Australian Government
Department of Health
Therapeutic Goods Administration

AusPAR Attachment 2

Extract from the Clinical Evaluation Report for loteprednol etabonate 0.5%

Proprietary Product Name: Lotemax

Sponsor: Bausch & Lomb Australia Pty Ltd

Date of first round CER: 5 April 2013

Date of second round CER: 28 August 2013

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health, and is responsible for for regulating medicines and medical devices.
- The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance), when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary for regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website < http://www.tga.gov.au>.

About the Extract from the Clinical Evaluation Report

- This document provides a more detailed evaluation of the clinical findings, extracted from the Clinical Evaluation Report (CER) prepared by the TGA. This extract does not include sections from the CER regarding product documentation or post market activities.
- The words [Information redacted], where they appear in this document, indicate that confidential information has been deleted.
- For the most recent Product Information (PI), please refer to the TGA website < http://www.tga.gov.au/hp/information-medicines-pi.htm>.

Contents

List of abbreviations

Abbreviation	Meaning
AAU	Acute anterior uveitis
ACI	Anterior chamber inflammation
ACR	Anterior chamber reaction (score total of cells plus flare)
AE	Adverse event
AH	Aqueous humor
Alrex	Loteprednol etabonate ophthalmic suspension, 0.2%
AUC	Area under the curve
BCI	Bulbar conjunctival injection
BID	Twice per day
CI	Confidence interval
CMH	Cochran-Mantel-Haenzel
CPT	Conjunctival provocation test
FBS	Foreign body sensation
GPC	Giant papillary conjunctivitis
IGA	Investigator global assessment
IND	Investigational New Drug
IOL	Intraocular lens
IOP	Intraocular pressure
ITT	Intent to treat
KP	Keratic precipitates
LE	Loteprednol etabonate
LOCF	Last observation carried forward
Lotemax	Loteprednol etabonate ophthalmic suspension, 0.5%
mg	Milligram (0.001 gram)
mm Hg	Millimeters of mercury
mL	Milliliter (0.001 liter)
ng	Nanogram (10^{-9} gram)
NOAEL	No observed adverse effect level
NSAID	Nonsteroidal anti-inflammatory drug
P-5604	Loteprednol etabonate
PA	Prednisolone acetate (1.0%)
PJ-90	Δ1-Cortienic acid (an inactive metabolite of LE)
PJ-91	Δ1-Cortienic acid etabonate (an inactive metabolite of LE)
PK	Pharmacokinetic
QD	One time per day
QID	Four times per day
SAE	Serious adverse event
SAC	Seasonal allergic conjunctivitis
UK	United Kingdom
µM	Micromolar (10^{-6} molar concentration)
VA	Visual acuity
Zylet	Loteprednol etabonate 0.5% and tobramycin 0.3% ophthalmic suspension

1. Introduction

The submission proposes registration of the Lotemax 0.5% Ophthalmic Suspension. Each mL of Lotemax contains 5 mg of loteprednol etabonate. Lotemax 0.5% Ophthalmic Suspension is supplied as a sterile suspension in a white low density polyethylene (LDPE) bottle with a controlled dropper tip and polypropylene cap. Tamper evidence is provided with a shrink band around the cap and neck area of the bottle. Lotemax 0.5% Ophthalmic Suspension is available in the following pack sizes: 2.5 ml, 5 ml, 10 ml and 15 ml.

2. Clinical rationale

Loteprednol etabonate (LE) has been developed by Bausch & Lomb as a family of three products which are approved in various countries worldwide. These are:

- Loteprednol etabonate 0.5% ophthalmic suspension (Lotemax)
- Loteprednol etabonate 0.2% ophthalmic suspension (Alrex)
- Loteprednol etabonate 0.5% and tobramycin 0.3% in an ophthalmic suspension (Zylet)

The current application to TGA is to register the first product of the Loteprednol etabonate family, Lotemax 0.5% Ophthalmic Suspension.

Loteprednol etabonate is a corticosteroid, an analog of prednisolone which was developed for use in ocular inflammatory conditions. Concerns about potential ocular toxicities associated with conventional steroids prompted a quest by Bausch and Lomb for new and safer glucocorticoids that could be used in the management of ocular inflammatory conditions.

While structurally similar to other corticosteroids, Loteprednol etabonate replaces the number 20 position ketone with an ester group. This structural modification sets Loteprednol etabonate apart from other corticosteroids by virtue of its metabolism. After performing its therapeutic effect, LE is inactivated rapidly by circulating esterases to PJ-91 (Δ1-cortienic acid etabonate) and subsequently to PJ-90 (Δ1-cortienic acid), both of these being inactive metabolites. Inactivation of LE takes place at the site of application, before the substance reaches the general circulation. In this way Loteprednol etabonate can achieve its therapeutic effects whilst minimizing the extent of unwanted side effects.

Topical corticosteroids marketed currently (for example Prednisolone, dexamethasone, et cetera) are associated with side effects such as increased intra-ocular pressure, cataract formation after long term use, decreased resistance to infection, and delayed wound healing. Results from multiple studies with Lotemax have demonstrated that treatment is associated with lower propensity for elevations in IOP compared to other steroids. Studies have proven that Lotemax has less IOP elevating effects than prednisolone acetate 1% eye drops in known steroid responders. However, if Lotemax is used for more than 10 days, IOP should be monitored as a precautionary measure.

3. Contents of the clinical dossier

3.1. Scope of the clinical dossier

The submission contained the following clinical information:

- 3 initial tolerability studies (HGP-ss-101; P-5604-102 and P-5604-104).

- 4 clinical pharmacology studies, including 4 that provided pharmacokinetic data (studies P-5604-112; P-5604-120; 358-005; 358-006) and none provided pharmacodynamic data.
- Pivotal efficacy/safety studies including 2 studies in post-cataract inflammation (125 and 127), 1 study in SAC (121), 2 studies in GPC (107 and 108) and 2 studies in AAU (122/1221 and 126).
- No dose-finding studies.
- Other efficacy/safety studies using proposed LE 0.5% (Lotemax) included 1 pilot study in SAC (114), 1 pilot study in GPC (106) and one study in AAC (141). There were 3 other studies which evaluated safety/ efficacy of LE 0.2% (Alrex) in treatment of SAC (studies 141 and 144) and 1 study in AAC (145).
- There were no pooled analyses, meta-analyses.

3.2. Paediatric data

The submission did not include paediatric data for Lotemax. However, a study has been performed to evaluate the safety and efficacy of the combination product; Loteprednol etabonate 0.5%/ Tobramycin 0.3% ophthalmic suspension compared to Loteprednol etabonate 0.5%, Tobramycin Ophthalmic Solution USP, 0.3%, and the vehicle of the combination product in paediatric subjects aged 0 to 6 years, for the treatment of blepharoconjunctivitis in 137 patients. The results showed that loteprednol etabonate 0.5%/ tobramycin 0.3% ophthalmic suspension had a similar ocular safety profile to Lotemax, tobramycin and vehicle in the management of blepharoconjunctivitis in paediatric subjects.

However, this limited data does not justify removal of statement regarding lack of adequate data in the proposed PI and SmPC.

Lotemax and Alrex were submitted and approved in the US prior to April 1999 when these products were excluded from the requirements of conducting a paediatric evaluation. In EU, Lotemax was considered an 'old' product that did not require development of a paediatric investigation plan. However, a statement is required in the SmPC regarding no paediatric evaluation has been conducted.

4. Pharmacokinetics

4.1. Studies providing pharmacokinetic data

Table 1 shows the studies relating to each pharmacokinetic topic.

Table 1. Submitted pharmacokinetic studies.

PK topic	Subtopic	Study ID	*
PK in healthy adults	General PK - Single dose- ocular tolerability study - Multi-dose - Single dose- oral	HGPss-101 P5064-120 5064-112	
	Bioequivalence† - Single dose - Multi-dose	None	

	Food effect	None	
PK in special populations	Target population §- Single dose - Multi-dose	358-005	
		358-006	
	Hepatic impairment	None	
	Renal impairment	None	
	Neonates/infants/children/adolescents	None	
	Elderly	None	
	{Other special populations}	None	
Genetic/gender-related PK	Males versus females	None	
PK interactions	With tobramycin	358-006	
Population PK analyses	Healthy subjects	None	
	Target population	None	
	Other	None	

* Indicates the primary aim of the study. † Bioequivalence of different formulations. § Subjects who would be eligible to receive the drug if approved for the proposed indication.

None of the pharmacokinetic studies had deficiencies that excluded their results from consideration.

4.2. Analytical Methods

Quantitative and selective analysis of LE and PJ-91 concentrations in human AH and plasma was performed using HPLC assays coupled with mass spectrometric detection. These methods were assessed for precision and accuracy based on the accepted approach at the time the studies were conducted.

4.3. Summary of pharmacokinetics

The information in the following summary is derived from conventional pharmacokinetic studies unless otherwise stated.

The ocular and systemic pharmacokinetics (PK) of loteprednol etabonate (LE) have been evaluated in rats, rabbits, dogs, and humans in a variety of in vitro and in vivo studies. Results from the nonclinical evaluation of LE demonstrate that it is rapidly absorbed into ocular tissues with minimal (for example, < 1 ng/ mL) systemic exposure following topical ocular administration. The binding of LE to plasma proteins is approximately 95% in dog blood, and LE does not partition extensively into the cellular fraction of blood. To the extent that LE reaches the systemic circulation, it distributes into tissues, and is readily metabolized to two inactive metabolites, PJ-91 and PJ-90. Following systemic administration to rats, LE is eliminated

primarily via the biliary/fecal route, with most of the dose eliminated in the form of a metabolite, PJ-90.

The PK properties of Lotemax in humans have been evaluated following single oral administration and following single and repeated topical ocular administration. Studies were conducted by Xenon Vision (Study 112) and Pharmos (Study 120) to assess the systemic exposure to LE and PJ-91 following oral and topical ocular administration, respectively, to healthy volunteers. In addition, studies were conducted by Bausch & Lomb and Pharmos to assess the ocular penetration of LE, in the presence (Zylet) or absence (Lotemax) of tobramycin, in aqueous humor (AH) following topical ocular instillation to subjects undergoing routine cataract surgery (pilot Study 358-005 and Study 358-006).

Topical ocular administration of Lotemax eight times daily for two days and then four times daily (QID) for 41 days, resulted in concentrations of LE and PJ-91 in plasma that were below the lower limit of quantitation (LLOQ) at all collection times (that is, < 1 ng/ mL). Interestingly, systemic exposure to LE and PJ-91 following oral administration of LE (approximately 0.5 mg/kg) was also relatively low, with measurable plasma LE concentrations (that is, > 5 ng/mL) observed in only two subjects and measurable PJ-91 concentrations in only one subject.

Topical ocular administration of Lotemax resulted in measurable LE concentrations in AH within 20 minutes after dosing, and concentrations of approximately 3.7 ng/ mL were observed at one hour after dosing. When dosed as a fixed combination with tobramycin (0.3%, Zylet), LE levels in AH were generally similar, though not completely bioequivalent to the levels observed in the Lotemax treatment group.

Taken together, results from the clinical PK studies with Lotemax indicate that LE rapidly penetrates into ocular tissues, while systemic exposure to LE and PJ-91 is very low (for example, < 1 ng/ mL), even with QID dosing for 43 days.

4.3.1. Pharmacokinetics in healthy subjects

4.3.1.1. Absorption

4.3.1.1.1. Sites and mechanisms of absorption

Results from the nonclinical evaluation of LE demonstrate that it is rapidly absorbed into ocular tissues with minimal (for example, < 1 ng/ mL) systemic exposure following topical ocular administration.

Results from a bioavailability study (Study 50644-120,) in 14 healthy volunteers established that plasma levels of loteprednol etabonate and Δ1 cortienic acid etabonate (PJ-91), its primary, inactive metabolite, were below the limit of quantitation (1 ng/ mL) at all sampling times. The results were obtained following the ocular administration of one drop in each eye of 0.5% loteprednol etabonate eight times daily for 2 days or 4 times daily for 42 days. This study suggests limited (< 1 ng/ mL) systemic absorption with Lotemax. Topical ocular administration of Lotemax to human subjects resulted in measurable LE concentrations in aqueous humor (AH) within 20 minutes after dosing, and concentrations of approximately 3.7 ng/ mL were observed at one hour after dosing.

A Phase I tolerability study evaluated 4 concentrations of LE (0.005%, 0.05%, 0.1% and 0.5%) in 14 healthy subjects, but no PK results were provided in the study report and it appears that only safety parameters were evaluated and all concentrations of LE were well-tolerated.

4.3.1.2. Bioavailability

4.3.1.2.1. Absolute bioavailability

Not applicable.

4.3.1.2.2. Bioavailability relative to an oral solution or micronised suspension

After single oral administration of 40 mg (equivalent to 8 bottles of 5 mL of proposed suspension) to 6 healthy adult male volunteers, both LE and PJ-91 (expected metabolite) were detected at very low levels (0.5-14 ng/ mL) (Study 5604-112).

4.3.1.2.3. Bioequivalence of clinical trial and market formulations

The Phase I clinical studies were conducted with a developmental formulation. An early developmental formulation was utilized in two initial Phase I studies. The Phase II clinical studies were also conducted with a developmental formulation. Ophthalmic suspensions containing 0.1% and 0.5% LE were utilized (these were also used in toxicology studies). The Phase II formula was rejected for commercial development because after six months at room temperature, the gelatin suspending agent was found to be physically unstable. The formulation for the Phase III studies is the same as that proposed for marketing, except that the clinical trial formulation was produced with a 5% BAK overage and the proposed marketing formulation is produced with a 2% BAK overage.

> Comments: Bioequivalence between the Phase III clinical trial and the proposed marketing formulation was not evaluated. However, the only difference between the two formulations was that the Phase III CT formulation had 5% BAK overage while the proposed marketing formulation had 2% BAK overage. Since BAK (benzalkonium) is a preservative and not an active ingredient and the overage difference is within 5%, this difference is not likely to affect interpretation regarding efficacy and safety of proposed marketing formulation of Lotemax based on the Phase III studies.

4.3.1.2.4. Bioequivalence of different dosage forms and strengths

Not applicable.

4.3.1.2.5. Bioequivalence to relevant registered products

Not applicable.

4.3.1.2.6. Influence of food

Not applicable.

4.3.1.2.7. Dose proportionality

Clinical PK studies have been conducted to evaluate the ocular penetration of LE and the systemic exposure to LE and PJ-91 following topical administration of Lotemax; however, the clinical PK properties of LE have not been assessed with administration of LE concentrations other than 0.5%. Results from animal PK studies suggest that ocular exposure to LE increases with increasing dose levels in most tissues.

4.3.1.2.8. Bioavailability during multiple-dosing

A single study (Study 120) was conducted to assess potential differences in systemic exposure following single versus repeated topical ocular administration of LE ophthalmic suspension. The LE levels in this study were below the lower limit of quantitation (1 ng/ mL) at all collection times after the first and last dose of the study. Overall, while the results from this study do not exclude the possibility that systemic levels of LE are slightly higher after repeated administration, the data suggest that any accumulation, if present, does not result in meaningful systemic exposure to LE.

4.3.1.2.9. Effect of administration timing

Not applicable.

4.3.1.3. Distribution

4.3.1.3.1. Volume of distribution

Topical ocular administration of Lotemax in humans resulted in measurable loteprednol etabonate concentrations in aqueous humour within 20 minutes after dosing, and concentrations of approximately 3.7 ng/ mL were observed at one hour after dosing. Loteprednol etabonate is highly protein bound in plasma, and distributes preferentially into the cellular components of blood.

4.3.1.4. Plasma protein binding

The binding of LE to plasma proteins is approximately 95% in dog blood, and LE does not partition extensively into the cellular fraction of blood.

4.3.1.4.1. Tissue distribution

To the extent that LE reaches the systemic circulation, it distributes into tissues, and is readily metabolized to two inactive metabolites, PJ-91 and PJ-90.

4.3.1.5. Metabolism

4.3.1.5.1. Interconversion between enantiomers

Not applicable.

4.3.1.5.2. Sites of metabolism and mechanisms / enzyme systems involved

Systemic metabolism in humans likely occurs in the liver. To the extent that loteprednol etabonate reaches the systemic circulation, it distributes into tissues, and is readily metabolised to two inactive metabolites, PJ-90 (Δ1-cortienic acid) and PJ-91 (Δ1-cortienic acid etabonate).

4.3.1.5.3. Non-renal clearance

Following systemic administration to rats, LE is eliminated primarily via the biliary/fecal route, with most of the dose eliminated in the form of a metabolite, PJ-90.

4.3.1.5.4. Metabolites identified in humans

4.3.1.5.4.1. Active metabolites

None.

4.3.1.5.4.2. Other metabolites

Not applicable.

4.3.1.5.5. Pharmacokinetics of metabolites

Not detectable.

4.3.1.5.6. Consequences of genetic polymorphism

Not applicable.

4.3.1.6. Excretion

4.3.1.6.1. Routes and mechanisms of excretion

Following systemic administration to rats, loteprednol etabonate is eliminated primarily via the biliary/faecal route, with most of the dose eliminated in the form of the metabolite, PJ-90.

4.3.1.6.2. Mass balance studies

No mass balance studies were conducted in humans.

4.3.1.6.3. Renal clearance

Not applicable.

4.3.1.7. Intra- and inter-individual variability of pharmacokinetics

No data was provided.

4.3.2. Pharmacokinetics in the target population

PKs of Lotemax were not specifically evaluated in the proposed target patient population. Studies 358-005 and 358-006 compared PKs of LE alone compared with that following administration of Zylet (LE plus tobramycin) and this is discussed further later.

> Comments: However, it is important to note that in studies 358-005 and 358-006, LE concentrations AH were only evaluated in the aqueous humor (AH) and systemic absorption of LE in the target patient population was not evaluated.

4.3.3. Pharmacokinetics in other special populations

4.3.3.1. Pharmacokinetics in subjects with impaired hepatic function

Not applicable.

4.3.3.2. Pharmacokinetics in subjects with impaired renal function

Not applicable.

4.3.3.3. Pharmacokinetics according to age

Not evaluated.

4.3.3.4. Pharmacokinetics related to genetic factors

Not evaluated.

4.3.3.5. Pharmacokinetics {in other special population / according to other population characteristic}

Not evaluated.

4.3.4. Pharmacokinetic interactions

4.3.4.1. Pharmacokinetic interactions demonstrated in human studies

In the pilot pharmacokinetic Study 358-005, LE concentrations were measurable in 44% (27161) of eyes receiving two or four drops of Lotemax or LET (LE 0.5% and tobramycin 0.3%, Zylet) and sampled 20 or 40 minutes after the last instillation. Furthermore, LE concentrations in AH were similar following administration of LE alone or in combination with tobramycin (LET or Zylet).

In a controlled Phase III study (358-006,) of ocular penetration, the levels of LE in the aqueous humor were found to be generally comparable between Lotemax (0.5% loteprednol etabonate) and LET following 1 day treatment pre-operatively in over 2000 subjects undergoing uncomplicated cataract surgery. Although not completely bioequivalent to the levels observed in the LE treatment group, the presence of tobramycin in the Zylet formulation did not decrease the penetration of LE into AH. There was no apparent safety issue in this patient population of LET versus Lotemax .

The ocular disposition of LE following co-administration with commonly-used ophthalmic agents showed no interactions when examined in a nonclinical study in rabbits (Study #BLP-358-P002); however, this was not evaluated in humans. The sponsors have only studied the effect of co-administration of LE and tobramycin on the resulting levels of LE in AH in humans.

4.3.4.2. Clinical implications of in vitro findings

No in vitro studies have been conducted that relate to the potential for PK drug interactions. Specifically, the effect of LE on the inhibition or induction of cytochrome P450 enyzmes has not been investigated.

Comments: The systemic exposure of LE following topical ocular exposure in humans is less than 1 ng/ mL (< 0.002 μM). At these very low levels, the possibility that LE would alter the metabolism of concomitantly administered drugs is very remote. However, potential drug interactions following administration of other ocular medications with LE were not evaluated in humans.

4.4. Evaluator's overall conclusions on pharmacokinetics

The available pharmacokinetic data from in vivo and in vitro studies indicate that loteprednol etabonate is readily absorbed into ocular tissues, with low systemic exposure following topical ocular administration. However, systemic absorption of LE has not been evaluated in the target patient population.

4.4.1. Absorption

Results from a bioavailability study in normal volunteers established that plasma levels of loteprednol etabonate and Δ1 cortienic acid etabonate (PJ-91), its primary, inactive metabolite, were below the limit of quantitation (1 ng/ mL) at all sampling times. The results were obtained following the ocular administration of one drop in each eye of 0.5% loteprednol etabonate eight times daily for 2 days or 4 times daily for 42 days. This study suggests that limited (< 1 ng/ mL) systemic absorption occurs with Lotemax.

4.4.2. Distribution

Topical ocular administration of Lotemax in humans resulted in measurable loteprednol etabonate concentrations in aqueous humour within 20 minutes after dosing, and concentrations of approximately 3.7 ng/ mL were observed at one hour after dosing. Loteprednol etabonate is highly protein bound in plasma, and distributes preferentially into the cellular components of blood.

4.4.3. Metabolism

Systemic metabolism in humans likely occurs in the liver. To the extent that loteprednol etabonate reaches the systemic circulation, it distributes into tissues, and is readily metabolised to two inactive metabolites, PJ-90 (Δ1-cortienic acid) and PJ-91 (Δ1-cortienic acid etabonate).

4.4.4. Excretion

Following systemic administration to rats, loteprednol etabonate is eliminated primarily via the biliary/faecal route, with most of the dose eliminated in the form of the metabolite, PJ-90.

The clinical PK properties of LE have not been assessed with administration of LE concentrations other than 0.5%. Results from animal PK studies suggest that ocular exposure to LE increases with increasing dose levels in most tissues.

Although not completely bioequivalent to the levels observed in the LE treatment group, the presence of tobramycin in the Zylet formulation did not decrease the penetration of LE into AH (Study 358-006). The ocular disposition of LE following co-administration with commonly-used ophthalmic agents has not been examined in human subjects although a nonclinical study in rabbits did not show any interaction.

5. Pharmacodynamics

5.1. Studies providing pharmacodynamic data

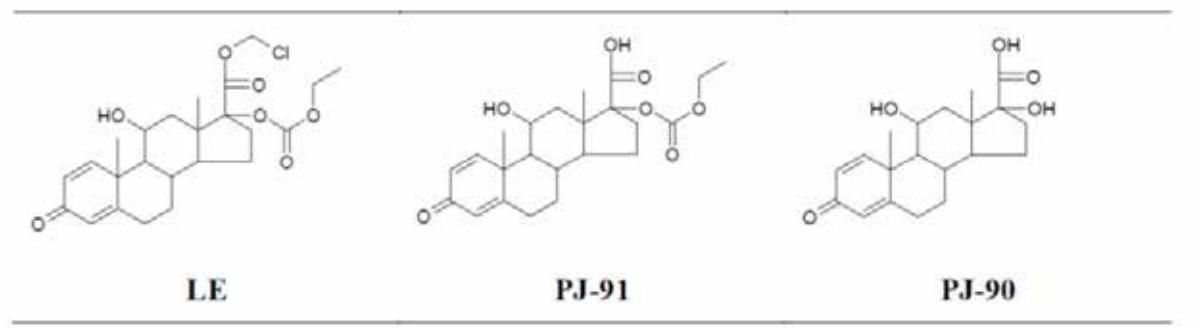
No pharmacodynamic studies were conducted.

5.2. Summary of pharmacodynamics

5.2.1. Mechanism of action

Loteprednol etabonate (LE) is a potent corticosteroid that has been formulated as an ophthalmic suspension. LE was derived from an inactive metabolite of prednisolone, cortienic acid, based on the 'inactive metabolite' approach.[1] Specifically, LE was designed with a 17-β-chloromethyl ester, but without the ketone group which is present at position 20 for other corticosteroids, such as prednisolone (Figure 1 below). The biologically labile 17-β-chloromethyl ester function, together with a labile 17-α-ethylcarbonate function result in metabolism of LE to the 17-β-carboxylate form (PJ-91, Δ1-cortienic acid etabonate) and subsequently to PJ-90 (Δ1-cortienic acid).

Figure 1: Chemical structure of loteprednol etabonate and metabolites



The active drug binds to the glucocorticoid receptor with an affinity that is 4.3-times greater than that for dexamethasone. In contrast, PJ-91 and PJ-90 are inactive at the glucocorticoid receptor,[2] which should minimize the potential for these metabolites to elevate intraocular pressure (IOP). The absence of the ketone group at position 20 should reduce the likelihood of molecular interaction with amino acid residues on the ocular lens, a process which may be involved in the formation of steroid-inducted cataracts.[3] In theory, the metabolism of LE to inactive metabolites and the absence of the ketone group at position 20 should offer a therapeutic advantage over conventional steroids by reducing the risk for steroid-induced cataracts and elevation of IOP. Furthermore, as a result of the limited systemic absorption after topical ocular administration, along with the rapid metabolism to inactive metabolites, systemic exposure to LE with ophthalmic use is negligible.

5.2.2. Pharmacodynamic effects

5.2.2.1. Primary pharmacodynamic effects

Study 141 was a prospective, double-blind, placebo-controlled, single centre paired comparison of LE 0.5% ophthalmic suspension (BID or QID) versus placebo (vehicle) in the antigen challenge model of acute allergic conjunctivitis. Sixty subjects who had a minimum pre-determined response to an ocular antigen challenge[4] were enrolled in the study and all subjects

[1] Bodor N. Novel approaches to the design of safer drugs: Soft drugs and site-specific chemical delivery systems. In: Advances in Drug Research. London: Academic Press; 1984. Vol 13, 255-331; Bodor N, Loftsson T, Wu WM. Metabolism, distribution, and transdermal permeation of a soft corticosteroid, loteprednol etabonate. Pharm Res. 1992;9:1275-1278.

[2] Druzgala P, Wu WM, Bodor N. Ocular absorption and distribution of loteprednol etabonate, a soft steroid, in rabbits eyes. Curr Eye Res. 1991;10:933-937.

[3] Manabe S, Bucala R, Cerami A. Nonenzymatic addition of glucocorticoids to lens proteins in steroid-induced cataracts. J Clin Invest. 1984;74:1803-1810.

[4] Subjects were administered a pre-study challenge on day 0 to determine their response to rising doses of allergen; on day 7 they were challenged with the highest dose of allergen used on day 0 to ensure that their response was still present and subjects who qualified then began their 28 day treatment period (with LE 0.5% and vehicle according to BID or QID dosing schedules). Subjects were rechallenged on day 21 at 15 mins after latest dose and on day 35, subjects were randomly divided into 2 groups for challenges at 2 hr and 8 hr after the final dose of study medication

received drug in one eye and vehicle in the contralateral eye. Subjects were randomised with respect to which eye received active drug with the first 30 subjects receiving the BID dosing schedule and next 30 subjects receiving the QID dosing schedule. LE 0.5% ophthalmic suspension eye drops (BID or QID) were significantly more effective than placebo for reducing mean redness and itching. Effects of treatment were still evident at the 8 hour challenge in the QID treatment group for both redness and itching, but only for redness in the BID group.

> Comments: This study evaluated the safety and efficacy of LE 0.5% ophthalmic suspension in the relief of signs and symptoms in the antigen challenge model of acute allergic conjunctivitis. Previous studies using this model have shown that it is sensitive to the effects of h1-antihistaminics, a1-adrenoceptor agonists and mast cell stabilisers.[5] The mid-potency corticosteroid, fluorometholone was also found effective in a conjunctival provocation test (CPT) model (Harper, 1995). Overall results of this study showed that LE 0.5% (BID or QID) was more effective than vehicle placebo in the control of signs and symptoms of acute allergic conjunctivitis induced by an antigen challenge. The procedure used in this study (CPT) is an acceptable model to detect anti-allergy actions of LE.

Study 145 was 2 separate studies with different objectives carried out under one protocol. The major study was a paired comparison design to evaluate effects of LE ophthalmic suspension at concentration of 0.1%, 0.2% and 0.3% for the relief of the signs and symptoms induced in the antigen model of acute allergic conjunctivitis. The goal of this study would be used subsequently in the treatment of environmental allergic conjunctivitis.

All LE concentrations were superior to placebo (vehicle for LE) in the relief of signs and symptoms. The 0.2% and 0.3% were statistically significantly superior to placebo in the reduction of itching at Visit 3 and 4 (2 hour challenge) and the 0.3% concentration alone at the 4-hour challenge. For mean redness, the 0.2% and 0.3% LE concentrations were statistically significantly superior to placebo at all challenge times with interocular differences exceeding one unit for both concentrations at the 4-hour challenges on Visit 4. There were no meaningful changes in other symptoms of chemosis, lid swelling and tearing although the trend was in favour of LE. Mucosal discharge was reported in very few subjects. There were no clinically meaningful elevations in IOP, but there was a trend indicating that the 0.3% formulation was causing some modest increases. Hence, the 0.2% concentration of LE was selected for evaluation in environmental seasonal allergic conjunctivitis studies.

The parallel group study showed that bilateral treatment with LE 0.5% was superior to placebo at both challenge times. The greater magnitude of efficacy observed at Visit 4, 2-hour challenge was consistent with the mode of action of corticosteroids which are known to be effective in the late phase allergic reactions.

> Comments: Alrex Ophthalmic Suspension (LE 0.2%) is approved for temporary relief of the signs and symptoms of seasonal allergic conjunctivitis in USA, Canada and some other countries. However, the sponsors have not applied for approval of LE 0.2% in this submission, only for LE 0.5% and based on the limited data provided in the above 2 studies, it appears that risk-benefit ratio for LE 0.5% may not be favourable for treatment of seasonal allergic conjunctivitis (due to trend of increased IOP observed with 0.3% LE compared with 0.1% and 0.2% LE in Study 145).

[5] Abelson MB, Chambers WA, Smith L. "Conjunctival Allergen Challenge. A Clinical Approach to Studying Allergic Conjunctival" Arch. Ophthalmol. Vol. 108: pp84-88, 1990; Abelson MB, Paradis A, George MA, Smith LM, Maguire L, Burns R. "Effects of Vasocon-A in the allergen challenge model of acute allergic conjunctivitis". Arch. Ophthalmol. Vol. 108: pp520-524, 1990; Rimas M, Kjellman NI, Blychert LO, Bjorksten B. "Topical levocabastine protects better than sodium cromolygate and placebo in conjunctival provocation tests". Allergy Vol.45: pp18-21, 1990.

5.2.2.2. Secondary pharmacodynamic effects

Not evaluated.

5.2.3. Time course of pharmacodynamic effects

Not evaluated.

5.2.4. Relationship between drug concentration and pharmacodynamic effects

Not evaluated.

5.2.5. Genetic-, gender- and age-related differences in pharmacodynamic response

Not evaluated.

5.2.6. Pharmacodynamic interactions

Not evaluated.

5.3. Evaluator's overall conclusions on pharmacodynamics

Results of Study 141 showed that LE 0.5% (BID or QID) was more effective than vehicle placebo in the control of signs and symptoms of acute allergic conjunctivitis induced by an antigen challenge.

Study 145 was a 2-part study; the paired comparison part of the study evaluated LE at concentrations of 0.1%, 0.2% and 0.3% with the 0.2% dose being selected for further evaluation in treatment of seasonal allergic conjunctivitis. The parallel group part of study 145 showed that bilateral treatment with LE 0.5% was superior to placebo at both challenge times. The greater magnitude of efficacy observed at Visit 4, 2-hour challenge was consistent with the mode of action of corticosteroids which are known to be effective in the late phase allergic reactions.

Based on the limited information provided (Studies 141 and 145), it appears that proposed dose of LE 0.5% may not be appropriate for treatment of seasonal allergic conjunctivitis, especially in light of the fact that the sponsors have specifically developed another LE formulation (0.2%; Alrex) for this indication. Furthermore, there was no dose-response analysis for LE in treatment of post-operative inflammation or for any of the other proposed indications.

6. Dosage selection for the pivotal studies

Only one dose of LE (0.5%) was used in all Phase II and III studies. There were no studies supporting the proposed strength and dosing regimen of Lotemax.

7. Clinical efficacy

7.1. Indication 1

Post-operative inflammation following ocular surgery

7.1.1. Pivotal efficacy studies

7.1.1.1. Study 125

7.1.1.1.1. Study design, objectives, locations and dates

This was a Phase III, randomised, double-blind, placebo-controlled, parallel group, multicentre study. The main objective was to compare the efficacy of loteprednol etabonate 0.5% (LE) to placebo (vehicle) in controlling the anterior chamber cell and flare reaction in patients

undergoing cataract surgery with intraocular lens (IOL) implantation. The secondary objective was to evaluate safety and ocular tolerance of LE. The study was conducted from May 1996 to September 1996 at 17 centres in the USA.

7.1.1.1.2. Inclusion and exclusion criteria

Adult patients exhibiting inflammation following surgery for cataract removal and intraocular lens (IOL) implantation with a combined anterior chamber cell and flare reaction rating of greater than 3 units at 22-24 hours following surgery (Visit 1). The main exclusion criteria were:- absent or minimal inflammation (sum of cell and flare score < 3 at Visit 1), pregnant/lactating females, previous allergic hypersensitivity to corticosteroids, loteprednol etabonate or any other component of the study medication, expected concurrent therapy with ocular NSAIDs, mast cell stabiliser, antihistamine decongestant for succeeding 15 days or within 2 days before Visit 1; therapy with systemic or topical corticosteroids within 2 weeks prior to start of study, any abnormality preventing applanation tonometry in either eye, IOP greater than 30mmHg; history of intraocular or laser surgery within past 6 months; presence of ocular pathology other than the cataract (such as vernal, giant papillary, viral or bacterial conjunctivitis, uveitis, retinopathies) or history of other serious ocular or systemic illness.

7.1.1.1.3. Study treatments

All subjects received either loteprednol etabonate 0.5% ophthalmic suspension (LE) or placebo (Vehicle); one drop was instilled 4 times daily at roughly 4 hour intervals in the operated eye for up to 14 days following surgery. Systemic steroids, NSAIDs, thyroxin, oestrogen replacements, insulin, hypoglycaemic agents, antihypertensives, anti-microbials were allowed. The following ocular medications were also allowed:- artificial tears, antibiotics, NSAIDs (only at time of surgery to prevent miosis), ocular hypotensives, antimuscarinics (atropine) in the post-operative period.

> Comments: The dose of LE (0.5%) selected for this study was based on previous studies conducted in giant papillary conjunctivitis, prophylaxis of seasonal allergic conjunctivitis and uveitis. No specific dose-ranging studies were conducted for the proposed indication of post-operative inflammation.

7.1.1.1.4. Efficacy variables and outcomes

The main efficacy variables were: evaluation of signs and symptoms of inflammation at baseline (between 23-24 hours after surgery) and then on days 3, 8, 15 and 17.

The primary efficacy outcome was the proportion of patients with anterior chamber inflammation (ACI) resolved (the sum of cell and flare scores was 0) by the final visit.

Secondary outcomes included resolution of cell and flare individually, the magnitude of change in the cell and flare ratings, treatment failure and investigator's Global Assessment. Treatment failures were defined as patients who discontinued early with inadequate control of their post-operative inflammation or patients who had a 3 unit increase in their ACI score over baseline.

Other efficacy outcome was assessment of rebound: patients returned 2 days after stopping treatment to ensure that inflammation had not rebounded after cessation of treatment (ACI scores at Visit 5 were greater than those at Visit 4).

Other supportive measures were ocular signs (chemosis, erythema, palpebral injection, bulbar injection, corneal oedema, hyphema and ciliary flush) and symptoms (pain, photophobia, itching, tearing, dryness, discharge and discomfort). Ocular safety evaluations included an external examination, slit lamp examination, tonometry and visual acuity.

7.1.1.1.5. Randomisation and blinding methods

It was a double-blind study. After confirming compliance with inclusion/ exclusion criteria, the eligible patients were randomised to either LE 0.5% or placebo. Randomisation was in blocks of

4 with equal allocation to LE and placebo. Sequential numbers were shipped to each site based on number of potential subjects expected to enrol. Some partial randomisation blocks were issued.

> Comments: Randomisation was not based on severity of anterior chamber inflammation (sum of cell and flare scores) at baseline. However, the proportion of patients having moderate or severe ACI scores at baseline was similar in the LE and placebo groups.

7.1.1.1.6. Analysis populations

Of the 227 patients, 5 patients had no valid on-treatment follow-up examination and so the intent-to-treat (ITT) population included 222 patients.

7.1.1.1.7. Sample size

Assuming a placebo resolution rate of 20% for the ACI score 15 days after surgery, the sample size of at least 91 subjects in each treatment group provided 80% power to detect a clinically significant 20% improvement over placebo with a type 1 error rate of 0.05.

7.1.1.1.8. Statistical methods

All statistical tests were 2-tailed with alpha = 0.05 using non-parameteric methods. The primary efficacy analysis to assess if resolution rate was different for LE versus placebo was determined using the Cochran-Mantel-Haenszel test controlling for investigator. Similar statistical tests were used to assess the secondary efficacy outcomes of individual cell and flare scores, treatment failure rates, investigator global assessment.

7.1.1.1.9. Participant flow

Of the 302 patients screened, 227 were randomised to treatment with LE (n = 110) or placebo (n = 117). The completion rate was much higher in the LE group compared with placebo (LE versus placebo: 90% versus 64%) with more placebo-treated patients discontinued due to lack of efficacy (LE versus placebo: 5% versus 29%).

7.1.1.1.10. Major protocol violations/deviations

Over 8.% (19/227) of the ITT patients were excluded from the per protocol (PP) analysis; hence the PP analysis set included 203 patients (LE = 101, placebo = 102).

7.1.1.1.11. Baseline data

The mean age was 71 years (38-92years); however, there were more patients aged >70 years in the LE group compared with placebo (66% versus 50%, p = 0.019). Majority of the patients were female (59%) Caucasian (89%) with light irides (59%),[6] had the cataracts removed by phacoemulsification (91%) with no significant differences between treatment groups. Both treatment groups had an ACI score of 3.8 units at baseline and the proportion of patients having moderate or severe ACI scores at baseline was similar in the LE and placebo groups.

7.1.1.1.12. Results for the primary efficacy outcome

At the final visit, greater proportion of subjects in the LE group (64%; 70/109) had resolution of cell and flare compared with placebo (29%; 33/113); the 35% difference between LE and placebo groups was statistically and clinically significant (p < 0.001). The resolution rates increased with time for patients remaining on treatment in both groups, but the difference in rates was statistically significantly (p < 0.003) in favour of LE at all visits; resolution rates in the LE group were 15%, 43% and 70% at Visit 2, 3 and 4, respectively (compared with 4%, 15% and 29%, respectively in the placebo group). Similar results were observed in the more conservative LOCF analysis. The per protocol analysis also showed similar results with

[6] Light irides- blue, green, light hazel or light grey; dark irides were dark brown, dark hazel, dark grey

resolution rate of 65% (60/101) in the LE group and 29% (30/102) in the placebo group (difference = 36%, p < 0.001).

At the final visit, the mean change from baseline was statistically significantly greater in the LE group compared with placebo (-2.9 versus -1.7 units, p < 0.001); in terms of observed severity, the LE patients had a mean score of 0.9% with only 11% of patients having moderate or greater ACIs compared to mean ACI of 2.1 for placebo with 36% of patients with moderate or greater ACIs.

7.1.1.1.13. Results for other efficacy outcomes

At the final visit, resolution rate for cell scores was significantly (p < 0.001) greater in the LE group (68%; 74/109) compared with placebo (35%; 39/112) (diff = 33%) and this difference was observed at all visits. The mean change from baseline in severity at final visit was 1.7 units with LE compared to -1.0 with placebo (difference equals -1unit, p < 0.001); in terms of observed severity, the LE patients had a mean cell rating of 0.5% with only 10% of patients with moderate or greater ratings compared to a mean of 1.2 for placebo with 37% of patients with moderate or greater rating.

Similar results for resolution rates for flare (LE versus placebo = 74% versus 43%; diff = 31%, p < 0.001) with significant differences observed at all visits. The mean change from baseline in severity was -1.3 units with LE compared to -0.8 with placebo (p < 0.001). In terms of observed severity, the LE patients had a mean cell rating of 0.4% with only 9% of patients with moderate or greater ratings compared to a mean of 0.9 for placebo with 24% of patients with moderate or greater rating.

Treatment failures included patients who discontinued early for inadequate control or who had an increase of > 3 in their ACI score. The difference in treatment failure rates was statistically and clinically significantly in favour or LE compared with placebo (LE = 6% (6/109) versus placebo = 30% (34/113), p < 0.001). The failures in the placebo group occurred throughout the 13-day period while all but one of the failures in the LE group occurred by day 7.

The mean assessment on the Investigator global rating was 1.0 (full to reasonable control) for LE and 2.2 (slight improvement) for placebo with a statistically significant difference in favour of LE (-1 unit, p < 0.001). Overall 79% (86/109) of the LE patients had reasonable control compared with 39% (44/111) of placebo patients.

The resolution rate and mean change from baseline favoured LE over placebo for all signs and symptoms with the exception of chemosis, dryness, itching and discharge.

At Visit 5 (2 days after treatment discontinuation), 70% (66/94) of patients in the LE group had resolution of cell and flare compared to 70% (69/98) of patients at Visit 4. Overall, 72% (68/94) remained unchanged from their Visit 4 values, 16% (15/94) were worse and 12% (11/94) improved. Hence, there was no evidence of rebound inflammation after cessation of LE therapy.

Logistic regression analysis for effect of age, gender, race, type of surgery, type of lens and baseline scores for ACI, cell and flare on the primary efficacy outcome showed significantly better resolution rates in patients with phacoemulsion surgery (p = 0.003), lower baseline ACI score (p = 0.039) and lower baseline cell score (p = 0.002).

7.1.1.2. Study 127

7.1.1.2.1. Study design, objectives, locations and dates

This study was conducted from May 1996 to October 1996 at 17 centres in the USA. Study design, objectives were similar to those described for Study 125 above.

7.1.1.2.2. Inclusion and exclusion criteria

These were similar to those described for Study 125 above.

7.1.1.2.3. Study treatments

These were similar to those described for Study 125 above.

7.1.1.2.4. Efficacy variables/ outcomes

These were similar to those described for Study 125 above.

7.1.1.2.5. Randomisation, blinding methods, sample size and statistical methods

These were similar to those described for Study 125 above.

Upon review of the final report for Study 127, dated 14 February, 1997, some confidence intervals were noted to be wider than anticipated and to not be consistent with the inference obtained from the p-values. The original confidence intervals around the difference in proportions between treatments in the anterior chamber inflammation score, anterior chamber cell score, anterior chamber flare score, and supportive signs and symptoms at each visit for Study 127 were planned to be calculated using standard normal approximations not adjusting for Investigator. However, the standard error term used in calculating the confidence intervals was incorrectly calculated using the number of resolved subjects as the denominator instead of the total number of subjects. This error in the standard error calculation lead to larger standard errors, as the number of resolved subjects is less than the total number of subjects, which lead to wider confidence intervals. Furthermore, the confidence intervals and p-values for the tests between proportions were estimated differently, with the p-value accounting for Investigator and the confidence interval not accounting for Investigator.

In this addendum, additional efficacy tables are provided for the above mentioned endpoints where p-values are calculated not controlling for Investigators (Pearson chi squared) [note: these p-values are not given to be a replacement to the original Cochran-Mantel-Haenszel p-values that adjust for Investigator; instead, they are given as a second p-value to test the consistency of results and to show a p-value of a similar construction to the confidence interval] and the normal approximation 95% confidence intervals are calculated using the correct denominator for the standard error.

> Comments: The results discussed below are based on data provided in the addendum of the CSR.

7.1.1.2.6. Analysis populations

Of the 203 enrolled patients, 1 patient (placebo group) had no valid on-treatment follow-up examinations and so the ITT analysis was performed on 202 subjects. The analysis of individual signs and symptoms from the ocular examination also required patient to have the sign or symptom under evaluation present at baseline. 'By Visit' analyses included only patients with valid visits in the interval. Per protocol analysis included ITT patients who failed the entry criteria or did not comply with protocol procedures. This analysis was similar to the ITT analysis with the Final visit (LOCF) as the primary endpoint and the 'by visit' analyses as supportive endpoints. Overall, 88% of the ITT patients were included in the PP analysis (178/203). All randomised patients were included in the safety evaluation (n = 203).

7.1.1.2.7. Participant flow

Of the 214 patients screened, 203 patients were enrolled and received treatment (LE = 102, placebo = 101) of whom 164 completed treatment [LE = 93% (95/102); placebo = 68% (69/101)]. Majority of discontinuations were due to inadequate anti-inflammatory effect [LE = 5% (5/102); placebo = 25% (25/101)].

7.1.1.2.8. Baseline data

Majority of the patients were female (58%), Caucasian (72%), had dark irides (51%) and had cataract extractions performed by phacoemulsification (79%) and received foldable lens implant (66-68%). The baseline demographic and disease characteristics were similar in the LE

and placebo groups. The baseline signs and symptoms of inflammation were also similar between treatment groups.

7.1.1.2.9. Results for the primary efficacy outcome

At the final visit, 55% of LE patients (56/102) had achieved resolution of cell and flare compared to 28% of placebo patients (28/100) and the 27% difference was statistically and clinically significant ($p < 0.001$). For both treatment groups, the resolution rates increased with time on treatment for the patients remaining on treatment at each of the scheduled visits. The difference was statistically significantly ($p < 0.008$) in favour of LE at Visits 3 and 4 only; resolution was observed in 10%, 34% and 58% of LE patients at Visit 2, 3 and 4, respectively compared with 9%, 17% and 39%, respectively for placebo. The resolution rates from the more conservative LOCF analysis were similar [10%, 34% and 55% for LE versus 9%, 15% and 28% for placebo ($p < 0.001$ at Visits 3 and 4)]. The PP analysis confirmed the results observed in the ITT analysis with 52% (49/94) of the LE patients compared to 29% (24/84) of placebo patients showing resolution of their cell and flare at final visit (diff = 23%, $p = 0.001$); the mean change from baseline was -2.5 units for LE and -1.7units for placebo.

At the final visit, the mean change from baseline was statistically significantly greater for LE compared with placebo [-2.6 versus -1.5 units; diff = -1 units, $p = 0.001$). In terms of observed severity, the LE patients had a mean ACI score of 0.9 with only 7% of patients with moderate or greater ACIs compared to a mean ACI of 2.2 for placebo with 35% of patients with moderate or greater ACIs.

7.1.1.2.10. Results for other efficacy outcomes

At final visit, 60% (61/102) had resolution of their cell compared with 31% (31/100) of placebo patients (diff = 29%, $p = 0.001$). The difference in resolution rates was statistically significantly ($p < 0.005$) in favour of LE at Visits 3 and 4; 13%, 39% and 63% of LE patients experienced resolution of cell at Visits 2, 3 and 4, respectively compared with 11%, 19% and 43%, respectively for placebo. At their final visit, the mean change from baseline was statistically significantly greater for LE compared with placebo [-1.6 versus -1.0 units; median diff = -1 units, $p = 0.001$). In terms of observed severity, the LE patients had a mean ACI score of 0.5 with only 8% of patients with moderate or greater ratings compared to a mean of 1.2 for placebo with 36% of patients with moderate or greater ratings.

At final visit, 67% (68/101) had resolution of their flare compared with 36% (36/100) of placebo patients (diff = 31%, $p < 0.001$). The difference in resolution rates was statistically significantly ($p < 0.003$) in favour of LE at Visits 3 and 4; 28%, 51% and 72% of LE patients experienced resolution of flare at Visits 2, 3 and 4, respectively compared with 17%, 35% and 50%, respectively for placebo. At their final visit, the mean change from baseline was statistically significantly greater for LE compared with placebo [-1.0 versus -0.5 units; median diff = 0 units, $p = 0.005$). In terms of observed severity, the LE patients had a mean flare rating of 0.4 with only 5% of patients with moderate or greater ratings compared to a mean of 0.9 for placebo with 20% of patients with moderate or greater ratings.

The incidence of treatment failures was statistically significantly lesser in the LE group (5%, 5/102) compared with placebo (25%, 25/100) (diff = 20%, 95% CI: -29.6, -10.6, $p < 0.001$). All of the treatment failures discontinued before day 15; increases in ACI of > 3 were recorded for only 3 patients (LE = 1; placebo = 2). The difference in the treatment failure rates as well as the difference in the time-course of failures was both clinically and statistically significant in favour of LE.

There were 102 LE patients and 98 placebo patients in the analysis of Investigator's Global Assessment. The mean assessment score was 0.8 (full to reasonable control) for LE compared with 2.0 (slight improvement for placebo (diff = -1 unit, $p < 0.001$) with 89% (91/102) of the LE patients reported to have at least reasonable control compared with 49% (48/98) placebo patients.

The resolution rates favoured LE for all signs and symptoms except dryness; the difference between LE and placebo was statistically significant ($p < 0.05$) for chemosis, erythema, bulbar injection, ciliary flush, pain, photophobia, tearing and discomfort. For dryness and hyphema, 10 or less patients (< 5% of the population) had a finding at baseline.

At Visit 5 (day 17, 2 days after end of treatment period), 63% (59/93) of LE patients had resolution of cell and flare compared with 58% (54/93) of LE patients at Visit 4. Of the 91 LE patients with valid visits at both Visit 4 and 5, 69% (63/91) of the patients remained unchanged from Visit 4, 9% (8/91) were worse and 22% (20/91) were improved. Hence, there was no evidence to suggest rebound inflammation after cessation of LE therapy. Resolution rates for other signs and symptoms behaved similarly, that is, the values at the off-therapy visit were similar to the last on-treatment visit.

Subgroup analysis showed that iris colour ($p = 0.004$) and surgery type ($p = 0.048$) had significant effects on the efficacy of LE; patients were more likely to have resolution of ACI if they had light irides (compared with dark irides) and phacoemulsification (compared with extracapsular cataract extraction). Furthermore, the treatment effect (LE –placebo) was greater in patients with more severe ACI ratings than those with milder ratings.

7.1.2. Other efficacy studies

Not applicable.

7.1.3. Analyses performed across trials (pooled analyses and meta-analyses)

Not applicable.

7.1.4. Evaluator's conclusions on clinical efficacy for indication 1 (Treatment of post-operative inflammation following ocular surgery)

Overall, efficacy of LE 0.5% was compared with that of placebo (vehicle for LE) in 2 well-conducted, Phase III studies involving 430 patients who had undergone cataract surgery.

LE 0.5% administered 4 times daily for up to 2 weeks following surgery showed clinically and statistically significantly greater reduction of anterior chamber inflammation (sum of cell and flare scores) with 55-64% of LE-treated patients showing resolution of symptoms (score of 0 at final visit) compared to placebo (28-29%). Furthermore, treatment failures (which included patients who discontinued early for inadequate control or who had an increase of > 3 in their ACI score) was also significantly lesser in the LE group (6%) compared with placebo (25-30%). The secondary endpoints of investigator global assessment and ocular signs and symptoms also showed favourable results for LE.

In both studies, patients were more likely to have resolution of ACI following LE treatment if they had phacoemulsification (compared with extracapsular cataract extraction).

Importantly, there was no evidence of rebound inflammation following assessment of anterior chamber cell and flare score, 2 days after stopping LE treatment in both studies.

Only one dose of LE (0.5%) was evaluated. The patient population evaluated in these studies was limited to patients undergoing cataract surgery, while the proposed indication is for a more generalised 'ocular surgery'. No studies were conducted to evaluate efficacy of LE in patients undergoing other ocular surgery.

7.2. Indication 2

Treatment of 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 conjunctivitis, when the

inherent hazard of steroid use is accepted to obtain an advisable diminution in oedema and inflammation.

7.2.1. Seasonal allergic conjunctivitis

7.2.1.1. Pivotal Study P5604-121

7.2.1.1.1. Study design, objectives, location, dates

P5604-121 was a Phase III, randomised, double-blind, placebo-controlled, parallel group prophylactic study to evaluate safety and efficacy of LE 0.5% in preventing the ocular signs and symptoms that accompany seasonal allergic conjunctivitis (SAC) during peak pollen levels. The study was conducted from August 1993 to March 1994 at 13 centres in the USA.

During the study all investigators were required to record local environmental allergen counts from the time of first screening visit until all patients completed the study. Diary cards were dispensed to patients with instructions to record the overall status of their ocular signs and symptoms.

The study was carried out during two separate pollen seasons: the ragweed pollen season (August to October 1993) and the mountain cedar pollen season (December 1993 to February 1994).

7.2.1.1.2. Inclusion/ exclusion criteria

The main inclusion criteria were adults aged 18-75 years with a history of seasonal allergic conjunctivitis for 2 previous years; evidence of positive history of a seasonal allergy (that is , mountain cedar, elm, oak, ragweed, et cetera) with either a positive skin (prick intradermal) or RAST test (within the past 36 months) to seasonal allergen present at investigative site at the time of the study. The main exclusion criteria were: - absent or minimal symptoms of SAC in previous year to allergens present at investigative site, no need for medication for signs/ symptoms of SAC in previous year; active signs and symptoms of SAC with greater than 2+ itching, 1+ bulbar conjunctival injection, 1+ palpebral conjunctival injection, 1+ tearing; pregnancy/ lactation; previous allergy to corticosteroids, LE or any component of study medications; concurrent therapy with NSAIDs, mast cells stabilisers, antihistamines, decongestants or beta-blockers during study periods; therapy with oral or topical corticosteroids within 2 weeks prior to study start; ocular surgery within past 6 months; other ocular pathology such as GPC, vernal, viral or bacterial conjunctivitis; IOP > 21mmHg,; best corrected distance visual acuity worse than or equal to 20/100 in either eye; anticipated travel for more than 24hours > 50 miles from home.

7.2.1.1.3. Study treatments

Patients were randomised to treatment with LE 0.5% or placebo (vehicle for LE 0.5% ophthalmic suspension); one drop was instilled in each eye 4 times daily for 6 weeks. No other concomitant ocular medications were allowed.

7.2.1.1.4. Efficacy variables and outcomes

The primary efficacy variable was a composite score equal to sum of individual scores for ocular itching and bulbar conjunctival injection. The secondary efficacy variable was the Investigator Global Assessment at the peak evaluation period (based on evaluation of patient ocular allergic signs and symptoms through patient diary entries) over period covering 2 previous visits and the current visit (for example. Visits 2 through visit 4), ophthalmic examination findings and weekly investigator clinical judgement. Other supportive endpoints were secondary composite score which was equal to sum of individual scores for tearing, erythema, chemosis and discomfort.

A positive response for the primary, secondary and supportive efficacy endpoints required that no rating of moderate or greater be recorded for either the individual variables of the composite

during the peak period. Other signs and symptoms were photophobia, foreign body sensation, discharge, burning stinging and corneal disease.

Most signs and symptoms were rated using a 4-point scale (0-3) with 0 = absent, 1 = mild, 2 = moderate, 3 = severe. For itching a 5-point scale was used where 0-absent, 1-trace, 2-mild, 3-moderate, 4-severe. The investigator global assessment used a 5-point scale where 0 = fairly controlled, 1 = reasonably controlled, 2 = slight improvement, 3 = unchanged, 4 = worse.

7.2.1.1.5. Randomisation and blinding

After meeting inclusion/ exclusion criteria, patients were randomised to treatment with LE 0.5% or placebo in a 1:1 ratio. The study was double blind.

7.2.1.1.6. Sample size and statistical methods

Assuming a placebo response rate of 30%-40% for clinician's and patient global assessment, the sample size of at least 80 patients in each treatment group would be able to detect differences of 20-25% from placebo group (assuming SD of 0.45) using 2-sided t-tests (alpha = -0.05). A per protocol analysis was also done which excluded 30 patients from the ITT patient population. In addition to the patients eliminated from the PP analysis, patients without full documentation of a history[7] of seasonal allergic conjunctivitis for previous 2 years to the allergen prevalent at the site at the time of the study were not included in a reanalysis of the primary efficacy parameter.

All analyses were carried on the mean rating of the left and right eyes under the assumption that both eyes were equally involved.

7.2.1.1.7. Participant flow

Of the 451 patients who were screened, 293 were randomised to treatment (LE = 146, placebo = 147). The treatment and study were completed by 86% (1226/146) of the LE patients and 83% (122/147) of the placebo patients; most common causes of early discontinuation were lack of efficacy (LE versus placebo: 2% versus 3%), AEs (4% versus 4%) and other reasons (8% versus 10%) with no significant difference between the LE and placebo groups.

7.2.1.1.8. Baseline data

Majority of the patients were female (63%), Caucasian (85%), with light irides and mean age of 42 years. All investigators except one were associated with either ragweed or mountain cedar but not both allergens. No difference was detected between treatment groups with approximately 50% of the patients in each treatment group during each allergen season. The baseline demographics were similar between treatment groups.

The protocol was designed to enter patients prior to any symptoms of seasonal allergic conjunctivitis; however, symptoms were absent in only 25% of patients overall, but there was no difference between treatment groups for absence or presence of symptoms. The investigator effect was significant ($p < 0.001$) ranging from all (100%) patients having at least mild symptoms to 33% of patients with symptoms. The composite scores were similar between the LE and the placebo group (1.16 and 1.17 with LE and placebo respectively, $p = 0.778$). However, there were significant differences between investigators with composite scores ranging from 0.5 to 1.9 ($p < 0.001$). Similar results were observed for mean baseline scores of itching (0.69 and 0.79, respectively, $p = 0.583$) and bulbar injection (0.46 and 0.44, respectively, $p = 0.79$).

7.2.1.1.9. Primary efficacy results

The mean scores for the primary composite endpoint was statistically significantly lesser in the LE group compared with placebo (LE versus placebo: 0.88 versus 1.50; diff = 0.7units, 95% CI: -0.47, -0.87 $p = 0.001$). LE was favoured by all investigators with estimated treatment effects

[7] During enrolment, some patients were initially enrolled into the study following only verbal confirmation and documentation to confirm diagnosis of SAC was done after enrolment.

ranging from 0.1 to 1.5 units. The response rate for the composite score was higher in LE patients compared with placebo (94% versus 78%, p < 0.001). Similar results were observed for mean itching scores (0.51 versus 0.88, diff = 0.4, 95% CI:-0.26, -0.56, p = 0.001; ranging from 0.04 to 1.2 units across investigators) and mean bulbar injection scores (0.37 versus 0.62, diff = 0.3 units, 95%: -0.17, -0.36, p = 0.001; ranging from 0.04 to 0.51 units across all investigators). The results of the PP analysis were similar to those of the ITT analysis with peak composite scores of 0.87 and 1.53 with LE and placebo, respectively (p < 0.001) and response rate also 16% higher in LE patients compared with placebo. Similar results were also observed in the 'Fully documented per protocol' analysis with peak composite scores of 0.94 and 1.58, respectively (p = 0.001) and 18% higher response rates with LE compared with placebo. The mean composite score during the peak pollen season increased by 0.34 units over baseline in the placebo group, but was reduced by 0.29 units in the LE group and although the change was not analysed statistically, the trend confirms the therapeutic effect of LE.

7.2.1.1.10. Other efficacy results

The secondary endpoint of mean peak Investigator Global Assessment scores was significantly (p < 0.001) better with LE (0.97) compared with placebo (1.38). A positive response was defined as rating of mostly (score = 1) or fully controlled (score = 0) and it was significantly higher with LE compared with placebo (86% versus 64%, diff = 22%, p < 0.001). These results were confirmed in the PP analysis with significantly (p < 0.001) better mean peak season score with LE (0.99) compared with placebo (1.38) and also higher response rates with LE (85% versus 63%, diff = 21%, p < 0.001.

The supportive composite score was created by the sum of the mean discomfort, chemosis, erythema and tearing scores for the peak pollen period with scores ranging from 0 to 12 (higher scores indicate greater severity of ocular symptoms/ signs). The mean peak ratings were significantly (p < 0.001) better with LE (0.96) compared with placebo (1.37). Significant differences were detected among investigators, but LE showed more favourable results for 9 of 11 investigators with estimated treatment effects ranging from -0.2 to 1.3 units with overall effect of 0.4 units (95% CI: -0.19, -0.65). LE was better than placebo for individual entities of this supportive composite endpoint with significant difference over placebo for discomfort (p = 0.001), erythema and tearing (p = 0.050) and chemosis (p < 0.011). The difference in response rates for the secondary composite and discomfort was marginally significant and it was significantly in favour of LE for tearing (p = 0.005). LE patients experienced mild or less discomfort, chemosis, erythema and tearing throughout the season than did placebo patients (LE = 77% versus placebo = 68%). The PP analysis were similar to those observed in the ITT analysis above.

The mean peak period scores and response rates for foreign body sensation, photophobia and discharge did not show any statistically significant difference between the LE and placebo groups. However, the peak period score and response rates for burning/stinging sensation and palpebral injection were significantly in favour of LE compared with placebo.

7.2.1.1.10.1. Subgroup analysis

There was no statistically significant difference between LE and placebo groups in response rates when the population was stratified by age, gender, race, iris pigmentation or baseline judgement, but there was significantly greater response rate for ragweed compared to mountain cedar (p = 0.035). There was no statistically significant difference between LE and placebo groups in peak scores when the population was stratified by gender, race, iris pigmentation, baseline judgement or allergen. The peak score for LE patients < 30 years (n = 51) was significantly less than those > 30years old (n = 237) (p = 0.047).

Comments: LE was more effective than placebo in all primary composite, secondary composite and investigator global assessment scores and in all individual parameters except chemosis providing evidence of efficacy as prophylactic treatment in patients with

history of SAC. However, the subgroup analysis indicated greater response with LE for ragweed compared with the mountain cedar allergens. Hence, LE may not be effective in prophylaxis of all allergens. This is especially important as this study was conducted only in the USA. The common allergens in Australia are different to those found in USA and efficacy of LE in prophylactic treatment of SAC was not evaluated in any Australian centre. Hence the evidence to support use of LE for prophylaxis or treatment of SAC is not convincing.

7.2.1.2. Study 114:

This was a prospective, double-blind, randomised, placebo-controlled, parallel group comparison of LE (0.5%) to its vehicle (placebo). Although this study was planned for 80 subjects, only 9 subjects with active signs and symptoms of SAC were enrolled and evaluated in this study. The study was stopped for reasons related to poor enrolment and financial considerations. Due to small sample size no statistical parametric analysis was done. The baseline mean primary composite score was 4.8 (0.3) and 4.4 (0.3) units in the LE and placebo group, respectively. There was a mean decrease of 2.6 units in the LE group within 15 minutes after first treatment and the severity of this composite score continued to decrease until day 12 (when it was 0.5 units with mean decrease of 4.3 units). The placebo group also showed a mean decrease of 3.0 units. Similar treatment effects were observed for the secondary composite score (bulbar chemosis, tearing, discharge and erythema), individual subjective measures (itching, tearing, discomfort, foreign body sensation and burning/ stinging) and individual objective measures (bulbar and palpebral injection, discharge, chemosis, corneal disease and erythema). The Physician global assessment mean values ranged from 0 to 0.8 units in the LE group and from 1.8 to 1.4 in the placebo group ($p = 0.040$). Overall, LE 0.5% was numerically more effective than placebo in treatment of SAC in this small subject population, although the difference was not statistically significant.

Comments: It is difficult to interpret significance of results due to very small sample size in this study.

7.2.2. Giant papillary conjunctivitis

7.2.2.1. Study 106

7.2.2.1.1. Study design, inclusion/ exclusion criteria:

This was a pilot randomised, placebo-controlled, parallel group, multicentre study to evaluate efficacy and safety of LE 0.5% compared with placebo (vehicle) in 113 patients with diagnosed Giant Papillary Conjunctivitis (GPC). The study was conducted from August 1990 to January 1991 at 7 centres in USA.

The main inclusion criteria were : adults (aged 18-55years) who had continuously worn contact lenses while awake for the past 48 hours, unless disease was severe; clinical diagnosis of bilateral contact lens GPC; active ocular signs and symptoms of GPC; papillae must be > 0.4 mm in diameter in each eye.

The main exclusion criteria were : previous allergy to prednisolone, LE or any component of the study medications; presence of other ocular disease (corneal abrasion or erosion, infection, inflammation, glaucoma, dry eye, et cetera) other than GPC; concomitant use of any medication (steroids, NSAIDs, analgesics, mast cell stabilisers, immunosuppressives, anticholinergic, et cetera) which may interfere with evaluation of patients response; IOP > 21mmHg; use of any ocular medication within past 48 hours; ocular surgery within past 6 months; concurrent contact lens wear during study; best corrected visual acuity worse than or equal to 20/100 in either eye; pregnant/ lactating females.

Comments: There was an amendment which allowed concurrent wear of contact lens during the study and the purpose of this amendment was to determine efficacy of LE in a subset of patients in which the source of the irritation was still present. In a separate

study it was demonstrated that LE eye drops suspension was compatible with a wide variety of contact lenses.

7.2.2.1.2. Study treatment and efficacy endpoints:

The 113 enrolled patients were randomly assigned to treatment with either LE 0.5% (n = 56) or the LE vehicle (Placebo, n = 57) and instructed to instil one drop into each eye four times daily for 4 weeks. Follow-up examinations were done on days 2, 3, 7, 14, 21 and 28 of double-blind therapy. Patients were randomised in blocks of 4 and each investigator completed at least one block of study medication.

The primary efficacy variables were reductions in papillae discharge, itching and discomfort (in descending order). Secondary parameters included ratings from the Physician's Clinical Judgement and the Patient Opinion relative to the patient's response to therapy. Efficacy was evaluated statistically by comparing means, mean changes and the mean percent change from baseline[8] for individual and grouped ocular sign and symptom scores at day 2 or 3, 7, 14, 21 and 28. Repeated measures analysis of variance and other appropriate statistical methods were employed. The primary analysis was performed on data from the single eye per patient having the higher composite 'baseline' scores for papillae, itching, discharge and discomfort. A second analysis was performed using the average of data from both eyes for each patient. Ocular symptoms were rated on a scale of 0 to 3 with 0 = absent, 1 = mild, 2 = moderate and 3 = severe.

7.2.2.1.3. Participant flow and baseline data:

Overall, 110 of the 113 patients completed treatment and the 3 discontinuations were due to reasons unrelated to study treatment.

The mean age of patients was 31 years with majority of patients being female (61%), Caucasian (92%) with iris colour black/brown (42%; 20% were hazel/ green and 38% were blue/ grey). Majority of patients wore soft lenses (91%; only 9% wore hard gas-permeable lenses); however, at one centre, 28% of patients wore hard lenses (72% wore soft lenses). The average duration of wear for the current lens type was longer for placebo patients (3.6 years) compared with LE (2.6 years), although the difference was not statistically significant (p = 0.175). Overall, 58% of the patients had previous episodes of GPC and the average length of the current episode was shorter in the LE group [mean (SD): 209 (391) days] compared with the placebo group [390 (1145) days] although interpretation was limited due high variability.

Treatment compliance was difficult to interpret as it was only documented by number of bottles, visit of dispensation and occasional comments included in the study evaluations. Overall, 3 patients dispensed only single bottle of medication (2.7%), 73 patients dispensed 2 bottles (64.6%) and 31 patients were dispensed 3 bottles (27.4%), 5 patients were dispensed 4 bottles (4.4%) and 1 patient had 6 bottles (0.9%).

7.2.2.1.4. Primary efficacy results

At baseline, the mean severity score for papillae was marginally less for LE than for placebo (2.02 and 2.16, respectively) and the mean expected AUC was 56.5 and 60.4 severity unit days for LE and placebo, respectively. Following 4 weeks treatment, the mean AUC for patients treated with LE was significantly lesser than that for placebo (43.1 and 52.9 severity unit days, respectively) with mean change from baseline of -13.4 and -5.7 severity unit days with LE and placebo, respectively ($p < 0.001$). The unadjusted mean percent improvement (decrease from expected) in AUC was 21% for LE and 10% for placebo. The repeated measures analysis of data across individual study visits showed only marginal significant difference between LE and placebo at Visit 2, but it was statistically significant at all other visits ($p < 0.001$). At the final visit (after 4 weeks of treatment), 16% of the LE patients were free of papillae compared to 2%

[8] Baseline was severity of signs and symptoms on day 0 before start of treatment and just after patients had removed contact lenses.

of placebo patients and improvement was observed in 72% of LE patients compared to 47% of placebo patients.

Prior to treatment, only 24% of the patients presented with discharge in association with their GPC with most of these patients only having mild severity (19/27, 70%) and 4 weeks of treatment with LE did not show any difference from placebo.

Most patients (82%) reported itching prior to initiating treatment. After 4 weeks of treatment, mean decrease in itching was 56% and 50% for LE and placebo, respectively with 93% and 85%, respectively reporting some improvement. Over the treatment period, 6 of the 20 patients without baseline itching reported at least one treatment emergent incidence of itching- 3 patients from each treatment group.

Prior to treatment, 76% of patients reported discomfort associated with their GPC and following 4 weeks of treatment, improvement was observed in 96% (41/42) of the LE patients compared to 86% (38/44) of the placebo patients; the average improvement in discomfort was 64% for LE and 58% for placebo.

> Comments: Of the primary efficacy parameters, only papillae showed a statistically and clinically significant reduction following 4 weeks of treatment with LE; discharge, itching and discomfort failed to show any significant improvement over placebo.

7.2.2.1.5. Secondary efficacy results:

Assessment of the Physician's clinical judgement at last visit showed that 11% of the LE patients and 30% of the placebo patients were rated as unimproved by the investigator (1 placebo patient had worsened). Overall 41% of the LE patients and 28% of the placebo patients had at least reasonable control of their symptoms at the end of the study. Repeated measures analysis showed that LE was favoured over placebo at all visits throughout the study with marginally significant difference between LE and placebo at Visit 2 ($p = 0.085$) and Visit 5 ($p = 0.055$) and significant difference observed at Visit 6 ($p = 0.009$).

A the last visit, 22% of the LE patients and 27% of the placebo patients considered themselves unimproved; 57% of LE patients and 48% of placebo patients felt their symptoms were reasonably controlled. However, there was no significant difference between LE and placebo for the secondary endpoint of 'patient's opinion'.

7.2.2.1.6. Other signs/ symptoms associated with GPC:

Prior to treatment, 75% of LE patients and 61% of placebo patients had bulbar injection with majority (88%) of patients having mild severity. Following 4 weeks of treatment, improvement was observed in significantly more LE patients (88%, 37/42) compared with placebo (74%, 26/35). There was significantly greater improvement in investigator 127's LE patients as 94%, (16/17) with bulbar injection at baseline showed improvement compared with only 47% (8/17) of placebo patients; it is important to note that this investigator had the largest group of patients that continued lens wear ($n = 20$).

Prior to treatment, 82% of LE patients and 91% of placebo patients presented with palpebral injection (48-52% had moderate or severe severity). Overall, there was no significant treatment difference following 4 weeks of treatment with exception of investigator 112 who showed significantly greater improvement with LE.

Prior to treatment, 50% of LE patients and 63% of placebo patients reported foreign body sensation (FBS) and most of these patients improved after 4 weeks of treatment with only 7% (2/28) of LE patients and 3% (1/36) of placebo patients failing to show at least some improvement. Of those without FBS symptoms at baseline, 21% (5/28) of the LE patients and 24% (5/21) of placebo patients reported FBS at least once over the course of the study. Overall, there was no statistically significant difference between LE and placebo although there was numerically greater improvements with LE throughout the study.

Prior to treatment, photophobia was reported in 34% of LE patients and 37% of placebo patients and following 4 weeks of treatment 84% (16/19) of LE patients and 95% of the placebo patients showed some improvement and the mean change for severity of photophobia at each visit favoured placebo.

Tearing was reported in 57% of LE and 63% of placebo patients prior to start of treatment. Improvement was observed in similar proportion of patients in the LE (94%, 30/32) and placebo (92%, 33/36) groups.

The incidence of erythema was low prior to start of treatment (20% and 10% in LE and placebo groups, respectively) and of these patients, improvement was noted in 75% (9/12) of LE patients and 82% (9/11) placebo patients.

A post-hoc analysis was done to determine if continued lens wear affects the efficacy of LE. A trend to superiority of LE over placebo was seen for papillae ($p = 0.005$), palpebral injection ($p = 0.048$) and bulbar injection ($p = 0.001$). None of the other endpoints showed any significant difference between LE and placebo; the main difference in this subgroup of lens wearers compared to general results is lack of statistically significant difference in physician's clinical judgement ($p = 0.235$). However, it is important to note that power to detect such differences was diminished due to post-hoc nature of this analysis.

> Comments: Discontinuation of therapy with or without any therapy is commonly used to treat GPC and it is known that most symptoms and some of the signs resolve rapidly. The slower resolving signs such as papillae respond better to therapy as was observed in this study. Post-hoc analysis in a small subset of patients who continued to wear lenses also showed statistically significant improvement in signs of palpebral and bulbar injection with favourable trends for itching and tearing. However, this needs to be evaluated in a prospective study as it would be of practical significance to assess efficacy and safety of LE in patient with GPC who wish to or are required to continue wearing their contact lenses. The LE eye drop suspension is compatible with most of the commonly used contact lenses; the vehicle used for LE suspension is a viscous soothing liquid and it may contribute to the overall improvement by improving lubrication of the conjunctiva or by dilution of the antigen. However, if the vehicle itself is therapeutic then the need for using a local steroid preparation is questionable. Hence, a larger study in patients who continue to wear their contact lenses while presenting with symptoms/ signs of GPC is required.
>
> Furthermore, symptoms/signs of GPC after stopping treatment were not evaluated in this study and any possible rebound effect was not assessed.

7.2.2.2. Study 107

7.2.2.2.1. Study design, inclusion/ exclusion criteria

Study P5604-107 was a prospective, double-blind, randomised, placebo-controlled, parallel group multicentre comparison of LE with placebo in patients with unilateral or bilateral contact lens associated GPC. The study was conducted from April 1993 to March 1994 at 18 centres in USA.

The inclusion/ exclusion criteria were similar to those described for Study 106 above with the following exceptions:- Ocular signs/ symptoms of GPC were defined in detail and included at least mild itching (Grade 2) and partially controlled or worse (Grade 2 or 3) lens intolerance in at least one eye. Furthermore, patients with contact lenses that were poorly fitted or in poor condition or required replacement were also excluded. Patients had the option to discontinue use of contact lenses or could continue to wear them in this study.

7.2.2.2.2. Study treatment and efficacy endpoints, statistical analysis:

Overall 233 patients were randomised to treatment with LE or placebo with one drop instilled in both eyes 4 times daily for 6 weeks.

Reductions in papillae (size and severity), lens intolerance and itching were the primary efficacy variables. Each of these scales required a score of 2 or more to meet the inclusion criteria and an improvement of at least one unit on the rating scale was defined as positive response. Difference in response rates between treatment groups were analysed using Cochran-Mantel-Haenszel tests controlling for investigator. The AUC was calculated using the trapezoidal rule for the first 42 days of treatment. Baseline was subtracted from the ratings for all variables except investigator and patient global assessments. AUC was analysed by 2-factor analysis of covariance in the case of signs/ symptoms and lens intolerance. The AUCs for investigator and patient global scores were analysed using 2-factor analysis of variance (the 2 factors were treatment group and investigator) and the covariate where applicable was the baseline rating. Secondary efficacy variables were conjunctival injection (palpebral and bulbar) and global assessments (investigator and patient). Other signs and symptoms that were evaluated included erythema, discharge, foreign body sensation, photophobia, tearing and corneal disease. During Visit 1, the worst eye was identified based primarily on papillae and lens intolerance. If both eyes were equally affected, the right eye was selected for evaluation of all efficacy endpoints.

The sample size of 206 evaluable patients was sufficient to detect a 20% difference in response rate between placebo and LE when the placebo rate was as high as 50% with a power of 80% at significance level of 0.05 (two-sided test).

7.2.2.2.3. Participant flow:

Of the 531 patients who were screened, 233 were randomised to treatment with LE (n = 110) and placebo (n = 113). Overall 91% of the patients in each treatment group completed the study and common reasons for discontinuation were AEs, lack of efficacy, other unrelated reasons with no significant difference between treatment groups. There were only minor protocol deviations with similar incidence in both treatment groups and no per protocol analysis was performed.

7.2.2.2.4. Baseline data:

The mean age was 33-34 years with 56-57% being > 30 years old. Majority of the patients were female (75%), Caucasian (89%), with light irides (58%), wore soft contact lenses (84%) and daily wear lenses (54%). Overall, 84% of the patients were still wearing their lenses on Visit 1 (baseline visit). The baseline demographics and other characteristics were similar between the LE and placebo groups.

7.2.2.2.5. Primary efficacy results:

7.2.2.2.5.1. Papillae

The response rate for papillae was significantly greater with LE (78%, 85/109) compared with placebo (51%, 56/110) (diff = 27%, 95% CI: 15%, 39%, p < 0.001). At all visits beginning with Visit 2, the response rate was statistically significantly (p < 0.044) greater in the LE group (21% to 89%) compared to the placebo-treated group (12%-55%). At day 49 (7 days after cessation of treatment), the response rate for LE remained significantly greater than for placebo (82% versus 52%, p < 0.001). The mean estimated difference in AUC[9] between treatment groups was -15.0 grade days (95% CI: -20.5, -9.4), that is the average severity of the condition in the LE group was approximately 0.4 grade units less than that in the placebo group. The mean change from baseline in severity score over the course of the study ranged from -0.2 to -1.2 in the LE

[9] AUC over the 42 day treatment period was a measure of change in severity of disease relative to baseline. Negative AUCs indicate improvement and the greater the absolute magnitude, the greater the improvement.

group and it was -0.1 to -0.7 in the placebo group; the difference of approximately 0.1 to 0.5 units in favour of LE was statistically significant at all visits except Visit 2 ($p < 0.001$).

7.2.2.2.5.2. Itching

Both treatment groups had mean baseline rating of 2.6 units with 50-53% of patients experiencing mild (Grade 2) itching at baseline. The response rate was significantly greater with LE (95%, 104/109) compared with placebo (81%, 89/110) (diff = 14%, 95% CI: 6%, 22%, $p = 0.001$). At the final visit, 70% of the LE patients had an itching score of 0 compared with 44% of the placebo patients.

The response rate in the LE group (89%-95%) was statistically significantly greater than the placebo group (77%-83%) only for visits beginning with Visit 4 ($p = 0.008$ to $p = 0.037$). At the off-therapy visit at day 49, the response rate showed no difference between the LE and placebo groups (85% versus 81%, $p = 0.394$). The estimated mean difference in AUC was -21.3 grade day (95%CI: -28.9, -13.7), that is, the severity of itching in the LE group was approximately 0.5 grade units less than in the placebo group throughout the study. Itching was a symptom expected to resolve early in treatment and for such symptoms the analysis of AUC also employed a 14 day interval which showed estimated treatment difference of -4.5 grade day (95% CI: -7.2, -1.8) or approximately 0.3 units for 14 days. The mean change from baseline in severity score over the course of the study ranged from -1.42 to -2.2 in the LE group and it was -1.2 to -1.6 in the placebo group; the difference of approximately 0.1 to 0.6 units in favour of LE was statistically significant at Visits 5 through Visit 8 ($p < 0.001$).

7.2.2.2.5.3. Lens intolerance

Both treatment groups had baseline ratings of 2.2units with significant difference among investigators for baseline rating without regard to treatment group ($p < 0.001$) with 0% to 71% patients in the uncontrolled category across investigators. The response rate was only marginally significantly greater than placebo (87% versus 77%, diff = 10%, 95% CI: 2%, 18%, $p = 0.053$). For 1 investigator, placebo was favoured over LE by 10%, 5 investigators showed identical rates and for 4 investigators, LE was favoured over placebo by 8% to 75%. For weeks 3 to 6, the response rates in the LE group (90%-94%) were significantly higher than those in the placebo group (74-79%) ($p = 0.001$ to $p = 0.003$). At weeks 1 and 2, the difference was not significant due to relatively high placebo response (69% at week 2). The estimated mean difference in AUC between LE and placebo was -16.3 grade day (95% CI: -24.1, -8.6) and the severity of lens intolerance throughout the study in the LE group was approximately 0.4 grade units less than that in the placebo group. The mean change from baseline in severity score ranged from -1.2 to -1.8 for LE and -0.9 to -1.2 for placebo with difference of 0.3 to 0.6 units being statistically significantly in favour of LE at weeks 4, 5 and 6 and at the final week ($p = 0.006$).

7.2.2.2.6. Secondary efficacy results

A positive response on the investigator's global rating was defined as a score of 2 or less. The response rate was significantly greater for LE (83%, 90/109) compared with placebo (57%, 63/110) with difference of 26% (95% CI: 14%, 38%, $p < 0.001$). At the final visit, 24% of the LE patients were rated as fully controlled compared with 10% of the placebo patients. At all visits beginning with Visit 2, the response rate in the LE group (39% to 91%) was statistically significantly ($p < 0.001$ to $p = 0.035$) greater than that in the placebo group (27%-58%). The estimated mean difference in AUC between LE and placebo was -29.1 grade day (95% CI: -36.1, -21.9) and the severity of the condition in the LE group throughout the study was approximately 0.7 grade units less than that in the placebo group.

The response rate of patients global rating at the final visit was significantly greater in the LE group (83%, 91/109) compared with placebo (61%, 67/110) with treatment difference of 22% (95% CI: 10%, 34%, $p < 0.001$). At the final visit, 43% of the LE patients rated their GPC as fully controlled compared to only 14% of the placebo patients. The mean estimated difference in AUC

between LE and placebo was -33.3 grade day (95% CI: -42, -24.6) and the severity of the condition in the LE group throughout the study was approximately 0.8 units less than that in the placebo group.

The baseline rating of palpebral conjunctival injection was 1.7 units in both the LE and placebo group. The response rate was significantly greater for LE (65%, 82/96) compared with placebo (40%, 39/97) with treatment difference of 25% (95% CI: 11%, 39%, $p < 0.001$). At the final visit, 32% (31/96) of the LE patients had a palpebral injection score of 0 compared with only 10% (10/97) of the placebo patients. The response rate for LE was significantly greater than placebo from Visit 4 through Visit 8. At the safety follow-up, the response rate for LE was still significantly greater than placebo (62% versus 45%, $p = 0.030$). The estimated mean difference in AUC between LE and placebo was -19.1 grade days (95% CI: -25.1, -13.1) and the severity of the condition in the LE group throughout the study was approximately 0.5 grade units less than that in the placebo group . The mean change from baseline in severity score in the LE group ranged from -0.2 to -0.9 at on-treatment visits compared with -0.1 to -0.4 in the placebo group and the difference of 0.1 to 0.6 units in favour of LE was statistically significant ($p < 0.001$ – $p = 0.015$).

The mean baseline rating for bulbar conjunctival injection was marginally statistically significantly higher in the LE group compared with placebo (1.1 versus 1.2 units, $p = 0.054$) and there were more LE patients with mild rating at baseline compared with placebo (92% versus 83%). The response rate for LE (72%, 56/78) was significantly greater than that for placebo (38%, 29/76) with treatment difference of 34% (95% CI: 19%, 49%, $p < 0.001$). At the final visit, 67% of LE patients had bulbar injection score of 0 compared to only 32% of placebo patients. At all therapy visits except Visit 2, the response rate in the LE patients (54-73%) was significantly ($p < 0.001$ to 0.011) greater than that in the placebo group (30-44%). At the off therapy safety visit, the response rate for LE remained significantly greater than that for placebo (78% versus 43%, $p < 0.001$). The estimated mean difference in AUC between LE and placebo was -17.2 grade day (95% CI: -22.5, -12) and the severity of the condition in the LE group throughout the study was approximately 0.4 grade units less than that in the placebo group. The mean change from baseline in severity score ranged from -0.3 to -0.7 in the LE group over the course of the study compared with -0.2 to -0.5 in the placebo group; the difference of 0.1 to 0.4 units in favour of LE was statistically significant at Visit 4 through Visit 8 ($p = 0.001$ to 0.041).

7.2.2.2.7. Other efficacy results

Erythema was reported in only 68 patients (31%) at baseline with greater but not significant improvement observed in the LE group at the final visit ($p = 0.318$) with similar response rates for LE (83%, 29/35) and placebo (73%, 24/33). The AUC was significantly in favour of LE ($p = 0.042$). Only 7 patients (3%) reported corneal disease at baseline and no statistical analysis was done on these data. Overall 74 patients (34%) reported discharge at baseline and the response rate at the final visit was significantly greater for LE (91%, 32/35) compared with placebo (72%, 28/39, $p = 0.032$). Overall, 186 patients (85%) reported a foreign body sensation at baseline with significantly greater response rate for LE compared with placebo ($p < 0.001$). Overall, 115 patients (53%) reported tearing at baseline and LE was significantly better than placebo ($p = 0.001$). Overall, 99 patients (45%) reported photophobia at baseline with significant benefit observed throughout the study for LE over placebo.

7.2.2.2.8. Subgroup analysis

In order to assess the impact of pre-study and baseline patient characteristics on the efficacy of LE, a detailed evaluation was done for papillae scores, the actual diagnostic indicator of GPC and the primary efficacy parameters of rate of positive response was analysed. There was a statistically significant greater response in terms of papillae for females (83%) treated with LE than males (61%) and also a marginally significant difference in response for Caucasians (81%)

treated with LE than other races (55%) although interpretation was limited due to small number of Non-Caucasians. There was no statistical significant difference between treatment groups in response rates when the population was stratified by age, iris pigmentation, lens wear measures (lens type, lens wear and wearing of lenses at Visit 1 or unilateral versus bilateral qualification of eyes for evaluation.

> Comments: LE treatment was more effective than placebo for 2 of the 3 primary efficacy parameters (papillae and itching) and was marginally significant for third parameter of lens intolerance. The rate of positive response to LE treatment in comparison to placebo met both statistical and clinical significance (patients showing a 1 grade improvement). Furthermore, the efficacy of LE was observed early by end of first week and was maintained throughout the study. LE also showed significant improvement compared to placebo for the secondary and supportive efficacy measures. There was no rebound or loss of efficacy for the 2 main parameters of papillae and itching measured 7 days after stopping treatment (on day 49).

7.2.2.3. Study 108

7.2.2.3.1. Study design, inclusion/ exclusion criteria:

Study P5604-108 was a prospective, double-blind, randomised, placebo-controlled, parallel group multicentre comparison of LE with placebo in 220 patients with unilateral or bilateral contact lens associated GPC. The study was conducted from May 1993 to February 1994 at 12 centres in USA.

The inclusion/ exclusion criteria, study treatments, efficacy endpoints, statistical analysis were similar to those described for Study 107 above.

7.2.2.3.2. Participant flow:

Of the 655 screened patients, 220 patients were randomised to treatment (LE = 111; Placebo = 109). Overall, 192 patients completed treatment and the common reasons for discontinuation were lack of efficacy (LE versus placebo: 1 versus 11), AEs (4 versus 3) and reasons unrelated to treatment (5 versus 4). Overall, all 220 patients were included in the ITT analysis and since only 4 patients had major protocol deviations/ violations, no per protocol analysis was done.

7.2.2.3.3. Baseline data:

The mean age of patients was 33-34 years and majority (56-62%) were aged > 30 years. Majority of the patients were females (76%), Caucasian (85%) with dark irides (53%), wore soft lenses (83%) which were daily wear lenses (74%). Overall, 88% were wearing lenses at Visit 1 (86% and 90% in LE and placebo groups, respectively); 33% had one qualified eye while 67% had both eyes qualified for analysis (and so the right eye was selected for efficacy analysis). The baseline patient characteristics were similar between the LE and placebo groups.

7.2.2.3.4. Primary efficacy results

7.2.2.3.4.1. Papillae

The baseline rating for papillae was 2.3 units in both groups. The response rate was significantly greater in the LE (75%, 83/111) group compared with placebo (50%, 55/109) with treatment difference of 25% (95%CI: 13%, 37%, $p < 0.001$). At the final visit, 29% of the LE patients had a papillae score of 0 compared to only 8% of placebo patients. At all visits on therapy beginning with Visit 3, the response rate in the LE group (48-81%) was significantly greater ($p < 0.001$ to 0.021) than that in the placebo group (24-59%). At day 49 (post-therapy safety visit), the response rate was still significantly greater for LE compared with placebo (81% versus 59%, $p = 0.003$). The difference between LE and placebo for AUC was -18.4 grade days (95% CI: -24.4, -12.4) and the mean severity of the condition in the LE group throughout the study was about 0.4 grade units less than in the placebo group.

7.2.2.3.4.2. Itching

Both treatment groups had mean baseline rating of 2.6 units with 30-78% of patients experiencing mild (Grade 2) and 0-23% experiencing severe itching at baseline. The response rate was significantly greater with LE (92%, 102/111) compared with placebo (76%, 83/109) (diff = 16%, 95% CI: 7%, 25%, p = 0.001). At the final visit, 66% of the LE patients had an itching score of 0 compared with 31% of the placebo patients. The response rate in the LE group (76%-95%) was statistically significantly greater than the placebo group (61%-86%) for all visits beginning with Visit 3 (p < 0.001 to 0.042). At the off-therapy visit at day 49, the response rate showed no difference between the LE and placebo groups (92% versus 84%, p = 0.094). The estimated mean difference in AUC was -25.4 grade days (95%CI: -33.8, -16.9), that is, the severity of itching in the LE group was approximately 0.6 grade units less than in the placebo group throughout the study. Itching was a symptom expected to resolve early in treatment and for such symptoms the analysis of AUC also employed a 14 day interval which showed estimated treatment difference of -5.6 Grade day (95% CI: -8.2, -2.9) or approximately 0.4 units for 14 days. The mean change from baseline in severity score over the course of the study ranged from -1.4 to -2.2 in the LE group and it was -0.9 to -1.6 in the placebo group; the difference of approximately 0.3 to 0.8 units in favour of LE was statistically significant for all visits (p less than or equal to 0.001 to 0.013).

7.2.2.3.4.3. Lens intolerance

Both treatment groups had baseline ratings of 2.3 units with significant difference among investigators for baseline rating without regard to treatment group (p < 0.001) with 0% to 100% patients in the uncontrolled category across investigators. The response rate was significantly greater in the LE group (84%, 93/111) compared with placebo (66%, 72/109) and the treatment difference was 18% (95% CI: 9%, 29%, p < 0.002). The response rates in the LE group were statistically significantly higher than placebo only at day 7 (76% versus 61%, p = 0.010) and day 35 (87% versus 74%, p = 0.048). The treatment difference was not statistically significant at other weeks due to a high placebo response. The estimated mean difference in AUC between LE and placebo was -13.0 grade days (95% CI: -20.7, -5.2) and the severity of lens intolerance throughout the study in the LE group was approximately 0.3 grade units less than that in the placebo group. The mean change from baseline in severity score ranged from -1.1 to -1.6 for LE and -0.9 to -1.3 for placebo with difference of 0.2 to 0.5 units being statistically significantly in favour of LE at weeks 1, 3 to 6 and at final week (p = 0.002 to 0.046).

7.2.2.3.5. Secondary efficacy results

A positive response on the investigator's global rating was defined as a score of 2 or less. The response rate was significantly greater for LE (88%, 98/111) compared with placebo (59%, 64/109) with difference of 29% (95% CI: 18%, 40%, p < 0.001). At the final visit, 40% of the LE patients were rated as fully controlled compared with 16% of the placebo patients. At all visits beginning with Visit 2, the response rate in the LE group (55% to 91%) was statistically significantly (p < 0.001 to p = 0.035) greater than that in the placebo group (39-67%). The estimated mean difference in AUC between LE and placebo was -28.8 grade days (95% CI: -38.2, 19.2) and the severity of the condition in the LE group throughout the study was approximately 0.7 grade units less than that in the placebo group.

The response rate for the patients global rating at the final visit was significantly greater in the LE group (86, 96/111) compared with placebo (62%, 68/109) with treatment difference of 24% (95% CI: 13%, 35%, p < 0.001). At the final visit, 45% of the LE patients rated their GPC as fully controlled compared to 28% of the placebo patients. At all visits except Visits 2 and 7, the response rate in the LE group (54-88%) was significantly greater than placebo (55-71%, p < 0.001 to -0.016). The mean estimated difference in AUC between LE and placebo was -23.6 grade days (95% CI: -34.6, 12.7) and the severity of the condition in the LE group throughout the study was approximately 0.6 units less than that in the placebo group.

The baseline rating of palpebral conjunctival injection was 1.8 units in both the LE and placebo group. The response rate was significantly greater for LE (72%, 76/106) compared with placebo (55%, 57/104) with treatment difference of 17% (95% CI: 4%, 30%, p = 0.012). At the final visit, 43% of the LE patients had a palpebral injection score of 0 compared with 23% of the placebo patients. The response rate for LE was significantly greater than placebo only at Visit 3 and final visit. At the safety follow-up visit, the response rate for LE was not significantly greater than placebo. The estimated mean difference in AUC between LE and placebo was -14.5 grade days (95% CI: -20.3, -8.6) and the severity of the condition in the LE group throughout the study was approximately 0.5 grade units less than that in the placebo group . The mean change from baseline in severity score in the LE group ranged from -0.5 to -1.1 at on-treatment visits compared with -0.3 to -0.8 in the placebo group and the difference of 0.2 to 0.4units in favour of LE was statistically significant (p = 0.001 to 0.023) at all treatment visits except Visits 4, 5 and 7.

The mean baseline rating for bulbar conjunctival injection was similar in the LE group compared with placebo (1.5 versus 1.6 units, p = 0.185). The response rate for LE (85%, 69/81) was significantly greater than that for placebo (47%, 35/74) with treatment difference of 38% (95% CI: 24%, 52%, p < 0.001). At the final visit, 69% of LE patients had bulbar injection score of 0 compared to 39% of placebo patients. At all therapy visits except Visit 2 and 6, the response rate in the LE patients (63-86%) was significantly (p < 0.001 to 0.021) greater than that in the placebo group (33-63%). At the off therapy safety visit, the response rate for LE remained significantly greater than that for placebo (89% versus 61%, p = 0.002). The estimated mean difference in AUC between LE and placebo was -13.4 grade day (95% CI: -21.3, -5.5) and the severity of the condition in the LE group throughout the study was approximately 0.3 grade units less than that in the placebo group. The mean change from baseline in severity score ranged from -0.6 to -1.3 in the LE group over the course of the study compared with -0.4 to -1.0 in the placebo group; the difference of 0.2 to 0.5units in favour of LE was statistically significant at all visits (p = 0.001 to 0.034).

7.2.2.3.6. Other efficacy results

Erythema was reported in 101patients (46%) at baseline with significantly greater improvement observed in the LE group at the final visit (p = 0.036). Only 8 patients (4%) reported corneal disease at baseline and no statistical analysis was done on these data. Overall 112 patients (51%) reported discharge at baseline and analysis of AUC suggested that LE was slightly better than placebo (p = 0.002). Overall, 188 patients (85%) reported a foreign body sensation at baseline with slight advantage of LE over placebo for response rates at final visit (p = 0.019). Overall, 150 patients (68%) reported tearing at baseline and LE was significantly better than placebo (p = 0.004). Overall, 112 patients (51%) reported photophobia at baseline and although marked reduction in this symptom was observed in both LE and placebo groups, LE was significantly better than placebo at final visit (p = 0.003).

7.2.2.3.7. Subgroup analysis

There was no statistical significant difference between treatment groups in response rates when the population was stratified by age, gender, race, iris pigmentation, lens wear measures (lens type, lens wear and wearing of lenses at Visit 1) or unilateral versus bilateral qualification of eyes for evaluation.

Comments: Treatment with LE for 6 weeks was more effective than placebo (vehicle for LE) in treatment of contact lens associated GPC with clinically relevant and statistically significant improvements in all 3 primary efficacy parameters of papillae, itching and lens intolerance. This was supported by significant improvements in the secondary (investigator/ patient global assessment and bulbar/ palpebral conjunctival injection) and other ocular signs and symptoms. Furthermore, there did not appear to be any rebound of signs/ symptoms of GPC following discontinuation of LE therapy; response

rates for LE, 7 days after discontinuation of treatment was similar to that observed at the end of the double-blind, 6-week treatment period.

7.2.3. Acute anterior uveitis

7.2.3.1. Study 122/1221

7.2.3.1.1. Study design, location, objectives

This was a double-blind, randomised, placebo-controlled, parallel group multicentre study in 162 patients with acute anterior uveitis. The study was conducted from October 1993 to September 1994 at 11 centres (8 in USA and 3 in UK). The main objective of the study was to compare efficacy and safety of LE 0.5% compared with prednisolone acetate 1% ophthalmic suspension in reducing the signs and symptoms of acute anterior uveitis.

7.2.3.1.2. Inclusion/ exclusion criteria

The main inclusion criteria were adults aged 18-75 years; clinical diagnosis of acute anterior uveitis with the following signs and symptoms:- an active anterior chamber cell reaction of at least 1.5 + and no presence of hypopyon, presence of at least 1 + ocular pain, photophobia and flare; presence of ciliary flush; if patient had previous episodes of AAU, the most recent attack should have been > 3 months prior to enrolment (later amended to at least 6 weeks).

The main exclusion criteria were:-. Any abnormality preventing reliable tonometry; ocular hypertension with IOP > 25mmHg in either eye; uncontrolled primary angle glaucoma (later amended to include all types of glaucoma); presence of hyphema, presumptive diagnosis, known history or clearly overt symptoms of AAU secondary to local or systemic infectious disease (TB, syphilis, herpes) or systemic inflammatory disease (such as systemic lupus erythematosus (SLE), Wegener's granulomatosis); concomitant posterior uveitis, choroiditis or significant macular oedema; unstable dosing regimen of any systemic or topical medication that could affect inflammatory response (for example corticosteroids, immunosuppressives, NSAID; history of severe/ serious ocular pathology or other medical conditions; allergy to corticosteroids, LE or any other component of study treatment; pregnancy/ lactation.

7.2.3.1.3. Study treatments

Patients were randomly assigned to treatment with either LE 0.5% or prednisolone acetate 1% ophthalmic suspensions and instructed to instil one drop into affected eye[10] 8 times daily for first 7 days, then 6 times daily until day 14 and then to 4 times daily until day 21. Thereafter, the daily dose was reduced according to one of 2 schedules based upon the anterior chamber cell rating till day 42.[11]. Follow up examinations occurred on Days 2, 7, 14, 21, 35 and 42 of blinded therapy. An off therapy examination was done on Day 49 or 7 days after study treatment discontinuation.

7.2.3.1.4. Efficacy endpoints

The primary efficacy variables were: the median time to a rating of 0 for the cell reaction in the anterior chamber; AUC as an estimate of severity over the first 21 days of treatment; proportion of patients with score of 0 cell reaction at the final visit; proportion of patients with at least one unit decrease in the anterior chamber cell rating.

Time to resolution of flare was a secondary variable. Other supportive variables were other signs and symptoms. Many of the signs and symptoms (ocular pain, photophobia, ciliary flush,

[10] The protocol did not specify if one or both eyes were to be treated in case of bilateral disease; however, all patients in the study only had one qualified/ affected eye.

[11] If by day 21, anterior chamber cell rating had reached 0, then the following schedule: days 22-25, three times daily; days 26-28- twice daily; days 29-35 once daily in morning. If the anterior chamber cell rating had not reached 0 by day21, then following schedule :- days 22 until AC rating reached 0 = four times daily; days 1-4 after 0 cell rating- 3 times daily; days 5-7 following 0 cell rating = twice daily; days 8-14 after 0 cell rating-once daily in morning.

keratic precipitates) were rated on a 4-point scale (0 to 3 with 0 = absent, 1 = mild, 2 = moderate and 3 = severe).

7.2.3.1.5. Randomisation, blinding, sample size and statistical methods

The study was double-blind and eligible patients were randomised to LE (n = 83) or prednisolone 1% (n = 79). There were no pilot data on which to estimate sample size. A minimum sample size of 120 evaluable patients (60 per group) would yield a power of 76% of correctly rejecting the null hypothesis of equal time to resolution at significance level of 0.05 and true median resolution times of 10 and 17 days for the two treatment groups. The power is increased to 96% if the true median resolution times are 7 and 14 days. Descriptive statistics by treatment group were presented for baseline rating, observed rating and change from baseline ratings on subsequent visits, final visit and the Visit 1-5 AUC of observed ratings. The proportion of patients with score of 0 and a change from baseline of 1 unit or more improvement from baseline was also tabulated for Visits 1-7 and final visit. Level of significance for rejection of null hypothesis was 0.05 and p-values > 0.05 and < 0.10 were identified as marginally significant. The null hypothesis of equality between treatment groups of the mean rank baseline rating, mean change from baseline at final and other visits was tested by the CMH chi-square test on ranked scores controlling for investigator. Equality between groups in time to resolution was tested by estimating the survival function using life table methods and log rank analysis. AUC was tested by analysis of covariance using baseline as covariate.

7.2.3.1.6. Analysis populations, participant flow, baseline data

Of the 205 screened patients, 162 were randomised to treatment (LE = 83; Prednisolone = 79). Treatment was completed by fewer LE patients (69%, 57/83) compared to the PA patients (86%, 68/79) with statistically significant association between treatment and proportion of patients completing treatment whether controlling for country or investigator. At US sites alone, the association was not significant (LE versus PA = 81% versus 85%, p = 0.0636) but the association was highly significant at the 3 UK sites (60% versus 87%, p = 0.004), Lack of efficacy was most common cause of discontinuation with 18 of 83 LE patients (22%) discontinued due to lack of efficacy compared with only 5% (4/75) in PA group. Overall, 14/18 LE patients who discontinued did so during first 10 days of therapy, but the other 4 patients responded initially to therapy but flared up upon tapering of the dose. Six patients were excluded from the ITT analysis as 4 patients were lost to follow-up and 2 developed AAU in the fellow eye. Eight additional patients were excluded from the PP analysis (3 in LE and 5 in PA group) due to use of prohibited concomitant ocular and systemic medications. However, since < 5% of the ITT was excluded from PP population, the PP analysis was not conducted. Majority of the patients were male (52%), Caucasian (72%) with mean age of 43 years. The baseline patient characteristics were similar in the LE and PA groups.

7.2.3.1.7. Primary efficacy results

The baseline anterior chamber (AC) cell rating was 2.5 and 2.6 in the LE and PA groups, respectively. The median time to reach a 0 cell rating was 23 and 20 days in LE and PA groups, respectively (p = 0.003). The anterior chamber cell severity through the first 21 days of therapy as reflected in the AUC were similar for both treatments (33.1 and 24.5 unit days, p = 0.211). The overall mean change form baseline to final visit in rating was marginally statistically significantly in favour of PA (-2.2 units) compared to LE (-1.6 units, p = 0.075). However, none of the mean cell rating changes from baseline at Visit 2 through Visit 7 were significantly different between groups (p = 0.268 to 0.918).

A positive response was defined as a score of 0 or an improvement of at least 1 unit from baseline. The proportion of patients meeting a score of 0 was significantly greater in the PA group (89%, 67/75) compared with LE group (64%, 52/81) and the difference of -25% between the PA and LE groups was statistically significant (95% CI: -38%, -12%, p < 0.001). Similar

results were observed for the proportion of patients achieving an improvement from baseline of 1 or more cell rating units (LE versus PA: 69% versus 93%, p < 0.001).

Comments: The positive response rate in both treatment groups was similar at each visit from Visit 2 through Visit 6 and the overall difference at the final visit was likely due to the greater number of patients in the LE group who being discontinued at Visit 2 had their unresolved ratings carried forward in the analysis. Overall, these results demonstrate that patients are less likely to respond to LE compared to PA.

7.2.3.1.8. Secondary and other efficacy results

The aqueous chamber flare rating is a measure of the protein present in the aqueous humor and the mean flare ratings were slightly higher in the LE group (2.0) compared with the PA group (1.8, p = 0.076). The median time to reach complete resolution (0 score) was significantly greater in the LE group compared with PA group (20 days versus 14 days, p = 0.002). The anterior chamber flare severity through the first 21 days of therapy also favoured PA (17.2 unit days) over LE (26.2 unit days, p = 0.041).

The mean change from baseline to final visit was similar in the LE (-1.2units) and PA (-1.5units, p = 0.116) groups. The response rate at the final visit was significantly higher in the PA group compared with the LE group; the proportion of patients meeting score of 0 by final visit was 63% (51/81) in the LE group and 87% (65/75) in the PA group (diff = -24%, 95% CI: -37%, -10%, p < 0.001) with similar results for proportion of patients with improvement from baseline of at least 1 unit.

The mean baseline ocular pain score was similar in the LE and PA groups (1.7 units each, p = 0.534). The median time to achieve resolution (score 0) was 7 days in both the LE and PA groups although the difference indicated significantly quicker resolution in the PA group (p = 0.045). The pain severity through first 21 days reflected by the AUC was also similar (LE = 15.1 unit days, PA = 11.2 unit days, p = 0.312). The overall change from baseline in mean pain score at final visit was similar in the LE (-1.2 units) and PA (-1.4units) groups (p = 0.229) and it was also similar at all other study visits. The response rate in terms of proportion of patients with score of 0 at final visit was slightly higher in the PA group (84%, 63/75) compared with the LE group (72%, 58/81) and the treatment difference of -12% was marginally significant (95% CI: -25%, -1%, p = 0.068). However, the proportion of patients showing improvement from baseline of 1 or more units was not significantly different (p = 0.129).

The mean photophobia score at baseline was similar in the LE (1.8) and PA (1.9) groups (p = 0.509). The median time to resolution was 8 days for both the PA and LE groups (0.829). The photophobia severity through the first 21 days of therapy reflected by the AUC was also similar for LE (17.3 unit-days) and PA (14.6 unit days) groups (p = 0.652). The mean change from baseline was -1.1 units and -1.5 units in the LE and PA groups, respectively, but the difference was not significant (p = 0.278). The proportion of patients achieving an improvement of 1 unit by final visit was 62% (50/81) in the LE group and 76% (57/75) in the PA group and the difference was not significant (p = 0.157).

The 2 treatment groups required to be identical in terms of ciliary flush with rating of 1 unit at baseline. The median time to resolution of ciliary flush was 7 days in both LE and PA groups, but the onset of resolution was quicker in the PA group (p = 0.026). The ciliary flush severity through first 21 days of therapy reflected in the AUC favoured PA (6.8 unit-days) over LE (10.4 unit-days, p = 0.005). The proportion of patients showing a positive response by the final visit (rating of 0 at final visit) was significantly higher in the PA group (93%, 70/75) compared with LE group (70%, 57/81, p < 0.001).

Keratic precipitates (KP) are inflammatory cells and white blood cells from the iris and ciliary body that enter the aqueous and adhere to the innermost corneal epithelium and are a typical finding in uveitis. A total of 111/156 patients presented with KP at Visit 1 (LE = 60, PA = 51) and the mean ratings were 1.3 and 1.2 for LE and PA, respectively (p = 0.412). The median time to

resolution of KP was slightly faster in the LE group compared with the PA group, although the difference was not significant (9 versus 12 days, p = 0.120). The KP severity through the first 21 days of therapy reflected in the AUC were similar for both treatments (LE = 14.5 unit-days, PA = 11.5 unit-days, p = 0.294). The overall median change from baseline in KP score was slightly greater in the PA group (-0.9units) compared to the LE group (-0.8 units, p = 0.032). A positive response was achieved in more PA patients compared to LE patients; the proportion of patients who achieved a score of 0 by the final visit was 80% and 70% in the PA and LE groups, respectively (p = 0.033), while the proportion of patients with improvement from baseline of at least 1 unit was 82% and 70%, respectively (p = 0.114).

Of all the other parameters which were evaluated, analysis was only done for those symptoms with sample size of > 40 patients showing these symptoms with score > 0 at baseline; hence, statistical analysis was only done for itching (26 LE and 21PA), tearing (47 LE and 38 PA), discomfort (55 LE and 42 PA), erythema (40LE and 38 PA), palpebral conjunctival injection (PCI) (30 LE, 26 PA) and bulbar conjunctival injection (76 LE and 62PA). The analysis of time to resolution, disease severity over 21 days (reflected by AUC) and proportion of patients achieving a score of 0 at final visit did not show any significant difference between LE and PA groups for itching, tearing, discomfort, erythema and palpebral conjunctival injection.

Overall, 138 patients presented with bulbar conjunctival injection (BCI) at baseline (rating of 1.4 and 1.6 units in the LE and PA groups, respectively, p = 0.067). The disease severity over first 21 days of therapy reflected by mean AUC was significantly lesser in the PA group (LE = 13.2, PA = 10.5 unit-days, p = 0.039). The proportion of patients achieving a BCI score of 0 at final visit was significantly greater in the PA group (68% and 85% in LE and PA groups, respectively, p = 0.017) as was the proportion of patients showing improvement from baseline of at least 1 unit (76% and 94%, respectively, p = 0.005). The mean rank change from baseline in BCI rating at the final visit was also significantly greater in the PA group (p = 0.002).

7.2.3.1.9. Subgroup analysis

The efficacy of LE in treatment of AAU was not affected by sex, race, iris pigmentation, HLA-B-27 response or site of uveitis. However, patients aged < 40 years were slower to achieve a 0 rating than older patients, but the difference was not statistically significant (median time to resolution was 28 days for < 40 year olds and 22 days for > 40 year old group. The severity of cell reaction over the 21 days of therapy was less severe in the older > 40 year group (28.9 unit days) compared with that in the younger < 40 year group (38.2 unit days, p = 0.038). The proportion of patients responding with either a cell rating of 0 or improvement of at least 1 unit the final visit favoured the older group although the differences were not statistically significant. Only 4 of the 81 LE patients presented at baseline with granulomatous anterior chamber reaction and none of these patients in this subgroup achieved cell rating of 0, while the median time to cell rating of 0 in the non-granulomatous group was 22 days (p = 0.032). Again none of the granulomatous subgroup patients reaction resolved (versus 68% of the nongranulomatous subgroup) and only 25% (versus 71% of the nongranulomatous subgroup) had improved by 1 or more units at the final visit.

> Comments: The rate of resolution was generally more rapid with PA compared to LE although this difference was more obvious for signs of anterior chamber reaction (cells and flare) and was less pronounced for primary symptoms of pain and photophobia associated with AAU. Overall, patients treated with PA showed a more rapid resolution of signs and symptoms of AAU and a greater proportion of patient's primary signs of AAU responded to PA treatment rather than to LE.
>
> The difference between PA and LE was more pronounced in the UK study sites while the US study sites failed to show significant difference between PA and LE. However, there were marked differences in the conduct of the trial in USA and UK which may have influenced the results. The most important difference was that UK sites tended to

discontinue treatment if the patients did not show very early signs of improvement. Since almost all such patients were in the LE treatment group, it may have biased results after Visit 2 against LE.

7.2.3.2. Study 126

7.2.3.2.1. Study design, objectives, location, dates

This was a double-blind, randomised, placebo-controlled, parallel group multicentre study in 175 patients with acute anterior uveitis. The study was conducted from 26 January 1996 to 7 October 1996 at 19 centres in USA. The main objective of the study was to compare efficacy and safety of LE 0.5% compared with prednisolone acetate 1% ophthalmic suspension in reducing the signs and symptoms of acute anterior uveitis. The study design, randomisation and blinding, were similar to those described for Study 122/1221 above.

7.2.3.2.2. Inclusion/ exclusion criteria:

The inclusion/ exclusion criteria were similar to those described for Study 122/1221 above.

7.2.3.2.3. Study treatment:

The dosing regimen used in this study was more intensive that that used in Study 122/1221 above. All randomised subjects received either LE 0.5% (n = 84) or PA 1% (n = 91) unilaterally for 28 days. The dosing regimen was Days 0-7- every 1 hour up to 16 times/ day; Days 8-14- every 2 hours up to 8 times daily; days 15-21- 4 times daily; Days 22-25- twice daily and Days 26-28- once daily in morning.

7.2.3.2.4. Efficacy endpoints:

Supportive efficacy variables were ocular signs (ciliary flush, keratic precipitates, PCI (palpebral conjunctival injection), BCI (bulbar conjunctival injection), corneal disease, erythema, chemosis and hyphema) and symptoms (itching, tearing, dryness, discharge and discomfort).

The primary efficacy outcome measure was the anterior chamber cell rating. The secondary outcome measure was rating for anterior chamber flare, pain and photophobia and the supportive outcome measures were other ocular signs and symptoms. The primary analytic endpoint of each of the above measures was % of patients with resolution (score of 0) at final visit; secondary endpoint was AUC survival analysis for disease severity and supportive analytical endpoint was proportion of patients with improvement of at least 1 unit from baseline at the final visit.

7.2.3.2.5. Sample size, analysis populations, statistical analysis:

A sample size of 80 gave the study 47% power with type 1 error rate of 0.05 to reject the null hypothesis (no difference in rate of resolution between LE and PA) using 2-tail test and assuming resolution rate at final visit of 92% and 82% with LE and PA, respectively. However, under a directional hypothesis (LE showing less resolution rate than PA) and one-tail testing the power with this sample size would be only 59%. However, LE as a conservative alternative to PA could be acceptable if its efficacy was no worse than that of PA by a specific amount, Makuch's and Simon's method provides the sample size such that with a specified power the upper confidence limit for a difference in efficacy does not exceed a specified difference under the assumption of equal efficacy between the 2 therapies. If the resolution rate were expected to be 92% and if the sponsor was 80% ($\beta = 0.2$) certain that the upper 95% confidence limit on the difference (PA – LE) did not exceed 10%, then each treatment group would have to be 91 patients. IF the difference to be detected were allowed to increase to 11% (LE = 81%), then the groups size should be 75.

The actual samples size in this study was 84 and 91 patients in LE and PA groups, respectively and it had 80% power to show that PA and LE was equal provided the upper limit of the 95% confidence limit for treatment difference (PA-LE) was < 11%.

Five of the 175 randomised patients failed to return for any on-treatment observations and so these patients were excluded from the ITT evaluable populations which now consisted of 170 patients (LE = 79, PA = 91). A per protocol efficacy population comprised of patients remaining on-treatment at least through Visit 5 (day 21) and adhering to the major requirements of the protocol (entry criteria, dosing and usage of concomitant medications); 6 LE and 10 PA patients were excluded from the PP analysis which was done in 154 patients (LE = 75, PA = 79).

7.2.3.2.6. Participant flow:

Overall, 175 patients were randomised to treatment of whom 137 completed treatment. The most common reasons for discontinuation were lack of efficacy (9 on LE and 7 on PA), AEs (2 each in LE and PA groups), lost to follow-up (LE = 6; PA = 3) and reasons unrelated to the study (LE = 6; PA = 3).

7.2.3.2.7. Baseline data

The mean age was 41-42 years (range 18-88 years) with 52-60% of patients aged < 40 years. Majority of the patients were male (52-55%), Caucasian (59-63%; 27-34% were Blacks) with dark irides (57-68%) and had iritis[12] (87-94%). Five LE patients (6%) had a positive HLA-B27 reaction at baseline compared to 10 PA (11%) patients. The remaining patients either had a negative or unknown HLA-B27 response. Majority of the patients presented with nongranulomatous inflammatory reaction (94-95%), had acute disease (58-62% compared to subacute or recurrent disease) and baseline cell scores of < 2 (67-68%). The baseline patient demographics and disease characteristics were similar in the LE and PA groups. Furthermore, the baseline mean ratings of the primary and secondary outcome measures were similar in both treatment groups.

7.2.3.2.8. Primary efficacy results

The proportion of patients achieving an anterior chamber cell rating score of 0 at final visit was significantly greater in the PA compared with the LE group (LE versus PA: 72% versus 87%, diff of LE – PA = -15%, 95% CI: -27%, -3%, p = 0.015). However, the proportion of patients remaining in the study who achieved a cell score of 0 increased in both treatment groups throughout the study and the treatment difference (LE-PA) ranged from -1% to -9% and was not statistically significant at any other time point.

Improvement in disease severity over 28 days of therapy reflected by AUC was not statistically significantly difference between the LE and PA groups (-33.6 and -43.8 unit-days, respectively, p = 0.285); the difference of 10.2 unit days over 28 days represented an advantage of PA over LE of 0.4 units per day. The analysis of the distribution of time to first resolution of anterior chamber cell showed no significant difference between the LE and PA groups over the course of therapy (p = 0.105) and for both groups, the median time to first resolution occurred during the interval encompassing Visit 3. The proportion of patients achieving an improvement from baseline of 1 or more rating units at final visit was significantly greater in the PA group (LE versus PA: 79% versus 91%, p = 0.030). At the final visit, the mean change from baseline was -1.5 and -1.9 units in the LE and PA groups, respectively (p = -0.154, CMH test for equality).

These results in the ITT population were supported by the PP analysis in which the proportion of patients with resolution of cell by the final visit was 72% (54/75) and 85% (67/79) for the LE and PA groups, respectively. Other measures of efficacy also showed similar results in the PP analysis.

[12] Site of uveitis was iritis in majority and only 6-13% had iridocyclitis.

7.2.3.2.9. Secondary efficacy results

The proportion of patients achieving a flare score of 0 on their final visit was significantly greater in the PA compared with the LE group (LE versus PA: 66% versus 82%; diff = -16%, 95% CI: -29%, -3%, p = 0.017).

However, the proportion of patients remaining in the study who achieved a flare score of 0 increased in both treatment groups throughout the study and the treatment difference (LE-PA) ranged from -4% to -9% and was not statistically significant at any other time point. Improvement in disease severity over 28 days of therapy reflected by AUC was not statistically significantly different between the LE and PA groups (-24.1 and -30.1 unit-days, respectively, p = 0.335); the difference of 6 unit days over 28 days represented an advantage of PA over LE of 0.2 units per day. The analysis of the distribution of time to first resolution of anterior chamber flare showed that flare tended to resolve earlier in the PA group compared with the LE group (p = 0.060). Over the course of therapy, the PA group tended to reach a 0 flare slightly ahead of the LE group with 84% (74/88) of PA patients reaching 0 flare at some time during the study compared with 67% (53/79) of LE patients. The median time to first resolution occurred during interval involving Visit 4 for the LE group and Visit 3 for the PA group and the survival curves were more divergent after 2 weeks of therapy. The proportion of patients achieving an improvement from baseline of 1 or more rating units at final visit was significantly greater in the PA group (LE versus PA: 80% versus 91%, p = 0.036). At the final visit, the mean change from baseline was -1.1 and 11.3 units in the LE and PA groups, respectively (p = 0.173, CMH test for equality).

The proportion of patients achieving a ocular pain score of 0 on their final visit was similar in the LE and PA groups (LE versus PA: 90% versus 85%) but the 5% difference in favour of LE was not statistically significant (95% CI: -5.8% to 14.6%, p = 0.474). The proportion of patients remaining in the study who achieved a pain score of 0 increased or remained the same for both treatment groups throughout the study and the treatment difference (LE-PA) ranged from -15% to +6% and was statistically significant at Visit 3. Improvement in disease severity over 28 days of therapy reflected by AUC was not statistically significantly different between the LE and PA groups (-34.9 and -39.9 unit-days, respectively, p = 0.292); the difference of 5 unit days over 28 days represented an advantage of PA over LE of 0.2 units per day. The analysis of the distribution of time to first resolution of ocular pain showed that pain tended to resolve at the same rate over the first week of treatment with median time to resolution occurring in period involving Visit 2. By the end of the study, similar proportion of patients in the LE and PA groups reached 0 pain sometime during the study (92% versus 91%, p = 0.748). The proportion of patients achieving an improvement from baseline of 1 or more rating units at final visit was similar in both treatment groups (LE versus PA: 94% versus 91%, p = 0.556). At the final visit, (p = 0.793, CMH test for equality).

The proportion of patients achieving a photophobia score of 0 on their final visit was similar in the LE and PA groups (LE versus PA: 79% versus 78%; diff = 1%, 95% CI:-11.5, 14.3, p = 0.973). The proportion of patients remaining in the study who achieved a photophobia score of 0 increased or remained the same for both treatment groups throughout the study and the treatment difference (LE-PA) ranged from -9% to +5% and was not statistically significant at any time. Improvement in disease severity over 28 days of therapy reflected by AUC was not statistically significantly different between the LE and PA groups (-32.6 and -37.5 unit-days, respectively, p = 0.175); the difference of 4.9 unit days over 28 days represented an advantage of PA over LE of 0.2 units per day. The analysis of the distribution of time to first resolution of photophobia showed that patients resolved at the same rate over the course of treatment = 0.702) and the median time to resolution occurred in the interval involving Visit 3 for both treatments. A similar proportion of patients in the LE and PA groups reached 0 photophobia score sometime during the study (92% versus 91%, p = 0.748). The proportion of patients achieving an improvement from baseline of 1 or more rating units at final visit was similar in

both treatment groups (LE versus PA: 85% versus 90%, p = 0.275). At the final visit, the mean change from baseline was -145 and -1.5 units in the LE and PA groups, respectively (p = 0.207, CMH test for equality).

7.2.3.2.10. Other efficacy results

Seven ocular signs (ciliary flush, keratic precipitates, PCI, BCI, corneal disease, erythema and chemosis) and five ocular symptoms (itching, tearing, dryness, discharge and discomfort) were evaluated as supportive efficacy measures. For most measures a complete analysis was done in terms of percent of patients resolved at final visit, AUC < time to resolution, proportion improving and change from baseline. However, for 4 of these measures with less than 40 patients presenting with positive findings at baseline (corneal disease, chemosis, dryness and discharge), only descriptive statistics were provided.

Of the 12 supportive measures, PA was numerically favoured over LE at the final visit for all 7 signs and for 2 of the symptoms (itching and tearing). LE was favoured for 3 symptoms (dryness, discharge and discomfort). Out of the 8 supportive measures with sufficient sample size to perform probability testing, 3 favoured PA (ciliary flush, keratic precipitates, BCI; p < 0.05) and one favoured LE (discomfort, p < 0.05).

7.2.3.2.11. Subgroup analysis:

An a priori exploratory analysis of 8 key pre-study characteristics (age, sex, race, iris pigmentation, site of uveitis, type of pathology, disease severity and baseline score) on efficacy outcome for anterior chamber cell rating was conducted. Age, race, iris pigmentation, site of uveitis and type of pathology (granulomatous versus nongranulomatous) did not have any impact on efficacy of LE in treatment of AAU.

There was some indication that women had a greater response to LE than men for 2 measures- distribution of time to first reduction and AUC. However, no statistically significant difference was observed in the primary outcome measure- proportion of patients with cell rating of 0 by final visit or mean change from baseline.

There was some indication that patients with acute disease had a greater response to LE than patients with non-acute disease for 2 measures of proportion of patients with cell rating of 0 by final visit and AUC. However, this statistical difference was not observed in distribution of time to first resolution or mean change from baseline measures.

For distribution of time to first resolution, LE patients with less severe disease at baseline (cell score < 2) resolved more rapidly (p = 0.002) compared to LE patients with more severe disease at baseline (score > 2). However, for AUC (p = 0.006), LE patients entering with more severe disease showed a greater improvement than those with milder disease. However, this statistical difference was not observed for in the primary outcome measure- proportion of patients with cell rating of 0 by final visit or mean change from baseline. Similar findings were observed in the PA group.

7.2.3.2.12. Off-therapy efficacy:

There were 135 patients with 0 rating for cell at Visit 6 (day 28) and 124 of these completed treatment and had an off-therapy Visit 7. Only 5 of these 124 patients had an increase in cell rating at this off-treatment visit; 4 of these 5 patients had an increase to 1 unit (1 LE and 3 PA) and one PA patient had an increase to 3 units. Hence, there was little evidence of rebound in either treatment group.

7.2.4. Other efficacy studies

Study 358-004 was a Phase III, randomised, double-blind, placebo-controlled study to evaluated the clinical bioequivalence of the LE component of LET (Zylet) to Lotemax in reducing the signs and symptoms associated with acute allergic conjunctivitis induced by a topical allergen challenge in 162 subjects. The study treatments of LE, LET or placebo were administered as one

eye drop instilled once daily for 2, 5 or 14 days. The primary efficacy parameters were conjunctival hyperemia and ocular itching; both LE and LET were more effective than placebo and the efficacy of LE and LET was similar.

Studies 143 and 144 were randomised, double-blind, parallel group studies which evaluated the efficacy and safety of LE 0.2% (Alrex) in the treatment of SAC following once daily dosing for 42 days. These studies involved 268 adult patients exhibiting signs and symptoms of environmental seasonal allergic conjunctivitis, coincident with elevated levels of an airborne pollen to which they had a demonstrated skin prick or RAST reaction. The primary efficacy sign was bulbar conjunctival injection (redness) and the primary efficacy symptom was itching; cure rates (proportion of patients with sign or symptom no longer present) for both redness and itching favoured LE after 2 weeks. Since the proposed drug Lotemax (LE 0.5%) was not evaluated in these studies, they have not been discussed in further detail in this evaluation report.

7.2.5. Evaluator's overall conclusions on clinical efficacy for indication 2.

7.2.5.1. Seasonal allergic conjunctivitis (SAC)

In the US Study 121, LE was more effective than placebo in all primary composite, secondary composite and investigator global assessment scores and in all individual parameters except chemosis providing evidence of efficacy as prophylactic treatment in patients with history of SAC. However, the subgroup analysis indicated greater response with LE for ragweed compared with the mountain cedar allergens. Hence, LE may not be effective in prophylaxis of SAC caused by all allergens. This is especially important as this study was conducted only in the USA. The common allergens in Australia are different to those found in USA and efficacy of LE in prophylactic treatment of SAC was not evaluated in any Australian centre. Study 114 which was designed to show efficacy of LE in treatment of patients with active SAC was not conclusive due to early termination of study and very small sample size (only 14 subjects enrolled compared to the initially planned 80 subjects per treatment group).

Overall, the evidence to support use of LE 0.5% for prophylaxis or treatment of SAC is not adequate. Furthermore, the sponsors have another formulation of LE (0.2%- Alrex) which is approved for treatment of SAC in USA, Canada and some other countries; it is not clear if the sponsors propose to apply for marketing approval of this lower concentration of LE (Alrex) in Australia.

7.2.5.2. GPC

Three multicentre, double-blind, parallel-group, placebo-controlled studies (Studies 106, 107, 108) were conducted to evaluate the safety and efficacy of Lotemax in the treatment of GPC associated with wearing contact lenses. The test medication, Lotemax or placebo, was administered four times a day for 28 days (Study 106) or for 42 days (Study 107 and Study 108).

Study 106 was a multicentre, randomised, double-masked, placebo controlled, parallel-group comparison of Lotemax and placebo in 113 subjects with bilateral GPC. Subjects receiving Lotemax demonstrated a significant reduction in the primary ocular sign of GPC (papillae, $p < 0.001$) and were rated better in the IGA ($p = 0.017$). Lotemax did not elevate IOP during the study and was clinically effective for the treatment of GPC. Symptoms/ signs of GPC after stopping treatment were not evaluated in this study and any possible rebound effect was not assessed.

The Phase III, randomised, double-masked, placebo-controlled, parallel-group studies 107 and 108 compared the safety and efficacy of Lotemax versus placebo in reducing the ocular signs and symptoms in 439 patients with contact lens-associated GPC. Papillae, itching, contact lens intolerance, other signs and symptoms of GPC (0-3 or 0-4 grading scales), and IOP were measured. In these studies, subjects were allowed to wear their contact lenses. This decision

was partially based upon the preference of myopic subjects not to return to spectacle correction, even with the presence of an inflammatory eye disorder.

In Study 107, LE treatment was more effective than placebo for 2 of the 3 primary efficacy parameters (papillae and itching) and was marginally significant for third parameters of lens intolerance. The proportion of subjects treated with Lotemax who at final visit demonstrated an improvement in papillae of at least one grade (78%, 85/109) was significantly greater than the proportion of those treated with placebo (51%, 56/110; $p < 0.001$). A treatment difference favouring Lotemax was seen with improvement in itching (95% [104/109] versus 81% [89/110]; $p = 0.001$) and lens intolerance (87% [95/109] versus 77%, [85/110]; $p = 0.053$). Furthermore, the efficacy of LE was observed early by end of first week and was maintained throughout the study. LE also showed significant improvement compared to placebo for the secondary and supportive efficacy measures.

In Study 108, treatment with LE for 6 weeks was more effective than placebo (vehicle for LE) in treatment of patients with GPC with clinically relevant and statistically significant improvements in all 3 primary efficacy parameters; the proportion of subjects treated with Lotemax demonstrating an improvement in papillae of at least one grade was significantly greater than those treated with placebo (75% [83/111] versus 50% [55/109], $p < 0.001$). A treatment difference favouring Lotemax was also seen with itching (92% [102/111] versus 76% [83/109], $p < 0.001$) and lens intolerance (84% [93/111] versus 66% [72/109], $p < 0.002$). This was supported by significant improvements in the secondary (investigator/ patient global assessment and bulbar/ palpebral conjunctival injection) and other ocular signs and symptoms.

In both Phase III studies 107 and 108, there did not appear to be any rebound of signs/ symptoms of GPC following discontinuation of LE therapy; response rates for LE, 7 days after discontinuation of treatment was similar to that observed at the end of the double-blind, 6-week treatment period.

Overall, there was adequate evidence to indicate efficacy of LE 0.5% for treatment of contact-lens associated GPC. However, efficacy and safety of LE 0.5% in the treatment of contact lens associated GPC was not evaluated beyond 6 weeks.

7.2.5.3. AAU

Two Phase III trials (Study 122/1221 and Study 126) were conducted to compare the safety and efficacy of Lotemax to prednisolone acetate 1.0% ophthalmic suspension in reducing the ocular signs and symptoms associated with acute anterior uveitis. Efficacy was evaluated by the proportion of subjects with a score of zero for key signs and symptoms of uveitis. The first study regimen (Study 122/1221) was 42 days of treatment, starting with a dose of eight times per day. The second study regimen (Study 126) was up to 28 days of treatment, starting with a dose of 16 times per day.

In Study 122/1221 (N = 162, Lotemax = 83, prednisolone acetate = 79), the proportion of subjects achieving resolution by their final visit (LOCF) was significantly ($p < 0.001$) lesser with LE 0.5% compared with PA 1% for both anterior chamber cells [LE versus PA: 64% (52/81) versus 89% (67/75)] and flare [63% (51/81) versus 87% (65/75)].

Similar results were observed in Study 126 (N = 175), with smaller proportion of subjects achieving resolution by their final visit (LOCF) in the LE group compared with PA for both anterior chamber cells [72% (58/81) versus 87% (77/89), $p = 0.015$] and flare [66% (52/79) versus 82% (72/88), $p = 0.017$].

The rate of resolution was generally more rapid with PA compared to LE although this difference was more obvious for signs of anterior chamber reaction (cells and flare) and was less pronounced for primary symptoms of pain and photophobia associated with AAU.

Overall, LE 0.5% did produce improvement of signs and symptoms of AAU although it was inferior to PA 1%. Hence, it would be prudent to mention this fact in the proposed indications section of proposed PI.

Overall, the evidence for efficacy of LE for the second generalised indication was not adequate. Efficacy of LE in SAC was not conclusive. LE was shown to be effective for treatment of contact lens associated GPC. Although LE was effective in patients with AAU, it was inferior to PA.

LE may prove to be useful in 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 conjunctivitis. However, the data submitted in this dossier only provided evidence for efficacy in contact lens associated GPC. Hence, there is no data to support or refute the claims of efficacy for the generalised indication of all steroid responsive inflammatory conditions.

8. Clinical safety

8.1. Studies providing evaluable safety data

The safety profile for LE as a single active agent, loteprednol etabonate (Lotemax or Alrex) is derived from 19 well-controlled clinical studies with topical ocular dosing and one study with oral dosing, as follows:

- One pharmacokinetic (PK) study in healthy volunteers with 40 mg oral LE (Study 112).
- One PK study in healthy volunteers (Study 120).
- Two safety studies in healthy volunteers (Studies 101 and 102).
- Four clinical pharmacology studies in sensitive volunteers (Studies 104,105,141 and 145).
- Ten clinical studies of Lotemax in subjects with clinical disorders (postoperative inflammation, giant papillary conjunctivitis (GPC), seasonal allergic conjunctivitis (SAC) and acute anterior uveitis).
- Two clinical studies of Alrex in subjects with SAC (143 and 144).

8.2. Pivotal efficacy studies

In the pivotal efficacy studies, the following safety data were collected:

Safety assessments included ocular examination for both eyes (at each visit) which included slit lamp examinations, patient ocular symptoms, IOP, visual acuity. Dilated fundoscopic examination was done for both eyes at screening at end of treatment. AEs were assessed as clinically significant changes from the ocular examination compared to before treatment (signs, symptoms, visual acuity and IOP); volunteered or observed events not captured on ocular examination and other systemic complaints. Clinical laboratory measurements were routinely measured only in the Zylet safety Study (358-003).

8.3. Pivotal studies that assessed safety as a primary outcome

Study 103 was a pivotal safety study.

8.3.1. Dose-response and non-pivotal efficacy studies

Not applicable as only one dose of LE (0.5%) was evaluated.

8.4. Clinical pharmacology studies

- One pharmacokinetic (PK) study in healthy volunteers with 40 mg oral LE (Study 112).
- One PK study in healthy volunteers (Study 120).
- Two safety studies in healthy volunteers (Studies 101 and 102).
- Four clinical pharmacology studies in sensitive volunteers (Studies 104,105,141 and 145).

8.5. Pivotal studies that assessed safety as a primary outcome

8.5.1. Study 103

In a double-masked, parallel-group Study 103, nineteen subjects with known IOP response to ocular corticosteroids were randomized to receive either Lotemax and PA (PredForte, Allergan) QID for up to 42 days (Bartlett et al, 1993b). Lotemax demonstrated a longer median time to raise IOP, and produced a lower mean endpoint IOP than PA. In these group of known corticosteroid responders, the IOP response to Lotemax was significantly less than that to PA based on several criteria. The proportion of subjects responding to PA with a significant elevation in IOP (greater than or equal to 10 mm Hg) was 55% (5/9), much greater than the proportion responding to Lotemax (1/10, 10%). The latency to significant elevations in IOP (greater than or equal to 10 mm Hg) was longer in the Lotemax phase than in the PA phase. The median time to response was 42 days for PA, and beyond that for Lotemax, as it was not capable of being estimated. The mean endpoint IOP was lower after treatment with Lotemax than after treatment with PA. At the end of the exposure period, the mean IOP was approximately 20 mm Hg in the Lotemax phase and 27 mm Hg in the PA phase. The area under the curve (AUC) for IOP elevation over 42 days for LE was approximately 25% of the elevation associated with PA. The mean area under the change from baseline IOP (LOCF) was 53.7 mm Hg x day for Lotemax, and 228.4 mm Hg x day for PA. This difference was statistically significant at p = 0.004.

8.6. Patient exposure

The safety assessment was performed on a population of 2210 subjects. These include 2204 subjects in 19 studies with topical ocular administration and six subjects in a single study with oral administration (Study 112). Of the 2204 subjects receiving topical ocular administration, 1209 received LE alone. Of these 1209 subjects, 973 received the highest (0.5%) currently marketed concentration, Lotemax. Of the 2204 subjects receiving topical ocular administration, 806 received vehicle and 198 received prednisolone acetate ophthalmic suspension, 1% (PA). The duration of dosing in the ocular studies ranged from one day (one drop) to 42 days. The frequency of dosing ranged from once per day (QD) up to 16 times per day (every hour during waking hours). This represents a total exposure of 34 570 LE subject-days, 26 611 of them with Lotemax. In the LE and Alrex studies, the mean age of subjects across treatment groups was 43-44 years (ranging from 17-99 years) and the majority of subjects were female (58%), Caucasian (80%) and had light iris pigmentation (51%). No integrated analysis has been performed to assess any effect of subpopulation characteristics on product safety or efficacy of LE.

8.7. Adverse events

8.7.1. All adverse events (irrespective of relationship to study treatment)

In the clinical program involving all strengths of LE, the majority of subjects received Lotemax (n = 973). Of the total population, 164 subjects received Alrex. A total of 2244 events were reported in 718 (59%) of the 1215 subjects exposed. Of these 2244 events, 1415 (63%) were ocular and 829 (37%) were non-ocular. Of these same 2244 events, 1768 (79%) were judged as unrelated to the study medication, and 476 (21%) were judged as related to the study

medication. Of the 476 events judged related to the study medication, 428 (19% of the total events) were ocular events. Thus, more than three fourths of the reported events were judged as unrelated to treatment. Adverse events related to LE were generally mild to moderate, nonserious and did not lead to discontinuation in the studies. All ocular events occurring with an incidence of greater than or equal to 1.0% were reported with a similar incidence in both the LE and vehicle treated groups.

8.7.2. Treatment-related adverse events (adverse drug reactions)

Ocular adverse reactions occurring in 5-15% of patients treated with LE ophthalmic suspension (0.2%-0.5%) in clinical studies included abnormal vision/blurring, burning on instillation, chemosis, discharge, dry eyes, epiphora, foreign body sensation, itching, injection, and photophobia. Other ocular adverse reactions occurring in less than 5% of patients include conjunctivitis, corneal abnormalities, eyelid erythema, keratoconjunctivitis, ocular irritation/pain/discomfort, papillae, and uveitis. Some of these events were similar to the underlying ocular disease being studied. Non-ocular adverse reactions occurred in less than 15% of patients. These include headache, rhinitis and pharyngitis.

8.7.3. Deaths and other serious adverse events

There were no deaths in any of the studies.

Of the 1215 subjects receiving LE, two (Lotemax) experienced an SAE. One subject had severe uveitis with increased IOP, judged by the Investigator as probably related to the study medication. The other subject had endophthalmitis, judged as possibly related. Both of these subjects were in a Phase III study for postoperative inflammation. Events in both of these subjects resolved. Of the 1215 subjects receiving LE, three (Lotemax) experienced SAEs (heart attack, congestive heart failure, and hospitalization for itching, cramps, and fatigue) that were judged by the Investigator as unrelated or remotely related to study medication. All three of these subjects were in a Phase III study for postoperative inflammation. All events resolved. One vehicle-treated subject (from a total of 806) also experienced an SAE (cystoid macula oedema), judged as not related to therapy.

8.7.4. Discontinuation due to adverse events

The overall rate for discontinuations due to AEs was similar in the LE (1.8%; 22/1215), vehicle (2.6%, 21/806) and PA (4.5%, 9/198) groups.

8.8. Laboratory tests

Clinical laboratory measurements were routinely measured only in the Zylet safety Study 358-003.

8.8.1. Vital signs

No significant difference in the incidence of clinically significant decreases in visual acuity (VA) was noted between subjects administered LE, PA or vehicle. Changes in VA were considered treatment emergent medical events if the decrease in VA was two lines or greater on the Snellen chart.

> Comments: Given that VA is a final common pathway for the function of the visual system, changes in this measure may be affected by disease state, therapeutic intervention, and many other factors. Using this very sensitive definition of a VA "event", the incidence within each study was similar for LE and the either positive- or negative-control. These results suggest there are no differences of clinical significance between LE and its vehicle, or between LE and PA in this measure.

8.8.2. Other safety parameter- IOP

In controlled, randomized studies, LE demonstrated a lower incidence of clinically significant increased IOP (greater than or equal to 10 mm Hg) than PA, and a similar incidence to vehicle,. The incidence of clinically significant increases in IOP (greater than or equal to 10 mm Hg) was evaluated in all subjects receiving planned treatment for 28 days or longer. The overall incidence of elevations in IOP in individuals treated with LE (any concentration) was 1.7% (15/901). This was similar to that seen in individuals treated with vehicle (0.5%, 3/583), and lower than that seen in individuals treated with PA (6.7%, 11/164). In subjects who did not wear contact lenses during the studies, only 0.6% (4/624) of all LE subjects had an IOP elevation of greater than or equal to 10 mm Hg.

8.8.3. Other safety parameter

Fourteen healthy subjects were randomized to instil either Lotemax (n = 10) or vehicle (n = 4) eight times daily on Days 0 and 1, and QID on Days 2 through 42 (Study 120). Levels of loteprednol or Δ1cortienic acid etabonate (PJ-91), the primary, inactive metabolite were below the level of quantitation (1 ng/mL) at all sampling times (below the limit of quantitation). Further, plasma cortisol levels were all within the normal range. In the same study, there was no evidence of hypothalamic-pituitary axis suppression, based upon plasma cortisol levels suggesting that negligible, systemic absorption occurs after ocular instillation of Lotemax.

8.9. Post-marketing experience

Loteprednol etabonate (as either Alrex or Lotemax) has been marketed in the US since March 1998. Zylet was launched in the US in December 2004. From approval to the present, the majority of this product was distributed in the US.

- Lotemax - loteprednol etabonate ophthalmic suspension, 0.5%, indicated for the treatment of 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 oedema and inflammation. Lotemax is also indicated for the treatment of postoperative inflammation following ocular surgery.
- Alrex - loteprednol etabonate ophthalmic suspension, 0.2%, indicated for temporary relief of signs and symptoms of seasonal allergic conjunctivitis.
- Zylet - loteprednol etabonate and tobramycin ophthalmic suspension 0.5%, 0.3%, indicated for steroid-responsive inflammatory ocular conditions for which a corticosteroid is indicated and where superficial bacterial ocular infection or a risk of bacterial ocular infection exists.

In addition to the US, Lotemax, Alrex, and Zylet have been approved in many countries throughout Latin America, the European Union (EU) and Asia/Pacific regions, and Canada.

From March 1998 through 31 December 2010 there have been over 29 million units of product containing LE sold. Assuming that each unit represents treatment for one patient, as this is the usual quantity prescribed per treatment, more than 29 million patients have been treated from March 1998 through 31 December 2010. For all three products, 708 patients reported 1668 signs and symptoms; 62% of them were non-medically confirmed.

Of these cases, 687 were spontaneous, and the majority were non serious (96%) and unexpected (61%). The frequency of these adverse reactions is very low in comparison with the maximum patient exposure (29,579,388 patients), assuming that each patient used one product box of the marketed products (Lotemax, Alrex, or Zylet). Twenty-one cases were reported from a field observation study of 831 subjects in Germany. Overall, 27 cases with Serious Adverse

events (SAEs) were reported. Two were reported in the German Field observation study, these were unexpected cases of endophthalmitis which were presumed and not confirmed. Twenty-five serious cases were reported spontaneously by health care professionals (20) and consumers (5). Among the spontaneous SAEs reported, 16 cases were unexpected and 9 cases were expected (IOP increase, glaucoma, cataract, and keratitis herpetic). The unexpected SAEs included severe corneal disorders; endophthalmitis; Toxic Anterior Segment Syndrome; retinal vein occlusion and macular oedema; hypersensitivity and dermatitis; arrhythmia and dyspnoea; glucose decrease headache; spontaneous abortion; throat tightness, flushing, and dizziness; paranoia and suicide attempt; and VIIth nerve paralysis. Causality included probably (12%), possibly (44%), unlikely related (40%), or unrelated (4%) to drug.

As expected, given the route of administration, 60% of the cases reported at least one ocular event; more than half of the signs and symptoms (828 of 1668) experienced involved the eye and adnexa.

The most frequently reported signs and symptoms were the following (n): eye irritation (132), eye pain/instillation site pain (103), ocular hyperaemia (84), drug ineffective/reduced effect (77), vision blurred (72), hypersensitivity (60), headache (60), intraocular pressure increase (50), condition aggravated (39), eye pruritus (31), lacrimation increased (28), eye swelling (25), eyelid oedema (23), dizziness (23), visual acuity reduced (22), dry eye (22), and eye discharge (21).

Six cases of drug exposure during pregnancy were recorded. Five cases were without any adverse events and one case was serious with spontaneous abortion. This case was assessed as unlikely related to loteprednol administration, as the spontaneous abortion occurred before 12 weeks of gestation.

Cumulatively (over 12 years) for Lotemax and Alrex, there have been a total of 585 cases with 1363 ADRs. Most of these reports were from the US, and 18 ADRs were both serious and unexpected. Cumulatively (over 6 years) for Zylet, there have been a total of 125 cases with 312 spontaneous ADRs (2 cases were reported also with Lotemax as the patients could have administered both drugs). All of the spontaneous ADRs were reported in the US and non-serious. The percentage of reports per estimated patient use is 0.002334% (585/25,060,468) for Lotemax and Alrex. For all products containing LE, the percentage is 0.002394% (708/29,579,388).

Taking into account safety data collected on Lotemax, Alrex, and Zylet from 09 March 1998 to 31 December 2010, the profile of the drug remains safe and in accord with the previous cumulative experience on LE.

8.10. Safety issues with the potential for major regulatory impact

8.10.1. Liver toxicity

Not applicable.

8.10.2. Haematological toxicity

Not applicable.

8.10.3. Serious skin reactions

Not applicable.

8.10.4. Cardiovascular safety

Not applicable.

8.10.5. Unwanted immunological events

Not applicable.

8.11. Other safety issues

8.11.1. Safety in special populations

The systemic drug levels of topical ophthalmic drug products are generally near lower limits of detection. Consequently, systemic interactions are unlikely and have been observed very infrequently.

No clinical differences were observed between geriatric and younger populations with Lotemax, Alrex, or Zylet.

Two clinical studies in the paediatric population were conducted with ophthalmic formulations containing the active substance loteprednol 0.5%. Although both studies were primarily conducted to investigate safety and efficacy of the product Zylet , which is a combination of loteprednol 0.5% and tobramycin 0.3%, paediatric patients were exposed to 0.5% loteprednol etabonate in both studies.

In the first study a total of 137 paediatric subjects were randomized into 4 groups (34-35 subjects per treatment group), 0 to 6 years of age, of either gender or any race, who had a clinical diagnosis of blepharoconjunctivitis in at least one eye. Parents/guardians were instructed to instil one or two drops of study medication four times a day (QID) for 14 days. The safety results of the study showed that all treatment groups (Zylet , LE suspension, tobramycin and vehicle) had a similar ocular safety profile in the management of blepharoconjunctivitis in paediatric subjects:

- ocular AEs were few in number and only two were judged by the Investigator as possibly related to study drug; they included eye pain (Zylet group) and conjunctivitis (Lotemax group).
- incidence of AEs in the study eye was not significantly different between all treatment groups.
- No ocular SAEs in any group, and no non-ocular SAEs attributed to study drug administration.
- Visual acuity changes were similar across treatment groups and trended toward improved visual acuity in the active treatment groups.

Although statistical significance was not seen with the primary endpoint, total grade of blepharoconjunctivitis, there were beneficial changes in individual signs seen with blepharoconjunctivitis in all four arms of the study; in particular improvement of lid erythema showed statistical significance of Zylet , over vehicle at Day 3 and Day 7. Based on these results it was concluded that this randomized, double-masked, parallel group, multicentre study comparing Zylet , with LE suspension (Lotemax), tobramycin, and vehicle ophthalmic formulations in the treatment of blepharoconjunctivitis in paediatric subjects showed that Zylet was safe and demonstrated efficacy.

The other study investigated the safety and efficacy of the product Zylet (loteprednol 0.5%/ tobramycin 0.3%) against vehicle in the treatment of eyelid inflammation in the paediatric population. A total of 108 paediatric patients were enrolled and 95 subjects completed the study. The efficacy endpoint of this study consisted of reduction of the baseline eyelid inflammatory condition and improvements in ocular signs (lid oedema, lid erythema, conjunctival injection, meibomian plugging). The safety endpoint was incidence of treatment emergent of adverse events, visual acuity and IOP. The safety results showed no ocular SAEs and only one non-ocular SAE, which was considered unrelated to the study drug by the Investigator. In total sixteen non-ocular AEs occurred in eight participants, most of the AEs were considered not related to the study medication; one case of rash was considered possibly related to the study drug. With regard to the treatment emergent ocular AEs there were in total 12 AEs. In total four AEs in the Zylet treated eyes were considered possibly related to the drug,

including conjunctivitis (2x), meibomianitis, and corneal staining. There were no significant differences between treatment groups in the rate of any AEs. The active treatment showed similar efficacy compared to vehicle with the exception of lid erythema where the difference between Zylet and vehicle was statistically significant at day 15 in favour for Zylet where the difference between Zylet and vehicle was statistically significant at day 15 in favour for Zylet .

The LE suspension eye drops (Lotemax and Alrex) are not approved for use in children as the efficacy and safety has not been established for this age group. The sponsor's claim that based on the results of the studies discussed above it can be concluded that there appear to be no unique safety concerns for the active substance loteprednol in the special group of paediatric patients.

> Comments: Although no specific clinical study on the efficacy or safety of Lotemax 0.5% suspension in paediatric patients was conducted, two clinical studies were performed that investigated the combination product loteprednol 0.5%/ tobramycin 0.3% in comparison to vehicle and to Lotemax and tobramycin mono-therapy respectively. These studies were conducted in the age group of zero to 6 years of ages. Both studies demonstrated the good tolerability and safety of the active treatments. Since the first launch of the LE suspension products about 8/406 (2%) AEs in Alrex and 7/1197 (0.5%) AEs in Lotemax were reported in children under 18 years of age. The reported AEs do not seem specific for this special population group. Although the safety of LE 0.5% ophthalmic suspension appeared to be similar to that of Zylet and vehicle in the studies involving children with blepharoconjunctivitis, there was no conclusive evidence of efficacy of LE 0.5% in these paediatric patients. Overall, there is inadequate evidence to support efficacy and safety of LE 0.5% in paediatric population for all the proposed indications.

No specific sub-group analysis was performed based upon extrinsic factors.

8.11.1.1. Use in Pregnancy and Lactation

For LE eye drops, no clinical data on exposed pregnancies are available from the clinical studies. Studies in animals have shown reproductive toxicity when LE is administered orally at 35 times the maximum clinical daily dose.

8.11.2. Safety related to drug-drug interactions and other interactions

Numerous concomitant medications were used during these clinical studies which include allowed and prescribed drugs, some of which treated the underlying disease (for example, anti-allergy agents) or in a few cases, ocular hypotensive agents. None of the events reported were associated with a deleterious effect of the combination of study and non-study drugs, and no drug interactions were noted.

8.12. Safety in the Zylet (combination of LE and tobramycin eye drops) studies:

Relatively few AEs were judged as related to Zylet. Those events which were judged related to Zylet were generally mild to moderate, non-serious, resolved without treatment, and, for the most part, did not interrupt continuation in the studies. There were no SAEs in the Zylet Studies #358-002, #358-003, #358-004 and #358-005. In Study #358-006 (older subjects with cataracts) there were 92 treatment emergent SAEs in 63 subjects, similarly distributed between treatment groups. All of these events were judged to be unrelated or unlikely related to study medication. In addition, there was one SAE with an onset prior to the surgery day (iritis, Lotemax/40). No clinically significant difference in the incidence of clinically significant decreases in VA was noted between Zylet and Lotemax or vehicle.

8.12.1. Other safety issues

No case of overdose has been reported. Acute over dosage is unlikely to occur via the ophthalmic route.

This product has no potential for drug abuse. No LE studies were specifically designed to evaluate withdrawal of study medication and/or rebound. No studies have been performed on the ability to drive and use machines after instillation. Based on the pharmacology of the drug, no effect is expected.

8.13. Evaluator's overall conclusions on clinical safety

In 25 studies of LE (20 with Lotemax or Alrex and five with Zylet) with dosing that ranged from a single treatment (two drops) to QID for 42 days, adverse events (AEs) were generally mild to moderate, non-serious, resolved without treatment, and, for the most part, did not interrupt continuation in the studies.

All 25 clinical studies undertaken with Lotemax, Alrex or Zylet were closely monitored for safety under current GCP guidelines as applied in the US and UK. All AEs, regardless of their relationship to study drug administration were documented and followed through to the resolution of the event.

Elevated IOP is associated with the chronic application of topical corticosteroids. IOP was closely monitored in all of the clinical studies.

Loteprednol etabonate demonstrated a lower incidence of clinically significant increas in IOP (greater than or equal to 10 mm Hg) than prednisolone acetate, and a similar incidence to placebo, in controlled, randomised studies. The incidence of clinically significant increases in IOP (greater than or equal to 10 mm Hg) was evaluated in all subjects receiving planned treatment for 28 days or longer. The overall incidence of elevations in IOP in individuals treated with loteprednol etabonate (0.1%, 0.2%, 0.3% and 0.5% concentrations) was 1.7% (15/901). This was similar to that seen in individuals treated with placebo (0.5%, 3/583), and lower than that seen in individuals treated with prednisolone acetate (6.7%, 11/164). In subjects who did not wear contact lenses during the studies, only 0.6% (4/624) of all loteprednol etabonate subjects had an IOP elevation of greater than or equal to 10 mm Hg.

In addition, a safety study was conducted in subjects with known IOP response to ocular corticosteroids (Study #103). The IOP response to LE was significantly less than that to PA using several criteria such as proportion of patients with significant elevation in IOP (> 10 mmHg) and median time significant IOP elevation.

Ocular adverse reactions occurring in 5-15% of patients treated with loteprednol etabonate ophthalmic suspension (0.2%-0.5%) in clinical studies included abnormal vision/blurring, burning on instillation, chemosis, discharge, dry eyes, epiphora, foreign body sensation, itching, injection, and photophobia. Other ocular adverse reactions occurring in less than 5% of patients include conjunctivitis, corneal abnormalities, eyelid erythema, keratoconjunctivitis, ocular irritation/pain/discomfort, papillae, and uveitis. Some of these events were similar to the underlying ocular disease being studied. Non-ocular adverse reactions occurred in less than 15% of patients. These include headache, rhinitis and pharyngitis.

In more than 12 years of post-marketing surveillance since approval in the US, there has been no change in the frequency or nature of AEs seen with Lotemax, Zylet or Alrex.

9. First round benefit-risk assessment

9.1. First round assessment of benefits

The benefits of Lotemax (LE 0.5%) in the proposed usage are:

- Results from the clinical pharmacokinetic studies with Lotemax indicate that loteprednol etabonate rapidly penetrates into ocular tissues, while systemic exposure to loteprednol etabonate and PJ-91 is very low (for example, < 1 ng/ mL), even with QID dosing for 43 days (plasma cortisol remained within normal levels). Based on results in healthy volunteers, the low systemic exposure to LE should not present a risk of undesired corticosteroid effects. However, systemic exposure following ocular instillation of LE 0.5% was not evaluated in the target patient population.
- Loteprednol etabonate (LE 0.5%) demonstrated a lower incidence of clinically significant increased IOP (greater than or equal to 10 mm Hg) than prednisolone acetate (PA 1%) , and a similar incidence to placebo, in controlled, randomised studies.
- Controlled clinical studies support the pharmacology of LE as a site-active corticosteroid, effective after topical ocular instillation in the treatment of post-operative ocular inflammation following cataract surgery and of steroid responsive ocular inflammatory conditions such as contact-lens associated GPC and acute anterior uveitis.

9.2. First round assessment of risks

The risks of Lotemax in the proposed usage are:

- Increased IOP although the risks was less than that associated with PA
- Efficacy only evaluated in post-operative inflammation following cataract surgery and not any other type of ocular surgery.
- Efficacy of LE 0.5% not established for treatment of seasonal allergic conjunctivitis (SAC). Furthermore, the sponsors have another product with lower concentration of LE (LE 0.2%, Alrex) which is proposed specifically for use in treatment of SAC and has already been approved for this purpose in USA and Canada. However, the sponsors are not seeking marketing approval for Alrex in Australia at this stage.
- For steroid responsive inflammatory ocular conditions, efficacy and safety of LE was only demonstrated in contact lens associated GPC and acute anterior uveitis. Furthermore, LE was not as effective as Prednisolone acetate 1% in treatment of acute anterior uveitis.
- Efficacy not established in paediatric population, although some evidence of safety from 2 clinical studies using LE 0.5%/ tobramycin 0.3% (Zylet) combination eye drops.

9.3. First round assessment of benefit-risk balance

The benefit-risk balance of Lotemax 0.5% is unfavourable given the proposed usage, but would become favourable if the changes recommended in Section 10 (below) are adopted.

10. First round recommendation regarding authorisation

It is recommended that Lotemax be rejected for the proposed indication of:

the treatment of post-operative inflammation following ocular surgery and

the treatment of 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 conjunctivitis, when the inherent hazard of steroid use is accepted to obtain an advisable diminution in oedema and inflammation.

However, there is sufficient data to support approval for the following alternative indication:

the treatment of post-operative inflammation following cataract surgery and

the treatment of steroid responsive inflammatory conditions of contact lens associated GPC and treatment of acute anterior uveitis, when the inherent hazard of steroid use is accepted to obtain an advisable diminution in oedema and inflammation.

For treatment of AAU, Lotemax is less effective than prednisolone acetate 1% in two 28-day controlled clinical trials where 72% of patients with Lotemax experienced resolution of anterior chamber cells compared to 87% of patients treated with prednisolone acetate 1%. The incidence of patients with clinically significant increases in IOP (> 10 mm Hg) was 1% with Lotemax and 6% with PA 1%. Lotemax should not be used in patients who require a more potent corticosteroid for this indication. Efficacy and safety beyond 6 weeks has not been evaluated.

Approval for the above modified indication is also subject to incorporation of suggested changes to the proposed PI and adequate response to the questions in this report.

11. Clinical questions

11.1. Pharmacokinetics

11.1.1. Question One

Following ocular administration of LE 0.5%, there was low systemic exposure in studies in healthy subjects; however, low systemic exposure of LE was not confirmed in studies in the target patient population. Could the sponsors justify why this has not been evaluated or if it has been why was it not included in the dossier?

11.1.2. Question Two

Only one concentration of LE (0.5%) was evaluated in the pharmacokinetic studies; please provide justification.

11.2. Pharmacodynamics

11.2.1. Question One

Study 145 evaluated 3 concentrations of LE (0.1%, 0.2%v and 0.3%) to determine the ideal concentration for treatment of SAC. The proposed dose of LE 0.5% was not evaluated in this study. Furthermore, only 1 concentration of LE 0.5% was evaluated in the Phase III clinical studies of post-operative inflammation following cataract surgery, contact lens associated GPC and AAU. Can the sponsors justify the lack of evaluation of dose-response of LE for the proposed indications?

11.3. Efficacy

None.

11.4. Safety

None.

12. Second round evaluation of clinical data submitted in response to questions

The initial question by the TGA is mentioned first followed by the sponsor's response in normal font and then the evaluator's comments on sponsor's response.

12.1. Pharmacokinetics

12.1.1. Question One

Following ocular administration of LE 0.5%, there was low systemic exposure in studies in healthy subjects; however, low systemic exposure of LE was not confirmed in studies in the target patient population. Could the sponsors justify why this has not been evaluated or if it has been why it was not included in the dossier?

12.1.1.1. Sponsor's response

The sponsors argue that following topical ocular administration, most of the drug is eliminated from the eye through nasolacrimal drainage, where it enters systemic circulation via the nasal cavity or gastrointestinal tract. Consequently, any difference in systemic exposure due to increased ocular penetration in an inflamed eye compared with a healthy eye is expected to be minimal and not biologically relevant. Furthermore, loteprednol etabonate (LE) was specifically designed to be metabolically labile resulting in rapid metabolism to inactive metabolites, thus systemic exposure to LE with ophthalmic use is negligible.

In two separate experiments, the ocular and systemic pharmacokinetics of LE were investigated following a topical ocular administration of Lotemax suspension, 0.5% to rabbits with inflamed eyes (Study # BL05020) or intact eyes (Study # BL08010). In both studies, systemic exposure to LE was consistently very low (< 1 ng/ mL). In a study with healthy volunteers (Study # P5604-120), where subjects received one drop in each eye 8 times daily for two days and then QID for 41 days, plasma levels of LE, as well as PJ-91, the primary metabolite of LE, were below the limit of quantitation (1 ng/ mL) and in many instances below the level of detection, Therefore, based on these data, evaluating systemic pharmacokinetics in the patient population was not deemed necessary.

12.1.1.2. Evaluator's comments on sponsor's response:

The explanation provided by the sponsors is acceptable.

12.1.2. Question Two

Only one concentration of LE (0.5%) was evaluated in the pharmacokinetic studies; please provide justification.

12.1.2.1. Sponsor's response:

A concentration of 0.5% LE was selected for the pharmacokinetic studies because it was the maximum concentration intended for clinical use. As part of an investigation to evaluate new formulations, the ocular and systemic pharmacokinetics of LE were evaluated in rabbits following topical ocular administration of LE at concentrations of 0.2%-1% (Study # BL08009 and Study # BL08010). The results of these studies revealed that systemic exposure to LE was low (< 1.4 ng/ mL, on average) at concentrations up to 1%.

In healthy volunteers (Study # P5604-120,), as plasma levels with ocular administration of LE 0.5% with frequent dosing and prolonged administration were below the limit of quantitation, it was concluded that systemic absorption of LE 0.5% administered less frequently over a shorter duration or if administered at a lower concentration would also be safe.

12.1.2.2. Evaluator's comments on sponsor's response:

The explanation provided by the sponsors is acceptable.

12.2. Pharmacodynamics:

Study 145 evaluated 3 concentrations of LE (0.1%, 0.2%v and 0.3%) to determine the ideal concentration for treatment of SAC. The proposed dose of LE 0.5% was not evaluated in this study. Furthermore, only 1 concentration of LE 0.5% was evaluated in the Phase III clinical studies of post-operative inflammation following cataract surgery, contact lens associated GPC and AAU. Can the sponsors justify the lack of evaluation of dose response of LE for the proposed indications?

12.2.1. Sponsor's response

Study #145 consisted of 2 parts with separate objectives and all subjects were instilled QID for 28 days.

- Paired comparison study: The objective was to compare 3 doses of LE suspension (0.1%, 0.2% and 0.3%) on the prevention of ocular signs and symptoms induced by an antigen challenge, this was a randomized, double-masked, placebo controlled, paired comparison study with one eye receiving LE and the contralateral eye receiving the vehicle. From the efficacy and safety results of this study, the 0.2% concentration was selected for environmental SAC studies.
- Parallel group study: The objective was to evaluate LE 0.5% suspension compared to vehicle on the prevention of ocular signs and symptoms induced by an antigen challenge, this was a randomized, double-masked, placebo controlled, parallel group study where subjects received either LE 0.5% or vehicle in both eyes. This parallel study demonstrated the superiority of LE 0.5% over the vehicle. (LE 0.5% was evaluated versus vehicle in a paired comparison in a previous study; Study #141).

LE 0.5% was evaluated in the Phase III clinical studies of post-operative inflammation following cataract surgery, contact lens associated GPC and AAU. The selection of the 0.5% concentration was based on different studies.

- The 0.5% clinical dose selection was in part supported by the nonclinical pharmacology study evaluating LE effect on corneal inflammation in rabbits (Study #PHA-30,) which demonstrated that LE is effective at concentrations of 0.5% with peak anti-inflammatory effect at 1% (refer to Table 2 below). Concentrations lower than 0.5% (0.05 and 0.1%) did not result in significant reductions in inflammation as compared to vehicle control.

Table 2. Effect of loteprednol etabonate on the inflammatory response in the cornea

DRUG	MEAN DECREASE IN CORNEAL INFLAMMATORY RESPONSE
Loteprednol etabonate 0.05%	6.6 (± 4.6)
Loteprednol etabonate 0.1%	4.6 (± 6.2)
Loteprednol etabonate 0.5%	18.4 (± 5.6)
Loteprednol etabonate 1.0%	39.3 (± 4.7)**
Loteprednol etabonate 2.0%	31.6 (± 2.9)**

* Therapy initiated 24 hours after induction of inflammation.

Table entries are the arithmetic means (± standard error) of data derived from the study of 12 eyes (12 rabbits). Values are expressed as percent difference from the mean of 12 vehicle treated control eyes (12 rabbits).

** values are significantly different ($p < 0.01$) from all others in the column but are not significantly different from each other.

- In a 28-day repeat ocular dose study in rabbits (Study # PTC-7,) data also supported the 0.5% clinical dose selection as the systemic no observed adverse effect level (NOAEL) was 0.7%. No ocular effects were observed at concentrations up to 5% LE. There were no effects in these studies which precluded the investigation of LE at 0.5% in the clinical setting.
- Finally, the selection of 0.5% was based primarily on the preponderance of the clinical data available. In the clinical safety studies, different concentrations of LE up to 0.5% were tested with no safety issues. For efficacy, in an allergen model study with rechallenge (Study # P5604-105,), the safety and effectiveness of LE 0.5% was compared to prednisolone acetate 1.0 % (PA) and vehicle. Subjects were randomized in a 2:1 ratio to receive LE or PA in one eye and vehicle in the contralateral eye. Results showed that ocular signs and symptoms were significantly better with LE or PA over vehicle with no statistically significant difference between LE 0.5% and PA 1% which is one of the reference treatments for ocular inflammation such as in post-operative inflammation and acute anterior uveitis. Furthermore, other Phase II studies, Study #141 and Study #145 (parallel group study) in the antigen challenge model, and Study #106 in giant papillary conjunctivitis, demonstrated a good efficacy versus safety profile with the 0.5% concentration. From the results of all these studies, LE 0.5% was selected to be used in the Phase III studies.

12.2.1.1. Evaluator's comments on sponsor's response:

The above explanation provided by the sponsors may justify selection of only 0.5% dose for the Phase III studies in treatment of ocular inflammation following cataract surgery, acute anterior uveitis (AAU) and contact-lens associated giant papillary conjunctivitis (GPC).

However, selection of LE 0.5% for treatment of seasonal allergic conjunctivitis was not justified based on the results of study 145. Alrex Ophthalmic Suspension (LE 0.2%) is approved for temporary relief of the signs and symptoms of seasonal allergic conjunctivitis in USA, Canada and some other countries. However, the 0.2% concentration of LE is not marketed in Australia and the sponsors have not applied for approval of LE 0.2% in this submission. Hence, based on the results observed in studies 141 and 145, it appears that risk-benefit ratio for LE 0.5% may not be favourable for treatment of seasonal allergic conjunctivitis (due to trend of increased IOP observed with 0.3% LE compared with 0.1% and 0.2% LE in study 145).

13. Second round benefit-risk assessment

13.1. Second round assessment of benefits

After consideration of responses to clinical questions, the benefits of Lotemax (0.5%) in the proposed usage are:

- Results from the clinical pharmacokinetic studies with Lotemax indicate that loteprednol etabonate rapidly penetrates into ocular tissues, while systemic exposure to loteprednol etabonate and PJ-91 is very low (for example, < 1 ng/ mL), even with QID dosing for 43 days (plasma cortisol remained within normal levels). Based on results in healthy volunteers, the low systemic exposure to LE should not present a risk of undesired corticosteroid effects.
- Loteprednol etabonate (LE 0.5%) demonstrated a lower incidence of clinically significant increased IOP (greater than or equal to 10 mm Hg) than prednisolone acetate (PA 1%), and a similar incidence to placebo, in controlled, randomised studies.
- Controlled clinical studies support the pharmacology of LE as a site-active corticosteroid, effective after topical ocular instillation in the treatment of post-operative ocular inflammation following cataract surgery and of steroid responsive ocular inflammatory conditions such as contact-lens associated GPC and acute anterior uveitis.

13.2. Second round assessment of risks

After consideration of the responses to clinical questions, the risks of Lotemax (0.5%) in the proposed usage are unchanged from those identified in the first round assessment of risks.

13.3. Second round assessment of benefit-risk balance

The benefit-risk balance of Lotemax 0.5% is unfavourable given the proposed usage, but would become favourable if the changes recommended in second round recommendation are adopted.

14. Second round recommendation regarding authorisation

It is recommended that Lotemax be rejected for the proposed indication of:

> *the treatment of post-operative inflammation following ocular surgery and*
>
> *the treatment of 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 conjunctivitis, when the inherent hazard of steroid use is accepted to obtain an advisable diminution in oedema and inflammation.*

However, there is sufficient data to support approval for the following alternative indication:

> *the treatment of post-operative inflammation following cataract surgery and*
>
> *the treatment of steroid responsive inflammatory conditions of contact lens associated GPC and treatment of acute anterior uveitis, when the inherent hazard of steroid use is accepted to obtain an advisable diminution in oedema and inflammation. For treatment of AAU, Lotemax is less effective than prednisolone acetate 1% in two 28-day controlled clinical trials where 72% of patients with Lotemax experienced resolution of anterior chamber cells compared to 87% of patients treated with prednisolone acetate 1%. The incidence of patients with clinically significant increases in IOP (> 10 mm Hg) was 1% with*

Lotemax and 6% with PA 1%. Lotemax should not be used in patients who require a more potent corticosteroid for this indication. Efficacy and safety beyond 6 weeks has not been evaluated.

Approval for the above modified indication is also subject to incorporation of suggested changes to the proposed PI which are beyond the scope of this AusPAR.

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