicron) gel 0.38% formulation would release a higher concentration of active drug than the LE gel 0.5% due to faster dissolution from the smaller particles. In the aqueous humor, the LE (submicron) gel 0.38% achieved a maximum mean concentration (C_{max}) of 0.0281 µg/mL and a mean area under the concentration versus time curve ($AUC_{0\text{-}24h}$) of 0.0421 µg·h/mL, whereas the LE micronized gel 0.5% achieved a C_{max} of 0.0112 µg/mL and an $AUC_{0\text{-}24h}$ of 0.0228 µg·h/mL; the differences were significant ($P = .00086$ for C_{max}, $P = .0005$ for $AUC_{0\text{-}24h}$).[14] LE (submicron) gel 0.38% also achieved similar C_{max} and $AUC_{0\text{-}24h}$ values compared with LE micronized gel 0.5% in the cornea and iris-ciliary body.[14]

Demonstrated Clinical Efficacy and Safety

LE (submicron) gel 0.38% was approved for administration 3 times a day based on the results of 2 randomized, multicenter, double-masked, parallel group, vehicle-controlled phase 3 clinical trials evaluating the safety and efficacy of 3-times-a-day dosing in the treatment of inflammation and pain in patients who underwent cataract extraction with intraocular lens implantation (**Table 4**).[12,13,20] The primary efficacy end points of both trials were the proportion of patients in the LE (submicron) gel 0.38% and vehicle groups

TABLE 4. Primary Efficacy and Safety Outcomes with Loteprednol Etabonate (Submicron) Gel 0.38% Three Times Daily[12,13,20]

		Trial 1	Trial 2
ClinicalTrials.gov Identifier		NCT01996839	NCT02786901
Design		Multicenter double-masked vehicle-controlled randomized parallel-group phase 3 study	
Patients		Adults (18 years and older) who had routine uncomplicated cataract surgery and ≥ grade 2 AC cells (6-15 cells) on postoperative day 1	
ITT population (n)			
LE (submicron) gel 0.38% 3 times daily		171	200
Vehicle		172	199
Primary efficacy outcomes[a]			
Proportion of patients with AC cell score = 0 (%)	LE (submicron) gel 0.38% 3 times daily	28.7[b]	30.5[c]
	Vehicle	9.3	20.1
Proportion of patients with pain score = 0 (%)	LE (submicron) gel 0.38% 3 times daily	73.1[b]	75.5[c]
	Vehicle	47.7	49.7
Selected safety outcomes			
≥1 ocular AE in the study eye (%)	LE (submicron) gel 0.38% 3 times daily	0	7.5
	Vehicle	2.3	10.1
Reported no drop sensation upon instillation		77.7%	76.4%
IOP elevation ≥10 mm Hg from baseline		0.3%	

AC indicates anterior chamber; AE, adverse event; IOP, intraocular pressure; ITT, intent to treat; LE, loteprednol etabonate.
[a]Primary efficacy outcomes included the proportion of patients with complete resolution of AC cells (cell score = 0) on postoperative day 8 (visit 5) and proportion of patients with no pain (pain score = 0) on postoperative day 8.
[b]$P < .0001$ (compared with vehicle).
[c]$P = .034$ (compared with vehicle).

with complete resolution of anterior chamber cells (cell score of 0) and complete resolution of pain (grade of 0) at postoperative day 8.[12,13] Compared with patients in the vehicle groups, significantly greater proportions of patients in the LE (submicron) gel 0.38% groups achieved complete resolution of anterior chamber cells by day 8, with a mean difference of 19% (95% CI, 11%-27%; P <.0001) in trial 1 and 10% (95% CI, 2%-19%; P = .034) in trial 2.[12,13,20] Significantly greater percentages of patients in the LE (submicron) gel 0.38% groups reported complete resolution of ocular pain at day 8 compared with those in the vehicle groups, with a mean difference of 25% (95% CI, 15%-35%; P <.0001) in trial 1 and 26% (95% CI, 17%-35%; P <.0001) in trial 2.[12,13,20]

At the assessment on day 3 (visit 4), which was 2 days after initiation of treatment, and all study visits afterward (day 8 [visit 5], day 15 [visit 6], and day 18 [visit 7]), significantly greater proportions of patients in the LE (submicron) gel 0.38% groups had complete resolution of ocular pain (grade 0) compared with the vehicle groups in trial 1 ($P \leq$.0161 for all visits) and trial 2 ($P \leq$.001 for all visits).[12,13] Additionally, fewer patients in the LE (submicron) gel 0.38% group required rescue medication before day 8 compared with the vehicle group in trial 1 (11.1% vs 41.9%; P <.0001) and trial 2 (10.0% vs 31.2%; P <.0001).[12,13]

Across both clinical trials, treatment with LE (submicron) gel 0.38% administered 3 times a day was shown to not elevate mean IOP, and mean IOP was similar among treatment groups postoperatively and consistently lower than baseline at each postbaseline visit.[12,13] Across both trials, just 1 study eye in the LE (submicron) gel 0.38% 3-times-a-day group had a clinically significant IOP elevation (≥10 mm Hg) from screening.[12,13] There were no treatment-emergent adverse drug reactions that occurred in more than 1% of patients and no reports of blurred vision associated with treatment. The majority (>75%) of patients in each trial reported they experienced no discomfort after drop instillation.[12,13]

Overall, treatment with LE (submicron) gel 0.38% after cataract surgery significantly improved resolution of inflammation and pain compared with a vehicle at day 8 (the primary efficacy end point), significantly reduced pain from day 3 onward, and reduced rescue medication use compared with a vehicle. It was safe and well tolerated, with minimal incidences of clinically significant IOP elevations.

Considerations for Selection of an Ocular Corticosteroid for Postoperative Intraocular and Ocular Surface Inflammation and Pain

With a rapidly aging and growing US adult population, the incidence of common ophthalmic procedures such as cataract, refractive, glaucoma, and corneal transplant surgeries are likely to increase substantially over the next few decades. The high demand for well-tolerated and effective topical ocular corticosteroids for postoperative intraocular and ocular surface pain and inflammation will remain. This need is underscored by the consequences of less than ideal control of postoperative inflammation, which may cause visually threatening ocular disease.

When an appropriate topical corticosteroid is selected, formulation considerations include those that offer optimal resolution of signs and symptoms of postoperative pain and inflammation and that address several patient-related challenges with administration and comfort. Nonadherence is a key component of therapeutic failure with topical ophthalmic drug therapy.

Several formulations of topical ocular corticosteroids are available for the postoperative management of inflammation and pain after ocular surgery (suspensions, ointments, emulsions, and gels). With suspension formulations, there are challenges related to the inadequate delivery of medication to the target tissue. Several studies have demonstrated that suspension formulations are associated with drug particle settling and clumping if not adequately shaken, which may result in inconsistent medication dosing and slower dissolution on eye. Unlike suspensions, emulsion and gel formulations offer dose uniformity without the need for vigorous shaking before use. Generic preparations, most often available in the form of a suspension, have less stringent FDA abbreviated new drug approval processes. Although they may offer short-term cost savings, this must be weighed against the potential long-term costs associated with treatment failures.

Other considerations when selecting an ophthalmic corticosteroid include the potential of a formulation to increase irritation and reflex tearing when formulated at a non-physiologic pH and increased preservative toxicity due to a higher concentration of BAK. Recently, existing therapeutic ocular agents have undergone novel physical manipulations (eg, reduction in drug particle size) to overcome barriers to drug delivery and improve bioavailability. There is an increased likelihood of class-associated AEs related to C-20 ketone steroids. Formulations that are associated with a lower incidence of elevated IOP are well tolerated and allow for reduced concentration, and dosing frequency should be strongly considered in the selection of appropriate topical ocular corticosteroids. Because a patient's successful recovery requires adherence with prescribed treatment, postoperative management should take into account the complexity of the regimen, the dosing schedule, and whether the medication requires shaking prior to instillation.

An innovative LE (submicron) ophthalmic gel 0.38% formulation was engineered with a drug particle size in the nanometer range for faster dissolution of the active ingredient in the tear film, increasing drug permeation into and through the cornea. Compared with other formulations, this results in 2 times greater penetration into the aqueous humor, and allows for a reduction in both dosing frequency and drug concentration. In addition, LE (submicron) gel 0.38% retains the formulation advancements of LE gel 0.5% in that the polycarbophil-containing gel prolongs drug residence time on the ocular surface,

further enhancing drug bioavailability. Importantly, LE (submicron) gel 0.38% exhibits a potent anti-inflammatory activity comparable to other LE formulations and is well tolerated with minimal potential for eliciting class-associated AEs presumably due to the unique retrometabolically designed LE molecule in combination with the lowered drug concentration and dosing regimen. In addition, the formulation is non-settling and delivers a consistent drug concentration with each drop without the need to shake the bottle, has a pH close to tears, has a low concentration of BAK, and does not result in blurred vision on instillation. Taken together, these formulation advancements provide physicians with a new efficacious treatment option for postsurgical inflammation and pain, with attributes that may improve patient convenience and adherence. ■

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REFERENCES

1. Blindness and vision impairment. World Health Organization website. who.int/news-room/fact-sheets/detail/blindness-and-visual-impairment. Published October 11, 2018. Accessed May 5, 2019.
2. Genetics Home Reference. Fuchs endothelial dystrophy. US National Library of Medicine website. ghr.nlm.nih.gov/condition/fuchs-endothelial-dystrophy. Published April 30, 2019. Accessed May 5, 2019.
3. Cataracts defined tables. National Eye Institute website. nei.nih.gov/eyedata/cataract/tables. Accessed May 3, 2019.
4. Projections for glaucoma. National Eye Institute website. nei.nih.gov/eyedata/glaucoma#5. Accessed May 3, 2019.
5. Projections for hyperopia. National Eye Institute website. nei.nih.gov/eyedata/hyperopia/tables#5. Accessed May 3, 2019.
6. Projections for myopia. National Eye Institute website. nei.nih.gov/eyedata/myopia#5. Accessed May 3, 2019.
7. Gollogly HE, Hodge DO, St Sauver JL, Erie JC. Increasing incidence of cataract surgery: population-based study. *J Cataract Refract Surg*. 2013;39(9):1383-1389. doi: 10.1016/j.jcrs.2013.03.027.
8. Number of LASIK surgeries in the U.S. 1996-2020. Statista website. statista.com/statistics/271478/number-of-lasik-surgeries-in-the-us/. Published July 18, 2016. Accessed May 3, 2019.
9. Park CY, Lee JK, Gore PK, Lim CY, Chuck RS. Keratoplasty in the United States: a 10-year review from 2005 through 2014. *Ophthalmology*. 2015;122(12):2432-2442. doi: 10.1016/j.ophtha.2015.08.017.
10. Statistical abstract of the United States: 2011. United States Census Bureau website. census.gov/library/publications/2010/compendia/statab/130ed.html. Updated September 26, 2015. Accessed December 28, 2018.
11. Patel A, Cholkar K, Agrahari V, Mitra AK. Ocular drug delivery systems: an overview. *World J Pharmacol*. 2013;2(2):47-64. doi: 10.5497/wjp.v2.i2.47.
12. Vittitow JL, LoBue T, Martel J. Safety and efficacy of a novel submicron loteprednol etabonate gel in the treatment of inflammation and pain post-cataract surgery. Presented at: the 2018 Annual Meeting of the Association for Research in Vision and Ophthalmology; April 29-May 3, 2018; Honolulu, HI. Abstract 2235.
13. Fong R, Silverstein BE, Peace JH, Williams JI, Vittitow JL. Submicron loteprednol etabonate ophthalmic gel 0.38% for the treatment of inflammation and pain after cataract surgery. *J Cataract Refract Surg*. 2018;44(10):1220-1229. doi: 10.1016/j.jcrs.2018.06.056.
14. Cavet ME, Glogowski S, Lowe ER, Phillips E. Rheological properties, dissolution kinetics, and ocular pharmacokinetics of submicron loteprednol etabonate ophthalmic gel 0.38% [Published online March 23, 2019]. *J Ocul Pharmacol Ther*. 2019. doi: 10.1089/jop.2018.0136.
15. Comstock TL, Sheppard JD. Loteprednol etabonate for inflammatory conditions of the anterior segment of the eye: twenty years of clinical experience with a retrometabolically designed corticosteroid. *Expert Opin Pharmacother*. 2018;19(4):337-353. doi: 10.1080/14656566.2018.1439920.
16. Coffey MJ, Decory HH, Lane SS. Development of a non-settling gel formulation of 0.5% loteprednol etabonate for anti-inflammatory use as an ophthalmic drop. *Clin Ophthalmol*. 2013;7:299-312. doi: 10.2147/OPTH.S40588.
17. Lotemax (loteprednol etabonate ophthalmic gel) 0.5% [prescribing information]. Bridgewater, NJ: Bausch & Lomb Incorporated; 2018.
18. Lotemax ointment (loteprednol etabonate ophthalmic ointment) 0.5% [prescribing information]. Bridgewater, NJ: Bausch & Lomb Incorporated; 2017.
19. Lotemax (loteprednol etabonate ophthalmic suspension) 0.5% [prescribing information]. Bridgewater, NJ: Bausch & Lomb Incorporated; 2016.
20. Lotemax SM (loteprednol etabonate ophthalmic gel) 0.38%. Bridgewater, NJ: Bausch & Lomb Incorporated; 2019.
21. Inveltys (loteprednol etabonate ophthalmic suspension) 1% [prescribing information]. Waltham, MA: Kala Pharmaceuticals, Inc; 2018.
22. Aptel F, Colin C, Kaderli S, et al. Management of postoperative inflammation after cataract and complex ocular surgeries: a systematic review and Delphi survey. *Br J Ophthalmol*. 2017;101(11):1-10. doi: 10.1136/bjophthalmol-2017-310324.
23. Rajpal RK, Roel L, Siou-Mermet R, Erb T. Efficacy and safety of loteprednol etabonate 0.5% gel in the treatment of ocular inflammation and pain after cataract surgery. *J Cataract Refract Surg*. 2013;39(2):158-167. doi: 10.1016/j.jcrs.2012.09.013.
24. DeCroos FC, Afshari NA. Perioperative antibiotics and anti-inflammatory agents in cataract surgery. *Curr Opin Ophthalmol*. 2008;19(1);22-26. doi: 10.1097/ICU.0b013e3282f30577.
25. Tripathi T, Alizadeh H. Significance of arachidonic acid in ocular infections and inflammation. *Inflamm Cell Signal*. 2014;1(5). doi: 10.14800/ics.301.
26. Gaynes BI, Onyekwuluje A. Topical ophthalmic NSAIDs: a discussion with focus on nepafenac ophthalmic suspension. *Clin Ophthalmol*. 2008;2(2):355-368. doi: 10.2147/OPTH.S1067.
27. Olson RJ, Braga-Mele R, Chen SH, et al. Cataract in the adult eye preferred practice pattern®. *Ophthalmology*. 2017;142(2):1-119. doi: 10.1016/j.ophtha.2016.09.027.
28. Hoffman RS, Braga-Mele R, Emerick G, et al; ASCRS Cataract Clinical Committee, American Glaucoma Society. Cataract surgery and nonsteroidal antiinflammatory drugs. *J Cataract Refract Surg*. 2016; 42(9):1368-1379. doi: 10.1016/j.jcrs.2016.06.006.
29. O'Brien TP. Emerging guidelines for use of NSAID therapy to optimize cataract surgery patient care. *Curr Med Res Opin*. 2005;21(7):1131-7. doi: 10.1185/030079905X50651.
30. Wielders LHP, Schouten JSAG, Winkens B, et al; ESCRS PREMED Study Group. European multicenter trial of the prevention of cystoid macular edema after cataract surgery in nondiabetics: ESCRS PREMED study report 1. *J Cataract Refract Surg*. 2018;44(4):429-439. doi: 10.1016/j.jcrs.2018.01.029.
31. Gaynes BI, Fiscella R. Topical nonsteroidal anti-inflammatory drugs for ophthalmic use: a safety review. *Drug Saf*. 2002;25(4):233-250. doi: 10.2165/00002018-200225040-00002.
32. Asai T, Nakagami T, Mochizuki M, Hata N, Tsuchiya T, Hotta Y. Three cases of corneal melting after instillation of a new nonsteroidal anti-inflammatory drug. *Cornea*. 2006;25(2):224-227. doi: 10.1097/01.ico.0000177835.93130.d4.
33. Wolf EJ, Kleiman LZ, Schrier A. Nepafenac-associated corneal melt. *J Cataract Refract Surg*. 2007;33(11):1974-1975. doi: 10.1016/j.jcrs.2007.06.043.
34. Harada K, Mohamed YH, Uematsu M, et al. Three cases of acute sterile corneal melt after cataract surgery. *Am J Ophthalmol Case Rep*. 2018;13:62-65. doi: 10.1016/j.ajoc.2018.12.004.
35. Prasher P. Acute corneal melt associated with topical bromfenac use. *Eye Contact Lens*. 2012;38(4):260-262. doi: 10.1097/ICL.0b013e318235c506.
36. Pleyer U, Ursell PG, Rama P. Intraocular pressure effects of common topical steroids for post-cataract inflammation: are they all the same? *Ophthalmol Ther*. 2013;2(2):55-72. doi: 10.1007/s40123-013-0020-5.
37. Comstock TL, Decory HH. Advances in corticosteroid therapy for ocular inflammation: loteprednol etabonate [published online March 28, 2012]. *Int J Inflam*. 2012;2012:789623. doi: 10.1155/2012/789623.
38. Kessel L, Tendal B, Jørgensen KJ, et al. Post-cataract prevention of inflammation and macular edema by steroid and nonsteroidal anti-inflammatory eye drops: a systematic review. *Ophthalmology*. 2014;121(10):1915-1924. doi: 10.1016/j.ophtha.2014.04.035.
39. Barnes PJ. How corticosteroids control inflammation: Quintiles Prize Lecture 2005. *Br J Pharmacol*. 2006;148(3):245-254. doi: 10.1038/sj.bjp.0706736.
40. Rhen T, Cidlowski JA. Antiinflammatory action of glucocorticoids: new mechanisms for old drugs. *N Engl J Med*. 2005;353(16):1711-1723. doi: 10.1056/NEJMra050541.
41. Revollo JR, Cidlowski JA. Mechanisms generating diversity in glucocorticoid receptor signaling. *Ann N Y Acad Sci*. 2009;1179:167-178. doi: 10.1111/j.1749-6632.2009.04986.x.
42. Sheppard JD, Comstock TL, Cavet ME. Impact of the topical ophthalmic corticosteroid loteprednol etabonate on intraocular pressure. *Adv Ther*. 2016;33(4):532-552. doi: 10.1007/s12325-016-0315-8.
43. Loteprednol Etabonate US Uveitis Study Group. Controlled evaluation of loteprednol etabonate and prednisolone acetate in the treatment of acute anterior uveitis. *Am J Ophthalmol*.1999;127(5):537-544.
44. Durezol (difluprednate ophthalmic emulsion) 0.5% [prescribing information]. Fort Worth, TX: Alcon Laboratories; 2017.
45. McGhee CN, Dean S, Danesh-Meyer H. Locally administered ocular corticosteroids: benefits and risks. *Drug Saf*. 2002;25(1):33-55. doi: 10.2165/00002018-200225010-00004.
46. Pred Forte (prednisolone acetate ophthalmic suspension, USP) 1% [prescribing information]. Madison, NJ: Allergan USA, Inc; 2018.
47. Flarex (fluorometholone acetate ophthalmic suspension) 0.1% [prescribing information]. Fort Worth, TX: Eyevance Pharmaceuticals, LLC; 2019.

48. FML (fluorometholone ophthalmic suspension, USP) 0.1% [prescribing information]. Madison, NJ: Allergan USA, Inc; 2018.
49. FML (fluorometholone ophthalmic ointment) 0.1% [prescribing information]. Madison, NJ: Allergan USA, Inc; 2018.
50. Maxidex (dexamethasone ophthalmic suspension) 0.1% [prescribing information]. Fort Worth, TX: Alcon Laboratories; 2018.
51. Pavesio CE1, Decory HH. Treatment of ocular inflammatory conditions with loteprednol etabonate. *Br J Ophthalmol.* 2008;92(4):455-459. doi: 10.1136/bjo.2007.132621.
52. James ER. The etiology of steroid cataract. *J Ocul Pharmacol Ther*. 2007;23(5):403-420. doi: 10.1089/jop.2006.0067.
53. Manabe S, Bucala R, Cerami A. Nonenzymatic addition of glucocorticoids to lens proteins in steroid-induced cataracts. *J Clin Invest*. 1984;74(5):1803-1810. doi: 10.1172/JCI111599.
54. Bodor N. Recent advances in retrometabolic design approaches. *J Control Release*. 1999;62(1-2):209-222. doi: 10.1016/S0168-3659(99)00040-1.
55. Bodor N, Buchwald P. Soft drug design: general principles and recent applications. *Med Res Rev.* 2000;20(1):58-101. doi: 10.1002/(SICI)1098-1128(200001)20:1<58::AID-MED3>3.0.CO;2-X.
56. Bodor N, Buchwald P. Drug targeting via retrometabolic approaches. *Pharmacol Ther*. 1997;76(1-3):1-27. doi: 10.1016/S0163-7258(97)00098-3.
57. Bielory BP, O'Brien TP, Bielory L. Management of seasonal allergic conjunctivitis: guide to therapy. *Acta Ophthalmol.* 2012;90(5):399-407. doi: 10.1111/j.1755-3768.2011.02272.x.
58. Druzgala P, Wu WM, Bodor N. Ocular absorption and distribution of loteprednol etabonate, a soft steroid, in rabbit eyes. *Curr Eye Res*. 1991;10(10):933-937. doi: 10.3109/02713689109020329.
59. Lane SS, Holland EJ. Loteprednol etabonate 0.5% versus prednisolone acetate 1.0% for the treatment of inflammation after cataract surgery. *J Cataract Refract Surg*. 2013;39(2):168-173. doi: 10.1016/j.jcrs.2012.10.039.
60. Abessi B, Brooksby LM, Schultze RL. Comparison of efficacy of difluprednate 0.05% and loteprednol gel 0.5% after cataract surgery. *Eye Contact Lens.* 2018;44(suppl 2):S37-S42. doi: 10.1097/ICL.0000000000000040.
61. Price MO, Feng MT, Scanameo A, Price FW Jr. Loteprednol etabonate 0.5% gel vs. prednisolone acetate 1% solution after descemet membrane endothelial keratoplasty: prospective randomized trial. *Cornea.* 2015;34(8):853-858. doi: 10.1097/ICO.0000000000000475.
62. Mifflin MD, Betts BS, Frederick PA, et al. Efficacy and safety of a 3-month loteprednol etabonate 0.5% gel taper for routine prophylaxis after photorefractive keratectomy compared to a 3-month prednisolone acetate 1% and fluorometholone 0.1% taper. *Clin Ophthalmol*. 2017;11:1113-1118. doi: 10.2147/OPTH.S138272.
63. Ilyas H, Slonim CB, Braswell GR, Favetta JR, Schulman M. Long-term safety of loteprednol etabonate 0.2% in the treatment of seasonal and perennial allergic conjunctivitis. *Eye Contact Lens*. 2004;30(1):10-13. doi: 10.1097/01.ICL.0000092071.82938.46.
64. Cavet ME, Sanfilippo CM, DeCory HH. Assessment of ophthalmic steroid class adverse event reports for loteprednol etabonate [ARVO abstract]. *Invest Ophthalmol Vis Sci*. 2017;58(8):1082.
65. Salinger CL, Gordon M, Jackson MA, Perl T, Donnenfeld E. A retrospective analysis of the postoperative use of loteprednol etabonate gel 0.5% following laser-assisted in situ keratomileusis or photorefractive keratectomy surgery. *Clin Ophthalmol*. 2015;9:2089-2097. doi: 10.2147/OPTH.S94332.
66. Loteprednol Etabonate US Uveitis Study Group. Controlled evaluation of loteprednol etabonate and prednisolone acetate in the treatment of acute anterior uveitis. *Am J Ophthalmol*. 1999;127(5):537-544. doi: 10.1016/S0002-9394(99)00034-3.
67. Holland EJ, Djalilian AR, Sanderson JP. Attenuation of ocular hypertension with the use of topical loteprednol etabonate 0.5% in steroid responders after corneal transplantation. *Cornea*. 2009;28(10):1139-1143. doi: 10.1097/ICO.0b013e3181a3c52f.
68. Smith S, Lorenz D, Peace J, McLeod K, Crockett R, Vogel R. Difluprednate ophthalmic emulsion 0.05% (Durezol) administered two times daily for managing ocular inflammation and pain following cataract surgery. *Clin Ophthalmol.* 2010;4:983-991. doi: 10.2147/opth.s10696.
69. Korenfeld MS, Silverstein SM, Cooke DL, Vogel R, Crockett RS; Difluprednate Ophthalmic Emulsion 0.05% (Durezol) Study Group. Difluprednate ophthalmic emulsion 0.05% for postoperative inflammation and pain. *J Cataract Refract Surg*. 2009;35(1):26-34. doi: 10.1016/j.jcrs.2008.09.024.
70. Rajpal RK, Fong R, Comstock TL. Loteprednol etabonate ophthalmic gel 0.5% following cataract surgery: integrated analysis of two clinical studies. *Adv Ther*. 2013;30(10):907-923. doi: 10.1007/s12325-013-0059-7.
71. Stewart R, Horwitz B, Howes J, Novack GD, Hart K. Double-masked, placebo-controlled evaluation of loteprednol etabonate 0.5% for postoperative inflammation. Loteprednol Etabonate Post-Operative Inflammation Study Group 1. *J Cataract Refract Surg*. 1998;24(11):1480-1489.
72. Gaudana R, Ananthula HK, Parenky A, Mitra AK. Ocular drug delivery. *AAPS J.* 2010;12(3):348-360. doi: 10.1208/s12248-010-9183-3.
73. Bourlais CL, Acar L, Zia H, Sado PA, Needham T, Leverge R. Ophthalmic drug delivery systems–recent advances. *Prog Retin Eye Res*. 1998;17(1):33-58. doi: 10.1016/S1350-9462(97)00002-5.
74. Davies NM. Biopharmaceutical considerations in topical ocular drug delivery. *Clin Exp Pharmacol Physiol*. 2000;27(7):558-562. doi: 10.1046/j.1440-1681.2000.03288.x.
75. Diestelhorst M, Kwon KA, Süverkrup R. Dose uniformity of ophthalmic suspensions. *J Cataract Refract Surg*. 1998;24(5):672-677. doi: 10.1016/S0886-3350(98)80264-2.
76. Stringer W, Bryant R. Dose uniformity of topical corticosteroid preparations: difluprednate ophthalmic emulsion 0.05% versus branded and generic prednisolone acetate ophthalmic suspension 1%. *Clin Ophthalmol*. 2010;4:1119-1124. doi: 10.2147/OPTH.S12441.
77. Marlowe ZT, Davio SR. Dose uniformity of loteprednol etabonate ophthalmic gel (0.5%) compared with branded and generic prednisolone acetate ophthalmic suspension (1%). *Clin Ophthalmol*. 2014;8:23-29. doi: 10.2147/OPTH.S55004.
78. Apt L, Henrick A, Silverman LM. Patient compliance with use of topical ophthalmic corticosteroid suspensions. *Am J Ophthalmol*. 1979;87(2):210-214. doi: 10.1016/0002-9394(79)90145-4.
79. Donnelly D. Instilling eyedrops: difficulties experienced by patients following cataract surgery. *J Adv Nurs*. 1987;12(2):235-243.
80. Kaur IP, Kanwar M. Ocular preparations: the formulation approach. *Drug Dev Ind Pharm*. 2002;28(5):473-493. doi: 10.1081/DDC-120003445.
81. Comstock TL, Paterno MR, Singh A, Erb T, Davis E. Safety and efficacy of loteprednol etabonate ophthalmic ointment 0.5% for the treatment of inflammation and pain following cataract surgery. *Clin Ophthalmol*. 2011;5:177-186. doi: 10.2147/OPTH.S16832.
82. Pirouzian A, Craven ER. Critical appraisal of loteprednol ointment, gel, and suspension in the treatment of postoperative inflammation and pain following ocular and corneal transplant surgery. *Clin Ophthalmol*. 2014;8:379-387. doi: 10.2147/OPTH.S30278.
83. Ingersoll KS, Cohen J. The impact of medication regimen factors on adherence to chronic treatment: a review of literature. *J Behav Med*. 2008;31(3):213-224. doi: 10.1007/s10865-007-9147-y.
84. Coleman CI, Limone B, Sobieraj DM, et al. Dosing frequency and medication adherence in chronic disease. *J Manag Care Pharm.* 2012;18(7):527-539. doi: 10.18553/jmcp.2012.18.7.527.
85. Ali Y, Lehmussaari K. Industrial perspective in ocular drug delivery. *Adv Drug Deliv Rev*. 2006;58(11):1258-1268. doi: 10.1016/j.addr.2006.07.022.
86. Code of Federal Regulations Title 21. Part 349.12 Ophthalmic demulcents. FDA website. accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=349.12. Revised April 1, 2018. Updated September 4, 2018. Accessed December 27, 2018.
87. Stevens CE, Bennion JL, Caldwell MC, Townley JR, Apsey DA, Schwertner HA. Dose uniformity of topical corticosteroids: a simulated trial of fluorometholone acetate 0.1% and loteprednol etabonate gel 0.5%. *J Ocul Pharmacol Ther*. 2017;33(2):111-114. doi: 10.1089/jop.2016.0151.
88. Kim T, Sall K, Holland EJ, Brazzell RK, Coultas S, Gupta PK. Safety and efficacy of twice daily administration of KPI-121 1% for ocular inflammation and pain following cataract surgery. *Clin Ophthalmol*. 2018;13:69-86. doi: 10.2147/OPTH.S185800.
89. Schopf L, Enlow E, Popov A, Bourassa J, Chen H. Ocular pharmacokinetics of a novel loteprednol etabonate 0.4% ophthalmic formulation. *Ophthalmol Ther*. 2014;3(1-2):63-72. doi: 10.1007/s40123-014-0021-z.
90. Kaur IP, Lal S, Rana C, Kakkar S, Singh H. Ocular preservatives: associated risks and newer options. *Cutan Ocul Toxicol*. 2009;28(3):93-103. doi: 10.1080/15569520902995834.
91. Loteprednol Etabonate Postoperative Inflammation Study Group 2. A double-masked, placebo-controlled evaluation of 0.5% loteprednol etabonate in the treatment of postoperative inflammation. *Ophthalmology*. 1998;105(9):1780-1786.