



# Dose Uniformity of Loteprednol Etabonate (Submicron) Ophthalmic Gel 0.38% Compared with Prednisolone Acetate Ophthalmic Suspension 1%

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Received: October 18, 2021 / Accepted: December 6, 2021 / Published online: December 17, 2021  
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## ABSTRACT

**Introduction:** Loteprednol etabonate (submicron) ophthalmic gel 0.38% (LE SM gel 0.38%) is a corticosteroid formulation designed to retain the nonsettling characteristics of loteprednol etabonate ophthalmic gel 0.5%, but with reduced drug particle size to improve ocular penetration, allowing for reduced dosing frequency. This study compared the dose uniformity of LE SM gel 0.38% with branded and generic prednisolone acetate (PA) 1% suspensions under simulated in-use dosing conditions.

**Methods:** Drug concentrations in drops of LE SM gel 0.38% and PA 1% suspensions, expressed from bottles that were shaken or not shaken, were determined during 2 weeks of simulated on-label dosing (LE SM gel 0.38%: three times daily; PA suspensions: four times daily). Sedimentation of drug particles was assessed for each product using dispersion analysis.

**Results:** The mean (SD) percent declared drug concentration of LE SM gel 0.38% over 2 weeks was 103.2% (1.3%) when the drug was dispensed from shaken bottles and 103.3% (1.5%)

when dispensed from unshaken bottles. However, for branded and generic PA suspensions, mean (SD) percent declared concentrations were 102.2% (1.4%) and 98.3% (2.9%), respectively, when dispensed from shaken bottles; and 89.2% (18.6%) and 78.3% (13.5%), respectively, when dispensed from unshaken bottles. Dispersion analysis showed that drug particles in LE SM gel 0.38% remained fully suspended under accelerated sedimentation conditions, whereas both branded and generic PA suspension drug particles settled out of suspension.

**Conclusions:** LE SM gel 0.38% delivered the drug consistently at the declared concentration over the entire 2 weeks of simulated in-use dosing conditions, regardless of whether the drug was dispensed from shaken or unshaken bottles. However, both branded and generic PA suspensions required the bottle to be shaken to provide a consistent drug concentration.

**Keywords:** Dose uniformity; Gel; Loteprednol etabonate; Nonsettling; Ophthalmic formulation; Prednisolone acetate; Simulated dosing; Suspension

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### Key Summary Points

Dose uniformity can be inconsistent with ophthalmic suspensions, as drug particles may settle over time and patients often fail to adequately shake the bottle prior to drop instillation.

Loteprednol etabonate (submicron) ophthalmic gel 0.38% (LE SM gel 0.38%) is indicated for the treatment of inflammation and pain following ocular surgery.

LE SM gel 0.38% was designed to retain the nonsettling characteristics of loteprednol etabonate ophthalmic gel 0.5% (LE gel 0.5%), but with reduced drug particle size to improve ocular penetration, allowing for reduced drug concentration and dosing frequency.

This study evaluated the dose uniformity of dispensed drops of LE SM gel 0.38% compared with branded and generic prednisolone acetate 1% suspensions under simulated in-use dosing conditions.

LE SM gel 0.38% retains the nonsettling properties of the LE gel 0.5% formulation, thereby providing uniform dosing and consistent effectiveness over the entire 2-week dosing regimen.

## INTRODUCTION

Topical ocular corticosteroids are considered the standard of care for postoperative inflammation and pain after ocular surgery [1, 2]. However, barriers to the optimal use of topical ocular corticosteroids exist, including potential adverse events, factors related to patient convenience (e.g., dosing frequency), and formulation-related challenges with drug delivery [1]. With respect to drug delivery, ophthalmic suspensions have the drawback that drug particles may settle over time and patients often fail to

adequately shake the bottle prior to instillation, resulting in inconsistencies in the uniformity of dispensed doses [1, 3, 4]. This may lead to the delivery of lower doses of drug initially and higher doses of drug later in treatment, which may compromise efficacy (by delivering inadequate doses early in treatment) and safety (as higher doses increase the potential for adverse ocular effects) [3].

Loteprednol etabonate (submicron) ophthalmic gel 0.38% (LE SM gel 0.38%; Lotemax<sup>®</sup> SM; Bausch + Lomb, Rochester, NY, USA), a next-generation corticosteroid formulation with reduced drug particle size and improved ocular penetration compared with loteprednol etabonate ophthalmic gel 0.5% (LE gel 0.5%; Lotemax<sup>®</sup>; Bausch + Lomb, Rochester, NY, USA), is indicated for the treatment of inflammation and pain following ocular surgery [1, 5–7]. The reduced drug particle size of LE SM gel 0.38% compared with LE gel 0.5% improves ocular penetration and enables a reduction in drug concentration and dosing frequency [1, 6].

Loteprednol etabonate, a C-20 ester-based ophthalmic corticosteroid, was retrometabolically designed to minimize the risk of adverse events while maintaining potency [1]. Loteprednol etabonate was first developed as a 0.5% suspension (0.5% and 1%), ointment (0.5%), and gel (0.5% and 0.38%) formulations [1]. The two gel formulations have a pH between 6 and 7, close to that of physiological tears; contain glycerin and propylene glycol, which have moisture retention properties; and contain a low concentration of the preservative benzalkonium chloride (0.003%), all of which may improve patient comfort upon instillation [1, 5, 8]. In addition, the polycarboxophil polymer-based gel formulations of LE gel 0.5% and LE SM gel 0.38% are semisolid at rest, which prevents settling of drug particles, alleviates the need for shaking prior to dose instillation (only one shake is required to stage the dropper tip), and should allow consistent dosing [3, 6, 9, 10]. This is in contrast to suspension formulations, which require vigorous shaking to resuspend drug particles prior to instillation [1, 11]. This study compared the dose uniformity of LE SM gel 0.38% to that of two prednisolone acetate

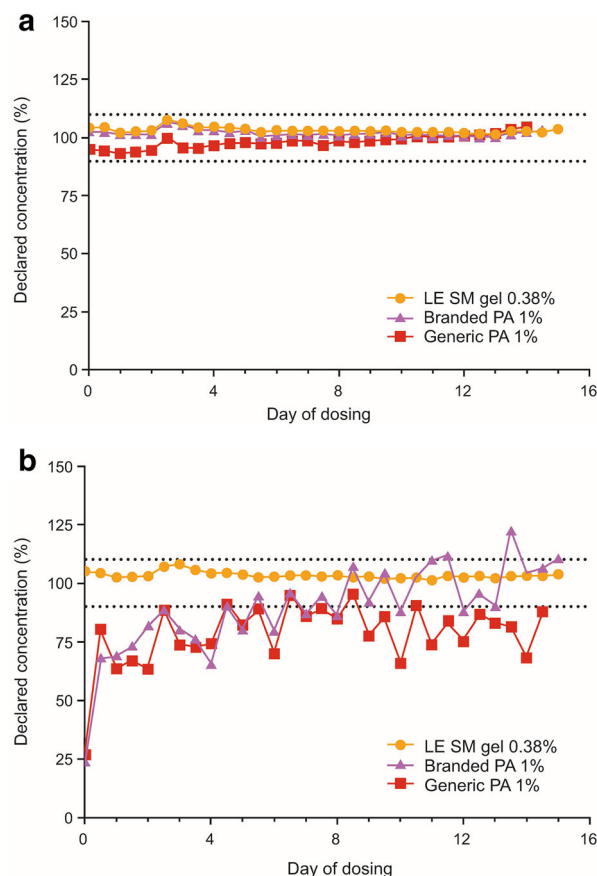
(1%) suspension products (branded and generic) under simulated in-use dosing conditions.

## METHODS

Commercially available lots of LE SM gel 0.38%, branded prednisolone acetate suspension 1% (Pred Forte®; Allergan, Madison NJ, USA), and generic prednisolone acetate suspension 1% (Pacific Pharma, Inc., Irvine, CA, USA) were evaluated in this study. For the dose uniformity analysis, two 5 mL bottles of these formulations were stored upright for 7 days prior to the start of the study. One bottle of each of these products (the same bottle each time) was shaken for 5 s immediately prior to drop expression, while the second set of bottles remained unshaken throughout the study. To simulate the dosing of the products, two drops were expressed from each bottle for 2 weeks, with dispensing time points following the product label recommendations [5, 11, 12]: LE SM gel 0.38% was dispensed three times a day (7 a.m., 12 p.m., and 10 p.m.;  $\pm 1$  h) and prednisolone acetate suspensions 1% were dispensed four times a day (7 a.m., 12 p.m., 5 p.m., and 10 p.m.;  $\pm 1$  h). The same analyst shook the designated bottles throughout the study to avoid introducing variability due to individual differences in shaking. The first and last daily dispensed drops were diluted (LE SM gel 0.38% samples were also filtered), and drug concentrations were determined using reverse-phase high-performance liquid chromatography (HPLC), as previously described [3]. OpenLab CDS software Rev C.01.07 SR4 (505) (Agilent Technologies, Inc., Santa Clara, CA, USA) was used to manually integrate the peak area counts for drug concentration analysis. All samples analyzed fell within the calibration curve. Sample drug concentrations were reported as the mean percent of the declared (labeled) concentration  $\pm$  standard deviation (SD).

To assess the rate of sedimentation, dispersion analysis was conducted for each product using a dispersion/stability analyzer (LUMiSizer, Model LS 611; LUM GmbH, Berlin, Germany), as previously described [3]. Commercial bottles of the products were shaken for 5 s prior to

transferring 0.4 mL samples to LUMiSizer cells, which were then centrifuged at 1000 rpm ( $\sim 120\times g$ ) for 24 h. Sedimentation rate plots were obtained using the integration (clarification) module of the LUMiSizer, which calculated the integral of the percent of transmittance raw data at each time point over 24 h. To document sedimentation, photographs were taken of the cells containing the samples immediately before and after centrifugation using an independent camera



**Fig. 1** Dose uniformity of LE SM gel 0.38% versus prednisolone acetate suspension 1% (branded and generic). Percent of declared drug concentration for the first and last daily dispensed drops over 2 weeks of simulated dosing is shown for bottles with (a) or without (b) shaking immediately prior to dispensing. Dotted lines indicate the range within 10% of the declared concentration (i.e., 90% to 110%). LE loteprednol etabonate, PA prednisolone acetate, SM submicron

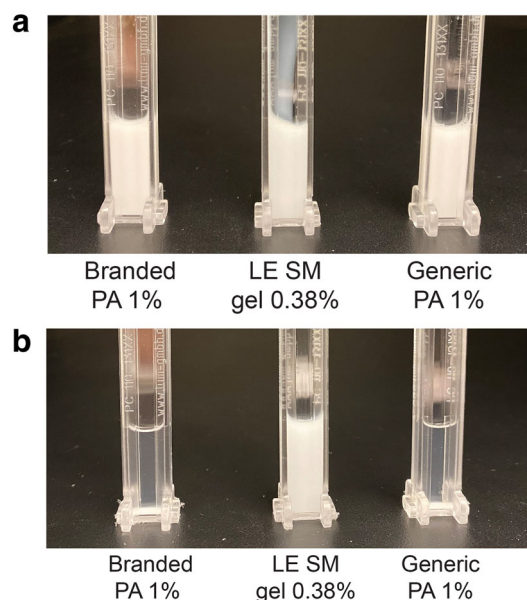
(Apple iPhone 11<sup>®</sup>, Apple Inc., Cupertino, CA, USA).

This study did not involve any human participants (or human tissue) or animal subjects.

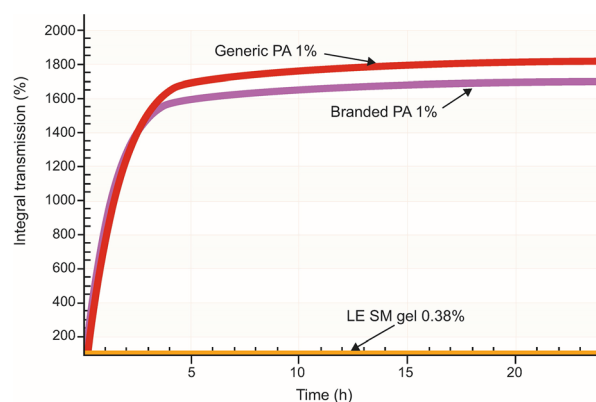
## RESULTS

Dispensed drops of LE SM gel 0.38% showed consistent on-target drug concentrations (i.e., within 90–110% of the declared, labeled concentration) at all measurement time points for the entire 2-week study period, independent of whether the bottles were shaken or not shaken (Fig. 1). The mean [SD] percent declared drug concentration of the LE SM gel 0.38% over the 2 weeks was similar whether the drug was dispensed from shaken or unshaken bottles (103.2% [1.3%] and 103.3% [1.5%], respectively). In contrast, dispensed drops of branded and generic suspensions of prednisolone acetate showed consistent on-target drug concentrations at all time points only when expressed from shaken bottles. Drug concentrations in drops of branded and generic formulations of prednisolone acetate suspension were highly variable when dispensed from bottles that were not shaken, reaching target concentrations at only a minority of the time points. The mean (SD) percent declared drug concentrations for the prednisolone acetate suspensions over the 2 weeks were on-target for drops expressed from shaken bottles (102.2% [1.4%] and 98.3% [2.9%], for branded and generic suspensions, respectively), but not for drops from bottles that were not shaken (89.2% [18.6%] and 78.3% [13.5%], respectively). Further, dispensed concentrations of prednisolone acetate suspensions were lowest at the start of the study. At the first time point, expressed drops of the prednisolone acetate suspensions were approximately 25% of the declared concentration, with no drops reaching the on-target range until day 4.

All three formulations appeared opaque, indicating well-dispersed drug particles prior to centrifugation for sedimentation analysis (Fig. 2). After centrifugation at approximately 120×*g* for 24 h, the sample of LE SM gel 0.38% remained opaque (i.e., drug particles were still well suspended). In contrast, samples of the



**Fig. 2** Sedimentation of LE SM gel 0.38% versus prednisolone acetate suspension 1% (branded and generic). Images are photographs of LE SM gel 0.38% and prednisolone acetate suspension 1% (branded and generic) before (a) and after (b) centrifugation at 1000 rpm ( $\sim 120\times g$ ) for 24 h. *LE* loteprednol etabonate, *PA* prednisolone acetate, *SM* submicron



**Fig. 3** Kinetics of sedimentation of LE SM gel 0.38% versus prednisolone acetate suspension 1% (branded and generic) at 1000 rpm ( $\sim 120\times g$ ) for 24 h. The percent integral transmission area under the curve as a function of time of centrifugation is plotted. *LE* loteprednol etabonate, *PA* prednisolone acetate, *SM* submicron



branded and generic formulations of prednisolone acetate suspension became translucent after centrifugation, and drug particles were observed to have settled out of suspension. Further, there was no indication of sedimentation of the LE SM gel 0.38% over the entire 24 h of centrifugation, as demonstrated by transmission analysis of sedimentation over time (Fig. 3). Conversely, samples of branded and generic prednisolone suspension rapidly sedimented over the course of the first 4–5 h of centrifugation, as indicated by increasing transmission during that time.

## DISCUSSION

The safety and efficacy of LE SM gel 0.38% in treating inflammation and pain following cataract surgery was demonstrated in two randomized, multicenter, double-masked, vehicle-controlled studies [13–15]. In the present study, dispensed drops of LE SM gel 0.38% showed consistent on-target drug concentrations for the entire 2-week study period, irrespective of whether the bottles were shaken or not. However, the branded and generic prednisolone suspensions required the bottle to be shaken to provide on-target drug concentrations. These findings were consistent with those observed with LE gel 0.5% in a similar study, confirming that the LE SM gel 0.38% formulation retains the dose uniformity and nonsettling properties of the LE gel 0.5% formulation [3].

Both the LE gel 0.5% and LE SM gel 0.38% formulations have similar rheological properties with nearly identical shear-thinning behavior and decreased viscosity on dilution with saline; however, the LE SM gel 0.38% formulation has a reduced drug particle size (an approximately five- to tenfold reduction in diameter), which results in improved drug dissolution, leading to enhanced ocular penetration and bioavailability in the anterior segment tissues most relevant to postsurgery inflammation [6, 7]. The reduced particle size in the LE SM gel 0.38% formulation allows for reductions in the active drug concentration and dosing frequency compared with the LE gel 0.5% formulation (three times daily vs. four times daily,

respectively) [7]. Although particle size is reduced in the LE SM gel 0.38% relative to the LE gel 0.5%, both formulations have similar nonsettling properties [7]. Furthermore, modifications made to the excipients in the LE SM gel 0.38% formulation to stabilize the drug particles (e.g., hypromellose) [1, 6] do not appear to affect the nonsettling characteristics of this formulation.

Despite clear instructions in the product label, compliance with dosing instructions (i.e., shaking the bottle adequately prior to instillation) is a major source of variability in dosing with ophthalmic suspensions [4]. Furthermore, dosing frequency has been identified as a barrier to adherence to eye drop regimens [1]. Most topical ocular corticosteroid formulations (including prednisolone acetate 1% suspension and LE gel 0.5%) require frequent (four times daily) dosing to achieve therapeutic levels of the active drug [1, 8, 11]. LE SM gel 0.38% allows for less frequent (three times daily) administration and, due to its nonsettling properties, requires only one shake (to load the dropper tip); thus, it is expected to improve patient convenience and potentially increase adherence [7].

The present study clearly demonstrates that for optimal and on-target dosing of branded and generic prednisolone acetate 1% suspensions, thorough shaking is required, particularly at the beginning of therapy, whereas shaking is not needed with LE SM gel 0.38% to resuspend the drug. Our *in vitro* study does not evaluate the possible impact of reduced delivery of prednisolone acetate with regard to efficacy. While there are no clinical studies comparing the efficacy of LE SM gel 0.38% with prednisolone acetate 1% suspensions, studies comparing LE gel 0.5% and prednisolone acetate 1% suspension demonstrated that the two corticosteroid products resulted in similar anti-inflammatory efficacy following ocular surgery [16–18]. However, clinical studies are performed under controlled conditions, and the patients in such studies are instructed and monitored on appropriate dosing and administration of the drugs. Thus, clinical trials are not expected to reflect real-world patient administration behaviors, and, in practice, patients may not always comply with dosing instructions [1, 4].

## CONCLUSION

LE SM gel 0.38% retains the nonsettling properties of the previous LE gel 0.5% formulation, thereby providing uniform dosing to allow for consistent effectiveness over the entire 2-week dosing regimen used in the treatment of inflammation and pain following ocular surgery.

## ACKNOWLEDGEMENTS

**Funding.** This study was funded by Bausch + Lomb (a division of Bausch Health US, LLC). The study sponsor also funded the journal's Rapid Service Fee.

**Medical Writing and Editorial Assistance.** Technical editorial and medical writing assistance was provided under the direction of the authors by Patricia A. Zipfel, PhD, and Pratibha Hebbar, PhD, Synchrony Medical Communications, LLC, West Chester, PA, USA, and funded by Bausch + Lomb (a division of Bausch Health US, LLC).

**Prior Presentation.** A portion of this work was previously presented at The Association for Research in Vision and Ophthalmology Annual Meeting, May 1–7, 2021 (virtual).

**Authorship.** All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article, take responsibility for the integrity of the work as a whole, and have given their approval for this version to be published.

**Author Contributions.** All authors contributed to the study conception and design. Material preparation, data collection, and analysis were performed by ZTM and MJC. The first draft of the manuscript was prepared by MEC and all authors reviewed and edited subsequent manuscript drafts. All authors read and approved the final manuscript.

**Disclosures.** Zora T. Marlowe is an employee of Bausch + Lomb (a division of Bausch Health US, LLC). Megan E. Cavet is an employee of Bausch + Lomb (a division of Bausch Health US, LLC). Martin J. Coffey is an employee of Bausch + Lomb (a division of Bausch Health US, LLC).

**Compliance with Ethics Guidelines.** This study did not involve any human participants (or human tissue) or animal subjects.

**Data Availability.** All data generated or analyzed during this study are included in this published article.

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