Clinical Drug Investigation (2020) 40:387–394
https://doi.org/10.1007/s40261-020-00899-2

ADIS DRUG EVALUATION

Loteprednol Etabonate (Submicron) Ophthalmic Gel 0.38%: A Review in Post-Operative Inflammation and Pain Following Ocular Surgery

Connie Kang[1] · Susan J. Keam[1] · Matt Shirley[1] · Yahiya Y. Syed[1]

Published online: 14 March 2020

Abstract

Loteprednol etabonate ophthalmic gel 0.38% (Lotemax® SM; hereafter referred to as loteprednol etabonate gel 0.38%) is a topical ophthalmic corticosteroid approved in the USA for the treatment of post-operative inflammation and pain following ocular surgery. This formulation provides improved drug delivery compared with loteprednol etabonate micronized gel 0.5%, with a smaller drug particle size (in the submicron range) to improve dissolution and penetration into ocular tissues, meaning less loteprednol etabonate is required to exert therapeutic effect. In two multicentre, randomized phase III trials, significantly more loteprednol etabonate gel 0.38% than vehicle recipients displayed complete resolution of ocular inflammation and ocular pain at day 8 post cataract surgery. Complete resolution of pain was seen as early as post-operative day 3. Treatment-related ocular adverse events in the loteprednol etabonate gel 0.38% group occurred in < 1% of subjects and included one incidence each of photophobia, cystoid macular oedema, eyelid oedema and instillation site pain. Treatment with loteprednol etabonate gel 0.38% had no meaningful impact on intraocular pressure (IOP) or visual acuity. Thus, loteprednol etabonate gel 0.38% extends the treatment options available in resolving post-operative inflammation and pain in patients who have undergone ocular surgery.

1 Introduction

Ocular pain and inflammation (e.g. anterior chamber reaction, redness, swelling, photophobia, tearing, decreased visual acuity and itching) are typical sequelae to ocular surgery, treatment of which can lead to better outcomes and patient satisfaction [1, 2]. Cataract surgery is one of the most commonly performed ocular surgeries [2, 3], and any ensuing post-operative inflammation and pain is usually treated by topical ophthalmic corticosteroids and topical ophthalmic non-steroidal anti-inflammatory drugs (NSAIDs), either alone or in combination [3, 4]. These drugs can also be useful in preventing complications arising from post-operative inflammation such as corneal or cystoid macular oedema [1, 2, 5].

Corticosteroids bind to glucocorticoid receptors, leading to gene regulation and the inhibition of inflammatory pathways. Ocular anti-inflammatory effects of corticosteroids include reductions in oedema, capillary and fibroblast proliferation, inhibited collagen and fibrin deposition, capillary

Loteprednol etabonate ophthalmic gel 0.38%: clinical considerations in post-operative inflammation and pain following ocular surgery

Greater dissolution and penetration into ocular tissue than the micronized gel 0.5% formulation because of the submicron drug particle size (median ranges between 0.4 and 0.6 μm).
Lower drug concentration per dose and less frequent administration than the micronized 0.5% gel.
Reduces post-operative inflammation and pain following cataract surgery.
Generally well tolerated with minimal impact on IOP.

Enhanced material for this Adis Drug Evaluation can be found at https://doi.org/10.6084/m9.figshare.11879742.

The manuscript was reviewed by: ***K. Sudhakar*** Department of Pharmaceutical Sciences, Lovely Professional University, Phagwara, India, ***E. Anastasopoulos*** 2nd Department of Ophthalmology, Faculty of Medicine, Aristotle University of Thessaloniki, Papageorgiou General Hospital, Thessaloniki, Greece.

✉ Connie Kang
demail@springer.com

[1] Springer Nature, Mairangi Bay, Private Bag 65901, Auckland 0754, New Zealand

constriction and scar tissue formation [3]. Ophthalmic steroid usage, however, is associated with adverse effects such as increased risk of infections (bacterial, viral and fungal), increased intraocular pressure (IOP), posterior subcapsular cataract formation and delayed healing [1, 5, 6]. While unlikely, systemic absorption of ophthalmic corticosteroids may lead to adrenal axis suppression and a reduction in endogenous plasma cortisol [7]. Low drug bioavailability (due to poor dissolution and tissue penetration) and rapid tear turnover can also lead to poor outcomes [8]. To improve on this, loteprednol etabonate, a topical ophthalmic corticosteroid, was retrometabolically designed to treat post-operative inflammation and pain at the intended site with minimal ocular and systemic adverse effects [3]. The development of this drug has been summarized elsewhere [9, 10].

Loteprednol etabonate is currently available in the USA formulated as a suspension (0.5% and 1%), ointment (0.5%) and gel (0.5% and 0.38%) [3]. The safety and efficacy of loteprednol etabonate ophthalmic gel 0.5% (Lotemax®) in treating post-operative inflammation and pain following cataract surgery is well established [3, 9]. Loteprednol etabonate is approved for reducing inflammation associated with other ocular surgeries (all formulations) [6, 11–14] and in the treatment of steroid-responsive inflammatory conditions of the eye (suspension formulation only) [12].

Loteprednol etabonate ophthalmic gel 0.38% (Lotemax® SM; hereafter referred to as loteprednol etabonate gel 0.38%) is a new formulation of loteprednol etabonate that has a smaller drug particle size (i.e. in the submicron particle size range) than the 0.5% micronized formulation, which allows for a lower drug concentration and less frequent administration. It has approval from the US Food and Drug Administration for use in patients with post-operative inflammation and pain following ocular surgery [6]. This article provides an overview of the pharmacological properties of loteprednol etabonate gel 0.38% and reviews clinical data relevant to its use in this setting.

2 Pharmacological Profile of Loteprednol Etabonate Gel 0.38%

Loteprednol etabonate is a carbon-20 ester-based ophthalmic corticosteroid which binds to glucocorticoid receptors and inhibits the inflammatory response [15, 16]. Loteprednol etabonate gel 0.38% retains the rheological and mucoadhesive properties of the previous 0.5% gel formulation but differs in drug particle size, drug concentration and formulation excipients [17]. Loteprednol etabonate particle size has been reduced in the submicron 0.38% gel, with the median particle diameter ranging between 0.4 and 0.6 μm (vs 3–5 μm in the micronized 0.5% gel) [15, 17]. The smaller particle size results in a greater total surface area of loteprednol etabonate particles exposed to tears, leading to faster dissolution and improved penetration through the ocular surface [15]. At the 30 s time point in a fixed-volume assay, the in vitro dissolution of loteprednol etabonate gel 0.38% was 2.6-fold higher than the 0.5% gel. When the same concentration (0.38%) of both submicron and micronized loteprednol etabonate were introduced to a flow-through dissolution assay, the maximum drug concentrations (C_{max}) were 72 μg/mL and 65 μg/mL, respectively. Doubling the concentration of micronized loteprednol etabonate gel in this assay did not improve the C_{max} of dissolved loteprednol etabonate; this suggests that the higher C_{max} for the submicron 0.38% gel was due to the smaller particle size [15].

The improved dissolution seen with the submicron loteprednol etabonate particles has facilitated a reduced loteprednol etabonate concentration in the submicron gel formulation (from 0.5 to 0.38%; a reduction of 24%); thus, when loteprednol etabonate gel 0.38% is administered at the approved dosage regimen, total daily drug exposure in human eyes is approximately a third to one half of that seen with the 0.5% micronized gel [6, 11]. It has also enabled less frequent drug administration (from four to three times daily) compared to the 0.5% gel, ointment and suspension [6, 11–13].

The rheological properties of loteprednol etabonate gel 0.38% are very similar to those of loteprednol etabonate gel 0.5% [15]. Loteprednol etabonate gel 0.38% is highly viscous at low shear stress and therefore is a non-settling semi-solid gel inside the bottle [15]; this means the bottle does not need to be shaken before instillation [10]. When high shear stress is applied (i.e. the bottle is squeezed) the viscosity decreases and the formulation is expressed as a liquid drop through the dropper tip [15]. This can be considered beneficial in terms of providing convenience and more consistent drug administration.

Loteprednol etabonate gel 0.38% contains the same concentration of polycarbophil as the 0.5% gel; polycarbophil gives the gel formulation its mucoadhesive and viscoelastic properties, which improve the structural integrity and ocular surface retention of the gel formulation [15]. Even with dilution from tears and the shear stress from blinking, the formulation attributes of loteprednol etabonate gel are expected to result in prolonged retention on the eye surface (in comparison with previous suspension formulations) and with reduced potential for blurred vision or sticky sensations [15]. The pH of the 0.38% gel is also the same as the 0.5% gel formulation (6.5), which is similar to the physiological pH of tear fluid (7.4) [10]. While the concentration of the preservative (benzalkonium chloride) in the 0.38% gel is the same as that in the 0.5% gel (0.003%), the total amount of preservative entering the eye (and potentially systemically) is reduced due to the lower dosage and dose frequency (one drop three times daily for the 0.38% gel

compared with up to two drops four times daily for the 0.5% gel) [15].

Some excipients used in loteprednol etabonate gel 0.5% have been changed to improve the stability of the new 0.38% formulation: tyloxapol (a surfactant and/or wetting agent) has been replaced with poloxamer 407; and hypromellose E4M (a suspending and/or viscosity-increasing agent with particle size-stabilizing and demulcent properties) has been added [15].

No ocular distribution studies have been conducted in humans [6]. In rabbits, loteprednol etabonate gel 0.38% exhibited high ocular penetration (loteprednol etabonate concentrations measurable within 5 min) and rapid absorption [loteprednol etabonate time to C_{max} (t_{max}) < 1 h] in all tested ocular tissues (Table 1) [15]. The area under the concentration–time curve from time zero to 24 h (AUC_{24}) of loteprednol etabonate was predictably highest in tear fluid and lowest in the aqueous humour. Loteprednol etabonate exposure was sustained, measurable up to 12 h in aqueous humour and up to 24 h in all other ocular tissues. The AUC_{24} for loteprednol etabonate gel 0.38% was significantly lower than for the 0.5% gel in the bulbar conjunctiva, but approximately double the C_{max} and AUC_{24} of the 0.5% gel in aqueous humour; all other values were similar (Table 1). The t_{max} varied between formulations across the ocular tissues. Consistent with its improved dissolution characteristics, loteprednol etabonate gel 0.38% was therefore highly absorbed from the conjunctiva into anterior segment tissues most relevant to post-operative inflammation (e.g. aqueous humour), and at a higher rate than the previous gel formulation, facilitating its anti-inflammatory effect [15].

Low levels of loteprednol etabonate (near the lower limit of quantitation) were detected in human plasma after administration of loteprednol etabonate gel 0.38% for up to 15 days in healthy adult subjects [6]. Following bilateral ocular administration of one drop three times daily, the loteprednol etabonate C_{max} was 0.13 ng/mL after a single dose, and 0.16 ng/mL after the last dose on day 15 [6]. Based on animal models and its retrometabolic design, loteprednol etabonate is expected to be rapidly metabolised into its major inactive metabolite, Δ^1-cortienic acid, in human plasma [16].

3 Therapeutic Efficacy of Loteprednol Etabonate Gel 0.38%

The efficacy of loteprednol etabonate gel 0.38% in reducing post-operative inflammation and pain following cataract surgery was evaluated in two phase III randomized, parallel-group, double-masked, vehicle-controlled, multicentre trials that were conducted in the USA (hereafter referred to as Study A [18] and Study B [19]). Results of the individual trials and an analysis of integrated data [17] are available.

Patients ≥ 18 years of age were eligible in both studies if they had: undergone routine uncomplicated cataract surgery by phacoemulsification with posterior chamber intraocular lens implantation in one eye (not in combination with any other surgery); a potential post-operative pinhole Snellen corrected distance visual acuity of ≥ 20/200 in the operated eye; and ≥ grade 2 anterior chamber (AC) cells (6–15 cells) on the first post-operative day [17–19]. Patient exclusion

Table 1 Pharmacokinetic properties of loteprednol etabonate (submicron) gel 0.38% versus loteprednol etabonate (micronized) gel 0.5% in anterior segment ocular tissues in rabbits [15]

Pharmacokinetic parameter[a]	Ocular tissue				
	Tear fluid	Bulbar conjunctiva	Cornea	Aqueous humour[b]	Iris/ciliary body
C_{max} (μg/g)					
LE (submicron) 0.38% gel	614	12.0	3.74	0.0281*	0.165
LE (micronized) 0.5% gel	871	16.4	2.38	0.0112	0.102
AUC_{24} (μg·h/g)					
LE (submicron) 0.38% gel	260	33.5*	11.7	0.0421**	0.338
LE (micronized) 0.5% gel	483	95.0	9.71	0.0228	0.385
t_{max} (h)					
LE (submicron) 0.38% gel	0.083	0.083	0.083	1	0.25
LE (micronized) 0.5% gel	0.25	0.25	0.083	0.5	0.083

AUC_{24} area under the concentration–time curve from time 0 to 24 h, *C_{max}* maximum concentration, *LE* loteprednol etabonate, *t_{max}* time to C_{max}

*$p < 0.01$, **$p = 0.0005$ (vs LE micronized 0.5% gel)

[a]Data shown are following a single ophthalmic dose ($n = 5$–6 study eyes per group per time point). C_{max} and AUC_{24} values are means

[b]Units for C_{max} and AUC_{24} are μg/mL and μg·h/mL, respectively

criteria included: history or presence of generalized systemic disease or serious ocular conditions (including cystoid macular oedema, glaucoma and ocular hypertension); prior ocular surgery (≤3 months in the study eye or ≤2 weeks in the fellow eye) or glaucoma-related surgery; IOP ≥ 21 mm Hg at screening or baseline; or ocular or systemic therapy (e.g. NSAIDs, mast cell stabilisers, antihistamines, decongestants, corticosteroids, glucocorticoids or immunosuppressants) required 7–30 days before cataract surgery or during the 18 days post-surgery [17–19].

Patients completed seven study visits: an initial screening visit ≤ 14 days prior to surgery; the day of the surgery; post-operative day 1 as the baseline visit; and post-operative days 3, 8, 15 and 18 [17]. In the two studies, patients ($n = 514$ [18] and 600 [19]) were randomized (2:2:1:1) to receive either loteprednol etabonate gel 0.38% twice daily (BID; approximately every 12 h) or three times daily (TID; approximately every 8 h), or vehicle BID or TID, for 14 days starting from post-operative day 1. This section will focus on data from patients who received TID dosing of loteprednol etabonate gel 0.38% (i.e. the approved regimen; Sect. 5) in comparison with data from vehicle recipients (with data for vehicle BID and TID dosing combined for analysis). Similarly, the integrated analysis was limited to patients ($n = 742$) who received loteprednol etabonate gel 0.38% TID or vehicle (BID or TID) [17].

The co-primary efficacy endpoints (evaluated hierarchically) were the proportions of patients with complete resolution of AC cells (i.e. no cells) and complete resolution of ocular pain (i.e. no pain) at post-operative day 8 in the intent-to-treat (ITT) population [17–19]. AC cell count is a measure of ocular inflammation and was assessed using a 5-point scale (0 = no cells, 1 = 1–5 cells, 2 = 6–15 cells, 3 = 16–30 cells, 4 = > 30 cells). Ocular pain was defined as foreign body sensation, stabbing, throbbing or aching pain and was assessed using a patient-graded 6-point scale (0 = none, 1 = minimal, 2 = mild, 3 = moderate, 4 = moderately severe, 5 = severe) [17]. Patients who received anti-inflammatory rescue medication (due to no change or worsening inflammation) or had missing data were considered treatment failures. In those requiring anti-inflammatory rescue medication, treatment was discontinued but patients were followed up to study completion [17, 18].

Baseline patient demographics were generally well balanced across treatment groups for both studies [18, 19]. In the integrated analysis, 77.6% of patients were white, 58.6% were female, and mean age was 68.9 years [17]. At baseline, AC cell score was 2.4 in both the loteprednol etabonate gel 0.38% and vehicle groups, and 50.1% and 49.9% of patients in the respective groups had pain, graded mostly as minimal (23.2% and 23.7%) or mild (18.6% and 16.4%). Overall, 80.3% of loteprednol etabonate gel 0.38% recipients completed the trials compared with 54.4% of vehicle recipients [17].

Short-term (14 days) treatment with loteprednol etabonate gel 0.38% TID was effective in treating post-operative ocular inflammation and pain following cataract surgery [17–19]. A significantly greater proportion of loteprednol etabonate gel 0.38% recipients than vehicle recipients achieved complete resolution of AC cells (score = 0) and complete resolution of ocular pain (score = 0) at post-operative day 8 in both individual trials and the integrated analysis (Table 2). Loteprednol etabonate gel 0.38% reduced ocular pain as early as post-operative day 3, with significantly more patients in this group achieving grade 0 pain compared with vehicle recipients [71.7% vs 50.4%; between-group difference 21.3% (95% CI 14.4%–28.1%); $p < 0.0001$] [17]. Significantly more patients achieved complete resolution of AC flare compared to vehicle from post-operative day 3 ($p < 0.005$); all other secondary endpoints (complete resolution of AC flare and combined AC cell and flare at days 3, 8, 15 and 18, and complete resolution of AC cells at days 3, 15 and 18) were significant from day 8 onwards (all $p < 0.0001$ vs vehicle). The mean reductions from baseline for AC cells, flare, and combined AC cells and flare were also significantly greater (all $p < 0.01$) for the loteprednol etabonate gel 0.38% group versus the vehicle group at every post-operative visit [17].

The proportion of patients who required rescue medication by day 8 was significantly lower in the loteprednol etabonate gel 0.38% group relative to the vehicle group [11.1% vs 41.9% in Study A and 10.0% vs 31.2% in Study B (both $p < 0.0001$)] [18, 19]. A similar result was seen at post-operative day 18 in the integrated analysis (18.4% vs 44.1%) [17]. The most frequently used rescue medication classes were topical corticosteroids (e.g. prednisolone or difluprednate) and/or NSAIDs (e.g. nepafenac or bromfenac) [17].

4 Tolerability of Loteprednol Etabonate Gel 0.38%

Loteprednol etabonate gel 0.38% was well tolerated in patients with post-operative ocular inflammation and pain following cataract surgery, based on data from two phase III trials [18, 19] and an integrated analysis [17] (Sect. 3). Analyses were conducted in the safety population, which excluded three patients from the ITT population [two patients from the loteprednol etabonate gel 0.38% group ($n = 369$) and one patient from the vehicle group ($n = 370$)]. The mean drug exposure was 13.1 and 10.7 days, respectively. In addition to the assessment of ocular and non-ocular adverse events (AEs), changes from baseline in visual acuity, IOP and ocular signs were evaluated [17].

In the integrated analysis, AEs of any cause were reported in 8.1% of loteprednol etabonate gel 0.38% recipients and 11.6% of vehicle recipients [17]. Reported AEs were consistent with those most commonly occurring after cataract

Table 2 Efficacy of loteprednol etabonate gel 0.38% at day 8 after cataract surgery in two randomized, double-masked phase III trials and an integrated analysis

Study	Treatment[b] (no. of pts)	Complete resolution (% of pts)[a]			
		AC cells[c]	Ocular pain[c]	AC flare[d]	AC cells + flare
Study A [18]	LE (171)	28.7	73.1	71.3	27.5
	Vehicle (172)[e]	9.3	47.7	41.3	9.3
	Difference[f] (95% CI)	19.4 (11.3–27.4)***	25.4 (15.4–35.4)***	30.1 (20.1–40.1)***	18.2 (10.2–26.2)***
Study B [19]	LE (200)	30.5	75.5	NA	NA
	Vehicle (199)[e]	20.1	49.7	NA	NA
	Difference[f] (95% CI) [6]	10 (2–19)*	26 (17–35)*	NA	NA
Integrated analysis of Studies A and B [17]	LE (371)	29.6	74.4	68.2	27.2
	Vehicle (371)	15.1	48.8	39.6	13.7
	Difference[f] (95% CI)	14.6 (8.7–20.5)***	25.6 (18.9–32.4)***	28.6 (21.7–35.4)***	13.5 (7.8–19.2)***

Data are in the intent-to-treat population. Both trials also included a LE twice daily treatment arm [$n = 171$ (Study A) and 201 (Study B)]; these data are not reported here

AC anterior chamber, *LE* loteprednol etabonate gel 0.38%, *NA* not available, *pts* patients

*$p < 0.05$, **$p \leq 0.01$, ***$p < 0.0001$ (two-sided)

[a]Complete resolutions for endpoints are defined as follows (as per respective rating scales): AC cells = no cells; ocular pain = 0 pain; AC flare = no AC flare; AC cells + flare = no AC cells + flare

[b]Pts received either one drop of LE or vehicle into the operated eye three times daily for 14 days following cataract surgery (beginning the day after surgery)

[c]Co-primary endpoints (see text for details of rating scales)

[d]AC flare determined using a 5-point scale (0 = none, 1 = mild, 2 = moderate, 3 = severe, 4 = very severe)

[e]Data from the two vehicle arms in the study (twice and three times daily) were reported as combined data

[f]Mean between-group difference for LE vs vehicle

surgery [19]. The majority of ocular and non-ocular AEs were mild or moderate in severity; no severe AEs were reported [17–19]. Serious AEs were not observed in the loteprednol etabonate gel 0.38% group [17]. Five patients from the integrated safety population withdrew from the study primarily due to an AE [two patients (0.5%) from the loteprednol etabonate gel 0.38% group and three patients (0.8%) from the vehicle group]; none of these events were considered treatment-related [17].

Ocular AEs in the study eye occurred in 2.4% of loteprednol etabonate gel 0.38% recipients and 6.2% of vehicle recipients, and were most commonly eye pain (0.3% vs 2.2%), photophobia (0.8% vs 1.4%) and corneal oedema (0% vs 1.4%) [17]. Treatment-related ocular AEs (irrespective of rescue medication use) were reported in 0.8% of patients in the loteprednol etabonate gel 0.38% group (photophobia, cystoid macular oedema, eyelid oedema and instillation site pain) and in 2.7% of patients in the vehicle group (conjunctival hyperaemia, corneal oedema, eye pain, ocular discomfort, general pain and administration site conditions). Significantly fewer patients from the loteprednol etabonate gel 0.38% group had worsening of photophobia and tearing symptoms when compared with the vehicle group at all on-treatment post-operative visits (all $p < 0.02$). The majority of patients in the respective groups (77.3% vs 81.0%) did not experience discomfort in the study eye (drop sensation) at day 8. Moderate discomfort was reported in 3.2% of loteprednol etabonate gel 0.38% recipients and 2.1% of vehicle recipients (all were Study B vehicle recipients). One patient from the loteprednol etabonate gel 0.38% group in Study B experienced severe drop discomfort [17, 19]. Non-ocular AEs occurred in 2.4% of loteprednol etabonate gel 0.38% recipients and 1.4% of vehicle recipients; headache (0.8% vs 0.3%) and bronchitis (0.5% vs 0%) were the most common [17]. No non-ocular AEs were considered treatment-related [17, 18].

Fewer loteprednol etabonate gel 0.38% recipients had worsening of various ocular signs on biomicroscopy compared with vehicle recipients at most visits, with the exception of worsening of AC cells and bulbar conjunctival injection at day 18 (both $p < 0.05$) [17]. Biomicroscopy did not show significant between-group differences with regards to external adnexa lids or lashes, hyphaema, posterior synechiae, precipitates, hypopyon or anterior vitreous haze [17]. Findings from fundoscopy performed at screening and day 15 were also comparable between the two groups, and abnormalities were not seen in most study eyes [17, 18].

A reduction in visual acuity of ≥ 3 lines by day 8 was seen in significantly ($p < 0.001$) fewer patients in the loteprednol etabonate gel 0.38% group relative to the vehicle group in

the integrated analysis (1.2% vs 5.9%) [17]. Between-group differences in visual acuity at the other time points were not statistically significant. Instillation of loteprednol etabonate gel 0.38% was not associated with blurred vision [17].

IOP at screening was similar in the loteprednol etabonate gel 0.38% and vehicle treatment arms (15.5 mmHg and 15.2 mmHg, respectively), and mean IOP decreased from baseline (post-operative day 1) in both groups at all subsequent post-operative visits [17]. One patient in the loteprednol etabonate gel 0.38% group in Study A experienced a clinically significant (defined as ≥ 10 mmHg) increase in IOP in the study eye [17, 18]. While treatment was discontinued in this patient, this AE was not considered to be serious or treatment-related and IOP had decreased to below screening level by day 8 [17].

5 Dosage and Administration of Loteprednol Etabonate Gel 0.38%

Loteprednol etabonate ophthalmic gel 0.38% is approved in the USA for the treatment of post-operative inflammation and pain following ocular surgery [6]. The recommended dosage is one drop of loteprednol etabonate gel instilled into the conjunctival sac of the affected eye three times daily, beginning the day after surgery and continuing throughout the first 2 weeks of the post-operative period. The bottle containing loteprednol etabonate gel should be inverted and shaken once to fill the tip before instillation [6].

The safety and efficacy of loteprednol etabonate gel 0.38% in paediatric patients have not been established [6]. As with other ophthalmic corticosteroids, loteprednol etabonate gel 0.38% is contraindicated in most viral diseases of the cornea and conjunctiva, including epithelial herpes simplex keratitis (dendritic keratitis), vaccinia and varicella, and also in mycobacterial infection of the eye and fungal diseases of ocular structures. Loteprednol etabonate gel 0.38% should be used with caution in patients with glaucoma; IOP should be monitored if the drug is used for more than 10 days [6].

Local prescribing information should be consulted for detailed information on loteprednol etabonate gel 0.38% regarding use in specific populations and other warnings and precautions.

6 Current Status of Loteprednol Etabonate Gel 0.38% in Post-operative Inflammation and Pain Following Ocular Surgery

Drug particle size reduction is a common method of improving drug delivery and exposure [8], and reducing the particle size to the submicron range (median ranging between 0.4 and 0.6 μm) has provided distinct advantages for loteprednol etabonate gel 0.38% over the loteprednol etabonate gel 0.5% formulation (median particle size ranging between 3 and 5 μm) (Sect. 3). The reduction in overall drug exposure with the submicron gel formulation (from lowering the loteprednol etabonate concentration and dosing frequency) can potentially reduce the risk of AEs further and ultimately yield a better safety and tolerability profile, while the less frequent dosage regimen can improve patient convenience and compliance [3, 15]. A comparative trial of loteprednol etabonate gel 0.38% and the 0.5% gel examining the potential for improved tolerability would be of high interest.

Loteprednol etabonate gel 0.38% has very similar rheological and viscoelastic properties to loteprednol etabonate gel 0.5% (Sect. 2) and the same concentration of the preservative benzalkonium chloride per dose (lowest amongst the loteprednol etabonate formulations) [6, 12–14]. Exposure to this preservative is reduced in patients receiving loteprednol etabonate gel 0.38% given the less frequent administration regimen, which could be beneficial for the patient as, among other toxic effects, benzalkonium chloride can cause damage to both surface and deeper ocular tissues [20]. The 1% suspension formulation of loteprednol etabonate (Inveltys®) utilises proprietary mucus-penetrating particle technology to enable twice daily dosing [14]. However, the 1% suspension has over three times more preservative (benzalkonium chloride) content than loteprednol etabonate gel 0.38% in addition to a higher concentration of active drug, which may impact treatment tolerability [6, 14].

Approval for loteprednol etabonate gel 0.38% was based on the results of two phase III vehicle-controlled studies demonstrating its efficacy and tolerability in patients with post-operative inflammation and pain following cataract surgery (Sects. 3, 4). Loteprednol etabonate gel 0.38% was more effective in resolving ocular inflammation and pain following cataract surgery than vehicle (Sect. 3) and was well tolerated (Sect. 4). The incidence of treatment-related ocular AEs were low (< 1% of patients) and these AEs likely resulted from the cataract surgery itself [17]. Loteprednol etabonate gel 0.38% recipients did not experience the same treatment-related ocular AEs as vehicle recipients (Sect. 4). Drop discomfort and blurred vision were not significant issues associated with gel instillation and effects on ocular signs were unremarkable and comparable between treatment groups. However, eligibility criteria for the two phase III trials were quite strict [17], which may limit the generalisability of the results in a real-world clinical setting in which many patients have complicated surgical requirements and/or multiple comorbidities or medications. Additionally, the use of loteprednol etabonate gel 0.38% following ocular surgeries other than cataract surgery has not been investigated.

A key issue associated with the use of ophthalmic corticosteroids, especially earlier formulations such as

prednisone and difluprednate, is the potential for elevated IOP [5]. Uncontrolled elevated IOP can cause damage to the optic nerve, leading to glaucoma and other AEs [18], and this risk is often a deciding factor for the choice of corticosteroid to use post-surgery [3, 5]. Loteprednol etabonate was designed to have minimal impact on IOP and marketed formulations of loteprednol etabonate have consistently shown favourable safety profiles in maintaining or reducing mean IOP irrespective of formulation, dosage or treatment duration [3, 21]. IOP changes were also minimal with loteprednol etabonate in known steroid responders [5]. Comparisons of loteprednol etabonate gel 0.5% with other steroids and NSAIDs have been summarized in previous reviews [9, 21]. Such comparisons are currently not available for the submicron 0.38% gel; however, results from the phase III trials indicate that this formulation will not result in clinically meaningful changes in IOP (Sect. 4). As with other ophthalmic corticosteroids, the US prescribing information does warn to monitor for IOP changes when loteprednol etabonate gel 0.38% is used for more than 10 days (approved treatment duration is 14 days) (Sect. 5) [6].

Ophthalmic steroid use is also associated with several other warnings including delayed healing, infections and cataract formation [6, 21]. The relative risk of posterior subcapsular cataract formation with loteprednol etabonate gel 0.38% use is unknown, though may be reduced by the comparatively short treatment duration [6]. Further investigation of these potential risks with loteprednol etabonate gel 0.38% treatment may be warranted.

Though the different ophthalmic formulations of loteprednol etabonate (0.38% and 0.5% gel [6, 11]; 0.5% ointment [13]; 0.5% and 1% suspension [12, 14]) are effective and well tolerated in the treatment of post-operative pain and inflammation, there are no direct head-to-head comparisons between these formulations, nor for loteprednol etabonate gel 0.38% against other drugs used in this indication (e.g. difluprednate 0.05%). The American Academy of Ophthalmology Preferred Practice Pattern [22] on cataract management recommends topical ophthalmic corticosteroids and NSAIDs for the post-operative management of inflammation and pain; however there is currently no consensus on an optimal step-wise treatment regimen [3, 22]. As such, treatment must be patient-specific and based upon the preference and experience of the surgeon [3, 22]. Clinical trials evaluating the efficacy and tolerability of loteprednol etabonate gel 0.38% against other steroids and NSAIDs used post-operatively may be useful. Pharmacoeconomic assessments of the cost-effectiveness of drugs used in the management of pain and inflammation following ocular surgery will also help determine the place of loteprednol etabonate gel 0.38% in this setting.

In conclusion, loteprednol etabonate ophthalmic gel 0.38% is an effective and well tolerated treatment which requires less frequent dosing, extending the options available for patients with post-operative inflammation and pain following ocular surgery.

Data Selection Loteprednol Etabonate Gel 0.38%: 39 records identified

Duplicates removed	2
Excluded during initial screening (e.g. press releases; news reports; not relevant drug/indication; preclinical study; reviews; case reports; not randomized trial)	2
Excluded during writing (e.g. reviews; duplicate data; small patient number; nonrandomized/phase I/II trials)	13
Cited efficacy/tolerability articles	3
Cited articles not efficacy/tolerability	19

Search Strategy: EMBASE, MEDLINE and PubMed from 1946 to present. Clinical trial registries/databases and websites were also searched for relevant data. Key words were loteprednol, LOTEMAX, cataract surgery. Records were limited to those in English language. Searches last updated 17 Feb 2020.

Acknowledgements During the peer review process the manufacturer of loteprednol etabonate gel 0.38% was also offered an opportunity to review this article. Changes resulting from comments received were made on the basis of scientific and editorial merit.

Compliance with Ethical Standards

Funding The preparation of this review was not supported by any external funding.

Conflicts of interest Connie Kang, Susan J. Keam, Matt Shirley and Yahiya Y. Syed are salaried employees of Adis International Ltd/Springer Nature, are responsible for the article content and declare no relevant conflicts of interest.

References

1. Kessel L, Tendal B, Jorgensen 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):1915–24.
2. El-Harazi SM, Feldman RM. Control of intra-ocular inflammation associated with cataract surgery. Curr Opin Ophthalmol. 2001;12(1):4–8.
3. Salinger CL, Gaynes BI, Rajpal RK. Innovations in topical ocular corticosteroid therapy for the management of postoperative ocular inflammation and pain. Am J Manag Care. 2019;25:215–26.
4. Malik A, Sadafale A, Gupta YK, et al. A comparative study of various topical nonsteroidal anti-inflammatory drugs to steroid drops for control of post cataract surgery inflammation. Oman J Ophthalmol. 2016;9(3):150–6.
5. 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;2:55–72.
6. Bausch & Lomb Incorporated. LOTEMAX SM (loteprednol etabonate ophthalmic gel) 0.38%, for topical ophthalmic use: US prescribing information. 2019. https://www.fda.gov. Accessed 17 Feb 2020.
7. McGhee CNJ, Dean S, Danesh-Meyer H. Locally administered ocular corticosteroids. Drug Saf. 2002;25(1):33–55.
8. Shen J, Lu GW, Hughes P. Targeted ocular drug delivery with pharmacokinetic/pharmacodynamic considerations. Pharm Res. 2018;35(11):217.
9. Lyseng-Williamson KA. Loteprednol etabonate ophthalmic gel 0.5%: a review of its use in post-operative inflammation and pain following ocular surgery. Drugs. 2013;73(9):949–58.
10. 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.
11. Bausch & Lomb Incorporated. LOTEMAX (loteprednol etabonate ophthalmic gel) 0.5%, for topical ophthalmic use: US prescribing information. 2018. https://www.fda.gov. Accessed 17 Feb 2020.
12. Bausch & Lomb Incorporated. LOTEMAX (loteprednol etabonate ophthalmic suspension) 0.5%, for topical ophthalmic use: US prescribing information. 1998. https://www.fda.gov. Accessed 17 Feb 2020.
13. Bausch & Lomb Incorporated. LOTEMAX (loteprednol etabonate ophthalmic ointment) 0.5%, for topical ophthalmic use: US prescribing information. 2011. https://www.fda.gov. Accessed 17 Feb 2020.
14. Kala Pharmaceuticals Inc. INVELTYS (loteprednol etabonate ophthalmic suspension) 1%, for topical ophthalmic use: US prescribing information. 2018. https://www.fda.gov. Accessed 17 Feb 2020.
15. Cavet ME, Glogowski S, Lowe ER, et al. Rheological properties, dissolution kinetics, and ocular pharmacokinetics of loteprednol etabonate (submicron) ophthalmic gel 0.38%. J Ocul Pharmacol Ther. 2019;35(5):291–300.
16. 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):337–53.
17. Fong R, Cavet ME, DeCory H, et al. Loteprednol etabonate (submicron) ophthalmic gel 0.38% dosed three times daily following cataract surgery: integrated analysis of two phase III clinical studies. Clin Ophthalmol. 2019;13:1427–38.
18. Fong R, Silverstein BE, Peace JH, et al. Submicron loteprednol etabonate ophthalmic gel 0.38% for the treatment of inflammation and pain after cataract surgery. J Cataract Refract Surg. 2018;44(10):1220–9.
19. 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 [abstract no. 2235 plus poster]. Invest Ophthalmol Vis Sci. 2018;59:9.
20. Datta S, Baudouin C, Brignole-Baudouin F, et al. The eye drop preservative benzalkonium chloride potently induces mitochondrial dysfunction and preferentially affects LHON mutant cells. Invest Ophthalmol Vis Sci. 2017;58:2406–12.
21. Sheppard JD, Comstock TL, Cavet ME. Impact of the topical ophthalmic corticosteroid loteprednol etabonate on intraocular pressure. Adv Ther. 2016;33:532–52.
22. Olson RJ, Braga-Mele R, Chen SH, et al. Cataract in the adult eye Preferred Practice Pattern®. Ophthalmology. 2017;124(4):1–119.