



Australian Government
Department of Health
Therapeutic Goods Administration

Australian Public Assessment Report for loteprednol etabonate

Proprietary Product Name: Lotemax

Sponsor: Bausch and Lomb Australia Pty Ltd

April 2014

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 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 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 AusPARs

- An Australian Public Assessment Record (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission.
- AusPARs are prepared and published by the TGA.
- An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations, and extensions of indications.
- An AusPAR is a static document, in that it will provide information that relates to a submission at a particular point in time.
- A new AusPAR will be developed to reflect changes to indications and/or major variations to a prescription medicine subject to evaluation by the TGA.

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List of abbreviations

Abbreviation	Meaning
AAC	Acute allergic conjunctivitis
AAU	Acute anterior uveitis
ACPM	Advisory Committee For Prescription Medicines
AE	Adverse event
AH	Aqueous humour
Alrex	Loteprednol etabonate ophthalmic suspension, 0.2%
C _{max}	Maximal concentration
CYP	Cytochrome P-450
ECG	Electrocardiogram
EP	European Pharmacopeia
GLP	Good laboratory practice
GMP	Good manufacturing practice
GPC	Giant papillary conjunctivitis
HDPE	High density polyethylene
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IGA	Investigator global assessment
IOP	Intraocular pressure
IV	Intravenous
LDPE	Low density polyethylene
LE	Loteprednol etabonate
LOCF	Last observation carried forward
LOQ	Limit of quantification
Lotemax	Loteprednol etabonate ophthalmic suspension, 0.5%
mg	Milligram (0.001 gram)
mL	Millilitre (0.001 litre)

Abbreviation	Meaning
mm Hg	Millimetres of mercury
MW	Molecular weight
ng	Nanogram (10 ⁻⁹ gram)
PA	Prednisolone acetate (1.0%)
PI	Product Information
PJ-90	Δ1-Cortienic acid (an inactive metabolite of LE)
PJ-91	Δ1-Cortienic acid etabonate (an inactive metabolite of LE)
PK	Pharmacokinetic
PO	Oral
PSC	Pharmaceutical subcommittee
RMP	Risk management plan
SAC	Seasonal allergic conjunctivitis
SAE	Serious adverse event
SC	Subcutaneous
TGA	Therapeutic Goods Administration
UK	United Kingdom
US	United States
USP	United States Pharmacopeia
Zylet	Loteprednol etabonate 0.5% and tobramycin 0.3% ophthalmic suspension
μM	Micromolar (10 ⁻⁶ molar concentration)

I. Introduction to product submission

Submission details

<i>Type of submission:</i>	New chemical entity
<i>Decision:</i>	Approved
<i>Date of decision:</i>	13 January 2014
<i>Active ingredient:</i>	Loteprednol etabonate
<i>Product name:</i>	Lotemax
<i>Sponsor's name and address:</i>	Bausch and Lomb Australia Pty Ltd PO Box 346 North Ryde BC NSW 1670
<i>Dose form:</i>	Eye drop suspension
<i>Strength:</i>	0.5%
<i>Pack size(s):</i>	2.5 mL, 5 mL, 10 mL and 15 mL
<i>Approved therapeutic use:</i>	Treatment of post-operative inflammation following cataract surgery Treatment of steroid responsive inflammatory conditions of contact lens associated giant papillary conjunctivitis (GPC).
<i>Route of administration:</i>	Topical
<i>Dosage:</i>	Post operative Inflammation: Apply one to two drops of Lotemax into the conjunctival sac of the operated eye(s) four times daily beginning 24 hours after surgery and continuing throughout the first 2 weeks of the post-operative period. Steroid Responsive Disease Treatment: Apply one to two drops of Lotemax into the conjunctival sac of the affected eyes four times daily. Systemic absorption of LE may be reduced by compressing the lacrimal sac at the medial canthus for a minute during and following the instillation of the drops (this blocks the passage of the drops via the naso-lacrimal duct to the wide absorptive area of the nasal and pharyngeal mucosa) .
<i>ARTG number:</i>	202525

Product background

Lotemax is a topical anti-inflammatory corticosteroid for ophthalmic use. Each mL of Lotemax contains 5 mg of loteprednol etabonate. Loteprednol etabonate is a corticosteroid analog of prednisolone which was developed for local use in ocular inflammatory conditions.

The proposed indication of Lotemax is for:

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.

Regulatory status

The product received initial registration on the Australian Register of Therapeutic Goods on 13 January 2014.

Loteprednol has been marketed in the United States of America (US) since 1998 for the indications of:

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

Loteprednol has also been approved in several countries throughout Latin America, Europe, Asia/Pacific and Canada.

In the US (and some other countries), 3 products with loteprednol are marketed:

- Lotemax: loteprednol etabonate ophthalmic suspension 0.5% (this submission)
- Alrex: loteprednol etabonate ophthalmic suspension 0.2%, for temporary relief of seasonal allergic conjunctivitis
- Zylet: loteprednol etabonate ophthalmic suspension 0.5% and tobramycin 0.3%, for steroid-responsive inflammatory ocular conditions and where superficial bacterial ocular infection or a risk of bacterial ocular infection exists.

There appear to be no plans to submit an application to register Alrex or Zylet in Australia.

This information was current at the time this application was considered.

Product Information

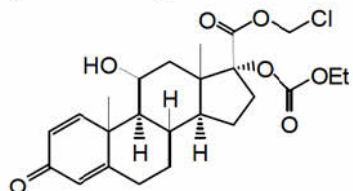
The approved Product Information (PI) current at the time this AusPAR was prepared can be found as Attachment 1.

II. Quality findings

Drug substance (active ingredient)

Lotemax eye drops is a suspension of the new chemical entity loteprednol etabonate at a concentration of 5 mg/mL (0.5% w.v).

Figure 1. loteprednol etabonate



$C_{24}H_{31}ClO_7$ Molecular Weight (MW) = 466.96 aqueous solubility = 0.008 mg/mL (0.0008 % w/v) pKa = none
optical rotation = +37° to +45°

The loteprednol etabonate is a corticosteroid related to and derived from prednisolone. As for other corticosteroids, the mode of action is reported to be unknown, but may be due to the induction of phospholipase A2 inhibitory proteins (lipocortins). It was designed to metabolise to inactive metabolites; Δ^1 -cortienic acid (termed PJ-90), and Δ^1 -cortienic acid etabonate (PJ-91).

Figure 2. PJ-90

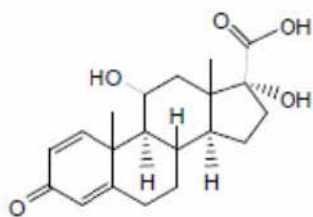
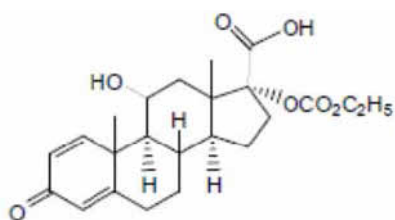


Figure 3. PJ-91



Drug product

Aspects relating to the sterilisation of the product were found to be acceptable by TGA.

There are no compendial monographs for the drug substance, but the specifications adopted for both the non-sterile and sterile materials were acceptable. In particular:

- The assay limits of for non-sterilised material and sterilised material have been justified.
- Some limits for synthetic impurities were above the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) qualification threshold, but it was accepted by the TGA that these limits were qualified.
- Tighter than ICH limits were adopted for the residual solvents present.

- The particle size is tightly controlled.
- The microbiological tests and limits were acceptable.

The product contains no unusual excipients for this dosage form. The drug substance does not dissolve in the base solution and is therefore suspended. The base solution contains povidone as a suspending agent, tyloxapol as a surfactant, disodium edetate as a chelator, water as the solvent and glycerol to make it isotonic. During manufacture the pH is adjusted and it is preserved with 0.20 mg/mL (0.020% w/v) benzalkonium chloride.

Manufacture is typical for an eye drop but involves no terminal sterilisation step. Thus, the sterile drug substance is suspended into the pre-sterilised base solution (sterilised by filtration) and the suspension then filled into pre-sterilised white low density polyethylene (LDPE) bottles with pre-sterilised dropper tip and pre-sterilised cap (all sterilised at a separate site with ethylene oxide).

- The relevant Office within TGA has stated that the site that sterilises the bottles dropper tips and caps requires Good Manufacturing Practice (GMP) clearance: an application has very recently been submitted for GMP Clearance but this has not yet to be decided.
- TGA has accepted that all aspects of manufacture are acceptable.
- There were no container safety issues including adequate control over the drop size delivered by the dropper tips.

There are no compendial monographs for the product but the specifications for the product ensure the general requirements for eye drops are met. The chemistry and physical tests and limits within the specifications and where required the release limits are tighter than the expiry limits to allow for change on storage. In particular:

- The assay limits are acceptable at release and expiry.
- The limits for the degradants are acceptable at release and expiry.
- Although the expiry limits are above the ICH qualification threshold, they are accepted as they are metabolites.
- There are no limits for other individual degradants above the ICH qualification threshold.
- The expiry limits for benzalkonium chloride and disodium edetate have been justified.
- The particle size distribution of the suspended particles is tightly controlled.

In relation to preservative efficacy, this will be tested only in the event of a benzalkonium chloride assay failure on stability, and if tested, then according to both United States Pharmacopeia (USP) and European Pharmacopeia (EP) requirements. This was acceptable to the TGA.

In relation to the shelf life, it was noted that after storage in the inverted position for greater than 9 months (that is, when tested at 12 months and beyond but not when tested at 9 months), the assay of the suspension in the bottles declined to unacceptable levels. This was found to be due to the settling of the suspended particles in recesses around the dropper orifice, which set and could not be dislodged by vigorous shaking. To alleviate concerns that this could occur in practice, the sponsor provided information that was able to assure the TGA that the product will be stored upright until dispensed to the patient and that this settling could not occur within the in use period. Thus, the chemical and physical data provided support an unopened shelf life of 2 years when stored below 25°C (15 months for the 2.5 mL volume product) and an opened shelf life of 4 weeks. The additional conditions “Do not freeze”, “Store in an upright position” and “Shake vigorously before using” will also apply. The TGA accepted that these shelf lives have also been

supported by preservative efficacy testing performed using both USP and EP methods and requirements.

Biopharmaceutics

This product is for ocular use and is intended to act without systemic absorption. As a consequence no bioavailability data were required to be submitted (and none were provided). The dataset did however include a pharmacokinetic study to determine the systemic levels of loteprednol etabonate and its metabolite PJ-91. The limit of quantification (LOQ) of these analytes in plasma is less than 1 ng/mL.

Advisory committee considerations

Details relating to this submission were presented at the 151st meeting of Pharmaceutical Subcommittee (PSC) of the Advisory Committee for Prescription Medicines (ACPM). The PSC had concerns over the settling of the suspension and the age of the validation studies. These issues were resolved to satisfaction of the TGA.

Quality summary and conclusions

Approval of the registration of the proposed product cannot be recommended on pharmaceutical chemistry grounds as the site that sterilises the container, dropper tip and cap has not been granted GMP Clearance. It is noted that the sponsor's justification for not requiring GMP Clearance was not acceptable to the TGA and GMP Clearance is required. The sponsor has recently submitted an application to TGA for GMP Clearance.

If GMP Clearance is issued approval could be recommended.

III. Nonclinical findings

Introduction

All pivotal safety-related studies were conducted under Good Laboratory Practice (GLP) conditions with the exception of one: an Ames test¹ for bacterial mutagenicity. However, this study was adequately documented and the circumstances under which it was conducted is not considered to be a major deficiency.

Pharmacology

Primary pharmacology

Loteprednol etabonate is a corticosteroid and an analogue of prednisolone (but an ester rather than a ketone). In vitro, the drug was shown to bind to the rat glucocorticoid receptor with nanomolar affinity (4.3-times greater than that of dexamethasone). Metabolites of loteprednol etabonate, PJ-91 (Δ 1- cortienic acid etabonate; 17 carboxylic acid derivative) and PJ-90 (Δ 1 - cortienic acid), displayed no glucocorticoid receptor affinity. Anti-inflammatory activity was demonstrated for loteprednol etabonate in vivo in various rabbit models of ocular inflammation following topical administration at strengths

¹ The Ames test is a widely employed method that uses bacteria to test to assess the mutagenic potential of chemical compounds.

greater than or equal to 0.5%, and also by the topical dermal and subcutaneous (SC) routes in other inflammatory models involving mice and/ or rats.

In pharmacodynamic drug interaction studies, the combination of loteprednol etabonate and the antibiotic agent besifloxacin had a mostly additive effect toward inhibition of interleukin-1 β -induced cytokine production in human corneal epithelial cells in vitro. In vivo in rabbit eyes, the inclusion of 0.3% tobramycin (another antibiotic agent; as in Tobrex eye drops) did not interfere with the anti-inflammatory effect of 0.5% loteprednol etabonate.

Secondary pharmacodynamics

Secondary pharmacodynamic pharmacology studies revealed a range of activities consistent with but less prominent than that of other corticosteroids. With regard to ocular effects (assessed in rabbits), these comprised inhibition of corneal wound healing (at 0.1% to 1.0%; similar or less severe compared with dexamethasone), decreased corneal scarring (at 0.1%; similar to dexamethasone) and small increases in intraocular pressure (at 0.1%; less severe compared with dexamethasone). Other activities shown for loteprednol etabonate were inhibition of dermal fibroblast proliferation (mouse; in vitro), atrophy of the skin and limited thymic suppression (with repeat topical dermal administration in rats), some anti-asthma activity (as inhibition of lipopolysaccharide-induced release of interleukin 1 β from human mixed mononuclear leukocytes in vitro, and inhibition of allergen-induced eosinophilia in guinea pigs and bronchoconstriction in sheep). In contrast to some other steroids, topical dermal administration of 0.1% loteprednol etabonate did not delay skin wound healing in hairless mice.

Loteprednol etabonate (less than or equal to 100 μ M) was not cytotoxic to ARPE 19 cells (an immortalised human retinal pigment epithelial cell line). No receptor screening assays were conducted.

Safety pharmacology

No specialised safety pharmacology studies were submitted. The absence of such studies is considered acceptable given clinical experience with the drug, prior data for the drug class, and limited systemic exposure in patients.

Pharmacokinetics

Limited systemic absorption of loteprednol etabonate following topical ocular administration was evident in rabbits, dogs and humans. Plasma levels of loteprednol etabonate were below the limit of quantitation in;

- rabbits (that is, less than 1.0 ng/mL) following bilateral administration of the clinical formulation at a dose of 50 μ L/eye (equals 250 μ g loteprednol etabonate/eye), and
- in dogs (that is, less than 4 ng/mL) following 4 times daily unilateral treatment with a 0.5% ointment formulation yielding an average dose of 1.63 mg loteprednol etabonate per eye, and also
- in healthy human adults (that is, less than 1 ng/mL) following repeated topical ocular administration of Lotemax (one drop into each eye 8 times daily for 2 days, then 4 times daily for 41 days).

Peak drug concentrations were typically observed in

- the tears, conjunctiva and cornea of rabbits 5 to 15 minutes after topical ocular administration of 0.5% loteprednol etabonate suspension, and

- in the aqueous humour at 0.5 to 1 hour post-dose.

The C_{max} in the aqueous humour was approximately 10 ng/mL.

Protein binding by loteprednol etabonate was shown to be high in dog plasma (approximately 95%) with more moderate binding seen for metabolite PJ-91 (approximately 73%).

In accordance with its high lipophilicity, a high red blood cell partition coefficient was found for loteprednol etabonate in dog blood. The examination of a limited set of tissues examined (liver, kidney, heart and lungs) in rats following oral administration of (^{14}C) loteprednol etabonate showed that the highest peak concentrations of loteprednol etabonate and PJ-91 were to be found in the liver (58- and 11-times higher compared with blood for the respective compounds).

Metabolism of loteprednol etabonate involves sequential hydrolysis to PJ-91 and PJ-90. Following topical ocular administration in rabbits, metabolites were detected in ocular tissues from the first time point examined (either 5 or 30 minutes post-dose). The levels of metabolites were higher than the parent drug in the rabbit cornea and aqueous humour (consistent with local metabolism in ocular tissues). Metabolism of loteprednol etabonate to PJ-90 and PJ-91 was shown to occur in rats after intravenous (IV) or oral (PO) administration. The formation of PJ-91 was seen in dogs after IV administration and in humans after PO administration (detection in blood, plasma, urine and/or bile). In an IV study in rats the primary route of excretion was shown to be the biliary/faecal route (as metabolites).

Pharmacokinetic drug interactions

No Cytochrome P-450 (CYP) inhibition or induction studies were conducted. This is considered acceptable given that the low systemic exposure in patients (plasma C_{max} , less than 1 ng/mL (that is, less than 2.14 nM)) renders interactions mediated by such effects of loteprednol etabonate unlikely.

The ocular disposition of loteprednol etabonate was not substantially altered by prior treatment (10 to 30 minutes pre-dose) with 0.5% proparacaine, 2.5% phenylephrine, 1% tropicamide, 0.5% apraclonidine or 0.3% ofloxacin in rabbits. No significant effect of 0.5% ketorolac or 4% xylocaine was seen either, but these drugs were administered 20 to 25 minutes after administration of loteprednol etabonate and significant absorption would already have occurred.

Toxicology

Acute toxicity

Single-dose toxicity studies were conducted by the PO and subcutaneous (SC) routes in mice and rats. The main experiments used an observation period of 14 days, in accordance with the European Union (EU) guideline of single-dose toxicity (3BS1a).² In mice, the lethal dose, 50% (LD_{50}) by the oral route, was in excess of 4000 mg/kg and the maximum non-lethal dose by the SC route was 1333.4 mg/kg. Maximum non-lethal doses were 4000 mg/kg PO and 1333.4 mg/kg SC in rats. These doses are more than 1000 to 6000 times higher than the maximum anticipated human dose on a mg/m^2 body surface area basis.

² European Medicines Agency, Questions and answers on the withdrawal of the 'Note for guidance on single dose toxicity', 24 June 2010.

Repeat-dose toxicity

Studies of up to 6 months duration in rabbits and 12 months duration in dogs involving repeated topical ocular administration of loteprednol etabonate suspension were conducted. The duration of these pivotal studies, the range of species, group sizes, the use of both sexes of the clinical route are consistent with ICH/EU guidelines. Other aspects of the pivotal studies do not meet the full requirements of the EU Guideline of Repeated Dose Toxicity (CPMP/SWP/1042/99),³ namely:

- the use of only a single dose level in the pivotal rabbit study (in addition to the control group) compared with the three recommended
- a frequency of administration that falls short of the proposed clinical dosing regimen,
- especially in the studies in dogs
 - up to 8 times daily (approximately 1.5 hours apart) in just the first week of the 6-month rabbit study then 4 times daily (approximately 2 hours apart), and once or twice daily (greater than or equal to 4 hours apart) in the in the 12-month dog study, compared with 4-times daily or up to hourly administration in humans
- the absence of toxicokinetic analyses (both species), and lack of examination of urinalysis (rabbits) and electrocardiogram (ECG) recordings (both species).

The pivotal studies were described as being conducted with the commercial Lotemax formulation but this was unable to be verified from information contained in the actual study reports. In particular, the description of the vehicle control in the dog study revealed an excipient profile not matching that of Lotemax. The highest strength of loteprednol etabonate tested in the pivotal studies was 0.5%, the same as that proposed for registration; strengths of up to 5.0% (though not formulated similarly to Lotemax) were tested in shorter studies (7 days and 4 weeks duration in rabbits). A series of other 4 week studies investigated gel and ointment dose forms, but these studies did not feature comprehensive histopathological examination. A 4-week study by the PO route in rats was also submitted. Under ICH guidance (M3(R2))⁴, studies of 4 weeks duration are sufficient to support a clinical duration of treatment of up to 2 weeks; treatment for up to 6 weeks, as proposed, should be supported by animal studies of at least 6 months duration.

Relative exposure

Exposure ratios achieved in studies that included comprehensive histopathological examination have been calculated below based on animal:human doses per eye following adjustment for differences in size across species (for assessment of local toxicity compared with acute local tolerance, which is assessed by direct comparison of strengths)) and doses adjusted for body surface area (for assessment of systemic toxicity). Comparisons are made with respect to two clinical dosing scenarios: the standard dose recommended for the treatment of post-operative inflammation following ocular surgery and for the treatment of various steroid-responsive inflammatory conditions (that is, two drops per eye 4 times daily), and the maximum recommended dose used in the first week of treatment of steroid-responsive inflammatory conditions (that is, one drop per eye every hour (assuming 18 treatment hours per day).

The maximum anticipated human dose was not achieved in the pivotal dog study, or for any sufficient period in the pivotal rabbit study, on either an ocular or systemic basis. Higher exposure multiples were obtained in a 4 week topical ocular study in rabbits and a 4-week oral study in rats. In accordance with ICH M3(R2),⁴ these 4-week studies are of

³ European Medicines Agency, "Guideline on repeated dose toxicity", 18 March 2010.

⁴ European Medicines Agency, "ICH guideline M3(R2) on non-clinical safety studies for the conduct of human clinical trials and marketing authorisation for pharmaceuticals. December 2009.

sufficient duration to support dosing at the higher proposed level for one week and at the standard dose level for up to 2 weeks.

Table 1. Relative exposure in repeat-dose toxicity studies featuring comprehensive histopathological examination

Species	Study duration/ treatment details		Dose per day			Exposure ratio				
			mg/ eye	mg/ kg	mg/ m ²	2 drops/eye, 4 times daily		1 drop/eye, hourly		
						ocular	systemic	ocular	systemic	
Rat (SD)	4 weeks (PO administration) [Study PTC/9]		–	0.5	3	–	1.8	–	0.8	
			–	5	30	–	18	–	8	
			–	50	300	–	178	–	79	
Rabbit (NZW)	4 weeks [Study PTC/7]	100 µL, once daily	0.1%	0.1	0.025	0.375	0.21	0.22	0.09	0.10
			0.7%	0.7	0.175	2.63	1.5	1.6	0.65	0.69
			5.0%	5	1.25	18.8	10	11	4.6	4.9
	6 months (pivotal) [Study PTC/89]	30 µL ´ 0.5%; eight times daily (first week only)	1.2	0.3	4.5	2.5	2.7	1.1	1.2	
			0.6	0.15	2.25	1.3	1.3	0.56	0.59	
Dog (Beagle)	12 months (pivotal) [Study PTC/74]	90 µL, once daily	0.05%	0.045	0.0036	0.072	0.044	0.043	0.02	0.02
		90 µL, twice daily	0.1%	0.18	0.0144	0.288	0.18	0.17	0.08	0.08
			0.5%	0.9	0.072	1.44	0.88	0.85	0.39	0.38
Human	2 drops/eye, 4 times daily	32 µL ´ 0.5%	1.28	0.0512	1.69	–	–	–	–	
	1 drop/eye, hourly		2.88	0.115	3.80	–	–	–	–	

Body weights of 4, 12.5 and 50 kg are assumed for rabbits, dogs and humans respectively; mg/kg to mg/m² conversion factors of 6, 15, 20 and 33 have been used for rats, rabbits, dogs and humans, respectively; ocular administration was unilateral in rabbits and dogs; bilateral administration is assumed in humans; hourly administration in humans is assumed to be for 18h per day; ocular exposure ratios are based on animal:human mg/eye doses following normalisation for ocular volume across species (based on vitreous volumes of 1.5, 3.2 and 4.0 mL in rabbits, dogs and humans, respectively).

Major findings

Loteprednol etabonate was well tolerated locally in all studies, including when administered to rabbits as a suspension containing 10 times the clinical strength of the active ingredient. Notable ocular effects were confined to minimal conjunctival redness towards the end of the treatment period in the 6 month rabbit study (0.6 mg/eye/day; relative exposure, 0.56), and corneal stromal deposits (ranging from a fine haze to crystalline deposits; at greater than or equal to 0.18 mg/eye/day), corneal opacity (at 0.9 mg/eye/day) and increased intraocular pressure (at greater than or equal to 0.18 mg/eye/day) in the 12 month dog study (relative exposure, 0.08 to 0.39). The corneal stromal deposits and corneal opacity in dogs developed after more than 13 and 39 weeks of treatment, respectively (that is, first evident at subsequent examinations conducted in Weeks 26 or 52). These effects and also a significantly more prominent increase in

intraocular pressure (IOP), were also seen in a 0.1% dexamethasone (0.18 mg/eye/day) comparator group that was included in the study. Intraocular pressure was not increased in rabbits treated with loteprednol etabonate.

Topical ocular administration of loteprednol etabonate for 12 months was not associated with any systemic histopathological changes in dogs. In the same study, dexamethasone-treated animals showed typical systemic corticosteroid effects (adrenal atrophy, lymphoid depletion in spleen, thymic involution and ballooned cells in the liver). Thymic involution was observed in loteprednol etabonate-treated rabbits in the pivotal 6 month study. The most prominent systemic effects of loteprednol etabonate were seen in the 4 week oral study in rats (consistent with the higher doses used and exposure achieved), with histopathological changes evident at greater than or equal to 5 mg/kg/day (relative exposure, 8 to 79) but comprising class effects only (thymic involution, splenic lymphoid depletion and adrenal cortical atrophy). Adrenal cortical atrophy was also reported as a histopathological change caused by loteprednol etabonate in rabbits in another 6 month topical ocular study (poorly documented; see Combination use below).

Three studies involving direct administration of metabolite PJ-90 were submitted. These showed a low order of acute toxicity by the SC route in rats and no significant ocular irritation or other local toxicity in rabbits with topical ocular administration of the 0.5% strength for up to 4 weeks at a dose of 0.5 mg/eye/day.

Genotoxicity

The potential genotoxicity of loteprednol etabonate was investigated in tests for mutagenicity in bacteria, an in vitro mouse lymphoma tk assay, an assay for clastogenicity in vitro (in human lymphocytes) and in the mouse bone marrow micronucleus test. The conduct of the studies was mostly in accordance with ICH guidelines. Drug concentrations in the in vitro studies were low, limited by solubility, but acceptable. No bacterial strain capable of detecting mutations at A-T sites (such as *S. typhimurium* TA102 or *E. coli* WP2 uvrA) was included in one of the two Ames tests submitted (the only one for which GLP status was confirmed, and which used a higher maximum concentration than the other study). Dose selection and use of the oral route in the in vivo mouse study is considered acceptable. Overall the genotoxicity program is considered adequate, and all studies returned negative results for loteprednol etabonate.

Carcinogenicity

No carcinogenicity studies were submitted. In accordance with ICH guidance (3BS8a)⁵, the absence of such studies is considered acceptable given the lack of significant systemic exposure in patients, that the duration of treatment does not exceed 3 months, the negative genotoxicity findings and the absence of other nonclinical findings that would give cause for concern.

Reproductive toxicity

Reproductive toxicity studies submitted by the sponsor covered all stages (fertility, early embryonic development, embryofetal development, and pre- and postnatal development). Numbers of animals and the timing/duration of treatment were appropriate. All studies were conducted by administration of the product via the oral route.

⁵ TGA Adopted ICH guidance "The need for carcinogenicity studies of pharmaceuticals", 1995

Relative exposure

Toxicokinetic analyses in the reproductive toxicity studies were very limited. Plasma levels were only assessed at single time points in pilot studies, and while loteprednol etabonate was not detectable in plasma, the assays were not of high sensitivity (lower limit of quantitation, 500 ng/mL). Relative exposure is estimated below based on animal:human doses adjusted for body surface area. The figures should be considered a very rough estimate given the comparison across routes (oral in animals; topical ocular in humans), but clinical exposure is seen to be surpassed at the highest dose levels and not at the lowest ones.

Table 2. Clinical Exposure

Species	Study/treatment	Dose		Exposure ratio		
		mg/kg/day	mg/m ² /day	2 drops/eye, 4 times daily	1 drop/eye, hourly	
Rat (OFA-SD)	Fertility & early embryonic development	♂/♀	0.5	3	1.8	0.8
			5	30	18	8
		♀	25	150	89	39
		♂	50	300	178	79
	Embryofetal development		0.5	3	1.8	0.8
			5	30	18	8
			50	300	178	79
			100	600	355	158
	Pre-/postnatal development		0.5	3	1.8	0.8
			5	30	18	8
		50	300	178	79	
Rabbit (NZW)	Embryofetal development		0.1	1.5	0.9	0.4
			0.5	7.5	4.4	2.0
			3	45	27	12
Human	2 drops/eye, 4 times daily	32 µL 0.5%	0.0512	1.69	-	-
	1 drop/eye, hourly		0.115	3.80	-	-

mg/kg to mg/m² conversion factors of 6, 15 and 33 have been used for rats, rabbits, and humans (50 kg), respectively;

PO administration in laboratory animal species; hourly administration in humans is assumed to be for 18h per day.

No data on placental transfer or excretion in milk were submitted.

Fertility was unaffected in male and female rats treated with loteprednol etabonate at respective doses of up to 50 and 25 mg/kg/day PO. Pre- and post-implantation losses were increased and live litter size decreased in rats at 25 mg/kg/day. Loteprednol etabonate was teratogenic in both laboratory animal species tested and is consistent with previous findings for the class. In rats, the incidence of fetuses with major external/visceral abnormalities (most commonly cleft palate; also umbilical hernia) was increased at greater than or equal to 50 mg/kg/day together with a reduction in mean fetal weight and retarded ossification of various bones; these doses were also maternotoxic (evident as suppression of maternal body weight gain or slight body weight loss). In rabbits, treatment at 3 mg/kg/day was associated with meningocele, retarded ossification, an increased incidence of limb flexure and decreased mean fetal weight were seen at this dose. Treatment was not associated with maternotoxicity during the actual

treatment period in rabbits (that is, gestation days 6 to 18; corresponding to the period of organogenesis), but body weight loss was seen in the four days after the cessation of dosing at 3 mg/kg/day. However, there was no significant effect on body weight at the end of the gestation period compared with controls. The no observable effect level (NOEL) for embryofetal development was 5 mg/kg/day PO in the rat and 0.5 mg/kg/day PO in the rabbit (0.8 to 2 times the maximum anticipated clinical dose based on body surface area-adjusted doses). In a pre-/postnatal development study in rats, loteprednol etabonate decreased pup birth weight at greater than or equal to 5 mg/kg/day PO, and decreased perinatal and postnatal survival, reduced postnatal body weight gain and delayed attainment of the righting reflex, startle response and pupillary light reflex in pups at 50 mg/kg/day. These effects occurred in the context of maternal toxicity (suppression of body weight gain). Pup development was unaffected at 0.5 mg/kg/day PO (0.8 times the clinical dose based on body surface area-adjusted doses).

Pregnancy classification

The sponsor has proposed Pregnancy Category B3.⁶ This category is considered appropriate given the nature of the animal findings, tempered by the exposure level in patients.

Antigenicity

Loteprednol etabonate (as a 0.5% cream) did not show skin sensitisation potential in guinea pigs.

Combination use

Ocular tolerance of 0.5% loteprednol etabonate in combination with 0.3% tobramycin or 10% sulfacetamide was demonstrated in 30-day studies in rabbits (up to 8 times daily administration at 100 µL/dose). A partial report for a 6-month repeat-dose toxicity study with 0.5% loteprednol etabonate alone and in combination with 0.3% tobramycin in rabbits was submitted (involving 6 times daily dosing with “one drop”). In the absence of documentation of histopathological findings and other details (including the actual dose volume administered) this study is not adequate for regulatory assessment. Adrenal cortical atrophy was reported as a histopathological finding with loteprednol etabonate treatment (with and without tobramycin; consistent with known effects of the corticosteroid class). None of the repeat-dose combination studies included microscopic examination of the minimum core list of tissues (recommended regardless of the route of administration) given in the EU Guideline on Repeated Dose Toxicity (CPMP/SWP/1042/99).⁷

Paediatric use

No specific studies in juvenile animals were submitted. Specific studies in juvenile animal studies are not considered necessary to support use of Lotemax in children given the nature of the findings seen in the existing studies conducted in young adult animals. However, the significance of the failure of the pivotal ocular repeat-dose studies to reach ocular and systemic exposure levels predicted in an adult patient (50 kg assumed body weight) is magnified with respect to use in children, where higher exposure can be anticipated compared with adults given the absence of dose adjustment.

⁶ Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human fetus having been observed. Studies in animals have shown evidence of an increased occurrence of fetal damage, the significance of which is considered uncertain in humans.

⁷ European Medicines Agency, “Guideline on repeated dose toxicity”, 18 March 2010.

<http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2010/03/WC500079536.pdf>

Nonclinical summary

- All pivotal safety-related studies, except for an Ames test for bacterial mutagenicity, were conducted according to GLP.
- Loteprednol etabonate was shown to bind to the rat glucocorticoid receptor, displaying higher affinity *cf.* dexamethasone. Anti-inflammatory activity following topical ocular administration of the clinically proposed strength (or higher) was shown in various rabbit models, and when administered by other routes in other species.
- Secondary pharmacodynamic studies revealed activities consistent with, or less prominent than, those observed for other corticosteroids (For example, increased intraocular pressure, inhibition of corneal wound healing). Receptor screening assays and safety pharmacology studies were not conducted.
- Topical ocular administration was shown to result in only limited systemic absorption in rabbits and dogs, as occurs in humans. Absorption into rabbit ocular tissues was rapid. Plasma protein binding by the drug was high (approximately 95%; assessed in dog plasma). Metabolism of loteprednol etabonate involves sequential hydrolysis to form two metabolites; neither is pharmacologically active at the glucocorticoid receptor.
- Loteprednol etabonate had a low order of acute toxicity by the PO and SC routes in mice and rats.
- Repeat-dose toxicity studies by the topical ocular route of up to 6 months duration in rats and 12 months duration in dogs were conducted. Ocular and systemic exposure to loteprednol etabonate at the dose levels tested in these longest studies is estimated to be below that anticipated in patients at the maximum recommended dose. Significant multiples of the anticipated human exposures were only obtained in 4-week studies in rats (PO administration) and rabbits (topical ocular administration). At 4 weeks, these studies fall short of the maximum anticipated duration of treatment of 6 weeks; the relevant ICH guideline recommends studies of 6 months duration in animals to support this length of duration of clinical treatment.
- The repeat-dose toxicity studies demonstrated that loteprednol etabonate was well tolerated locally in the eye. All ocular and systemic findings represented only known corticosteroid class effects. These comprised corneal stromal deposits, corneal opacity and increased intraocular pressure in dogs; thymic involution and (reportedly) adrenal cortical atrophy in rabbits; and thymic involution, splenic lymphoid depletion and adrenal cortical atrophy in rats.
- Loteprednol etabonate was not genotoxic in a battery of *in vitro* and *in vivo* tests. Carcinogenicity studies have not been conducted and are not required for this product under ICH guidance.
- Reproductive toxicity studies, conducted by the oral route, showed no impairment of fertility (in rats), teratogenicity and other adverse effects on embryofetal development (in both rats and rabbits), and adverse effects on pre-/postnatal development (rats).
- No specific studies in juvenile animals were submitted.
- Loteprednol etabonate (as a 0.5% cream) was not a skin sensitiser in guinea pigs.

Nonclinical conclusions and recommendation

- The nonclinical data package suffers from deficiencies with respect to the investigation of repeat-dose toxicity. Local ocular tolerance (that is, the potential for irritation) has

been adequately addressed but the assessment of the other aspects of general toxicity, ocular toxicity and systemic toxicity relies on studies of adequate duration but where exposure was subclinical (that is, the 6 month rabbit and 12-month dog studies) or otherwise studies where high relative exposure was obtained but the duration of treatment is insufficient to support a clinical treatment regime of longer than 2 weeks duration (that is, 4-week studies in rats (involving oral administration) and in rabbits). However, given the overall program and that these studies have only revealed effects consistent with or less prominent than those of other members of the corticosteroid class, these deficiencies are not considered so major that registration should be opposed.

- The absence of certain studies that would typically be expected for a new chemical entity (most notably, those on safety pharmacology and carcinogenicity) is considered acceptable given existing experience with the drug and drug class and/or the pattern of clinical use and exposure level.
- Primary pharmacology studies, showing anti-inflammatory activity following topical ocular administration of the proposed clinical strength, support the drug's use for the proposed indications.
- Loteprednol etabonate, like other corticosteroids, was shown to be teratogenic in laboratory animal species. Pregnancy Category B3,⁸ as the sponsor proposes, is considered appropriate for the product given the route of administration and resultant clinical exposure level.
- While noting that only qualified support can be given, there are no nonclinical objections to the registration of Lotemax for the proposed indications.

IV. Clinical findings

A summary of the clinical findings is presented in this section. Further details of these clinical findings can be found in Attachment 2.

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.

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).

⁸ Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human fetus having been observed. Studies in animals have shown evidence of an increased occurrence of fetal damage, the significance of which is considered uncertain in humans.

- 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 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 (Δ^1 -cortienic acid etabonate) and subsequently to PJ-90 (Δ^1 -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 (IOP), 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 intraocular pressure (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.

Contents of the clinical dossier

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 seasonal allergic conjunctivitis (SAC) (121), 2 studies in giant papillary conjunctivitis (GPC) (107 and 108) and 2 studies in acute anterior uveitis (AAU) (122/1221 and 126).
- No dose-finding studies.
- Other efficacy/safety studies using proposed LE 0.5% (Lotemax) included 1 pilot study in seasonal allergic conjunctivitis (SAC) (114), 1 pilot study in giant papillary conjunctivitis (GPC) (106) and one study in acute allergic conjunctivitis (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 or meta-analyses.

Pharmacokinetics

Studies providing pharmacokinetic data

Table 3 shows the studies relating to each pharmacokinetic topic.

Table 3. Studies providing pharmacokinetic data

PK topic	Subtopic	Study ID
PK in healthy adults	General PK - Single dose-ocular tolerability study	HGPss-101
	- Multi-dose	P5064-120
	- Single dose- oral	5064-112
	Bioequivalence† - Single dose	None
	- Multi dose	
	Food effect	None
PK in special populations	Target population § - Single dose	358-005
	- Multi-dose	358-006
	Hepatic impairment	None
	Renal impairment	None
	Neonates/infants/children/adol escents	None
	Elderly	None
	{Other special population}	None
Genetic/gender-related PK	Males vs. 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.

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.

Absorption

Results from a bioavailability study in normal volunteers established that plasma levels of loteprednol etabonate and $\Delta 1$ - 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 (less than 1 ng/ mL) systemic absorption occurs with Lotemax.

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.

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 ($\Delta 1$ -cortienic acid) and PJ-91 ($\Delta 1$ -cortienic acid etabonate).

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 pharmacokinetic (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 aqueous humour (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.

Pharmacodynamics

Limited information was provided from two studies (141 and 145). See Attachment 2 for further details.

Evaluator's overall conclusions on pharmacodynamics

Results of Study 141 showed that LE 0.5% (twice daily or four times daily) 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 two 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.

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.

Efficacy

Studies providing efficacy data for Indication 1

Treatment of post-operative inflammation following ocular surgery

Studies 125 and 127.

Evaluator's conclusions of efficacy for Indication 1

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 to 64% of LE-treated patients showing resolution of symptoms (score of 0 at final visit) compared to placebo (28 to 29%). Furthermore, treatment failures (which included patients who discontinued early for inadequate control or who had an increase of greater than 3 in their anterior chamber inflammation (ACI) score) was also significantly lesser in the LE group (6%) compared with placebo (25 to 30%). The secondary endpoints of investigator global assessment (IGA) 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.

Studies providing efficacy data for 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.

Seasonal allergic conjunctivitis (SAC): Studies P5604-121 and Study 114.

Giant papillary conjunctivitis (GPC): Study 106, 107 and 108.

Acute anterior uveitis (AAU): Study 122/1221 and 126.

Other efficacy studies: Study 358-004, 143 and 144.

Evaluator's conclusions of efficacy for Indication 2

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.

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 Investigator global assessment (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 out of 109) was significantly greater than the proportion of those treated with placebo (51%, 56 out of 110; $p < 0.001$). A treatment difference favouring Lotemax was seen with improvement in itching (95% (104 out of 109) versus 81% (89 out of 110); $p = 0.001$) and lens intolerance (87% (95 out of 109) versus 77%, (85 out of 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 out of 111) versus 50% (55 out of 109), $p < 0.001$). A treatment difference favouring Lotemax was also seen with itching (92% (102 out of 111) versus 76% (83 out of 109), $p < 0.001$) and lens intolerance (84% (93 out of 111) versus 66% (72 out of 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 or 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.

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 (last observation carried forward (LOCF)) was significantly ($p < 0.001$) lesser with LE 0.5% compared with prednisolone acetate (PA) 1% for both anterior chamber cells (LE versus PA: 64% (52 out of 81) versus 89% (67 out of 75)) and flare (63% (51 out of 81) versus 87% (65 out of 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 out of 81) versus 87% (77 out of 89), $p = 0.015$) and flare (66% (52 out of 79) versus 82% (72 out of 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, and 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.

Safety

Studies providing evaluable safety data

The safety profile for LE as a single active agent, loteprednol etobonate (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).

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 to 44 years (ranging from 17 to 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.

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 conjunctivides, 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 out of 25,060,468) for Lotemax and Alrex. For all products containing LE, the percentage is 0.002394% (708 out of 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.

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 four times daily 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 United Kingdom (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 increased 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 out of 901). This was similar to that seen in individuals treated with placebo (0.5%, 3 out of 583), and lower than that seen in individuals treated with prednisolone acetate (6.7%, 11 out of 164). In subjects who did not wear contact lenses during the studies, only 0.6% (4 out of 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 (greater than 10 mmHg) and median time significant IOP elevation.

Ocular adverse reactions occurring in 5 to 15% of patients treated with loteprednol etabonate ophthalmic suspension (0.2% to 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 Alex.

First round benefit-risk assessment

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, less than 1 ng/mL), even with four times daily 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.

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%, Alex) 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 Alex 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.

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 (below) are adopted.

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 (greater than 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.

Clinical questions

Pharmacokinetics

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 why was it not included in the dossier?

Question Two

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

Pharmacodynamics

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?

Efficacy

None.

Safety

None.

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 and then the evaluator's comments on sponsor's response.

Pharmacokinetics***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?

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 (less than 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 four times daily 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.

Evaluator's comments on sponsor's response

The explanation provided by the sponsors is acceptable.

Question Two

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

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% to 1% (Study BL08009 and Study BL08010.) The results of these studies revealed that systemic exposure to LE was low (less than 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.

Evaluator's comments on sponsor's response

The explanation provided by the sponsors is acceptable.

Pharmacodynamics***Question One***

Study 145 evaluated 3 concentrations of LE (0.1%, 0.2% 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?

Sponsor's response

Study 145 consisted of 2 parts with separate objectives and all subjects were instilled four times daily 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 the Table 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 4. 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 to 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.

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. Alex 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).

Second round benefit-risk assessment

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, less than 1 ng/mL), even with four times daily 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.

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.

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.

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 (greater than 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.

V. Pharmacovigilance findings

Risk management plan

The sponsor submitted a Risk Management Plan (RMP version 01, dated 31 October 2012 (data lock point 31 March 2012)) which was reviewed by the TGA. A summary of the RMP appears in the following table.

Safety specification

The sponsor categorised the risks as important identified risks and other identified risks, important potential risks and other potential risks (Table 5).

Table 5. Ongoing safety concerns

Risk	Details
Important identified risks	<ul style="list-style-type: none"> · Intraocular Pressure (IOP), Glaucoma, Blindness · Visual disorders
Other identified risks	<ul style="list-style-type: none"> · Headache, Dizziness · Ocular discomfort/Local intolerance
Important potential risks	<ul style="list-style-type: none"> · Corneal disorders · Ocular infections · Cataract formation · Keratitis
Other potential risks	<ul style="list-style-type: none"> · Blood glucose increased · Drug ineffective
Important missing information	<ul style="list-style-type: none"> · None

Lotemax suspension eye drops are not approved for use in children as the efficacy and safety has not been established for this age group.

For Lotemax suspension, no clinical data on exposed pregnancies are available from the clinical studies since this was an exclusion criterion. Studies in animals have shown reproductive toxicity when LE is administered orally at 35 times the maximum clinical daily dose for humans.

Loteprednol is classified under Pregnancy Category B3. There are no adequate and well controlled studies in pregnant women. LE should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Teratogenic effects

Loteprednol etabonate has been shown to be (when administered orally to rabbits during organogenesis at a dose of 3 mg/kg/day, a dose which caused no maternal toxicity);

- embryotoxic (delayed ossification) and
- teratogenic (increased incidence of meningocele, abnormal left common carotid artery, and limb flexures).

Comment: It is recommended to the delegate that paediatric use and use in pregnancy be listed as important missing information and close monitoring of paediatric off label use and use by pregnant women be reported and discussed in PSURs Pharmacovigilance plan

The sponsor reports that since the most common ocular AEs reported were consistent with the underlying diseases studied and because there are no specific concerns about the safety of the LE suspension routine pharmacovigilance practices are sufficient to monitor post-marketing Lotemax.

The following studies are part of a pharmaco-epidemiological programme as required for registration of the LE suspension 0.5% product (Lotemax) in several countries in the Asian-Pacific region.

- Study # 623
 - Post Marketing Surveillance Study conducted in Thailand with Lotemax.
 - § It consists of the collection of adverse events and serious AE data from dispensed drugs for 2 years in 243 sites which are listed by the Thai Health Authorities.
 - § As of March 2012, no AE or SAEs were reported on the 122 reports sent to Thai FDA.
 - § Due for completion in February 2013
- Study # 628.
 - Post Marketing Surveillance Study that will be conducted in Korea with Lotemax eye drops suspension.
 - § It will be conducted in approximately 600 subjects in approximately 30 sites for 6 years from the approval of the product.
 - § As of 06 August 2012, 494 persons were recruited. No serious adverse events were reported.
 - § Due for completion in June 2014
- Study # 641.
 - Post Marketing Surveillance Study conducted in Philippines with Lotemax.
 - § It will be conducted in approximately 150 subjects in 1 site.
 - § At this time, no patients were enrolled.
 - § Due for completion in December 2012

The evaluator requested the sponsor provide the TGA with an update regarding the Studies 623 and 641. In regard to the pharmacovigilance plan and the appropriateness of milestones the evaluator had no objection to the specified pharmacovigilance plan.

Risk minimisation activities

The sponsor states that routine risk minimisation activities (product labelling) are sufficient to mitigate the important identified and potential risks.

In regard to the proposed routine risk minimisation activities, the draft product information document is considered satisfactory.

The proposed Australian CMI states that in severe cases your doctor may recommend that you put one to two drops in the affected eyes hourly. This statement is at odds with the proposed dosage and administration (Australian PI).

In regard to the proposed routine risk minimisation activities, it is recommended to the Delegate that the draft consumer medicine information document be revised as follows: strike through text to be deleted from Australian CMI. In severe cases your doctor may recommend that you put one to two drops in the affected eyes hourly

The evaluator considered that the planned actions were considered acceptable and appropriate.

Table 5 - Summary of risk management plan

Safety concern	Proposed pharmacovigilance	Proposed risk minimisation activities
Important Identified Risks		
Increase of Intraocular pressure (IOP) / glaucoma Blindness	Routine PV activity Routine activity is considered sufficient because the reaction might be serious but the risk of IOP increase is clearly known for the steroids. The potential of LE to increase IOP is lower than for other steroids especially in short term use. For duration of use longer than 10 days IOP should be monitored. Listed in SmPC and PI Adverse Event section 4.8. and viii): Listed as adverse event Warnings and Precautions section 4.4 and vi) Advice to do ocular examination if duration of treatment is longer than 10 days with monitoring of IOP	Routine
Visual disorders Visual acuity reduced Visual field defects Vision blurred Visual impairment	Routine pharmacovigilance is considered sufficient because the reactions are non-serious in most cases. In five cases only a link to increase IOP could be drawn. In most cases visual disorders were reported together with ocular discomfort or local intolerance effects. Adverse Event section 4.8. and viii): Listed as adverse event Warnings and Precautions section 4.4 /4.6 Advice to do ocular examination if duration of treatment is longer than 10 days with monitoring of IOP. Advice that patient should be re-evaluated if symptoms do not improve after 2 days of treatment	Routine
Important Potential Risks		
Corneal disorders Corneal perforation/ Corneal scar/ corneal epithelium defect	Routine pharmacovigilance. Although some reactions may be serious, routine activity is considered sufficient because the rate is very low. Corneal events Listed in Adverse Events section Warnings and Precautions section 4.4 and vi) Prolonged use In patients with underlying corneal diseases may lead to corneal perforation. Advice to do ocular examination if duration of treatment is longer than 10 days with monitoring of IOP Advice that patient should be re-evaluated if symptoms. Advice that patient should be re-evaluated if symptoms do not improve after 2 days of treatment	Routine
Ocular infections Endophthalmitis	Warnings and Precautions section 4.4 and vi) Advice to do ocular examination if duration of treatment is longer than 10 days with monitoring of IOP Advice that patient should be re-evaluated if symptoms do not improve after 2 days of treatment Storage conditions in PI section xi) Discard bottle 4 weeks after opening Routine activity is considered sufficient because the reaction, although serious, is very rare. A causal link to LE use is considered only remote.	Routine

Safety concern	Proposed pharmacovigilance	Proposed risk minimisation activities
Important potential risks		
Cataract formation Subcapsular cataract	Routine Pharmacovigilance SmPC and PI Adverse Events section 4.8 and viii) Warning and precautions section 4.4. and vi) Prolonged use in patients may lead to posterior subcapsular cataract formation. Advice to do ocular examination if duration of treatment is longer than 10 days with monitoring of IOP	Routine
Keratitis Ulcerative Keratitis Punctate Keratitis	Routine Pharmacovigilance Adverse Events section 4.8 and viii) Warning and precautions section 4.4. and vi) Prolonged use in patients with underlying corneal diseases may lead to corneal perforation. Advice to do ocular examination if duration of treatment is longer than 10 days with monitoring of IOP Advice that patient should be re-evaluated if symptoms	Routine
Other identified risks		
Headache Migraine Dizziness	Routine PV activity Routine activity is considered sufficient because the reactions are non-serious and listed in the SmPC and have a very low impact on patient's safety.	Routine
Ocular discomfort/ ocular intolerance Eye pain, Eye pruritus Eye irritation Ocular hyperaemia Lacrimation increased Photophobia Foreign body sensation in eye	Routine PV activity Routine activity is considered sufficient because the reactions are non-serious and listed in the SmPC and have a very low impact on patient's safety.	Routine
Other potential risks		
Drug ineffective	Routine pharmacovigilance is considered sufficient because the reaction is non-serious and rare.	Routine
Blood glucose increased	Routine pharmacovigilance is considered sufficient because the reaction is non-serious and very rare.	Routine

Reconciliation of issues outlined in the RMP report

The following table provides a summary of the OPR evaluation of the RMP issues raised with the sponsor, sponsors responses and OPR evaluation of these responses.

Table 6. Reconciliation of issues outlined in the RMP report

Recommendation in RMP evaluation report	Sponsor's response	OPR evaluator's comment
Safety considerations may be raised by the nonclinical and clinical evaluators through the consolidated section 31 request and/or the Nonclinical and Clinical Evaluation Reports respectively. It is important to ensure that the information provided in response to these include a consideration of the relevance for the Risk Management Plan, and any specific information needed to address this issue in the RMP. For any safety considerations so raised, the sponsor should provide information that is relevant and necessary to address the issue in the RMP.	'There were no safety questions raised by nonclinical and clinical evaluators in this Consolidated S31. The Nonclinical and Clinical Evaluation Reports are not yet available to B&L. B&L provides an assurance that any safety considerations raised in the nonclinical and clinical evaluation reports, B&L will provide information that is relevant and necessary to address the issue in the RMP.'	The sponsor's response is satisfactory.

Recommendation in RMP evaluation report	Sponsor's response	OPR evaluator's comment
<p>The sponsor is requested to provide the TGA with an update regarding the study 623 and 641.</p>	<p>Update of Study #623:</p> <p>Study #623 is a Post Marketing Surveillance Study conducted in Thailand with Lotemax.</p> <p>The objective of this study is to monitor the safety of the use of Lotemax 0.5% eye drops suspension. The study design consists of the collection of non-serious and serious adverse event data from dispensed drugs for 2 years in 243 sites which are listed by the Thai Health Authorities (TFDA).</p> <p>The Start Date was on 4-Jan-2011. The End Date of the study was on 3-Jan-2013. During the study in total data from 827 patients exposed were collected from 236 study sites.</p> <p>Overall three (3) non-serious Adverse Events (AE) cases were reported:</p> <p>1) Case no. 24 reported on 2nd May 2012 (BL-2012-000616) – spike in IOP (outcome: resolved with sequelae)</p> <p>2) Case no. 44 reported on 3rd July 2012 (BL-2012-000617) – spike in IOP (outcome: resolved with sequelae – continued usage of Lotemax but in lower dose)</p> <p>3) Case no. 57 reported on 14th July 2012 (BL-2012-002125) – spike in IOP (steroid responder- continued usage of Lotemax but in lower dose).</p> <p>B&L is awaiting approval from Thai FDA, expected in the month of August 2013.</p>	<p>The updates provided by the sponsor regarding study #623 are satisfactory.</p> <p>The evaluator noted the decision of suspending study #641 and the justification provided by the sponsor.</p> <p>The evaluator recommends that the sponsor undertake to provide further updates and final results of the post-marketing surveillance studies #623, #624 and #628 to the TGA in future Periodic Safety Update Reports.</p> <p>It is recommended that results of these studies are communicated to the TGA at the same time as they are communicated to other regulatory agencies.</p>

Recommendation in RMP evaluation report	Sponsor's response	OPR evaluator's comment
	<p>Update of Study #641:</p> <p>Study #641 is based on the Philippine legislation which required post-marketing safety surveillance (PMS) study as a prerequisite for approval of new chemical entities (NCE). The protocol for such a study had to be submitted and approved by the Philippines FDA before the NCE registration application could be filed. The study protocol of Study #641 had been approved and the study had been flagged in the dossier/RMP. However the study had not been initiated yet and no patients were enrolled.</p> <p>Due to changes in the Philippines legislation which were issued in February 2013, this type of studies is no longer a requirement. As this study was no longer required B&L decided to suspend the study. The study closure letter will be submitted to the Institutional Review Board (IRB) in May 2013.</p> <p>The design of Study #641 was a Post-marketing surveillance to evaluate the safety and efficacy of Lotemax in an open label non-comparative study conducted in a sample Filipino population of the Lotemax Monitored Release Program (150 subjects at one site).</p> <p>The objectives of the study were to obtain confirmatory information regarding the safety profile of the product when used as a topical formulation for the treatment of post-operative inflammation, of for the treatment of steroid-responsive inflammatory conditions of the palpebral and bulbar conjunctiva, cornea and anterior segment of the globe in the Filipino population.</p> <p>Based on the fact that Lotemax eye drops suspension has been launched since 1998 and is marketed in many countries worldwide, there is a long experience of safety data from clinical studies and post-marketing data. Therefore Study # 641 would have limited or no contribution to the safety data for any identified risks. The contribution would be the collection of data from the Filipino population, however there were other studies conducted in Asia with many subjects and no difference in the safety data was found in different populations.</p> <p>Thus B&L considers that the suspension of Study # 641 has no relevant impact on the safety and efficacy information and on the conclusions of any identified risks in the Risk Management Plan of Lotemax.</p>	

Recommendation in RMP evaluation report	Sponsor's response	OPR evaluator's comment
<p>It is recommended to the delegate that paediatric use and use in pregnancy be listed as important missing information and close monitoring of paediatric off label use and use by pregnant women be reported and discussed in PSURs. In regard to the proposed routine risk minimisation activities, the draft product information document is considered satisfactory.</p>	<p>"B&L is in agreement with the evaluator's recommendation to include the paediatric use and use during pregnancy in the safety concern section "important missing information". In addition a close monitoring of paediatric off label use as well as by pregnant women will be presented and discussed in future PSURs."</p>	<p>The sponsor's response is satisfactory.</p>
<p>The proposed Australian CMI states that in severe cases your doctor may recommend that you put one to two drops in the affected eyes hourly. This statement is at odds with the proposed dosage and administration (Australian PI). It is recommended to the Delegate that the draft consumer medicine information document be revised as follows: strike through text to be deleted from Australian CMI.</p> <p>In severe cases your doctor may recommend that you put one to two drops in the affected eyes hourly.</p>	<p>"B&L agrees to revise the proposed CMI and to change the dosage instruction in order to align on the PI for the hourly administration. This is justified to clarify the inconsistency.</p> <p>The Dosage and administration in Lotemax PI states:</p> <p>Post-Operative Inflammation</p> <p>Apply one to two drops of Lotemax into the conjunctival sac of the operated eye(s) four times daily beginning 24 hours after surgery and continuing throughout the first 2 weeks of the post-operative period.</p> <p>Steroid Responsive Disease Treatment</p> <p>Apply one to two drops of Lotemax into the conjunctival sac of the affected eye(s) four times daily. During the initial treatment within the first week, the dosing may be increased, up to 1 drop every hour, if necessary. Care should be taken not to discontinue therapy prematurely.</p> <p>In order to be consistent with the PI, the CMI will be revised as:</p> <p>"In severe cases your doctor may recommend that you put one drop in the affected eye(s) hourly."</p> <p>The CMI will be updated when the Delegates Overview is received.'</p>	<p>The updated text in the proposed CMI appears to be consistent with that in the PI. The sponsor's response is satisfactory.</p>

Outstanding issues

Details on the following outstanding issue are outlined in the table 'Reconciliation of issues outlined in the RMP report'.

Recommendation

The OPR evaluator noted the decision of suspending Study #641 and the justification provided by the sponsor.

The evaluator recommends that the sponsor undertake to provide further updates and final results of the post-marketing surveillance Studies #623, #624 and #628 to the TGA in future Periodic Safety Update Reports.

It is recommended that results of these studies are communicated to the TGA at the same time as they are communicated to other regulatory agencies.

Summary of the RMP in the Australian context

The OPR evaluator noted that the summary of the RMP does not reflect proposed risk minimisation activities in Australia. It is recommended that the sponsor includes a

summary table of the RMP in Australian context to show risk minimisation activities planned in Australia.

Non-clinical data: The nonclinical evaluator noted that nonclinical data are not accurately described in the Safety Specification of the draft Risk Management Plan in a number of cases. The sponsor should revise the description of nonclinical data in the safety specification of the RMP as recommended by the nonclinical evaluator.

Advice from the Advisory Committee on the Safety of Medicines (ACSOM)

ACSOM advice was not sought for this submission.

Suggested wording for conditions of registration

RMP

Implement RMP version 01, dated 31 October 2012 (data lock point 31 March 2012); and any future updates as a condition of registration.

VI. Overall conclusion and risk/benefit assessment

The submission was summarised in the following Delegate's overview and recommendations:

Introduction

Ocular inflammation is common after ophthalmic surgery, particularly after removal of cataracts combined with intraocular lens insertion. This manifests as iritis, corneal oedema, increased cells and protein flare) in the anterior chamber, accompanied by hyperalgesia.

Although recent advances in surgical techniques (for example, smaller incisions) have improved cataract surgical outcomes, postoperative inflammation and pain remain a major source of discomfort for patients. If left untreated, postoperative inflammation can lead to suboptimal vision results or complications such as cystoid macular oedema.

Non-surgical causes of ocular inflammation include contact lens associated giant papillary conjunctivitis and acute anterior uveitis.

Corticosteroids are effective in suppressing both the early and late phase of ocular inflammation. The topical ocular corticosteroids that are currently marketed (for example, prednisolone, dexamethasone) have well characterised adverse events: increased intraocular pressure, cataract formation, decreased resistance to infection, and delayed wound healing.

Loteprednol etabonate (LE), a corticosteroid analog of prednisolone, was developed for use in ocular inflammatory conditions.

Quality

The evaluator recommended approval subject to GMP clearance for the site that sterilises the container, dropper tip and cap. The sponsor submitted an application to the TGA for GMP clearance during the evaluation.

The product contains no unusual excipients. Loteprednol does not dissolve in the base solution and is therefore suspended.

Lotemax was considered at the 151st meeting of the PSC, who had concerns about settling of the suspension and age of the validation studies. These concerns were resolved.

Nonclinical

The evaluator recommended approval. PI changes recommended by the nonclinical evaluator were adopted by the sponsor during the evaluation.

Clinical

The clinical evaluator recommended approval for the indications of

*post-operative inflammation following cataract surgery, and
contact lens associated giant papillary conjunctivitis, and
acute anterior uveitis.*

The data evaluated included:

- 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.
- 7 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).
- Other efficacy/safety studies using proposed LE 0.5% (Lotemax) included 1 pilot study in SAC (114), 1 pilot study in GPC (106) and 1 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).
- No dose-finding studies or pooled studies/meta-analyses were submitted.

Pharmacology

Loteprednol is readily absorbed into ocular tissues. Following ocular administration, most of the drug is eliminated from the eye through nasolacrimal drainage, where it enters the systemic circulation via the nasal cavity or gastrointestinal tract. Loteprednol is rapidly metabolised to inactive products and systemic exposure is low.

Efficacy

Post-operative inflammation following cataract surgery

Two Phase III studies: 125 (1996-1997) and 127 (1996-1997)

Loteprednol 0.5% administered 4 times daily for up to 2 weeks after surgery showed clinically important and statistically significant differences versus placebo on resolution of anterior chamber inflammation (55% to 64% versus 28% to 29%). No studies were provided in the dossier for other types of surgery. During the evaluation, the sponsor agreed to narrow the part of the indication that refers to surgery from "postoperative inflammation following ocular surgery" (indication in the United States and other some countries) to post-operative inflammation following cataract surgery".

Contact lens associated giant papillary conjunctivitis

Two Phase III studies: 106 (1990-T991), 107 (1993-1994), 108 0993-1994)

The results of the three studies were variable, but provide sufficient evidence that treatment with loteprednol produces clinically important improvements for papillae, itching and lens intolerance; versus placebo. A caveat is that the efficacy and safety of loteprednol 0.5% was not evaluated beyond 6 weeks.

Acute anterior uveitis

Two Phase III studies: 1/2/1221 (1993-1994), 126 (1996)

The results show that loteprednol 0.5% is less effective than prednisolone acetate 1% (resolution at Day 28: 72% versus 87%); however, increase in intra-ocular pressure was lower (greater than 10 mmHg: 1% versus 6%). This information has been included in the Indication section of the PI.

Seasonal allergic conjunctivitis

The clinical evaluator was concerned allergens in Australia are different from those found in the United States and that no study had been done in Australia. The Alrex formulation of loteprednol 0.2% is approved for treatment of seasonal allergic conjunctivitis in United States, Canada, and some other countries. The sponsor agreed to remove the indication of seasonal allergic conjunctivitis during the evaluation.

Other inflammatory conditions listed in the US PI

No data were submitted for other steroid responsive inflammatory conditions of the palpebral and bulbar conjunctiva, cornea or anterior segment.

Safety

In 25 studies of loteprednol (as Lotemax: 0.5%, Alrex: 0.2%, Zylet with tobramycin: 0.5%/0.3%) adverse events were generally mild to moderate, non-serious, resolved without treatment, and did not lead to discontinuation of treatment. Dosing ranged from a single treatment to four times daily for 42 days.

Ocular adverse events include blurred vision, itching, and photophobia. Non-ocular adverse events include headache, rhinitis, and pharyngitis.

Loteprednol is less likely to lead to increase in intra-ocular pressure than prednisolone (greater than 10 mmHg: 1.7% versus 6.7%).

Loteprednol has been marketed in the United States since 1998. As of 2010, more than 29 million units had been sold. No change in the frequency or nature of adverse events has been seen.

Risk management plan

The outstanding issues in the second round evaluation of the Risk Management Plan have been addressed.

Risk-benefit analysis**Delegate considerations**

Although loteprednol 0.5% is a new chemical entity for the purposes of registration in Australia, it has been marketed in the United States since 1998; and it is marketed in several other countries.

During the evaluation, the indications were narrowed from inflammation:

- following ocular surgery.
- due to other steroid responsive conditions of the eye (multiple conditions were listed)

to inflammation:

- following cataract surgery.
- due to contact lens associated giant papillary conjunctivitis.
- due to acute anterior uveitis.

These indications better reflect the submitted data. There is the potential for off-label use (for example, for seasonal allergic conjunctivitis).

Taking into account the quality, efficacy, and safety for the proposed indications, the Delegate has no reason to say, at this time, that the application for Lotemax should not be approved for registration.

Proposed action

There is no reason to say, at this time, that the application for Lotemax should not be approved for registration.

Request for ACPM advice

The committee is requested to provide advice on any issues that it thinks may be relevant to a decision on whether or not to approve this application for registration of a new chemical entity onto the Australian market.

Response from sponsor

General

Bausch and Lomb concurs with all comments and recommendations mentioned in the evaluation reports. The sponsor believes that all issues raised in the evaluation reports have been resolved to TGA's satisfaction.

Quality evaluation

The GMP clearance for the outstanding site has been issued for Bausch and Lomb.

Nonclinical evaluation

The PI has been updated to include all the changes recommended by the evaluator.

Clinical evaluation

Indication

Bausch and Lomb has narrowed the indication consistent with the TGA recommendation.

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 (greater than 10 mmHg) was 1% with Lotemax and 6% with prednisolone acetate 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.

Efficacy

Bausch and Lomb has noted the TGA comments on seasonal allergic conjunctivitis and other inflammatory conditions (palpebral and bulbar conjunctiva, cornea or anterior segments) and have removed these conditions from the PI.

The PI has been updated to reflect the TGA recommendation.

In regard to the TGA comment on the potential for off label use of Lotemax (for example for seasonal allergic conjunctivitis), the sponsor considers that the chance for off label use is very unlikely, however, if it occurs, there should not be any safety concern for the following reasons:

- The submitted study (121) for seasonal allergic conjunctivitis, a Phase III, randomised double blind, placebo controlled, parallel group demonstrated that Lotemax, when compared to placebo, is more effective in preventing the signs and symptoms of allergic conjunctivitis, This study also showed that Lotemax did not cause an elevation in IOP (greater than or equal to 10 mmHg) in any of these patients over 6 weeks course of treatment.
- In 25 clinical studies undertaken with loteprednol etabonate (0.2% and 0.5%) and with combination of loteprednol etabonate 0.5% and tobramycin 0.3%, loteprednol etabonate demonstrated a lower incidence of clinically significant increased IOP (greater than or equal to 10 mmHg) than prednisolone acetate, and a similar or slightly higher incidence to placebo, in controlled randomised studies.
- Therefore there is no safety concern if Lotemax is used off label (for SAC).
- In addition, as the information in relation to seasonal allergic conjunctivitis has been removed from the PI, the chance for off label use for SAC is remove.

Safety

Lotemax has demonstrated an acceptable ocular safety profile. The IOP response to loteprednol etabonate was significantly less than prednisolone acetate.

RMP evaluation

Recommendation for RMP has been adopted. The RMP was updated and submitted during the second round response (RMP version 02 dated 6 September 2013).

Advisory Committee Considerations

The Advisory Committee on Prescription Medicines (ACPM), having considered the evaluations and the Delegate's overview, as well as the sponsor's response to these documents, advised the following:

The submission seeks to register a new chemical entity.

The ACPM, taking into account the submitted evidence of efficacy, safety and quality, agreed with the Delegate and considered Lotemax eye drops containing 0.5% of loteprednol etabonate to have an overall positive benefit-risk profile for the following indications;

Treatment of post-operative inflammation following cataract surgery and

Treatment of steroid responsive inflammatory conditions of contact lens associated GPC

Proposed conditions of registration:

The ACPM agreed with the Delegate on the proposed conditions of registration and specifically advised on the inclusion of the following:

- Subject to satisfactory negotiation of the Risk Management Plan most recently approved by the TGA.
- Negotiation of Product Information and Consumer Medicines Information to the satisfaction of the TGA.

Proposed Product Information (PI)/Consumer Medicine Information (CMI) amendments:

The ACPM advised that the product information should clearly state that efficacy and safety beyond 6 weeks has not been evaluated.

The ACPM advised that the implementation by the sponsor of the recommendations outlined above to the satisfaction of the TGA, in addition to the evidence of efficacy and safety provided would support the safe and effective use of these products.

The ACPM concluded that the evidence provided in the sponsor's submission did not satisfactorily establish the safety and efficacy of Lotemax eye drops containing 0.5% of loteprednol etabonate for the following indication;

- Treatment of acute anterior uveitis, when the inherent hazard of steroid use is accepted to obtain an advisable diminution in oedema and inflammation.

In making this recommendation the ACPM

- expressed concern that for the treatment of AAU, Lotemax is less effective than prednisolone acetate 1% in two 28-day controlled clinical trials.
- Noted the extensive exclusion criteria for these trials which reduced applicability to the likely population which would require such treatment.
- Was of the view that Lotemax was less efficacious and with no proven, clinically meaningful safety benefit over existing therapies.

Outcome

Based on a review of quality, safety and efficacy, TGA approved the registration of Lotemax eye drop suspension containing loteprednol etabonate 0.5% indicated for:

treatment of post-operative inflammation following cataract surgery and treatment of steroid responsive inflammatory conditions of contact lens associated giant papillary conjunctivitis (GPC).

Specific conditions of registration applying to these therapeutic goods

1. The Lotemax (loteprednol etabonate) Risk Management Plan (RMP), Version 01 dated 31 October 2012 (data lock point (DLP) 31 March 2012), and any subsequent revisions and updates, as agreed with the TGA will be implemented in Australia.

Attachment 1. Product Information

The Product Information approved at the time this AusPAR was published is at Attachment 1. For the most recent Product Information please refer to the TGA website at <<http://www.tga.gov.au/hp/information-medicines-pi.htm>>.

Attachment 2. Extract from the Clinical Evaluation Report

Therapeutic Goods Administration

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