

Public Assessment Report

Alrex 0.2% Eye Drop Suspension

(loteprednol etabonate)

PL 00033/0160

**ALREX 0.2% EYE DROP SUSPENSION
(LOTEPREDNOL ETABONATE)**

PL 00033/0160

UKPAR

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LAY SUMMARY

The Medicines and Healthcare products Regulatory Agency (MHRA) has granted Chauvin Pharmaceuticals Limited a Marketing Authorisation (licence) for the medicinal product Alrex 0.2% Eye Drop Suspension (PL 00033/0160). This is a prescription only medicine [POM] for treating seasonal allergic (“hay fever”) conjunctivitis.

Seasonal allergic conjunctivitis affects between 5% and 22% of the general population and it is a response of the eye to specific irritants in the air. The active ingredient in this product, loteprednol etabonate, suppresses the response to these irritants, although there is no general agreement on how this suppression is achieved.

The clinical data presented to the MHRA, before licensing, demonstrated that Alrex 0.2% Eye Drop Suspension is effective in the treatment of seasonal allergic conjunctivitis. There were no significant safety concerns and it was decided that the benefits of using Alrex outweigh the risks, hence a Marketing Authorisation has been granted.

ALREX 0.2% EYE DROP SUSPENSION

(LOTEPREDNOL ETABONATE)

PL 00033/0160

SCIENTIFIC DISCUSSION

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INTRODUCTION

Based on the review of the data on quality, safety and efficacy the UK granted a marketing authorisation for the medicinal product Alrex 0.2% Eye Drop Suspension (loteprednol etabonate) (PL 00033/0160) to Chauvin Pharmaceuticals Limited on 17 July 2006. The product is a prescription only medicine.

The application was submitted as a full application according to Article 8.3(i) of Directive 2001/83/EC.

Alrex 0.2% Eye Drop Suspension contains the active ingredient loteprednol etabonate, with the chemical name chloromethyl 17 α [(ethoxy-carbonyl)oxy]-11 β -hydroxy-3-oxoandrosta-1,4-diene-17 β -carboxylate.

Alrex 0.2% Eye Drop Suspension is indicated for the symptomatic treatment of seasonal allergic conjunctivitis.

Loteprednol etabonate belongs to a new class of corticosteroids. Corticosteroids suppress the inflammatory response to inciting agents of a mechanical, chemical or immunological nature. No generally accepted explanation of this steroid property has been advanced.

The active ingredient loteprednol etabonate was first authorised in the United States in 1998. It has also been licensed as a 0.5% eye drop suspension in the UK.

PHARMACEUTICAL ASSESSMENT

LICENCE NO: PL 00033/0160
PROPRIETARY NAME: Alrex 0.2% Eye drop Suspension
ACTIVE(S): Loteprednol etabonate
COMPANY NAME: Chauvin Pharmaceuticals Limited
E.C. ARTICLE: 8.3(i)
LEGAL STATUS: POM

INTRODUCTION

This is an application for a new drug, loteprednol etabonate, which is formulated as an eye drop suspension to be used for the symptomatic treatment of seasonal allergic conjunctivitis. It is preserved with benzalkonium chloride. It is stated that the drug belongs to a new class of corticosteroids with potent anti-inflammatory activity. *In vivo* transformation of hydrocortisone and its analogues produces cortienic acid as an inactive metabolite. This drug is an ester of Δ^1 cortienic acid etabonate [PJ-91].

METHOD OF PREPARATION

A satisfactory description of the method of manufacture is provided.

The process validation studies are acceptable.

DRUG SUBSTANCE

Drug substance specification

A satisfactory drug substance specification is provided.

OTHER INGREDIENTS

Suitable sources of all the excipients have been identified.

CONTAINER AND CLOSURE SYSTEM

The product is packed in either 7.5ml or 10ml size low density polyethylene containers containing either 5ml or 10ml of the suspension. The closure is a pink polypropylene cap.

CONTROL TESTS ON THE FINISHED MEDICINAL PRODUCT

Finished product specification

A satisfactory finished product specification is provided.

STABILITY

Stability tests on the finished medicinal product

The stability data were generated at 25°C/40%RH and 40°C/20%RH which is generally in line with the CPMP guidance for products in semi-permeable containers.

The results were within the specifications.

EXPERT REPORT

A satisfactory statement has been provided.

PRODUCT NAME & APPEARANCE.

The product name is acceptable and the appearance is satisfactory.

SUMMARY OF PRODUCT CHARACTERISTICS PATIENT INFORMATION LEAFLET LABELLING

These are generally acceptable, from a pharmaceutical perspective.

CONCLUSIONS

Marketing authorisation should be granted.

Note regarding consideration by Chemistry, Pharmacy and Standards Sub-committee:

This application was presented to the Chemistry, Pharmacy and Standards Sub-committee on 19 March 2003. The Sub-committee advised the grant of a Marketing Authorisation once the applicant had complied with certain conditions.

PRECLINICAL ASSESSMENT

LICENCE NO: PL 00033/0160
PROPRIETARY NAME: Alrex 0.2% Eye drop Suspension
ACTIVE(S): Loteprednol etabonate
COMPANY NAME: Chauvin Pharmaceuticals Limited
E.C. ARTICLE: 8.3(i)
LEGAL STATUS: POM

INTRODUCTION

This is a stand-alone application for Alrex 0.2% Eye Drop Suspension submitted in accordance with Article 8.3(i) of Directive 2001/83/EC.

The product is a sterile multidose eye drop containing a new active ingredient, loteprednol etabonate (LE), at 0.2%w/v which is equivalent to 0.08mg loteprednol per eye drop. Loteprednol etabonate or chloromethyl 17 α [(ethoxy-carbonyl)oxy]-11 β -hydroxy-3-oxoandrosta-1,4-diene-17 β -carboxylate is a new corticosteroid with anti-inflammatory activity. It is stated to undergo local transformation into inactive metabolites, thereby reducing the local and systemic side effects experienced with conventional corticosteroid therapy.

Alrex is indicated for the treatment of seasonal allergic conjunctivitis. The proposed dosage schedule is to apply one drop 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 one drop every hour, if necessary.

Assuming that one drop is 32 μ L, the maximum daily dose would be 32 μ L x 2 eyes x 16 treatment hours, or 1.024mL/day. The maximum dose of loteprednol, assuming that the specific gravity of the formulated product is approximately 1.0, would be 1.024mL x 0.08/100 – about 0.82 μ g/day or about 0.013 μ g/kg/day assuming 60kg bodyweight.

GLP ASPECTS

The single dose and repeated dose toxicity studies, as well as the mutagenicity and reproductive toxicity studies were conducted in compliance with GLP. The pharmacodynamic studies are not required and were not conducted in compliance with GLP. Many of the pharmacokinetic studies were not conducted in compliance with GLP, even though this is required as they form part of the safety studies.

The Expert has stated that although the reported detail and standard of presentation of some of these reports are variable, in general the conclusions reached appeared to be supported by the data presented.

PHARMACODYNAMICS

Pharmacodynamics for the proposed indication

LE is an analogue of prednisolone but it is an ester rather than a ketone. It is rapidly metabolised by tissue esterases to the carboxylic acid PJ-91 which can be metabolised to the inactive PJ-90. PJ-91 does not bind to glucocorticoid receptors and does not have the typical

activity of a corticosteroid. It is stated that the absence of a keto group at position 20 eliminates the adduction with lysine which would form in the crystalline lens, reducing the formation of corticosteroid-induced cataracts.

LE was evaluated in a number of anti-inflammatory screening tests in comparison with hydrocortisone-17-butyrate (HCB), hydrocortisone-17-butyrate propionate (HCBP), clobetasol-17-propionate (CBP), betamethasone-17-valerate (BMV) and dexamethasone sodium phosphate (DMS).

Four comparative studies of the potency of LE, HCB and BMV in the croton oil oedema model were conducted, two studies in mice and two in rats, with varying treatment schedules. The relative potencies of the three corticosteroids varied in the different models; LE was active in this model. In two other models involving local action, histamine-induced vascular permeability and dinitrofluorobenzene-induced dermatitis, LE was slightly more active than DMS in the former and appeared to be marginally more active than HCBP in the latter, although in this case the difference in activity did not attain statistical significance. LE demonstrated a similar potency to both DMS and HCB in a model of homologous passive cutaneous anaphylaxis.

LE was less active than both HCB and DMS in both the rat carragenin-induced skin and paw oedema models and was inactive in the adjuvant-induced arthritis model. In the cotton pellet granuloma assay, both BMV and HCB showed anti-inflammatory activity over a wide dose range. In this assay, treatment with both BMV and HCB resulted in between 20% and 80% thymic suppression over a dose range from 75-1000 µg/pellet, whereas the thymic suppression resulting from treatment with LE over a dose range of 100-5000 µg/pellet was approximately 20%. This study indicates that LE exhibits anti-granuloma activity at doses below those that cause thymic suppression.

LE was compared with flurbiprofen sodium and DMS using a series of ocular inflammatory models (paracentesis, nitrogen mustard 1% and 4%, shigella endotoxin and immune uveitis) each with the common endpoint of determination of total protein infiltration into the anterior chamber. With the exception of the nitrogen mustard 4% model, animals pre-treated with LE showed less total protein migration into the anterior chamber, although the reductions were generally not statistically significant.

The anti-inflammatory efficacy of LE 1% and prednisolone acetate 1% were compared in an endotoxin-induced model of ocular inflammation in rabbits. LE was shown to be as effective as the comparator, both in lowering leukocyte infiltration in the aqueous humour and in reducing cellular accumulation in the iris-ciliary body as measured by myeloperoxidase activity. Animals treated with either compound exhibited a crossover effect in the untreated, contra-lateral eye.

LE, fluoromethalone (FML) and dexamethasone (Dexa) were compared using a similar model of endotoxin-induced (300ng *E.coli* lipopolysaccharide (LPS) in each eye) ocular inflammation compared with both FML and Dexa. However, LE reduced both the inflammatory response and protein infiltration into the aqueous humour in comparison with the saline-treated control group.

A further study was conducted in the rabbit to evaluate the effect of LE in a chronic model of uveitis. A higher concentration (1%) of LE was used. Leukocyte infiltration into the aqueous humour of animals treated with LE (1%) was reduced compared with saline-treated controls and was also lower than in animals treated with FML or Dexa. Similarly, protein infiltration

into the aqueous humour in animals receiving LE (1%) was lower than in controls, but LE was less effective than FML or Dexa in reducing protein infiltration.

Another evaluation of the anti-inflammatory activity of LE was a study designed to compare the effectiveness of a range of concentrations of LE (0.05%, 0.1%, 0.5%, 1.0% and 2.0%) with two concentrations of prednisolone acetate (0.125% and 1.0%). Concentrations of LE <0.5% were not effective, 0.5% LE was equally as effective as 0.125% prednisolone acetate in reducing corneal inflammation and LE achieved its peak activity at 1.0%, at which concentration it was equally as effective as 1.0% prednisolone acetate. Further studies were conducted to evaluate the effect of commencing treatment prior to the induction of inflammation. This had no effect on the anti-inflammatory activity of either steroid.

A further element of this study was a comparison of inhibition of full thickness corneal wound healing of LE vehicle, LE (1%), prednisolone acetate 1% (Pred), and dexamethasone sodium phosphate 1% (DMS). LE (1%) and Pred (1%) produced a statistically significant decrease in the IOP required for wound rupture when compared with LE vehicle. The decrease produced by DMS was even greater.

LE is presumed to act at the glucocorticoid (Type II) receptors. In rat lung cytosol preparations, LE was shown to displace tritiated triamcinolone acetonide from glucocorticoid receptor binding sites ligand with a potency of 1.5 times that of dexamethasone. This was considered to possibly indicate either binding to transcortin or enzymatic inactivation of the compound. In the presence of corticenic acid which saturated the transcortin binding sites, LE demonstrated a potency of 4.3 times that of DMS.

A further study was conducted to determine the relative binding efficiencies of LE and its metabolites PJ-91 and PJ-90 using a similar rat lung cytosol preparation to that described above. These data indicate that LE binds competitively to transcortin, in common with other non-fluorinated corticosteroids. PJ-91 did not displace tritiated triamcinolone acetonide from the glucocorticoid (Type II) receptor, indicating that it lacks significant glucocorticoid activity.

Secondary pharmacology

Topically applied LE had no adverse effect on wound healing in the skin of hairless mice. By contrast, betamethasone valerate and prednicarbate delayed wound healing in this model.

In a rabbit corneal wound model, both LE and DMS delayed all types of reparative activity and reduced cornea scarring. Both steroids had their greatest effect on day 7 post-operatively.

Multiple administration of LE (0.1%) to the eyes of normotensive rabbits did not result in any sustained increase in intraocular pressure (IOP). By contrast, DMS (0.1%) in the same dosing regimen produced a sustainable increase of IOP.

The applicant presented a compilation of study results lacking in individual animal data. In rats, topically applied LE appeared to cause less skin atrophy than HCB or BMV. Also LE appeared to be less likely to reduce thymus weight compared with comparator products. The expert noted that there appeared to be doubts as to the procedural precision in these studies.

LE, betamethasone and prednicarbate significantly decreased cell growth in cultured 3T3 Balb C mouse fibroblasts and dermal fibroblasts from newborn hairless mice.

LE demonstrated activity in several models of experimental asthma. It was only effective when administered by inhalation. In an *in vitro* model using human lymphocytes, the lipopolysaccharide-induced formation of Interleukin-1 β was inhibited.

Safety pharmacology

No safety pharmacology studies have been included in this application. The clinical data have demonstrated that limited to non-detectable systemic absorption of LE occurs following oral and ocular administration and therefore systemic bioavailability is not applicable. The risk of undesired corticosteroid effects is very low. Therefore, the retrospective generation of safety pharmacology data is unnecessary.

Pharmacodynamic drug interactions

In an endotoxin-induced model of ocular inflammation in rabbits, LE (0.3%) alone or in combination with tobramycin (0.3%) exhibited similar anti-inflammatory properties. Tobramycin did not interfere with the anti-inflammatory effect of LE.

Assessor's comment

LE is a corticosteroid of similar potency to DMS or BMV. Receptor binding studies indicate that LE has a binding affinity greater than that of DMS to glucocorticoid (Type II) receptors and that LE binds competitively to transcortin. PJ-91 lacks glucocorticoid activity.

LE reduces corneal scarring post-surgery. Ocular treatment with LE produces negligible increases in IOP when compared with DMS. Topically applied LE elicits less skin atrophy and thymic involution than comparator products.

PHARMACOKINETICS

Absorption

LE is to be applied topically to the eye for a local effect. Nevertheless, two studies were conducted using the oral route of administration. Rats and dogs were dosed by oral gavage with a suspension of LE at a single dose of 5mg/kg/body weight. In the rat, blood levels of LE were unchanged for the duration of the study at a low level (200ng/ml). The applicant hypothesized that the slow absorption was the result of low aqueous solubility of the molecule. In the dog, blood levels of LE were below the limits of detection.

Distribution

¹⁴C – LE was administered as 50 μ l drops, three per eye, at 5-minute intervals to both eyes of groups of three or four rabbits. The total dose per animal was 3 μ moles or 26 μ CI. The results demonstrated good ocular penetration of LE to the ocular tissues. The highest concentration of LE was consistently found in the conjunctiva throughout the study period and significant concentrations of LE were also detected in the cornea and iris ciliary body. Metabolite concentrations (PJ-91 + PJ-90) in the cornea exceeded the concentrations of LE detected in this tissue, indicating that the cornea may be a significant site of metabolism of LE. Blood levels of LE and its metabolites were below the limits of detection throughout the study period.

Further studies of the distribution of LE and the metabolites PJ-90 and PJ-91 in the ocular tissues of the rabbit were conducted using an appropriate method. In the pilot study, rabbits received a single intraocular dose of 30µl of LE in each eye. Peak concentrations of LE and PJ-91 were observed in all tissues by 0.5 h except for PJ-91 levels in the iris ciliary body (ICB) which peaked at 2 h. Appreciable accumulation of LE was observed in the aqueous humour (AH), cornea and ICB. Cornea and ICB levels of LE were ~6.4 fold and ~4 fold those in the AH, respectively, at 0.5 h. PJ-91 accumulation in cornea and ICB was also observed and was consistent with intraocular metabolism. In contrast, PJ-90 was not detected in any ocular tissue.

The effects of intraocular administration of a higher dose (2 x 32µl per eye) of LE were also evaluated in a study which also examined the effects of concomitant drugs used in cataract extraction procedures on the ocular distribution of LE and compared the distribution of LE in this tissue following administration of 2 drops (~2 x 32µl) of LE or two drops of LE (0.5%) and tobramycin. LE concentrations in aqueous humour were generally similar in all test groups. It can be concluded that treatment with concomitant drugs had no effect on LE concentration in the aqueous humour. Treatment with concomitant drugs had no effect on LE or PJ-91 concentration in the cornea.

Comparison of the data from this study in which animals received 2 x 32µl of LE with those from a study in which animals received a single drop of LE suggests that the LE concentrations in the cornea increased disproportionately with increasing dose. In contrast, LE concentrations in the cornea iris ciliary body were approximately dose-proportional at 0.5 h after administration of either one or two drops of LE.

Metabolism

In the rat, following intravenous administration at dose levels up to 20mg/kg, total clearance of LE from blood was dose-dependent and decreased with increasing dose. All clearances were greater than hepatic blood flow, indicating that blood or other organs contribute to the metabolism of LE. Both mean resident time and $t_{1/2}$ increased with dose, indicating saturation of the enzymes responsible for LE metabolism in blood or other organs. High concentrations of the metabolite PJ-91 and the putative metabolite PJ-90, but not LE, were found in the bile and the elimination rates of both compounds in the bile were high. These results suggest the liver is an important site of metabolism. *In vitro*, LE was stable in dog blood or plasma.

Excretion

In the rat study described above, high concentrations of PJ-91 and the putative metabolite PJ-90, but not LE, were found in the bile and the elimination rates of both metabolites in the bile were high. PJ-90 was not detected in urine or blood. These results indicate that biliary excretion of the metabolites of LE is a significant route of elimination.

Pharmacokinetic drug interactions

No data

Other pharmacokinetic studies

None.

Assessor's comment

The data available indicate that LE is rapidly metabolised following intravenous administration. Following ocular administration, there was good penetration to ocular tissues while blood levels were below the limits of detection. PJ-91 has a short plasma elimination half-life.

TOXICOLOGY

Single dose toxicity studies

Studies were conducted using the oral and subcutaneous routes of administration in the mouse and rat. In the oral studies test substance availability limited the dose level used to 4g/kg/body weight.

The acute oral and subcutaneous maximum tolerated dose (MTD) in the mouse and rat for LE was $\geq 4,000$ mg/kg/body weight and $>1,333$ mg/kg/body weight respectively for both species. Apparent reduction in spleen size was noted in both species following subcutaneous administration which may have been treatment-related. Otherwise there were no unusual toxic effects.

The MTD of PJ-90 was >100 mg/kg/body weight when administered subcutaneously in the rat.

Combinations of LE (0.5%) suspension with sulfacetamide (10%w/v) or tobramycin (0.3%w/v) were not toxic by the oral route to mice or rats at a dose volume of 20ml/kg/body weight.

Repeated dose toxicity studies

A total of eight studies were conducted including one dose range finding study. All studies except one (oral) used the ocular route of administration. There was one 28-day oral route rat study, a 7-day range-finding study, two 28-day, two 30-day and one 26-week study in the rabbit and a 52-week study in the dog.

In the oral dose 28-day study in the rat, the dose levels were up to 50mg/kg/day. In the studies using the ocular route of administration, the test substances were administered to one eye of the test animal. The dose volume in the rabbit 26-week and dog 52-week studies were 30 μ l while in all the other studies the volume was 0.1ml. The rabbit 7-day dose range finding study and the 28-day definitive study were both conducted using a maximum concentration of LE of 5.0%. There was also a 28-day rabbit study evaluating the potential effect of PJ-90 at a concentration of 0.5%. There were two rabbit studies of 30 days duration using a combination of drugs. In the first study LE (0.5%) was administered with tobramycin (0.3%) while in the second LE (0.5%) was given in combination with sulfacetamide sodium (10%). In the latter study, there were dosing regimens of 2, 4 or 8 times per day. In the former study IOP was assessed. In the rabbit 26-week study LE (0.5%) was administered as eight doses at intervals of not less than 1.5 hours in the first 7 days and subsequently 4 doses at intervals of not less than 2 hours. In the dog 52-week study, the effects of a range of concentrations of LE (0.05%, 0.1%, 0.5%) was compared with dexamethasone (0.1%). With the exception of the LE 0.1% group, all animals received 6 x 30 μ L drops of the test substance or vehicle daily in two sub-doses of approximately 90 μ l at least 4 hours apart while the LE (0.1%) group received a single sub-dose of 90 μ l daily.

In the 28-day study in the rat and rabbit by the oral and ocular routes respectively, increased alanine aminotransferase (ALT) and glucose levels occurred at high dose levels in both species but there was no histological change in the liver. These effects occurred only at high multiples of the anticipated human dose. No changes in glucose occurred in the 26-week rabbit or 52-week dog study. There were no adverse ocular effects observed following administration of LE in combination with sulfacetamide sodium. No adverse effects were apparent following ocular administration of PJ-90 for 28 days.

There were no significant treatment-related adverse effects in the 26-week rabbit or 52-week dog studies. In the dog study an increasing incidence of stromal anomalies ranging from fine haze of crystalline deposits in the treated cornea of animals receiving LE (0.5%) or LE (0.1%) occurred between weeks 26 and 52. The incidence was lower than in the dexamethasone treated group. IOP increased in the LE treated animals, but to a lesser amount than in dexamethasone-treated animals.

Genotoxicity

There were four *in vitro* studies and one *in vivo* study. The GLP status of some of the early studies is unknown, however they appear to have been adequately conducted and reported. The remaining studies were conducted in accordance with GLP.

Assessor's table

Type of test Study ID	Test system	Concentrations range / Metabolising system	Results
Gene mutations in bacteria PTC/1431	<i>S. typhimurium</i> TA1535, TA1537, TA1538, TA100, TA98	+/- S9 0.1 to 100 µg/plate	Negative
Gene mutations in mammalian cells PTC/24596	L5178Y TK +/- Mouse lymphoma cells	0.075 to 1.5 µg /mL	Negative
DNA damage/repair in bacteria PTC/1430	<i>B. subtilis</i> H17 Rec+, M45 Rec-	1.2 to 12,000 µg/mL	Negative
Chromosomal aberration <i>in vitro</i> PTC/10	Human lymphocyte	6.25 to 50 µg/mL	Negative
Chromosomal aberration <i>in vitro</i> PTC/24595	Male/Female CD1 Mice	1,000, 2,000, 4,000 mg/kg p.o.	Negative

In two of the *in vitro* tests, the gene mutations in bacteria and the chromosome aberration in mammalian cells, the maximum practical dose was stated to be limited by precipitation of LE. In the gene mutation in mammalian cells assay, the highest concentration used was stated to be limited by the solubility of LE in the solvent dimethylsulphoxide (DMSO). It is usual to conduct a mouse micronucleus test to a MTD or a dose showing a toxic effect to the bone marrow by alteration of the polychromatic erythrocytes/normochromatic erythrocytes (PCE/NCE) ratio. In this study, there was no decrease in the PCE/NCE. There was no dose range finding study. The Expert proposes that in view of the intended clinical use, the maximum dose selected was 4,000mg/kg. In comparison to the calculated minimum

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haemorrhagic dose (MHD) of LE (0.03 μ /kg) the top dose in this study equates to a multiple of greater than 133 million times the anticipated human dose.

Carcinogenicity studies

No data. This was considered acceptable in view of the proposed therapeutic use of the product, the lack of systemic exposure in humans following therapeutic use and the negative genotoxicity package.

Reproductive and developmental toxicity

Fertility and early embryonic development

In both a dose range finding and the definitive study, rats were dosed by oral gavage with micronised LE in a suspension in 1% aqueous methylcellulose. In the dose range finding study conducted at dose levels up to 100mg/kg/day there was treatment-related toxicity in both the F0 and F1 generations including dose-related reductions in body weight and food consumption, and adverse effects on various reproductive parameters.

In the definitive study, the dose levels were 0.5, 5 or 50mg/kg/day (males) and 0.5, 5, 25mg/kg/day (females). The study report states that analyses of the dose formulation indicated that during week 1 low-dose males may have received less than the intended dose, but that for the remainder of the study, all animals received the test article at doses close to the intended concentration. The top dose was toxic 5/30 males and 1/30 females being sacrificed because of poor condition. One male was found dead. There was a dose-related reduction in body weight gain in all treated female groups from week 2 to study termination and in mid- and top-dose males from day 8 pre-mating to study termination. Food consumption was reduced in both sexes during the study. Pre- and post-implantation losses were increased while numbers of corpora lutea, implantation sites and live foetuses were reduced at the top dose. There was an increased incidence of external, visceral and skeletal abnormalities and variants at the mid- and top-dose; these were of a type associated with corticosteroid exposure. Umbilical hernia was reported in 3 foetuses from the top-dose group and since a similar finding was reported in two mid-dose and one top-dose pups in the littering phase of this study and several pups in the peri- and post-natal study, these abnormalities were considered to be treatment-related. No developmental abnormalities were apparent in the low dose foetuses which represents an exposure in excess of 16,000 times the anticipated human dose.

There was evidence of toxicity in the F1 generation for pups of mid- and top dose F0 animals. However, no adverse effects occurred in F1 pups during post-weaning. The mating performance of the F1 and F2 generation were unaffected by treatment.

Embryo-foetal development

Rat

Groups of 24 dams were dosed daily by oral gavage with suspensions of LE on gestation days 6 to 15 at 0, 0.5, 5, 50 and 100 mg/kg/day and were selected on the basis of a dose range finding study.

There were no treatment-related deaths or overt signs of toxicity. There was a significant reduction in maternal body weight gain during the dosing period at \geq 5mg/kg/day. At 50 and

100 mg/kg/day, there was a reduction in food intake. The number of live foetuses was slightly reduced and post-implantation loss significantly increased at 100mg/kg/day.

Foetal weights were significantly lower at 50 and 100 mg/kg/day. The incidence of foetuses with major or minor abnormalities and retardation of skeletal ossification was higher at 50 and 100 mg/kg/day. The most common abnormality was cleft palate and this together with other major abnormalities occurred only at 50 and 100 mg/kg/day. The minor abnormalities were related to growth retardation and immaturity of foetuses related to retarded or non-ossification of various bones. The highest incidence was at 50 and 100 mg/kg/day. The NOEL was 5mg/kg/day.

Reproductive (Teratogenic) Studies in the Rat

Parameter	Control	0.5	5.0	50.0	100	Kruskal – Wallis Test
RAT						
External and Visceral Examination						
Total number of foetuses examined	323	338	293	300	288	
Number with minor abnormalities only	42	57	32	34	59	
Mean % ^a	12.7	16.6	10.1	11.4	22.0	NS
Number with major abnormalities only	0	0	0	14	11	
Mean % ^a	0.0	0.0	0.0	6.8+++	3.9+++	P<0.001
Skeletal Examination						
Total number of foetuses examined	216	225	196	200	192	
Number with minor abnormalities only	29	27	25	58	87	
Mean % ^a	12.2	12.1	16.1	29.8+	46.9+++	P<0.01
Number with major abnormalities only	0	0	0	4	4	
Mean % ^a	0.0	0.0	0.0	4.0	2.3	NS

+ = significantly different from control, p<0.05, multiple comparison test

+++ = significantly different from control, p<0.001, multiple comparison test

^a Mean % represents mean of the percentage of foetuses in each litter exhibiting each category of abnormality

Rabbit

Groups of 16 NZW does were dosed with suspensions of LE by oral gavage at dose levels of 0, 0.1, 0.5 or 3.0 mg/kg/day from days 6 to 18 of gestation. The dose levels were selected on the basis of a dose ranging study.

There were no treatment-related deaths or overt signs of toxicity. At 3 mg/kg/day maternal body weight was increased during the dosing period but lower after the end of the dosing period and similar to controls at the end of pregnancy. There was no consistent dose-related effect on food consumption. Foetal body weights at 3mg/kg/day were reduced. Also, there was slight embryonic/foetal development retardation observed as lower foetal weights and an increase in skeletal minor abnormalities. Major abnormalities occurred at 3mg/kg/day only and were principally meningocele. The increased incidence of minor external/visceral abnormalities in treated animals did not reach statistical significance. The principal observation was an abnormal left common carotid artery and at 3mg/kg/day a higher

incidence of limb flexures. The number of foetuses showing retarded ossification was statistically significant at 3mg/kg/day.

Reproductive (Teratogenic) Studies in the Rabbit

Parameter	Control	0.1 mg/kg	5.0 mg/kg	3.0 mg/kg	Kruskal – Wallis Test
RAT					
External and Visceral Examination					
Total number of foetuses examined	123	106	119	121	
Number with minor abnormalities only	22	30	41	44	
Mean % ^a	17.8	25.1	29.1	31.9	NS
Number with major abnormalities only	2	2	5	6	
Mean %	3.0	2.1	4.2	4.8	NS
Skeletal Examination					
Total number of foetuses examined	123	106	119	121	
Number with minor abnormalities only	12	15	18	35	
Mean %	11.1	11.6	17.2	27.8+	P<0.05
Number with major abnormalities only	0	1	2	2	
Mean %	0.0	1.1	2.1	1.6	NS
Combined Examination					
Total number of foetuses examined	123	106	119	121	
Number with any major abnormalities only	2	2	5	8	
Mean %	3.0	2.1	4.2	6.4	NS

+ = significantly different from control, p<0.05, multiple comparison test

Pre-natal and post-natal development, including maternal function

Groups of 20 dams were dosed by oral gavage with a suspension of LE from gestation day 15 to day 20 *post partum* at 0, 0.5, 5 or 50 mg/kg/day. The dams and offspring were autopsied on day 21 *post partum*.

Treatment-related overt signs of toxicity occurred at 50mg/kg/day. Four dams had poor conditions during the lactation period, 3 of which were killed prematurely. There was a dose-related decrease in maternal body weight gain at all treatment levels, although this was only slight at 0.5mg/kg/day. Food consumption was reduced at 5 and 50 mg/kg/day.

There were no treatment-related maternal autopsy findings except for top-dose dam which was killed prematurely. Pup survival at 50mg/kg/day was adversely affected with fewer than 50% of pups surviving to weaning. Pup bodyweight at 5 and 50 mg/kg/day were reduced at birth; at 50mg/kg/day the body weight remained reduced throughout lactation. During lactation there was a high incidence of small, hypothermic, dead and missing pups at 50mg/kg/day. Five pups at 50mg/kg/day and one at 5mg/kg/day had a major abnormality of umbilical herniation or related abnormality. At weaning, there were no treatment-related autopsy findings for the offspring at any dose level.

Peri and Post Natal Toxicity Study

Group	Number Pregnant	Gestation Index	Mean duration of gestation (days) ± S.D	Mean duration of parturition (days) ± S.D	Mean number of pups born ± S.D	Mean live birth index	Mean Viability Index	Mean Lactation index	Mean Cumulative Survival index	Sex Ratio At Birth M:F
Control	20	100	21.6±0.3	2.4±0.7	14.3±2.2	94.3	87.9	100.0	82.5	54:46
0.5 mg/kg	20	100	21.6±0.1	2.7±0.1	13.7±2.5	90.2	83.0	100.0	81.0	47:53
5.0 mg/kg	20	95	21.8±0.4	2.7±0.8	13.7±1.5	89.8	86.8	100.0	80.7	50:50
50 mg/kg	20	95	22.1±0.5	2.7±1.6	13.0±3.3	87.2	65.3++	80.0++	47.8++	49:51
Analysis of variance			NS	NS	NS					
Kruskal- Wallis test						NS	p<0.01	p<0.05	p<0.01	NS
Fisher exact Probability test		NS								

++ = significantly different from control, p<0.01, multiple comparison test

Studies in which offspring (juveniles) are dosed and/or further evaluated

No data.

Local tolerance

Two eye irritation studies conducted in rabbits with different formulations of LE and a third study with PJ-90 revealed no significant ocular irritation.

Further studies in the rabbit with combination products containing LE and either sulphacetamide or tobramycin revealed no significant ocular irritation.

Other toxicity studies

Protein binding

In vitro in the dog LE and PJ-91 were approximately 95% and 73% bound to plasma proteins respectively.

Hydrolysis in plasma and in human liver in vitro

LE was stable in the dog whole blood and plasma with $t_{1/2}$ values of 18 and 22 hours respectively. PJ-91 was not detected. Since the plasma $t_{1/2}$ of LE *in vivo* is about 2.8 hours, this indicates that significant metabolism does not occur in blood or plasma.

In a separate study, there was no evidence of hydrolysis of LE in rabbit, dog or human plasma. LE was rapidly hydrolysed in rat plasma, almost 100% hydrolysis having occurred in 30 minutes. Homogenised biopsy samples of human liver metabolised 27% of LE in 30 minutes.

Gastrointestinal indications

A number of studies were conducted to evaluate the possibility of using LE in the treatment of gastrointestinal inflammation but these are not relevant to this application.

Antigenicity

In a delayed contact hypersensitivity study (Buehler technique) conducted in guinea pigs, LE as a 0.5% cream formulation did not induce sensitisation.

Immunotoxicity

No data provided.

Dependence

No data provided.

Studies on impurities

Two metabolites PJ-90 and PJ-91 are specified to be present in the finished product at concentrations not greater than 1%w/w. The estimated total daily intake for these metabolites at the maximum dose is 20.5µg, which is below the threshold for qualification. Nevertheless both metabolites can be considered qualified on the basis of the toxicity studies conducted.

Ecotoxicity/Environmental risk

An environmental risk assessment has not been conducted. The expert highlights the fact that the proposed indication is treatment of seasonal allergic conjunctivitis and small volumes will be used. Residues in multidose containers are likely to be minimal. Ecotoxicologically significant environmental release is unlikely.

ASSESSOR'S OVERALL CONCLUSIONS ON TOXICOLOGY

LE is a corticosteroid. It has anti-inflammatory activity in a wide variety of animal models of ocular inflammation. Its rapid metabolism at the site of application results in low systemic absorption with consequent low potential of corticosteroid adverse effects.

Several studies in the rat and rabbit using the oral and ocular routes of administration revealed the liver as a potential target organ based on biochemical changes. However, there were no histological changes in either species, indicating that a hypertrophic effect consistent with the liver being a major metabolic site occurred.

There were adverse effects in the reproductive toxicity studies including embryotoxic effects characterised by growth retardation and, at dose levels at which there was evidence of maternal toxicity, teratogenicity in the rat with equivocal evidence of teratogenicity in the rabbit. However, in humans LE concentrations are below the LOQ under therapeutic conditions of use, therefore the risk to reproduction is minimal.

There were several deficiencies in the preclinical package of studies which have been highlighted in this report and addressed in detail in the expert's report. However, in view of the minimal, if any, systemic exposure to LE reported in the clinical studies following therapeutic use and the clinical experience, the shortcomings in the preclinical data are not an impediment to granting a marketing authorisation.

CLINICAL ASSESSMENT

LICENCE NO: PL 00033/0160
PROPRIETARY NAME: Alrex 0.2% Eye Drop Suspension
ACTIVE(S): Loteprednol etabonate
COMPANY NAME: Chauvin Pharmaceuticals Limited
E.C. ARTICLE: 8.3(i)
LEGAL STATUS: POM

INTRODUCTION

This is a national complete application for a marketing authorisation for Alrex 0.2% w/v Eye Drop Suspension, PL 00033/0160, with Chauvin Pharmaceuticals Ltd as the marketing authorisation holder. The application has been submitted under Article 8.3(i) of Directive 2001/83/EC.

Seasonal allergic conjunctivitis affects between 5% and 22% of the general population and it is a Type I hypersensitive response to specific airborne antigens. Allergic and inflammatory conditions of the eye have traditionally been treated using a range of corticosteroids. Their use can be associated with several undesirable side effects including raised intraocular pressure (IOP), increased incidence of posterior subcapsular cataracts and susceptibility to eye infections.

Alrex contains a new active substance, loteprednol etabonate (LE), which is intended for the treatment of seasonal allergic conjunctivitis. LE is a corticosteroid that undergoes local transformation to inactive metabolites, thus reducing the local and systemic side effects experienced with conventional corticosteroid therapy.

LE was first authorised in the United States in 1998 and is currently licensed in the UK as a 0.5% eye drop suspension for the treatment of post-operative inflammation following ocular surgery.

There are currently several topical ocular corticosteroids available for seasonal allergic conjunctivitis in the UK, including prednisolone acetate 1%, which has been used as a control in several clinical studies.

CLINICAL INDICATIONS

Symptomatic treatment of seasonal allergic conjunctivitis.

DOSE AND DOSAGE SCHEDULES

As per Summary of Product Characteristics (SPC) Section 4.2.

CLINICAL PHARMACOLOGY

Pharmacodynamics

Loteprednol etabonate (LE), is an analogue of prednisolone but unlike other corticosteroids it is an ester rather than a ketone. It is rapidly metabolised by tissue esterases to an inactive

compound (PJ-91) *in vivo*. PJ-91 does not bind to glucocorticoid receptors. This is probably the reason for the reduced propensity of LE to elevate the intraocular pressure (IOP) compared with other steroids. Its lability to blood and liver enzymes reduces the likelihood of systemic side effects, and the absence of the keto group at position 20 eliminates the adduction with lysine which would form in the crystalline lens, thus reducing the formation of corticosteroid-induced cataracts.

Pharmacodynamics of LE were investigated in 5 clinical studies using different concentrations up to 0.5%, which additionally evaluated efficacy and safety.

Conjunctival Provocation Test (CPT)

The CPT is a controlled experimental model where antigen dosage and length of exposure can be monitored and adjusted, thereby providing information on the appropriate dosing and duration of action of ophthalmic anti-allergic medications.

Study P-5604: 104 Dose regimen evaluation of LE

Objectives

To evaluate the safety and efficacy of three dosing regimens of LE ophthalmic suspension in inhibiting the inflammatory response, using the allergen controlled model.

Design and method

Clinical phase II, double blind, randomised, cross-over, placebo controlled study.

30 adults (17 F, 13 M, aged 22-47 years) with known ocular sensitivity to various allergens were recruited. Subjects were assigned to receive test medication in one eye while the contralateral eye served as a placebo control during three pre-treatment regimens: Period 1 = 15 min drug pre-treatment regimen (n =30); 0.1% LE vs placebo; 1 dose
Period 2 = 24 hour pre-treatment regimen (n = 29); 0.1% LE vs placebo; 5 doses
Period 3 = 48 hour pre-treatment regimen (n = 21); 0.5% vs placebo; 9 doses
Each period was separated by 7 days.

Efficacy variables were reductions in eyelid swelling, chemosis, redness, tearing and itching. Safety evaluations included external examination, slit-lamp biomicroscopy, applanation tonometry and visual acuity (VA) prior to enrolment and at scheduled times during the study. Systemic evaluations were recorded through patient comments.

Results

All three regimens were well tolerated with no serious adverse event (SAE) reported and only minor events noted. However, statistically significant treatment effects were lacking for every sign and symptom.

Conclusion

LE 0.1% and 0.5% are well tolerated and safe but its effectiveness has not been confirmed in this study.

Study P-5604: 105 Pilot efficacy evaluation of LE in CPT

Objectives

To evaluate the efficacy and safety of LE 0.5% ophthalmic suspension in controlling the ocular reactions following CPT and to compare LE effectiveness with that of Prednisolone Acetate (PA) and placebo.

Design and method

Clinical phase II, double blind, randomised (2:1 ratio for LE 0.5% and PA 1%), parallel group comparison of LE 0.5% and PA 1% with a placebo controlled contralateral eye. 42 adults aged 18-55 years participated in this study.

One drop of test medication was applied in each eye at 30 min and 15 min prior to CPT. Without further treatment, the eyes were re-challenged with another CPT 2 hours later.

Primary efficacy parameter was the composite CPT reaction score by the sum of ocular itching, conjunctival hyperaemia and chemosis. Safety evaluations were as for study 104.

Results

The test medications were well tolerated and no clinically significant adverse event (AE) was reported. There were statistically significant differences for both active treatments compared with placebo for all primary efficacy variables but there were no statistically significant differences between LE 0.5% and PA groups. After the rechallenge CPT, there was a statistically significant difference in the incidence of hyperaemia and chemosis in favour of eyes treated with LE or PA, when compared with placebo.

Conclusion

LE 0.5% and PA 1% are both safe and equally effective in treating the late phase reaction to an ocular allergen in susceptible individuals.

Dose escalation studies

Study P-5604: 101 Open dose escalating study of LE in 14 healthy volunteers

Objectives

To establish the tolerability of escalating dilutions of LE from 0.005% up to 0.5%, to assess its effect on IOP and to record any other effects.

Design and method

Open, randomised two period, clinical phase I study.

14 male healthy volunteers (aged 19-28 years) were randomly assigned to one of 4 treatment groups:

Group 1 (n=3) received medication A (0.005%) and then B (0.05%)

Group 2 (n=3) received medication B (0.05%) and then C (0.1%)

Group 3 (n=3) received medication C (0.1%) and then D (0.5%)

Group 4 (n=5) received medication D (0.5%) and then D (0.5%)

Each subject received one drop of study medication twice at weekly intervals.

Ocular safety evaluations (IOP, VA, colour vision, slit lamp biomicroscopy and ophthalmic examinations) were done pre-treatment and at scheduled times 24 hours post-dose.

Results

All concentrations were well tolerated with no or minimal effects on IOP. No clinically significant reactions were reported.

Conclusion

A single dose of LE ophthalmic suspension up to 0.5% is safe.

Study P-5604: 102 Phase I study to evaluate the safety and tolerance of multiple doses of LE 0.5% ophthalmic suspension

Objectives

To evaluate the safety of LE 0.5% ophthalmic suspension administered *qds* for 28 days and to evaluate the effect on the structures and functions of the eye.

Design and method

Double blind, randomised, placebo controlled study. 12 male subjects aged 18-45 years were recruited. 10 received either LE 0.5% or placebo in one eye and placebo on the contra-lateral eye. 2 subjects received placebo in both eyes. Treatments were administered four times a day during 28 days.

Ocular safety evaluations as for Study 101 above. Additionally, systemic safety evaluations were conducted including vital signs, blood sampling for plasma levels of the drugs and metabolites and haematology, biochemistry and urine analysis.

Results

It was well tolerated and burning eye was the most frequent AE reported.

Conclusion

LE 0.5% ophthalmic suspension is safe when given *qds* for 28 days.

Effects of IOP

Study P-5604: 103 Safety evaluation of the IOP to LE 0.5% in known steroid responsive individuals

Objectives

To compare the effects of LE 0.5% and Prednisolone acetate (PA) 1% on the IOP of steroid responders subjects (subjects with a documented history of ≥ 6 mmHg elevation of IOP in 6 weeks or less with topical dexamethasone 0.1% or PA 1% administration).

Design and method

Double blind, clinical phase I, randomised, parallel group study-period 1; protocol later amended to allow some patients to crossover-period 2.

19 adults aged 18-75 were randomised to receive LE 0.5% (n=10) or PA 1% (n=9), one drop into each eye *qds* for 42 days. Subsequent amendments allowed treatment to one eye only and patients to crossover (9 patients) and receive alternative treatment.

Primary variable was the change in the IOP from pre-study baseline.

Results

Elevation of IOP with LE was 25% of the elevation associated with PA. 55% of subjects in the PA group had a significant IOP elevation (≥ 10 mmHg) compared with 10% in the LE group during the first period of the study. Additionally, the mean time to significant IOP elevation in the PA group was shorter than the LE group and the mean endpoint IOP was lower after treatment with LE (~ 20 mmHg) than after treatment with PA (~ 27 mmHg).

Conclusion

LE 0.5% has a lower propensity to elevate the IOP than PA 1%.

Pharmacodynamics assessor's overall comment

The effect on the elevation of the IOP is lower compared with prednisolone acetate 1% and systemic pharmacodynamic effects were not detected. These results are obtained using a higher strength than the proposed product, further supporting the present application.

PHARMACOKINETICS

The pharmacokinetics of LE has been evaluated after oral and topical ocular administration.

Oral dosing

Study P-5604: 112

Objectives

To evaluate the safety and detect blood levels of LE and its major metabolite (PJ-91) after it is administered as a single oral dose.

Design and method

Open, single centre, clinical phase I study.

6 healthy male volunteers of the same race and aged 22-28 years received 40 mg LE 0.1% ophthalmic solution as a single oral dose. Blood samples were taken pre-treatment and at 0.25, 0.5, 1, 2, 3, 4, 6, 8, 12, 24, 36 and 48 hours after dosing. All subjects completed the study.

Results

Both LE and PJ-91 were detected in the plasma at very low levels (0.5 ng/ml to 14 ng/ml). As it was a small study no statistical analysis was performed.

Assessor's comment

This was a very small study involving a product concentration lower than the proposed product.

Topical dosing

Study P-5604: 120

Objectives

To determine levels of LE and its major metabolite PJ-91 in plasma and circulating cortisol levels following ocular administration of LE ophthalmic suspension.

Design and method

Single-centre, clinical phase I, double-blind, randomised, placebo controlled, parallel group study.

14 adults (12 females, 2 males, aged 19-44 years) were administered one drop of LE 0.5% ophthalmic suspension or placebo (LE n=10, Placebo n=4) into each eye 8 times daily on days 0 and 1, four times daily on days 2 through 42. Total duration of treatment was 43 days.

Primary variables were detection and quantitation of LE and PJ-91 in the blood after ocular administration and changes in circulating cortisol from baseline levels.

Results

All patients completed the study. Plasma levels of LE and PJ-91 were below level of quantitation (1 ng/ml) and in many cases below the level of plasma detection. Plasma cortisol levels were all within the normal range.

Conclusion

Following ocular administration of LE 0.5% to healthy volunteers blood levels of LE and PJ-91 were below limits of quantitation. There was no evidence of adrenal suppression.

Assessor's comment

Although this was a small study, the absence of adrenal suppression using 0.5% concentration favours the safety of the applied product.

Pharmacokinetics assessor's overall comment

Although concentrations of the active drug in the target compartment (aqueous humour) could be obtained by paracentesis, the applicant considers it an invasive procedure, which could result in an alteration of the intraocular distribution of the drug. This is the reason why no studies on the concentration of LE in the target tissues are available. The studies presented have demonstrated that limited to non-detectable systemic absorption of LE is observed following oral and ocular administrations and therefore systemic bioavailability is not applicable in this case. This means that the risk of systemic exposure to undesired corticosteroid effects is very low. Although no formal interaction studies were conducted, the applicant states that numerous concomitant medications were used during the clinical studies and no events that could have been caused by drug interactions were reported.

CLINICAL EFFICACY

Two dose response studies were conducted using the antigen model of acute allergic conjunctivitis. Study 141 was designed to validate the CPT for detecting anti-allergy activity of LE. Study 145 was designed to evaluate the appropriate dose of LE for Phase III SAC trials.

Two placebo controlled pivotal studies (studies 143 and 144) involving a total of 268 patients and using the environmental model have been conducted to support the use of LE 0.2% in the treatment of SAC.

LE 0.5% eye drops suspension was also developed in the United States for other indications. Some of the clinical studies conducted for its development are included in this section and also under “CLINICAL SAFETY”.

Dose response

Study P-5604: 141

Objectives

To compare two dose regimens of LE 0.5% on the prevention of signs and symptoms induced by an ocular antigen challenge, and to evaluate the duration of this effect.

Design & method

Single centre, clinical phase II, randomised, double blind, placebo controlled, paired comparison study.

60 adults aged 19-65 years were randomised to receive LE and placebo in respective eyes twice daily (n= 30) or four times a day (n= 30) during 28 days. Antigen challenges were carried out initially, at baseline and after 14 days of pre-treatment (15 minutes after the last dose) and after 28 days (2 hours or 8 hours after the final dose).

Primary efficacy variables included itching and mean redness scores.

Results

LE 0.5% reduced redness at all times on days 21 and 35 with both regimens. Itching was also reduced at all times on days 21 and 35 after a 2 hour challenge with both regimens and on day 35 after the 8 hour challenge with the *qds* dosing. LE failed to reduce itching at all time points at the 8 hour challenge following *bd* dosing.

Conclusion

LE was more effective than placebo but effects of treatment were still evident at the 8 hour challenge in the *qds* group.

Study P-5604: 145

Objectives

- (a) To compare 3 doses of LE ophthalmic suspension (0.1%, 0.2%, 0.3%) on the prevention of signs and symptoms induced by an ocular antigen challenge, and to evaluate the duration of this effect.
- (b) To evaluate LE 0.5% ophthalmic suspension compared with placebo on the prevention of signs and symptoms induced by an ocular antigen challenge.

Design & method

Single centre, clinical phase II, double-blind, randomised, placebo controlled study, paired comparison study (0.1%, 0.2%, 0.3%) and parallel group study (0.5%).

120 adults aged 19-66 years were recruited and all received the test drug as one drop *qds* for 28 days (from day 7 to day 35). Antigen challenges were carried out on days 0 (to determine response to rising doses of allergen), 7 (using the highest dose of day 0 to check the response was still present, baseline), 21 (challenge at 30 min post treatment) and 35 (challenge at 2 hours post treatment for all concentrations and at 4 hours for 0.1%, 0.2% and 0.3%).

0.1% group- n= 28

0.2% group- n= 31

0.3% group- n= 29

0.5% group- n= 32

Primary efficacy variables in the paired comparison groups were interocular differences in itching and mean redness. Second variables assessed chemosis, tearing and lid swelling. In the parallel group the same parameters were recorded but the variables were the differences in mean scores between the subjects that received active medication and those who received placebo. Mucous discharge was evaluated in all subjects.

Results

116 subjects completed the study. In the paired-comparison groups LE at all concentrations was significantly more effective than placebo for the primary variables, with the 0.3% formulation being the most effective and 0.1% the least effective. In the parallel-comparison group, subjects treated with the 0.5% formulation showed greater reductions in signs and symptoms than those did in the placebo group.

The 0.2% formulation showed statistically significant differences compared with placebo for itching and redness on day 21 at all times. On day 35 after 2 hours challenge, itching was still better at all times (statistically significant) although redness was only better at 3 min post-challenge. On day 35 after 4 hours challenge itching was better at 20 minutes and redness at 10 and 20 minutes (statistically significant).

Conclusion

LE ophthalmic suspension at concentrations 0.1%, 0.2%, 0.3% and 0.5% was more effective than placebo.

Assessor's comment

Due to the lack of statistically significant differences between the 0.1% formulation and placebo the 0.2% formulation was chosen as the optimal concentration to take into the pivotal phase III studies. The results from study 141 favoured the *qds* regimen.

Efficacy in SAC

Study P-5604: 143

Objectives

To evaluate the efficacy and safety of LE 0.2% ophthalmic suspension in the treatment of environmental SAC.

Design & method

Randomised, double-blind, placebo controlled, parallel group, multicentre, clinical phase III study.

133 adults aged 20-73 years and with a positive allergy test were recruited: 66 received LE 0.2% and 67 received placebo. All treatments administered were given as one drop into each eye four times a day during 6 weeks.

Daily pollen counts were recorded for each of the cities where the study sites were located and the active pollen season was defined as pollen counts consistently greater than 100/m³. All the subjects exhibited signs and symptoms of SAC at the time of elevated levels of airborne pollen.

On the day of enrolment signs and symptoms were evaluated at baseline and at 1 and 2 hours after the first dose. They were further evaluated on days 2 or 3, 7, 14, 28 and 42.

Primary efficacy variables included bulbar conjunctival injection and ocular itching. The primary efficacy analysis was mean change from baseline for the first two weeks. Secondary efficacy variable was Investigator Global Assessment and the analysis was the mean change from baseline following the first dose. Supportive efficacy variables were discomfort, foreign body sensation (FBS), burning/itching, photophobia, tearing, discharge, palpebral conjunctival injection, chemosis and erythema.

Results

126 patients completed the study. 4 discontinued due to medical events (2 in each group), one was lost to follow up and 2 discontinued for reasons unrelated to the study.

Summary of results:

	2 hours after first dose		First 2 weeks		End of first two weeks: Cure rate ²	
	Treatment effect	p	Treatment effect ¹	p	LE	Placebo
Bulbar injection	-0.40	< 0.001	-0.54	<0.001	31%	9%
Itching	-0.02	0.861	-0.62	<0.001	54%	38%

¹(LE-Placebo): negative numbers indicate LE favoured over placebo

²Cure rate is defined as the proportion of patients with the sign or symptom no longer present

LE was more effective for the primary and secondary variables than placebo and in most of the supportive analysis (statistically significant). The investigator global assessment was statistically significant in favour of LE for the first two weeks with 79% of LE patients mostly or fully controlled.

Conclusion

LE 0.2% is more effective than placebo in the treatment of SAC.

Study P-5604: 144

Objectives

To evaluate the efficacy and safety of LE 0.2% ophthalmic suspension in the treatment of environmental SAC.

Design & method

Randomised, double-blind, placebo controlled, parallel group, multicentre, clinical phase III study.

135 adults aged 19-74 years and with a positive allergy test were recruited: 67 received LE 0.2% and 68 received placebo. All treatments administered were given as one drop into each eye four times a day during 6 weeks.

Daily pollen counts were recorded for each of the cities where the study sites were located and the active pollen season was defined as pollen counts consistently greater than 100/m³. All the subjects exhibited signs and symptoms of SAC at the time of elevated levels of airborne pollen.

On the day of enrolment signs and symptoms were evaluated at baseline and at 1 and 2 hours after the first dose. They were further evaluated on days 2 or 3, 7, 14, 28 and 42.

Primary and secondary efficacy variables and analysis as for study 143.

Results

128 patients completed the study. 3 discontinued due to medical events (2 on placebo and one on LE), three were lost to follow up and one discontinued for reasons unrelated to the study.

LE was more effective for the primary and secondary variables than placebo and in most of the supportive analysis (statistically significant).

Summary of results:

	2 hours after first dose		First 2 weeks		End of first two weeks: Cure rate ²	
	Treatment effect ¹	p	Treatment effect ¹	p	LE	Placebo
Bulbar injection	-0.29	< 0.001	-0.52	<0.001	36%	15%
Itching	0.09	0.592	-0.40	<0.008	58%	38%

¹(LE-Placebo): negative numbers indicate LE favoured over placebo

²Cure rate is defined as the proportion of patients with the sign or symptom no longer present

The investigator global assessment was statistically significant in favour of LE for the first two weeks with 80% of LE patients mostly or fully controlled.

Conclusion

LE 0.2% is more effective than placebo.

Clinical efficacy assessor's overall comment

Both pivotal studies showed similar results confirming that LE 0.2% was more effective than placebo in the treatment of SAC. This was more evident 2 hours following the first dose and continued for two weeks. Only visits occurring before the end of the pollen season were included in the supportive analysis of visits 5 (day 28) and 6 (day 42). However, the pollen season was shorter than the study period and therefore the efficacy analysis was greatly decreased at visits 5 and 6. This explains the fact that results at the end of the study period were not statistically significant.

The strong placebo response is probably due to the fact that its vehicle contains inactive components that have demulcent effects, frequent application of eye drops has a rinsing action

allowing removal of pollen and, in the initial few hours of the study, the patients were inside offices away from the environmental challenge.

STATISTICAL ASSESSMENT

This assessment considers the evidence of efficacy for Alrex 0.2% (loteprednol etabonate) in seasonal allergic conjunctivitis (SAC). One dose finding trial (P-5604-145) and two pivotal trials are presented (P-5604-143 and P-5604-144). The following is a brief description of trial design and a critique of the trial methodology.

Design of the concentration-finding Trial

An allergen-challenge study was conducted to assess the relative efficacy and safety of Alrex 0.1%, 0.2% and 0.3%. The study separately compared Alrex 0.5% with vehicle control. The former part of the study was a randomised, double-blind, placebo-controlled, single-centre study. Ninety patients received either Alrex 0.1%, 0.2% or 0.3% in one eye and vehicle control in the contralateral eye. A random scheme determined what treatment was administered to which eye.

The applicant concludes that all concentrations were effective versus vehicle control, that 0.3% was most effective and that 0.1% was least effective. However, because of the increased side-effects at 0.3%, the applicant decided that a concentration of 0.2% would be used in the Phase III studies.

Comments on methodology

Numerous statistical analyses were conducted at numerous timepoints. This does not appear to have been accounted for in the interpretation of the trial results. Data on one of the primary protocol endpoints, bulbar conjunctival injection, have not been presented.

None of the concentrations showed universal superiority over vehicle control and there was no statistical evidence of concentration-response. However, there were trends to support the applicant's conclusion of increased efficacy at higher concentrations. If there are safety concerns at the 0.3% concentration, a choice of 0.2% may be considered reasonable.

Design of the pivotal trial

Trials 143 and 144 were similar in design. They were multicentre, randomised (1:1), double-blind, 6-week, placebo-controlled trials in 133 and 143 patients respectively.

The primary endpoints were bulbar conjunctival injection and itching, both measured on rating scales (0-3 and 0-4 respectively) at each visit. Daily diary cards were also completed, immediately after the first treatment of the day and immediately prior to the last treatment of the day.

The primary timepoint was after 2 weeks of treatment although secondary analyses were conducted at 1 hour, 2 hours, 1 day, 4 weeks and 6 weeks (or end of allergy season, whichever came first). For analyses at 4 weeks and 6 weeks, only visits that met the criteria for "active pollen season" were included (pollen count >100/m³). As both eyes were treated simultaneously with the same randomised treatment, data were meaned across eyes prior to statistical analysis.

The primary analysis method was ANOVA on change from baseline. The model included terms for centre, treatment and their interaction. In the analysis of bulbar conjunctival injection, baseline was included as a covariate. The primary analysis population was a modified ITT population including all randomised patients with at least 1 follow-up evaluation. Last observation carried forward (LOCF) was used for withdrawals prior to visit 6. Cochran-Mantel-Haenszel tests, adjusted for site, were used to assess the proportion of responders.

Intra-ocular pressure (IOP) was measured at each visit. The mean change in IOP was analysed using ANCOVA, with baseline as covariate.

Alrex 0.2% showed statistically significant advantages over vehicle control on itching and bulbar conjunctival injection. Itching was also assessed via daily diary card. A significant advantage over placebo (at week 2) was observed both immediately after the first treatment of the day and immediately prior to the last treatment of the day. The effect on itching was not observed in the first two hours of treatment.

Mean changes in IOP were significantly greater on Alrex (Trial 143: 1.14, 95%CI [0.55, 1.73], Trial 144: 0.6, 95%CI [0.11, 1.10]). No patient had a rise in IOP >10mmHg at any visit in trial 143, two patients had a rise of greater than 10mmHg in trial 144, one in each treatment group.

Comments on methodology

These are straightforward trials. The trials were conducted in accordance with the trial protocols. There were few withdrawals prior to the primary timepoint and few exclusions from the ITT population, despite the applicant's slightly restrictive criteria (ITT populations should, where possible, account for all randomised patients). The methods of statistical analysis were straightforward and the results had extreme levels of statistical significance and were consistent across the two pivotal trials. The clinical relevance of the results must be considered.

There were some minor issues relating to the statistical analysis. Firstly, there are multiple primary endpoints and multiple timepoints in each trial. However, given that results on the two pre-specified primary analyses were significant, this is not considered problematic. Secondly, there were centre-by-treatment interactions in both trials. However, the interactions were quantitative, meaning that the treatment effects at each centre favoured Alrex, but differed in magnitude. Such interactions are not of major concern. Finally, the omission of a term for baseline as a covariate in the ANOVA model for itching seems reasonable as all patients had an itching score of 4 at entry.

The trial employed a between-subject comparison, testing one treatment per subject rather than one treatment per eye, which would have enabled within-subject comparisons and a potential decrease in the required number of patients. This is not considered to devalue the trial actually performed.

Neither trial includes a licensed comparator. This does not preclude licensure or weaken the evidence for absolute efficacy. However, such a comparison would have been of interest.

There are two potential limitations to the generalisability of the trial results. First, only 133 patients were randomised out of a total of 387 screened. All patients were required to have severe itching and moderate to severe bulbar conjunctival injection at enrolment. Clinical

judgement should consider whether this is representative of the population indicated and, in particular, whether the trial results can be extrapolated to milder disease. Second, there is no evidence of continuing efficacy after more than 2 weeks of treatment. Analyses of data from weeks 4–6 were heavily affected by excluded data due to the end of the pollen season (It was protocolled that data would not be excluded from the primary analysis because of low pollen counts. This is appropriate in a trial aiming to demonstrate superiority). Therefore longer-term efficacy has been extrapolated from the evidence of short-term (2-week) efficacy. Clinical judgement should consider whether this is reasonable.

Statistical assessor’s overall conclusions

The trial designs and statistical analyses are straightforward and the trial data are considered reliable. There is statistical evidence of efficacy relative to placebo with regards to itching and bulbar conjunctival injection after 2 weeks of treatment. Longer-term efficacy has not been established and must be extrapolated from the 2-week data. There is evidence of increased IOP with Alex. The clinical relevance of the magnitude of these effects should be considered. Clinical judgement should also consider whether the trial results can be extrapolated to the proposed patient population.

OVERALL ASSESSMENT OF EFFICACY

The dose response studies demonstrated that LE 0.2% administered four times a day represented the optimal strength and dosage for the intended indication. The two pivotal studies were well conducted and have confirmed that LE 0.2% administered as a *qds* regimen is more effective than placebo in treating the signs and symptoms of SAC. The efficacy of LE was demonstrated in primary measures as well as secondary and supportive measures. Due to unexpected shortening of the pollen season there was only statistically significant efficacy over placebo for the first two weeks of treatment. However, this situation just reflects the normal environment, as pollen counts tend to fluctuate within the pollen season.

CLINICAL SAFETY

The safety profile is based on studies using LE 0.2% and LE 0.5%. Although the 0.5% formulation was developed for other indications apart from SAC, such as giant papillary conjunctivitis (GPC), acute anterior uveitis (AAU) and post-operative inflammation, it provides supportive data.

Ocular safety data was mainly evaluated through external examination, slit-lamp examination, tonometry and visual acuity (VA) prior to start and at scheduled times during the study period. Systemic safety was evaluated by subject comment during follow-up.

Summary of adverse events

Population exposed

The safety profile was based on 1215 normal volunteers and patients exposed to ocular or oral LE. The vast majority of the subjects were treated with 0.5% LE.

Subject population exposed to LE (ocular administration)

Concentration	Indication	N	Total
0.5% LE	Postoperative inflammation	212	973
	SAC	150	
	GPC	277	
	Uveitis	167	
	Other	167	
0.2% LE	SAC	133	164
	Other	31	
Other concentrations		102	102
Total			1209

Adverse events (AEs)

AEs related to LE (all concentrations) were generally mild to moderate, non-serious, resolved without treatment, and, for the most part, did not interrupt continuation of the clinical studies. 59% of the subjects exposed to LE reported an AE with 63% classified as ocular and 37% non-ocular. Overall, only 21% of all AEs were considered related to study medication.

This review will focus on the large, controlled phase III studies. Of the 879 subjects receiving LE in these studies, 68% reported an event (69% ocular and 31% non-ocular), similar to that in the prednisolone acetate (PA) group (67%) and less than the placebo group (80%).

Ocular events

The most frequent events were abnormal vision (mainly transient decreases in VA, itching and elevated IOP).

	LE	Placebo	PA
Abnormal vision	13 %	13 %	28 %
Itching	13 %	21 %	6 %
Elevation IOP	12 %	5 %	24 %

Elevation of IOP did not always mean an increase of ≥ 10 mmHg from baseline, which is the level considered to be clinically significant. Of patients treated with LE (any concentration) for at least 4 weeks and with dosing as frequently as every hour, only 2% had an elevation in the IOP of ≥ 10 mmHg compared with 0.5% in the placebo group and 6.7% in the PA group. When reviewing the pivotal studies that involved the 0.2% formulation, only one patient in the LE group (total LE 0.2% treated patients = 133) had a clinically significant increase in the IOP.

The incidence of clinically significant decreases in VA (a decrease 2 lines or greater in the Snellen chart) was similar between the LE, PA or placebo groups. Both pivotal studies did not report any significant decrease in VA amongst the LE treated patients.

Other less frequent ocular events reported in the LE treated patients included epiphora (11%), injection (9%), discomfort and photophobia (8% each), ocular discharge and foreign body sensation, FBS (7% each). In the placebo group, the incidences were higher than those in the LE group.

Assessor's comment

One must consider the patient populations for the control groups. PA patients had uveitis, a disease with low itching and high number of complaints regarding vision. On the other hand, placebo patients are mainly from the allergy and GPC studies where itching is a major symptom.

Non-ocular events

Non-ocular events related to therapy were generally rare, mild to moderate, non-serious, resolved without treatment and did not interrupt continuation in the studies.

The most frequent events in the LE group were headache and rhinitis (13% each), cough and pharyngitis (3% each) followed by common cold and sinusitis (2% each). Seen at an incidence of 1% were flu syndrome, allergic reaction, pain and fever. The incidence of these events was similar or higher in the control groups.

Results from a bioavailability study in normal volunteers established that the plasma levels of LE and its inactive metabolite, PJ-91, were below the limit of quantitation. The results were obtained following the ocular administration of one drop in each eye of 0.5% LE 8 times daily for 2 days or 4 times daily for 42 days. Plasma cortisol levels were within normal range confirming the absence of HPA suppression.

Serious events

Serious AEs were reported by 5 subjects with only 2 being related to study medication. All of the events occurred in phase III studies for postoperative inflammation. No serious AEs were reported in studies using 0.2% formulation or for SAC.

Patients discontinued due to AE

The overall rate for termination of LE treated subjects due to AE was 1.8% compared with 2.6% in the vehicle group and 4.5% in the PA group. In the studies involving 0.2% formulation, 3 subjects discontinued in the LE group (2 subjects discontinued due to AE related to study medication, increased IOP in one subject and headache and acute pharyngeal reaction in another subject) compared with 4 in the placebo group: increased IOP (n=1), eye spasm upon instillation of study drug (n=1), itching (n=1) and viral conjunctivitis (n=1).

Postmarketing surveillance

Since LE 0.2% was launched in the US, from March 1998 to August 2002 there were 80 spontaneously reported events representing 0.0024% per estimated patient use. There were no serious or unexpected AEs.

OVERALL COMMENT ON SAFETY

The safety studies presented for the 0.5% strength provide an extended database for assessment of safety at a higher dose than the present application. In this exaggerated exposure, the safety of LE is satisfactory. Overall, safety of LE 0.2% is relatively high compared with other corticosteroids, and acceptable for the intended patient population.

EXPERT REPORT

The clinical expert report was satisfactory.

APPLICATION FORM

This conformed to EC requirements and is satisfactory.

DISCUSSION

Loteprednol etabonate is a novel compound designed as a site-active corticosteroid. Although structurally similar to other corticosteroids, the number 20-position ketone group is absent. LE was designed to exert immediate anti-inflammatory activity within the eye upon instillation, followed by rapid hydrolysis to an inactive metabolite, providing the benefits of corticosteroid activity in the treatment of SAC without the risk of local and systemic side-effects caused by traditional corticosteroids.

One study has confirmed that LE is well absorbed into the eye, the target site, but has limited systemic exposure. Two pivotal studies have been submitted and both have demonstrated that LE 0.2% was more effective than placebo in treating the signs and symptoms of SAC. Its efficacy was demonstrated in primary as well as secondary and supportive measures. Only one LE-treated patient, out of a total exposure of 133 patients, and one placebo-treated patient developed an IOP >10 mmHg.

The safety studies presented for the 0.5% strength provide an extended database for assessment of safety. Overall, safety of LE 0.2% is acceptable for the intended patient population. Additionally, since LE 0.2% was launched in the US in 1998, no serious or unexpected AE has been reported further supporting the present application.

PRECLINICAL/CLINICAL ASSESSORS' RECOMMENDATION

The Committee on Safety of Medicines is asked to consider the evidence presented, the Applicant's Expert Reports and the comments and conclusions of the assessors and to advise the Licensing Authority.

COMMITTEE ON SAFETY OF MEDICINES RECOMMENDATION –
27 March 2003

The UK Advisory Committee considered the licence application on 27 March 2003 and advised the grant of a Marketing Authorisation provided the applicant revised certain sections of the Summary of Product Characteristics, Patient Information Leaflet and Labelling.

The changes requested by the UK Advisory committee were made and a marketing authorisation for Alex 0.2% Eye Drop Suspension was granted on 17 July 2006.

OVERALL CONCLUSION AND RISK-BENEFIT ASSESSMENT

QUALITY

The important quality characteristics of Alex 0.2% Eye Drop Suspension are well defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

PRECLINICAL

Loteprednol etabonate (LE) is a corticosteroid of similar potency to dexamethasone sodium phosphate or betamethasone-17-valerate. Pharmacodynamic studies have demonstrated anti-inflammatory properties in various animal models.

The reproductive toxicity studies revealed adverse effects in animals. However, in humans, the concentrations of LE are below the limit of quantitation under therapeutic conditions of use, therefore the risk to reproduction is minimal.

EFFICACY

The indication requested is symptomatic treatment of seasonal allergic conjunctivitis.

The two pivotal studies confirmed that LE 0.2% administered as a four-times-daily regimen is more effective than placebo in treating the signs and symptoms of SAC. The efficacy of LE was demonstrated in primary measures as well as secondary and supportive measures.

Overall, safety of LE 0.2% is relatively high compared with other corticosteroids, and acceptable for the intended patient population.

RISK-BENEFIT ASSESSMENT

The quality of the product is acceptable, no significant preclinical or clinical safety concerns were identified, and adequate efficacy has been demonstrated for this medicinal product. The risk-benefit assessment is therefore considered to be favourable.

ALREX 0.2% EYE DROP SUSPENSION

(LOTEPREDNOL ETABONATE)

PL 00033/0160

STEPS TAKEN FOR ASSESMENT

1	The MHRA received the marketing authorisation application for Alrex 0.2% Eye Drop Suspension on 30 December 2002.
2	The MHRA's assessment of the submitted data was completed on 3 March 2003.
3	The application was presented to the Chemistry, Pharmacy and Standards Sub-committee on 19 March 2003. The Sub-committee advised the grant of a Marketing Authorisation once the applicant had complied with certain conditions.
4	The MHRA's assessment report was considered by the Committee on Safety of Medicines (CSM) on 27 March 2003.
5	The applicant was informed that CSM recommended approval of the application subject to amendments to the product particulars (SPC, PIL and Labelling) on 9 April 2003.
6	The applicant informed the MHRA that it would accept the CSM recommendation on 4 September 2003.
7	Further information (quality) was requested from the applicant on 12 January 2004.
8	The applicant and the MHRA held a meeting on 18 June 2004 to discuss the quality objections raised.
9	The applicant submitted its response to the quality objections on 6 August 2004.
10	Further information (quality) was requested from the applicant on 3 March 2005.
11	The applicant and the MHRA held a teleconference on 3 August 2005 to further discuss some of the quality objections raised.
12	The applicant submitted its response to the quality objections on 25 August 2005.
13	Further information was requested from the company on 31 January 2006.
14	The applicant submitted its response to further information request on 15 March 2006.
15	Updated product particulars were requested from the applicant on 24 April 2006.
16	The applicant submitted its response to request for updated product particulars on 6 July 2006.
17	The MHRA completed its assessment of the updated product particulars on 11 July 2006.
18	The application was determined on 17 July 2006.

**ALREX 0.2% EYE DROP SUSPENSION
(LOTEPREDNOL ETABONATE)**

PL 00033/0160

STEPS TAKEN AFTER AUTHORISATION - SUMMARY

Date submitted	Application type	Scope	Outcome

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Alrex 0.2% Eye Drop Suspension ▼

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Loteprednol etabonate 0.2% w/v. Each drop contains 0.08 mg loteprednol etabonate.

For excipients, see Section 6.1.

3. PHARMACEUTICAL FORM

Eye Drops, suspension.

Milky-white sterile suspension.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

Symptomatic treatment of seasonal allergic conjunctivitis.

4.2. Posology and method of administration

Adults and Elderly:

Apply one drop 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 one drop every hour, if necessary. Treatment should not exceed six weeks. If more than one topical ophthalmic medicinal product is being used, the medicinal products should be administered at least 10 minutes apart.

Children and Adolescents:

Alrex should not be used in the paediatric age group until further data becomes available.

Shake the bottle vigorously to produce a uniform milky-white suspension before using.

This product is sterile when packaged. Patients should be advised not to allow the dropper tip to touch any surface, as this may contaminate the suspension. As with all ophthalmic preparations containing benzalkonium chloride, patients should be advised not to wear soft contact lenses when using Alex.

4.3. Contraindications

Alex is contraindicated in most viral diseases of the cornea and conjunctiva including epithelial herpes simplex keratitis (dendritic keratitis), vaccinia, varicella, untreated purulent ocular infections, glaucoma, eyes with suspected or confirmed infection, amoebic infections and also in mycobacterial infection of the eye and fungal diseases of ocular structures.

It is also contraindicated in individuals with known hypersensitivity to the active substance, to any of the excipients, and to other corticosteroids.

4.4. Special warnings and precautions for use

Prolonged use of corticosteroids may result in glaucoma with damage to the optic nerve, defects in visual acuity and fields of vision, and in posterior subcapsular cataract formation.

Prolonged use of corticosteroids may suppress the host response and may increase the possibility of secondary ocular infections. In those diseases causing thinning of the cornea or sclera, perforations have been known to occur with the use of topical steroids. In acute purulent conditions of the eye, steroids may mask infection or enhance existing infection. Appropriate anti-infective agents should be used if infection is present.

If signs and symptoms fail to improve after two days, the patient should be re-evaluated.

If this product is used for 10 days or longer, intraocular pressure should be monitored.

Alex contains benzalkonium chloride as a preservative, which is known to discolour soft contact lenses and should not be used whilst the patient is wearing soft contact lenses. Patients can have the contact lenses reinserted 10-15 minutes after Alex has been administered.

Benzalkonium chloride has been reported rarely to cause punctate keratopathy and toxic ulcerative keratopathy.

4.5. Interactions with other medicinal products and other forms of interaction

Since loteprednol etabonate is barely detected in plasma levels following the topical administration of Alrex eye drops, it is not expected to affect the pharmacokinetics of systemically administered drugs.

However, the low potential of loteprednol etabonate eye drops to increase the intraocular pressure may be adversely affected by systemically administered drugs with anticholinergic activity. In patients receiving concomitant ocular hypotensive therapy, the addition of loteprednol etabonate may increase intraocular pressure and decrease the apparent ocular hypotensive effect of these medications. Concurrent administration of cycloplegics may increase the risk of raised intraocular pressure.

4.6. Pregnancy and lactation

Pregnancy

There are no adequate data on the use of Alrex eye drops in pregnant women. Studies in animals with loteprednol etabonate have shown embryotoxic and teratogenic effects when administered orally at 35 times the maximum clinical dose (see Section 5.3). The potential risk for humans is unknown and Alrex eye drops should not be used in pregnancy unless considered essential by the physician.

Lactation

Insufficient data are available to support the use of Alrex eye drops in lactating women. Therefore, such use is contraindicated.

4.7. Effects on ability to drive and use machines

No studies have been performed on the ability to drive and use machines after instillation. Based on the pharmacology of the drug no effect is expected. However, instillation of eye drops may cause transient blurring of vision. Patients should be warned not to drive or operate machinery until their vision is clear.

4.8. Undesirable effects

Ocular adverse events reported as related to the use of the study medication, loteprednol etabonate ophthalmic suspension (0.005%-0.5%), under controlled clinical conditions were as follows:

Eye Disorders:

Common:	Increase in intraocular pressure, ocular itching, injection, burning/stinging, foreign body sensation, abnormal vision, ocular discharge, dry eyes, photophobia, ocular discomfort, chemosis and blurred vision.
Uncommon:	Eyelid erythema, eye pain and irritation of the eye.
Rare:	Sticky eye.

The following have been reported in clinical trials: epiphora, uveitis, keratic precipitates, intraocular inflammation (anterior chamber flare/cell), iritis, corneal disorder, ciliary hyperemia, keratitis, macular oedema, conjunctival papillae, conjunctival oedema, hyphema, anterior chamber inflammation, general eye inflammation (ophthalmitis) and synechia of the anterior chamber.

It should be noted that reactions associated with ophthalmic steroids include elevated intraocular pressure in steroid responsive patients, which may be associated with optic nerve damage, visual acuity and field defects, posterior subcapsular cataract formation, secondary ocular infection from pathogens including herpes simplex and perforation of the globe where there is thinning of the cornea or sclera.

In controlled randomised studies of individuals treated for 28 days or longer with loteprednol etabonate, the incidence of significant elevation of intra-ocular pressure (≥ 10 mmHg) was 2% (15/901) among patients receiving loteprednol etabonate, 7% (11/164) among patients receiving 1% prednisolone acetate and 0.5% (3/583) among patients receiving placebo.

Non-ocular adverse events reported as related to the use of the study medication, loteprednol etabonate ophthalmic suspension (0.005%-0.5%), under controlled clinical conditions were as follows:

Body as a whole:

Common:	Headache.
Uncommon:	Asthenia.
Rare:	Fever, pain, face oedema, chills and chest pain.

Digestive system:

Rare:	Nausea, diarrhoea and vomiting.
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Nervous system:

Rare:	Nervousness.
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Respiratory system:

Uncommon:	Rhinitis and pharyngitis.
Rare:	Increased cough.

Cardiovascular system:

Rare: Migraine.

Skin and appendages:

Rare: Rash and urticaria.

Special senses:

Rare: Taste disturbances.

Urogenital system:

Rare: Urinary tract infection.

4.9. Overdose

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

Oral ingestion of the contents of one bottle (up to 10 ml) is unlikely to cause any serious adverse events.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Corticosteroids suppress the inflammatory response to inciting agents of mechanical, chemical or immunological nature. No generally accepted explanation of this steroid property has been advanced. Loteprednol etabonate is a new class of corticosteroid with potent anti-inflammatory activity designed to be active at the site of action.

Animal studies have shown that loteprednol etabonate has a binding affinity to steroid receptors that is 4.3 times greater than dexamethasone. This new class of steroids are bioactive molecules whose in vivo transformation to non-toxic substances can be predicted from their chemistry and knowledge of enzymatic pathways in the body. Cortienic acid is an inactive metabolite of hydrocortisone and analogues of cortienic acid are also devoid of corticosteroid activity. Loteprednol etabonate is an ester derivative of one of these analogues, Δ^1 cortienic acid etabonate (PJ-91).

Placebo controlled studies demonstrated that Alex is significantly more effective than placebo for the treatment of seasonal allergic conjunctivitis. In patients with documented histories of seasonal allergic conjunctivitis to two distinct pollens, Alex, when administered for up to three weeks prior to the maximum pollen counts demonstrated a statistically significant lower symptomatology than in patients who received placebo.

Corticosteroids are capable of producing a rise in intra-ocular pressure in susceptible individuals. In a small study, loteprednol etabonate demonstrated a significantly longer time to produce the rise in pressure than did prednisolone acetate. The overall incidence of patients who had an IOP elevation of ≥ 10 mmHg was lower in the loteprednol etabonate treated patients. In many patients treated with loteprednol etabonate the ultimate rise in IOP never achieved the levels seen in patients treated with prednisolone acetate. In clinical trials only 2% of all patients had an IOP elevation of ≥ 10 mmHg. In patients who did not wear contact lenses 0.4% (1:226) of all patients had an elevated IOP related treatment whereas 5.0% (11:219) of all patients who wore contact lenses experienced an IOP elevation. In the small percentage of patients who did show a significant rise in IOP, pressure rapidly returned to normal on discontinuation of the drug.

5.2. Pharmacokinetic properties

Results from oral and ocular administration of loteprednol etabonate in normal volunteers have shown that there is a low or undetectable concentrations of either unchanged material or the metabolite. Results from a bioavailability study established that plasma concentrations of loteprednol etabonate following ocular administration of one drop in each eye of loteprednol etabonate 0.5% ophthalmic suspension eight times daily for two days or four times daily for 42 days were below the limit of quantitation (1 ng/mL) and detection (500 pg/mL) at all sampling times. In the same study, plasma cortisol concentrations were measured and no evidence of adrenal cortex suppression was observed. All cortisol measurements were within normal range. This study suggests that limited, if any, systemic absorption occurs with loteprednol etabonate 0.5% ophthalmic suspension.

5.3. Preclinical safety data

Both the acute and the repeated dose toxicology studies demonstrated that the drug was well tolerated and did not show unusual toxicity. Embryotoxic and teratogenic effects were observed in reproductive toxicity studies in rabbits at oral doses 35 times the maximum daily clinical dose and in rats at oral doses greater than 60 times the maximum daily clinical dose.

Mild ocular irritation was noted with both the acute and repeated dose rabbit ocular studies.

Preclinical effects were observed only at exposures considered sufficiently in excess of the maximum human exposure indicating little relevance to clinical use.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Glycerol
Povidone
Tyloxapol
Benzalkonium chloride
Edetate disodium dihydrogen
Purified water
Hydrochloride acid
Sodium hydroxide

6.2. Incompatibilities

In the absence of incompatibility studies, this medicinal product should not be mixed with other medicinal products.

6.3. Shelf life

36 months (unopened)
28 days after first opening the bottle

6.4. Special precautions for storage

Do not store above 25°C. Do not freeze

6.5. Nature and contents of container

Alrex is available in the following packaging configurations:

5.0 ml: supplied in a white low density polyethylene bottle (7.5 mL) with a white control drop tip and a pink polypropylene cap

10 ml: supplied in a white low density polyethylene bottle (10 mL) with a white control drop tip and a pink polypropylene cap

6.6. Instruction for use and handling

Discard any unused contents 28 days after first opening bottle.

7. MARKETING AUTHORISATION HOLDER

Chauvin Pharmaceuticals Ltd
Bausch & Lomb House
106 London Road
Kingston-Upon-Thames
Surrey
KT2 6TN

8. MARKETING AUTHORISATION NUMBER

PL 00033/0160

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

17/07/2006

10. DATE OF REVISION OF THE TEXT

17/07/2006

Patient Information Leaflet

**ALREX 0.2% EYE DROP SUSPENSION
(LOTEPREDNOL ETABONATE)**

PL 00033/0160

**BAUSCH
& LOMB**

Alrex™ 0.2%
eye drops suspension
loteprednol etabonate
PACKAGE LEAFLET



Read all of this leaflet carefully before you start using this medicine.

- Keep this leaflet. You may need to read it again.
- If you have any questions, please ask your doctor or your pharmacist.
- This medicine has been prescribed only for you. Do not give it to others. It may harm them, even if their symptoms are the same as yours.

In this leaflet:

1. What Alrex™ eye drops is and what it is used for
2. Before you use Alrex™ eye drops
3. How to use Alrex™ eye drops
4. Possible side effects
5. Storing Alrex™ eye drops

Alrex™ eye drops is an eye drops suspension
(loteprednol etabonate)

- The active ingredient is loteprednol etabonate. Each ml contains 2 mg (0.2% w/v) loteprednol etabonate
- Alrex™ eye drops also contains: Edetate Disodium Dihydrate, Glycerol, Povidone, Purified Water and Tyloxapol.
- Benzalkonium Chloride (0.01% w/v) is added as a preservative.

Marketing Authorisation Holder

Chauvin Pharmaceuticals Ltd.
106 London Road
Kingston-Upon-Thames
Surrey
KT2 6TN, UK
PL 00033/0160

Manufacturing by

Bausch & Lomb Incorporated
8500 Hidden River Parkway
Tampa, Florida 33637
USA

1. WHAT Alrex™ EYE DROPS IS AND WHAT IT IS USED FOR

Alrex™ eye drops is used for the treatment of signs and symptoms of seasonal allergic conjunctivitis. Sometimes the eye may become inflamed (red and painful) because of irritants such as pollen. Loteprednol etabonate is one of a group of medicines called corticosteroids. It acts by reducing inflammation and eases the symptoms. Because it is used in low doses directly where it is needed, its action is only at this place. Alrex™ eye drops is available in 5ml or 10ml bottles.

2. BEFORE YOU USE Alrex™ EYE DROPS

Do not use Alrex™ eye drops:

- if you are allergic to loteprednol or any of the other ingredients.
- if you are under 18 years of age.
- if you have eye diseases caused by viruses such as herpes simplex, vaccinia, and varicella.
- if you have eye diseases caused by bacteria and fungi.
- if you think you have any other eye infection.
- if you have been allergic to any other corticosteroid (also called "steroids").
- If you have glaucoma, which is a condition that occurs when the pressure in the eye increases for a period of time. This can cause damage to the optic nerve and problems with vision. Tell your doctor if you already have glaucoma or have been told that you have increased pressure in the eye.

Take special care with Alrex™ eye drops:

- Tell your doctor if pain develops, or if redness, itching, or inflammation gets worse.
- See your doctor if your symptoms do not get better within two days. He/she may want to re-evaluate your condition.
- You should not use Alrex™ eye drops longer than 10 days without having the pressure in your eye checked by your doctor.
- Long-term use of Alrex™ eye drops or other eye drops that contain steroids may lower your ability to fight infections and may increase your chance of getting an eye infection.
- Using steroid eye drops may make viral diseases of the eye, such as herpes simplex, worse and last longer.
- Long term use of Alrex™ eye drops or other eye drops that contain steroids may result in glaucoma and cataracts.

Pregnancy

If you are pregnant or intending to become pregnant, ask your doctor or pharmacist for advice before taking any medicine.

Breast-feeding

If you are breast-feeding, ask your doctor or pharmacist for advice before taking any medicine.



Important information about some of the ingredients of AlexTM eye drops

You should not wear soft contact lenses when using AlexTM eye drops. This product contains benzalkonium chloride, as a preservative, which is known to discolour contact lenses and should not be used whilst wearing soft contact lenses. Contact lenses can be reinserted 10-15 minutes after AlexTM eye drops has been administered.

Benzalkonium chloride has been reported to cause damage to the surface of the eye. This is rare and may be temporary or permanent depending on the extent of exposure.

Taking other medicines

Please inform your doctor or pharmacist if you are taking or have taken recently any other medicines, even those not prescribed. AlexTM may affect the way other medicines work, for example, medicines taken to control the ocular pressure.

3. HOW TO USE AlexTM EYE DROPS

- Always use your medicine as your doctor tells you to.

For Adults:

- Shake AlexTM eye drops vigorously before using.
- Apply one drop of AlexTM eye drops into the gap between your eyeball and eyelid, four times a day or as directed.
- If applying more than one drop, wait 30 seconds before the second drop is applied to the eye.
- Do not allow the tip of the dropper to touch any surface because this may contaminate the medicine. Your doctor will tell you how long your treatment with AlexTM eye drops will last. Do not stop treatment without talking with your doctor.
- You will usually only use this medicine for six weeks, unless specifically instructed by your doctor.

Do not use AlexTM eye drops in children.

If you are using another medicine in the eye, wait at least 10 minutes before applying.

If you forget to use AlexTM eye drops, wait until the next dose and then continue as before.

If you use more AlexTM eye drops than you should, tell your doctor or a pharmacist.

Eye drops can cause your vision to be blurred. This usually passes quickly. Do not drive or use machines until your vision is clear.

4. POSSIBLE SIDE EFFECTS

Like all medicines, AlexTM eye drops can have unwanted effects. The most common side effects in patients treated with AlexTM eye drops are:

- Blurred or abnormal vision
- Burning when putting drops in the eye or at any time while on the medication
- Swelling or discharge from the eyes
- Increased pressure within the eye
- Painful, dry or sticky eyes
- Tearing
- Sensation of having an object in your eye
- Itching in the eye or on the eyelid
- Redness in the eye or on the eyelid
- Photophobia (discomfort on exposure to light)

Other unwanted effects might include:

- Headache or migraine, cough or sore throat, runny nose, fatigue, nervousness, nausea, diarrhoea, vomiting, chest pain, facial swelling, fever, general pain, rash, taste disturbances or urine infection.

If you notice these or any other effects, tell your doctor or a pharmacist.

5. STORING AlexTM EYE DROPS

KEEP ALEXTM EYE DROPS OUT OF THE REACH AND SIGHT OF CHILDREN.

Store upright not above 25°C.

DO NOT FREEZE

Use by date

- Do not use after the expiry date stated on the carton and bottle.
- Discard any unused contents 28 days after first opening the bottle.

This leaflet was last approved on {date}

DO NOT USE IF PROTECTIVE SEAL IS BROKEN.

Further information

For any information about this medicine, please contact Bausch & Lomb, 106 London Road, Kingston-Upon-Thames, Surrey, KT2 6TN, UK.

Alex is a trademark of Bausch & Lomb Incorporated.

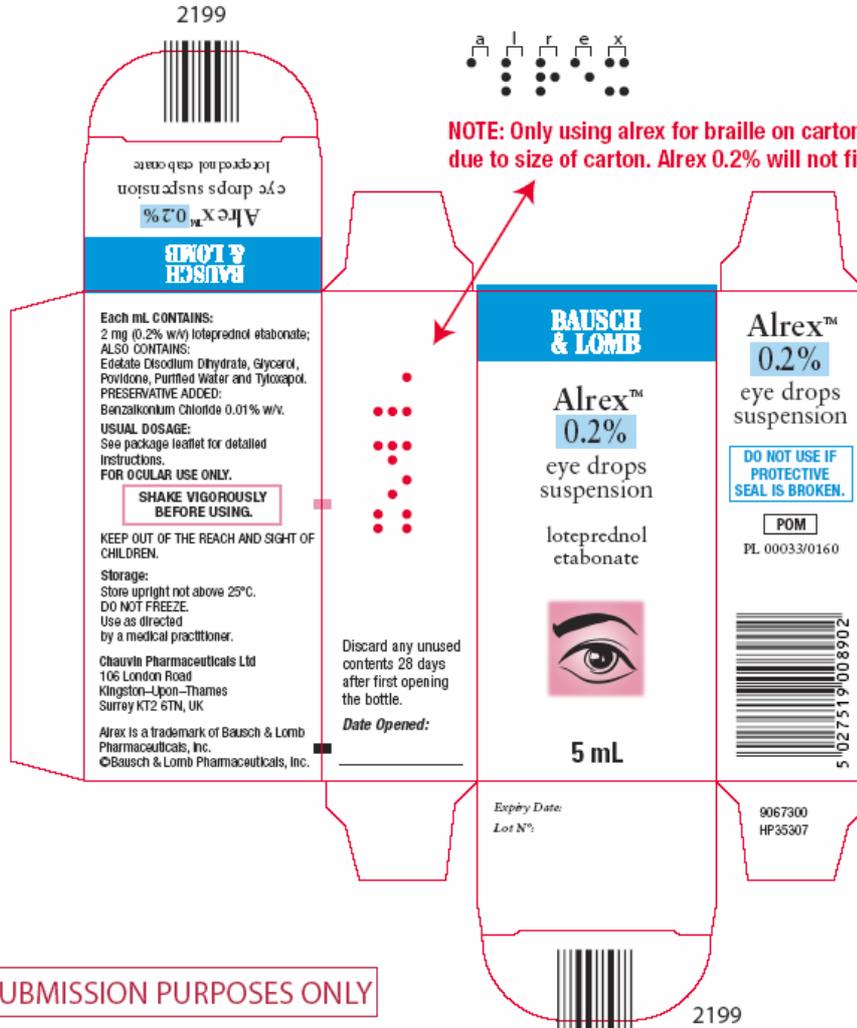
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R2/05-01
Prod. No. 353

Labels/Packaging

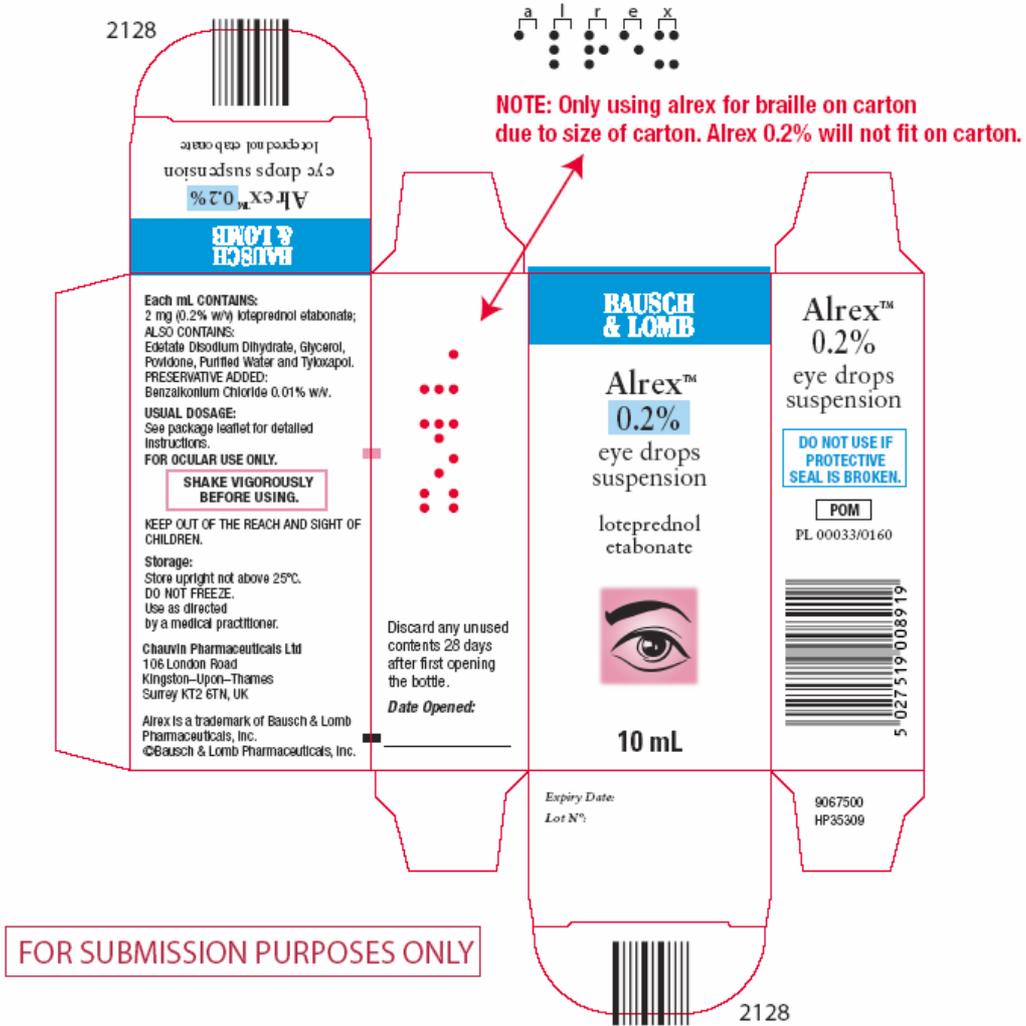
ALREX 0.2% EYE DROP SUSPENSION (LOTEPREDNOL ETABONATE)

PL 00033/0160



ALREX 0.2% EYE DROP SUSPENSION (LOTEPREDNOL ETABONATE)

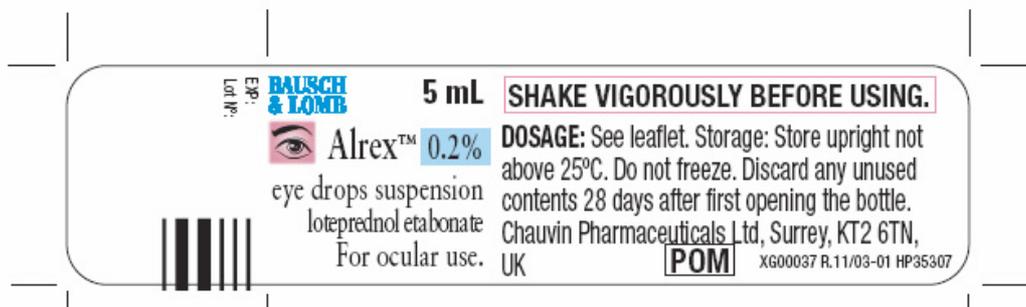
PL 00033/0160



**ALREX 0.2% EYE DROP SUSPENSION
(LOTEPREDNOL ETABONATE)**

PL 00033/0160

Bottle label 5ml



**ALREX 0.2% EYE DROP SUSPENSION
(LOTEPREDNOL ETABONATE)**

PL 00033/0160

Bottle label 10ml

