DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

JUN 27 2000

TRANSMITTED VIA FACSIMILE

Anna Wysowskyj
Senior Manager, Regulatory Affairs
Bausch & Lomb Pharmaceuticals, Inc.
8500 Hidden River Parkway
Tampa, FL 33637

RE: NDA 20-803 Alrex (loteprednol etabonate ophthalmic suspension, 0.2%)
MACMIS ID # 8889

Dear Ms. Wysowskyj:

This letter refers to Bausch & Lomb Pharmaceuticals, Inc.'s (B&L) submission, dated March 3, 2000, of promotional materials under cover of Form FDA 2253 for Alrex. The submission included a professional sales aid (PH1498), and a 4" x 6" magnet (PH1522) titled, "All the signs, all the symptoms." The Division of Drug Marketing, Advertising, and Communications (DDMAC) has reviewed the promotional materials and has concluded that they are false or misleading under the Federal Food, Drug, and Cosmetic Act and its implementing regulations. Our specific objections follow:

Misleading Claims of Superior Efficacy

In the promotional materials, you present a table titled, "Only Alrex scores against all the signs and symptoms of seasonal allergic conjunctivitis." The table includes the drugs Alrex, Acular, Alocril, Patanol, and Zaditor, and shows 10 symptoms of seasonal allergic conjunctivitis. Only Alrex is depicted to be effective for all the symptoms. The other products are depicted only to be effective for 1 symptom--itching. The table is misleading because you claim Alrex is superior to the other products based on labeled indications, but only Alrex and Acular have the same indications for use. Further, your comparison to Acular lacks adequate evidence in the form of adequate and well controlled head-to-head clinical trials.

The other products are indicated for vernal conjunctivitis, vernal keratoconjunctivitis, vernal keratitis, and allergic conjunctivitis. Thus, comparing Alrex to other drugs with different indications is misleading because the other drugs were developed for different uses in different patient populations. For example, drugs to treat vernal conjunctivitis would alleviate itching, conjunctival hyperemia, mucoid discharge, and papillary hypertrophy.

Anna Wysowskyj
Bausch & Lomb Pharmaceuticals, Inc.
NDA 20-803

Requested Actions

In order to address these objections, we request that you immediately cease the dissemination of these violative promotional materials and all similar promotional materials that contain the same or similar messages.

You should respond in writing to us regarding this issue by July 12, 2000. Your response should include B&L's intent to comply with the above request, the date that it ceased disseminating these and any other violative promotional materials with the same or similar messages, and a list of the discontinued materials.

If you have any questions, please contact me by facsimile at (301) 594-6771, or by written communication at the Division of Drug Marketing, Advertising, and Communications, HFD-42; Room 17B-20; 5600 Fishers Lane; Rockville, MD 20857. We remind you that only written communications are considered official.

In all future correspondence regarding this matter, please refer to MACMIS # 8889 and NDA 20-803.

Sincerely,

Warren F. Rumble
Regulatory Review Officer
Division of Drug Marketing,
Advertising and Communications

When you **must deliver** against seasonal allergic conjunctivitis...

ONLY ALREX® IS PROVEN TO COVER ALL THE SIGNS, ALL THE SYMPTOMS

Alrex®

loteprednol etabonate ophthalmic suspension 0.2%

All signs are clear

ALREX® (loteprednol etabonate ophthalmic suspension, 0.2%)
BRIEF SUMMARY

INDICATIONS AND USAGE:
ALREX® Ophthalmic Suspension is indicated for the temporary relief of the signs and symptoms of seasonal allergic conjunctivitis.

CONTRAINDICATIONS:
ALREX®, as with other ophthalmic corticosteroids, is contraindicated in most viral diseases of the cornea and conjunctiva including epithelial herpes simplex keratitis (dendritic keratitis), vaccinia, and varicella, and also in mycobacterial infection of the eye and fungal diseases of ocular structures. ALREX® is also contraindicated in individuals with known or suspected hypersensitivity to any of the ingredients of this preparation and to other corticosteroids.

WARNINGS:
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. Steroids should be used with caution in the presence of glaucoma.

Prolonged use of corticosteroids may suppress the host response and thus increase the hazard 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.

Use of ocular steroids may prolong the course and may exacerbate the severity of many viral infections of the eye (including herpes simplex). Employment of a corticosteroid medication in the treatment of patients with a history of herpes simplex requires great caution.

PRECAUTIONS:
General: For ophthalmic use only. The initial prescription and renewal of the medication order beyond 14 days should be made by a physician only after examination of the patient with the aid of magnification, such as slit lamp biomicroscopy and, where appropriate, fluorescein staining.

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.

Fungal infections of the cornea are particularly prone to develop coincidentally with long-term local steroid application. Fungus invasion must be considered in any persistent corneal ulceration where a steroid has been used or is in use. Fungal cultures should be taken when appropriate.

Information for Patients: 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. If redness or itching becomes aggravated, the patient should be advised to consult a physician.

Patients should be advised not to wear a contact lens if their eye is red. ALREX® should not be used to treat contact lens related irritation. The preservative in ALREX®, benzalkonium chloride, may be absorbed by soft contact lenses. Patients who wear soft contact lenses **and whose eyes are not red,** should be instructed to wait at least ten minutes after instilling ALREX® before they insert their contact lenses.

Carcinogenesis, mutagenesis, impairment of fertility: Long-term animal studies have not been conducted to evaluate the carcinogenic potential of loteprednol etabonate. Loteprednol etabonate was not genotoxic *in vitro* in the Ames test, the mouse lymphoma tk assay, or in a chromosome aberration test in human lymphocytes, or *in vivo* in the single dose mouse micronucleus assay. Treatment of male and female rats with up to 50 mg/kg/day and 25 mg/kg/day of loteprednol etabonate, respectively, (1500 and 750 times the maximum clinical dose, respectively) prior to and during mating did not impair fertility in either gender.

Pregnancy: Teratogenic effects: Pregnancy Category C. Loteprednol etabonate has been shown to be embryotoxic (delayed ossification) and teratogenic (increased incidence of meningocele, abnormal left common carotid artery, and limb flexures) when administered orally to rabbits during organogenesis at a dose of 3 mg/kg/day (85 times the maximum daily clinical dose), a dose which caused no maternal toxicity. The no-observed-effect-level (NOEL) for these effects was 0.5 mg/kg/day (15 times the maximum daily clinical dose). Oral treatment of rats during organogenesis resulted in teratogenicity (absent innominate artery at ≥5mg/kg/day doses, and cleft palate and umbilical hernia at ≥50 mg/kg/day) and embryotoxicity (increased post-implantation losses at 100 mg/kg/day and decreased fetal body weight and skeletal ossification with ≥50 mg/kg/day). Treatment of rats with 0.5 mg/kg/day (15 times the maximum clinical dose) during organogenesis did not result in any reproductive toxicity. Loteprednol etabonate was maternally toxic (significantly reduced body weight gain during treatment) when administered to pregnant rats during organogenesis at doses of ≥5 mg/kg/day.

Oral exposure of female rats to 50 mg/kg/day of loteprednol etabonate from the start of the fetal period through the end of lactation, a maternally toxic treatment regimen (significantly decreased body weight gain), gave rise to decreased growth and survival, and retarded development in the offspring during lactation; the NOEL for these effects was 5 mg/kg/day. Loteprednol etabonate had no effect on the duration of gestation or parturition when administered orally to pregnant rats at doses up to 50 mg/kg/day during the fetal period.

Nursing Mothers: It is not known whether topical ophthalmic administration of corticosteroids could result in sufficient systemic absorption to produce detectable quantities in human milk. Systemic steroids appear in human milk and could suppress growth, interfere with endogenous corticosteroid production, or cause other untoward effects. Caution should be exercised when ALREX® is administered to a nursing woman.

Pediatric Use: Safety and effectiveness in pediatric patients have not been established.

ADVERSE REACTIONS:
Reactions associated with ophthalmic steroids include elevated intraocular pressure, 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.

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

Non-ocular adverse reactions occurred in less than 15% of patients. These include headache, rhinitis and pharyngitis.

In a summation of controlled, randomized studies of individuals treated for 28 days or longer with loteprednol etabonate, the incidence of significant elevation of intraocular pressure (≥10 mm Hg) 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. Among the smaller group of patients who were studied with ALREX®, the incidence of clinically significant increases in IOP (≥10 mm Hg) was 1% (1/133) with ALREX® and 1% (1/135) with placebo.

Manufactured by
Bausch & Lomb Pharmaceuticals, Inc., Tampa, Florida 33637
under Agreement with Pharmos Corporation.
U.S. Patent No. 4,996,335
U.S. Patent No. 5,540,930

REFERENCES

1. Dell SJ, Lowry GM, Northcutt JA, Howes J, Novack GD, Hart K. A randomized, double-masked, placebo-controlled parallel study of 0.2% loteprednol etabonate in patients with seasonal allergic conjunctivitis. *J Allergy Clin Immunol.* 1998;102:251-255.
2. Shulman DG, Lothringer LL, Rubin JM, et al. A randomized, double-masked, placebo-controlled parallel study of loteprednol etabonate 0.2% in patients with seasonal allergic conjunctivitis. *Ophthalmology.* 1999;106:362-369.
3. Data on file, Bausch & Lomb Pharmaceuticals, Inc.

PH# 1498

BAUSCH & LOMB

POWERFUL RELIEF
of the Whole Symptom Complex

- Clinically and statistically significant relief of itching and redness within 2 hours[1,2]
- Physicians' Global Assessments significantly favored ALREX®[2]*

80% Of 65 patients on ALREX® fully or reasonably controlled vs baseline ($P<0.001$)[2]

40% Of 66 patients on placebo fully or reasonably controlled vs baseline ($P<0.001$)[2]

*Physicians' Global Assessments used a 5-point scale (0 to 4), where 0=fully controlled; 1=reasonably controlled; 2=slight improvement; 3=unchanged; and 4=worse.

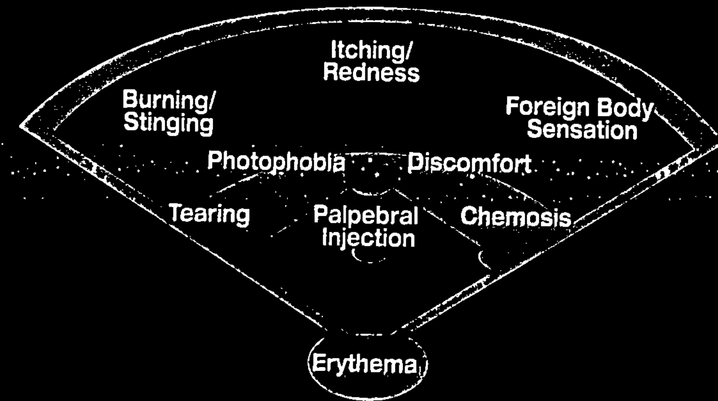
ONLY ALREX® scores against all the signs and all the symptoms of seasonal allergic conjunctivitis†

Alrex®

	Itching	Redness	Burning/ Stinging	Foreign Body Sensation	Tearing	Photophobia	Discomfort	Chemosis	Palpebral Injection	Erythema	TOTAL SCORE
ALREX® (loteprednol etabonate ophthalmic suspension, 0.2%)	1	1	1	1	1	1	1	1	1	1	10
Acular® (ketorolac tromethamine ophthalmic solution, 0.5%)	1	0	0	0	0	0	0	0	0	0	1
Alocril™ (nedocromil sodium ophthalmic solution, 2%)	1	0	0	0	0	0	0	0	0	0	1
Patanol® (olopatadine hydrochloride ophthalmic solution, 0.1%)	1	0	0	0	0	0	0	0	0	0	1
Zaditor™ (ketotifen fumarate ophthalmic solution, 0.025%)	1	0	0	0	0	0	0	0	0	0	1

†Based on the approved indications for each product.[3]

- ALREX® was favored over placebo for all of the following outcome measures[1,2]



- Corticosteroid strength with minimal risk of IOP rise[1]
  — In two well-controlled, 6-week, clinical trials, <1% of patients (n=1/133) had clinically significant† IOP rise — same as placebo (n=1/135)[1]

† Clinically significant IOP rise ... ≥10 mm Hg.

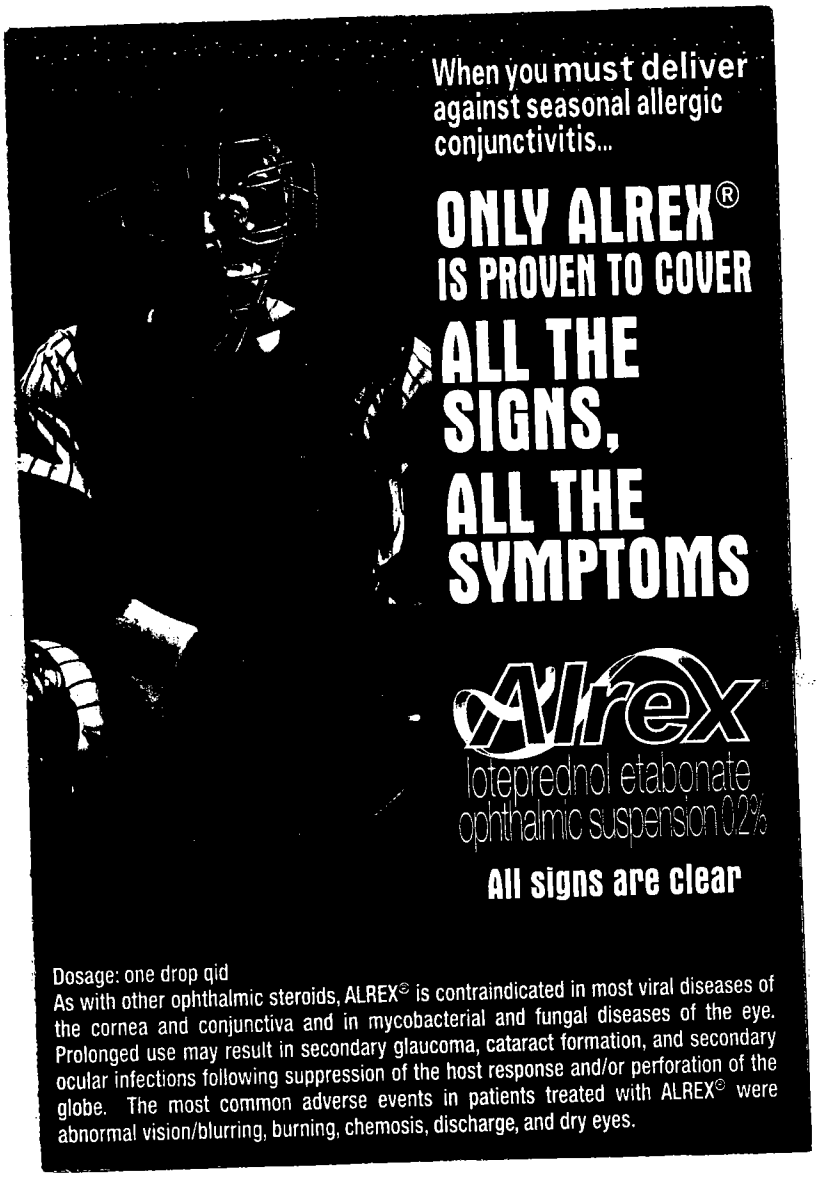
Dosage: one drop qid

As with other ophthalmic steroids, ALREX® is contraindicated in most viral diseases of the cornea and conjunctiva and in mycobacterial and fungal diseases of the eye. Prolonged use may result in secondary glaucoma, cataract formation, and secondary ocular infections following suppression of the host response and/or perforation of the globe. The most common adverse events in patients treated with ALREX® were abnormal vision/blurring, burning, chemosis, discharge, and dry eyes.

Alrex®
loteprednol etabonate ophthalmic suspension 0.2%

All signs are clear

PLEASE SEE ENCLOSED BRIEF SUMMARY OF PRESCRIBING INFORMATION.


When you must deliver against seasonal allergic conjunctivitis...
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IS PROVEN TO COVER
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Alrex
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ophthalmic suspension 0.2%
All signs are clear
Dosage: one drop qid
As with other ophthalmic steroids, ALREX© is contraindicated in most viral diseases of the cornea and conjunctiva and in mycobacterial and fungal diseases of the eye. Prolonged use may result in secondary glaucoma, cataract formation, and secondary ocular infections following suppression of the host response and/or perforation of the globe. The most common adverse events in patients treated with ALREX© were abnormal vision/blurring, burning, chemosis, discharge, and dry eyes.

ONLY ALREX® scores against all the signs and all the symptoms of seasonal allergic conjunctivitis†

	Itching	Redness	Burning/ Stinging	Foreign Body Sensation	Tearing	Photophobia	Discomfort	Chemosis	Palpebral Injection	Erythema	TOTAL SCORE
ALREX® (loteprednol etabonate ophthalmic suspension, 0.2%)	1	1	1	1	1	1	1	1	1	1	10
Acular™ (ketorolac tromethamine ophthalmic solution, 0.5%)	1	0	0	0	0	0	0	0	0	0	1
Alocril™ (nedocromil sodium ophthalmic solution, 2%)	1	0	0	0	0	0	0	0	0	0	1
Patanol™ (olopatadine hydrochloride ophthalmic solution, 0.1%)	1	0	0	0	0	0	0	0	0	0	1
Zaditor™ (ketotifen fumarate ophthalmic solution, 0.025%)	1	0	0	0	0	0	0	0	0	0	1

†Based on the approved indications for each product.

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Pharmaceuticals

PH1522 REV. 01/00.2