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 (SEE WARNINGS).

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: Patients should be advised not to allow the dropper tip to touch any surface, as this may contaminate the suspension. If pain develops, redness, itching or inflammation becomes aggravated, the patient should be advised to consult a physician. As with all ophthalmic preparations containing benzalkonium chloride, patients should be advised not to wear soft contact lenses when using LOTEMAX™.

Carcinogenesis, Mutagenesis, and Impairment of Fertility: Loteprednol etabonate was shown to be non-mutagenic in a series of *in vivo* and *in vitro* studies. Fertility was not affected in one study in rats using doses up to 40 times the human topical dose in males and 20 times the human topical dose in females. No studies have been conducted to evaluate the possibility of carcinogenicity with loteprednol etabonate.

Pregnancy: Pregnancy Category C. Loteprednol etabonate has been shown to be ~~weakly~~ teratogenic in rabbits when administered orally on days 6 to 18 of gestation in doses of up to ➔30 times the human topical dose (3 mg/kg/day). Fetal abnormalities included meningocele, abnormal left common carotid artery and limb flexures. There are no adequate and well controlled studies in pregnant women. LOTEMAX should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

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 ~~which~~ could suppress growth, interfere with endogenous corticosteroid production, or cause other untoward effects. Caution should be exercised when LOTEMAX 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 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 1.7% (14/823) among patients receiving loteprednol etabonate, 6.3% among patients receiving 1% prednisolone acetate (5/79) and 0.5% among patients receiving placebo (3/583).

DOSAGE AND ADMINISTRATION:

SHAKE WELL BEFORE USING.

Post-Operative Inflammation:
Apply one to two drops of LOTEMAX into the conjunctival sac of the affected eye(s) four times daily beginning 24 hours after surgery and continuing throughout the first 2 weeks of the postoperative period.

Giant Papillary Conjunctivitis:
Apply one to two drops of LOTEMAX into the conjunctival sac of the affected eye(s) four times daily for up to six weeks. Contact lenses should be discontinued for at least the first 48 hours of treatment with LOTEMAX. After the first 48 hours, patients should wait at least 10 minutes after dosing LOTEMAX to re-insert contact lenses. If no improvement after two weeks, consult physician. Care should be taken not to discontinue therapy prematurely.

HOW SUPPLIED:
LOTEMAX™ (loteprednol etabonate ophthalmic suspension) is supplied in a plastic bottle with a controlled drop tip in the following sizes:

2.5 mL	(NDC 24208-299-25) - AB29904
5 mL	(NDC 24208-299-05) - AB29907
10 mL	(NDC 24208-299-10) - AB29909
15 mL	(NDC 24208-299-15) - AB29911

DO NOT USE IF NECKBAND IMPRINTED WITH ??? IS NOT INTACT.

Storage: Store upright between 15° - 25°C (59° - 77°F). DO NOT FREEZE.

KEEP OUT OF REACH OF CHILDREN.

Caution: Federal law prohibits dispensing without prescription.

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

 XO50317 Rev. 3/97-7C

12 Conclusions

a. The submitted studies in NDA 20-583 demonstrate safety and efficacy for the treatment of giant papillary conjunctivitis.

b. The submitted studies in NDA 20-583 demonstrate less effectiveness than prednisolone acetate in the treatment of uveitis.

c. The submitted studies in NDA 20-841 demonstrate safety and effectiveness for the treatment of post-cataract inflammation.

13 Recommendations

1. Following resolution of the chemistry/manufacturing issues and labeling issues, NDA 20-583 is recommended for approval for the treatment of giant papillary conjunctivitis and post-operative inflammation following cataract surgery. Approval for the steroid class indication is **not recommended**, unless it is accompanied by clear statements that the product is not as effective as other steroids (prednisolone acetate suspension, 1%) and that patients in whom a stronger steroid is needed should not use this product.

2. The applicant should submit revised labeling consistent with the recommendations in this review.

3. Issues related to water loss and the formation of "aggregate" material after storage of inverted containers will need to be resolved prior to approval.
   A. What is the aggregate composed of?
   B. Does the aggregate recombine with the suspension on shaking? If so, how quickly?
   C. Can the aggregate be cleared by dispensing a couple of drops of the suspension? If so, does this affect the composition of the rest of the suspension?

4. Issues related to sterility testing will need to be resolved prior to approval.

Wiley A. Chambers, M.D.
Medical Officer, Ophthalmology

cc: NDA 20-583
NDA 20-841
HFD-550
HFD-340/Carreras
HFD-550/PM/Holmes
HFD-830/CHEM/Fenselau
HFD-805/MICRO/Cooney
HFD-550/PHARM/Weir
HFD-550/MO/Chambers

Medical Officer's Review of NDA 20-583
Amendment

NDA #20-583	Telecons:	8/20/97 & 8/22/97
M.O. Review #3	Review completed:	8/21/97
	Revised:	8/22/97

Generic name: Loteprednol etabonate ophthalmic suspension, 0.5%
Proposed trade name: Lotemax
Chemical name: Chloromethyl-17α-[(ethoxycarbonyl-oxy]-11ß-hydroxy-3-oxoandrosta-1,4-diene-17 carboxylate

Sponsor: Pharmos Corporation
2 Innovation Drive, Suite A
Alachua, FL 32615

Pharmacologic Category: Steroid

Proposed Indication(s): Treatment of steroid responsive inflammatory conditions of the palpebral and bulbar conjunctiva, cornea and anterior segment of the eye.

Dosage Form and Route of Administration: Ophthalmic suspension for topical ocular administration

NDA Drug Classification: 1S

Labeling Review

Reviewer recommended additions are identified by shading. Reviewer recommended additions are identified by redlining and deletions are identified by ~~a strikeout line~~. This review incorporates requested indications from NDA 20-583 as well as those from NDA 20-841.

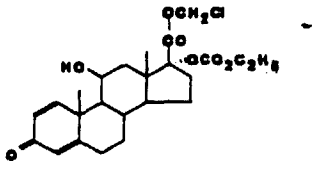
This review is based on discussions with the applicant on 8/20/97 and 8/22/97, with the understanding that the Office of Drug Evaluation V has not yet commented on the labeling and will have the final authority over the labeling.

LOTEMAX™
loteprednol etabonate ophthalmic suspension, 0.5%

STERILE OPHTHALMIC SUSPENSION

DESCRIPTION:
LOTEMAX™ (loteprednol etabonate ophthalmic suspension) contains a sterile, topical anti-inflammatory corticosteroid for ophthalmic use. Loteprednol etabonate is a white to off-white powder.

Loteprednol etabonate is represented by the following structural formula:



$C_{24}H_{31}ClO_7$ Mol. Wt. 466.96

Chemical name: chloromethyl 17α-[(ethoxycarbonyl)oxy]-11β-hydroxy-3-oxoandrosta-1,4-diene-17β-carboxylate

Each mL contains: ACTIVE: Loteprednol Etabonate 5 mg (0.5%);
INACTIVES: Glycerin, Povidone, Tyloxapol, Edetate Disodium, and Purified Water. Hydrochloric Acid and/or Sodium Hydroxide may be added to adjust the pH to 5.3-5.6. The suspension is essentially isotonic with a tonicity of 250 to 310.
PRESERVATIVE ADDED: Benzalkonium Chloride 0.01%.

CLINICAL PHARMACOLOGY:
Corticosteroids inhibit the inflammatory response to a variety of inciting agents and probably delay or slow healing. They inhibit the edema, fibrin deposition, capillary dilation, leukocyte migration, capillary proliferation, fibroblast proliferation, deposition of collagen, and scar formation associated with inflammation. There is no generally accepted explanation for the mechanism of action of ocular corticosteroids. However, corticosteroids are thought to act by the induction of phospholipase A_2 inhibitory proteins, collectively called lipocortins. It is postulated that these proteins control the biosynthesis of potent mediators of inflammation such as prostaglandins and leukotrienes by inhibiting the release of their common precursor arachidonic acid. Arachidonic acid is released from membrane phospholipids by phospholipase A_2. Corticosteroids are capable of producing a rise in intraocular pressure.

Loteprednol etabonate is structurally similar to other corticosteroids. However, the number 20 position ketone group is absent and it is synthesized through structural modifications of prednisolone-related compounds so that it will undergo a predictable transformation to an inactive metabolite. It is highly lipid soluble which enhances its penetration into cells. Therefore, loteprednol etabonate is designed to exert its effects and be hydrolyzed to an inactive metabolite. Based upon *in vivo* and *in vitro* preclinical metabolism studies, loteprednol etabonate undergoes extensive metabolism to inactive carboxylic acid metabolites.

Results from a bioavailability study in normal volunteers established that plasma levels of loteprednol etabonate and Δ^1 cortienic acid etabonate (PJ 91), its primary, inactive metabolite, were below the limit of quantitation (1 ng/mL) at all sampling times. The results were obtained following the ocular administration of one drop in each eye of 0.5% loteprednol etabonate 8 times daily for 2 days or 4 times daily for 42 days. This study suggests that limited (<1 ng/mL) systemic absorption occurs with LOTEMAX ~~Ophthalmic Suspension~~.

Clinical Studies:

Post-operative Inflammation:

Placebo-controlled clinical studies demonstrated that LOTEMAX is effective for the treatment of anterior chamber inflammation as measured by cell and flare.

Uveitis:

Controlled clinical studies of patients with uveitis demonstrated that LOTEMAX was less effective than prednisolone acetate 1%. Overall, 72% of patients treated with LOTEMAX experienced resolution of anterior chamber cell by day 28, compared to 87% of patients treated with 1% prednisolone acetate. The incidence of patients with clinically significant increases in IOP (≥10mmHg) was 1% with LOTEMAX and 6% with 1% prednisolone acetate.

Giant Papillary Conjunctivitis:

Placebo controlled clinical studies demonstrated that LOTEMAX was effective in reducing the signs and symptoms of giant papillary conjunctivitis after 1 week of treatment and continuing for up to 6 weeks.

Seasonal Allergic Conjunctivitis: A placebo controlled clinical study demonstrated that LOTEMAX was ~~more~~ effective in reducing the signs and symptoms of allergic conjunctivitis during peak periods of pollen exposure.

INDICATIONS AND USAGE:
LOTEMAX is indicated for the treatment of steroid responsive inflammatory conditions of the palpebral and bulbar conjunctiva, cornea, and anterior segment of the globe such as allergic conjunctivitis, acne rosacea, superficial punctate keratitis, herpes zoster keratitis, iritis, cyclitis, selected infective conjunctivitides, when the inherent hazard of steriod use is accepted to obtain an advisable diminution in edema and inflammation.

LOTEMAX is less effective than another agent in the treatment of uveitic inflammation and should not be used in patients who require a more potent corticosteroid for ~~their~~this inflammatory condition (see Clinical Pharmacology).

LOTEMAX is also indicated for the treatment of post-operative inflammation following ocular surgery.

CONTRAINDICATIONS:
LOTEMAX, 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. LOTEMAX 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.

The use of steroids after cataract surgery may delay healing and increase the incidence of bleb formation.

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 even though it may be difficult in children and uncooperative patients (see WARNINGS).

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 pain develops, redness, itching or inflammation becomes aggravated, the patient should be advised to consult a physician. As with all ophthalmic preparations containing benzalkonium chloride, patients should be advised not to wear soft contact lenses when using LOTEMAX™.

Carcinogenesis, Mutagenesis, and Impairment of Fertility: Loteprednol etabonate was shown to be non-mutagenic in a series of *in vivo* and *in vitro* studies. Fertility was not affected in one study in rats using doses up to 40 times the human topical dose in males and 20 times the human topical dose in females. No studies have been conducted to evaluate the possibility of carcinogenicity with loteprednol etabonate.

Pregnancy: Teratogenic effects: Pregnancy Category C. Loteprednol etabonate has been shown to be teratogenic in rabbits when administered orally on days 6 to 18 of gestation in doses of up to 30 times the human topical dose (3 mg/kg/day). Fetal abnormalities included meningocele, abnormal left common carotid artery and limb flexures. There are no adequate and well controlled studies in pregnant women.

LOTEMAX should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

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 LOTEMAX 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 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

DOSAGE AND ADMINISTRATION:

SHAKE WELL BEFORE USING.

Steroid Responsive Disease Treatment: Apply one to two drops of LOTEMAX into the conjunctival sac of the affect eye(s) four times daily. During the initial treatment within the first week, the dosing may be increased, up to 1 drop every hour, if necessary. Care should be taken not to discontinue therapy prematurely. If signs and symptoms fail to improve after two days, the patient should be re-evaluated (See PRECAUTIONS).

Post-Operative Inflammation:
Apply one to two drops of LOTEMAX into the conjunctival sac of the affected eye(s) four times daily beginning 24 hours after surgery and continuing throughout the first 2 weeks of the postoperative period.

HOW SUPPLIED:
LOTEMAX™ (loteprednol etabonate ophthalmic suspension) is supplied in a plastic bottle with a controlled drop tip in the following sizes:

2.5 mL	(NDC 24208-299-25) - AB29904
5 mL	(NDC 24208-299-05) - AB29907
10 mL	(NDC 24208-299-10) - AB29909
15 mL	(NDC 24208-299-15) - AB29911

DO NOT USE IF NECKBAND IMPRINTED WITH "Protective Seal" and yellow mortar and pestle IS NOT INTACT.

Storage: Store upright between 15° - 25°C (59° - 77°F). DO NOT FREEZE.

KEEP OUT OF REACH OF CHILDREN.

Caution: Federal law prohibits dispensing without prescription.

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

 XO50317 Rev. 3/97-7C

12 Conclusions

a. The submitted studies in NDA 20-583 demonstrate safety and efficacy for the treatment of giant papillary conjunctivitis.

b. The submitted studies in NDA 20-583 demonstrate less effectiveness than prednisolone acetate in the treatment of uveitis.

c. The submitted studies in NDA 20-841 demonstrate safety and effectiveness for the treatment of post-cataract inflammation.

13 Recommendations

1. Following resolution of the chemistry/manufacturing issues and labeling issues, NDA 20-583 is recommended for approval for the treatment of giant papillary conjunctivitis and post-operative inflammation following cataract surgery. Approval for the steroid class indication is **not recommended**, unless it is accompanied by clear statements that the product is not as effective as other steroids (prednisolone acetate suspension, 1%) and that patients in whom a stronger steroid is needed should not use this product.

2. The applicant should submit revised labeling consistent with the recommendations in this review.

3. Issues related to water loss and the formation of "aggregate" material after storage of inverted containers will need to be resolved prior to approval.
   A. What is the aggregate composed of?
   B. Does the aggregate recombine with the suspension on shaking? If so, how quickly?
   C. Can the aggregate be cleared by dispensing a couple of drops of the suspension? If so, does this affect the composition of the rest of the suspension?

4. Issues related to sterility testing will need to be resolved prior to approval.

MO
Wiley A. Chambers, M.D.
Medical Officer, Ophthalmology

cc: NDA 20-583
NDA 20-841
HFD-550
HFD-550/PM/Holmes
HFD-830/CHEM/Fenselau
HFD-805/MICRO/Cooney
HFD-550/PHARM/Weir
HFD-550/MO/Chambers

550
Lotemax

FEB 5 1998

Medical Officer's Review of NDA 20-583
Amendment

NDA #20-583
NDA #20-841
M.O. Review #4

Submit Date: 1/21/98
Review completed: 2/ 5/98

Generic name:	Loteprednol etabonate ophthalmic suspension, 0.5%
Proposed trade name:	Lotemax
Chemical name:	Chloromethyl-17α-[(ethoxycarbonyl-oxy]-11ß-hydroxy-3-oxoandrosta-1,4-diene-17 carboxylate
Sponsor:	Pharmos Corporation 33 Wood Ave, South, Suite 466 Iselin, NJ 08830
Agent:	Bausch & Lomb Pharmaceuticals 8500 Hidden River Parkway Tampa, FL 33637 (813) 975-7727
Pharmacologic Category:	Steroid
Proposed Indication(s):	Treatment of steroid responsive inflammatory conditions of the palpebral and bulbar conjunctiva, cornea and anterior segment of the eye.
Dosage Form and Route of Administration:	Ophthalmic suspension for topical ocular administration
NDA Drug Classification:	1S

Labeling Review

Reviewer recommended additions are identified by shading. Reviewer recommended additions are identified by redlining and deletions are identified by ~~a strikeout line.~~ This review incorporates requested indications from NDA 20-583 as well as those from NDA 20-841.

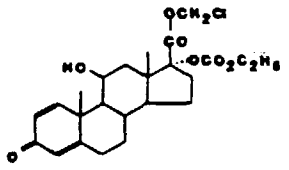
This review is based on discussions with the applicant, with the understanding that the Office of Drug Evaluation V has not yet commented on the labeling and will have the final authority over the labeling.

LOTEMAX™
loteprednol etabonate ophthalmic suspension, 0.5%

STERILE OPHTHALMIC SUSPENSION

DESCRIPTION:
LOTEMAX™ (loteprednol etabonate ophthalmic suspension) contains a sterile, topical anti-inflammatory corticosteroid for ophthalmic use. Loteprednol etabonate is a white to off-white powder.

Loteprednol etabonate is represented by the following structural formula:



$C_{24}H_{31}ClO_7$ Mol. Wt. 466.96

Chemical name: chloromethyl 17α-[(ethoxycarbonyl)oxy]-11β-hydroxy-3-oxoandrosta-1,4-diene-17β-carboxylate

Each mL contains:
ACTIVE: Loteprednol Etabonate 5 mg (0.5%);
INACTIVES: Glycerin, Povidone, Tyloxapol, Edetate Disodium and Purified Water. Hydrochloric Acid and/or Sodium Hydroxide may be added to adjust the pH to 5.3-5.6. The suspension is essentially isotonic with a tonicity of 250 to 310 mOsmol/kg.
PRESERVATIVE ADDED: Benzalkonium Chloride 0.01%.

CLINICAL PHARMACOLOGY:
Corticosteroids inhibit the inflammatory response to a variety of inciting agents and probably delay or slow healing. They inhibit the edema, fibrin deposition, capillary dilation, leukocyte migration, capillary proliferation, fibroblast proliferation, deposition of collagen, and scar formation associated with inflammation. There is no generally accepted explanation for the mechanism of action of ocular corticosteroids. However, corticosteroids are thought to act by the induction of phospholipase A_2 inhibitory proteins, collectively called lipocortins. It is postulated that these proteins control the biosynthesis of potent mediators of inflammation such as prostaglandins and leukotrienes by inhibiting the release of their common precursor arachidonic acid. Arachidonic acid is released from membrane phospholipids by phospholipase A_2. Corticosteroids are capable of producing a rise in ifitraocular pressure.

Loteprednol etabonate is structurally similar to other corticosteroids. However, the number 20 position ketone group is absent. It is highly lipid soluble which enhances its penetration into cells. Loteprednol etabonate is synthesized through structural modifications of prednisolone-related compounds so that it will undergo a predictable transformation to an inactive metabolite. Based upon *in vivo* and *in vitro* preclinical metabolism studies, loteprednol etabonate undergoes extensive metabolism to inactive carboxylic acid metabolites.

Results from a bioavailability study in normal volunteers established that plasma levels of loteprednol etabonate and Δ^1 cortienic acid etabonate (PJ 91), its primary, inactive metabolite, were below the limit of quantitation (1 ng/mL) at all sampling times. The results were obtained following the ocular administration of one drop in each eye of 0.5% loteprednol etabonate 8 times daily for 2 days or 4 times daily for 42 days. This study suggests that limited (<1 ng/mL) systemic absorption occurs with LOTEMAX.

Clinical Studies:

Post-operative Inflammation: Placebo-controlled clinical studies demonstrated that LOTEMAX is effective for the treatment of anterior chamber inflammation as measured by cell and flare.

Uveitis: Controlled clinical studies of patients with uveitis demonstrated that LOTEMAX was less effective than prednisolone acetate 1%. Overall, 72% of patients treated with LOTEMAX experienced resolution of anterior chamber cell by day 28, compared to 87% of patients treated with 1% prednisolone acetate. The incidence of patients with clinically significant increases in IOP (≥10mmHg) was 1% with LOTEMAX and 6% with 1% prednisolone acetate.

Giant Papillary Conjunctivitis:

Placebo controlled clinical studies demonstrated that LOTEMAX was effective in reducing the signs and symptoms of giant papillary conjunctivitis after 1 week of treatment and continuing for up to 6 weeks while on treatment.

Seasonal Allergic Conjunctivitis: A placebo controlled clinical study demonstrated that LOTEMAX was effective in reducing the signs and symptoms of allergic conjunctivitis during peak periods of pollen exposure.

INDICATIONS AND USAGE:
LOTEMAX is indicated for the treatment of steroid responsive inflammatory conditions of the palpebral and bulbar conjunctiva, cornea, and anterior segment of the globe such as allergic conjunctivitis, acne rosacea, superficial punctate keratitis, herpes zoster keratitis, iritis, cyclitis, selected infective conjunctivitides, when the inherent hazard of steriod use is accepted to obtain an advisable diminution in edema and inflammation.

LOTEMAX is less effective than prednisolone acetate 1% in two 28-day controlled clinical studies in acute anterior uveitis, where 72% of patients with LOTEMAX experienced resolution of anterior chamber cells, compared to 87% of patients treated with prednisolone acetate 1%. The incidence of patients with clinically significant increases in IOP (≥10 mmHg) was 1% with LOTEMAX and 6% with prednisolone acetate 1%. LOTEMAX should not be used in patients who require a more potent corticosteroid for this indication.

LOTEMAX is also indicated for the treatment of post-operative inflammation following ocular surgery.

CONTRAINDICATIONS:
LOTEMAX, 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. LOTEMAX 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.

The use of steroids after cataract surgery may delay healing and increase the incidence of bleb formation.

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 even though it may be difficult in children and uncooperative patients (see WARNINGS).

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 pain develops, redness, itching or inflammation becomes aggravated, the patient should be advised to consult a physician. As with all ophthalmic preparations containing benzalkonium chloride, patients should be advised not to wear soft contact lenses when using LOTEMAX™.

Carcinogenesis, Mutagenesis, and Impairment of Fertility: Loteprednol etabonate was shown to be non-mutagenic in a series of *in vivo* and *in vitro* studies. Fertility was not affected in one study in rats using doses up to 40 times the human topical dose in males and 20 times the human topical dose in females. No studies have been conducted to evaluate the possibility of carcinogenicity with loteprednol etabonate.

Pregnancy: Teratogenic effects: Pregnancy Category C. Loteprednol etabonate has been shown to be teratogenic in rabbits when administered orally on days 6 to 18 of gestation in doses of up to 30 times the human topical dose (3 mg/kg/day). Fetal abnormalities included meningocele, abnormal left common carotid artery and limb flexures. There are no adequate and well controlled studies in pregnant women. LOTEMAX should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

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 LOTEMAX 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 controlled, randomized studies of individuals treated for 28 days or longer with loteprednol etabonate, the incidence of significant elevation of intraocular pressure ($\geq$ 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.

DOSAGE AND ADMINISTRATION:
SHAKE VIGOROUSLY BEFORE USING.

Steroid Responsive Disease Treatment: Apply one to two drops of LOTEMAX into the conjunctival sac of the affect eye(s) four times daily. During the initial treatment within the first week, the dosing may be increased, up to 1 drop every hour, if necessary. Care should be taken not to discontinue therapy prematurely. If signs and symptoms fail to improve after two days, the patient should be re-evaluated (See PRECAUTIONS).

Post-Operative Inflammation:
Apply one to two drops of LOTEMAX into the conjunctival sac of the operated eye(s) four times daily beginning 24 hours after surgery and continuing throughout the first 2 weeks of the postoperative period.

HOW SUPPLIED:
LOTEMAX™ (loteprednol etabonate ophthalmic suspension) is supplied in a plastic bottle with a controlled drop tip in the following sizes:

2.5 mL	(NDC 24208-299-25) - AB29904
5 mL	(NDC 24208-299-05) - AB29907
10 mL	(NDC 24208-299-10) - AB29909
15 mL	(NDC 24208-299-15) - AB29911

DO NOT USE IF NECKBAND IMPRINTED WITH "Protective Seal" and YELLOW *(mortar and pestle graphic)* IS NOT INTACT.

Storage: Store upright between 15° - 25°C (59° - 77°F). DO NOT FREEZE.

KEEP OUT OF REACH OF CHILDREN.

Caution: Federal law prohibits dispensing without prescription.

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

XO50317 (Folded)
XM10039 (Flat)
Rev. 12/97-7L

APPEARS THIS WAY
ON ORIGINAL

13 **Recommendations**

NDAs 20-583 and 20-841 are recommended for approval for the treatment of steroid responsive disease and inflammation following cataract surgery with the labeling identified in this review. Approval for the steroid class indication is recommended, only with the language included in the above proposed labeling that the product is not as effective as prednisolone acetate suspension, 1% and that patients in whom a stronger steroid is needed should not use this product.

Wiley A. Chambers, M.D.
Medical Officer, Ophthalmology

cc: NDA 20-583
NDA 20-841
HFD-550
HFD-550/PM/LoBianco
HFD-830/CHEM/Fenselau
HFD-805/MICRO/Cooney
HFD-550/PHARM/Weir
HFD-550/MO/Chambers

APPEARS THIS WAY
ON ORIGINAL

Medical Officer's Review of NDA 20-583 & 20-841
Amendment

NDA #20-583
NDA #20-841
M.O. Review #5

Submit Dates: 12/10&11/97, 1/14&21/98
Review completed: 2/23/98

Generic name: Loteprednol etabonate ophthalmic suspension, 0.5%
Proposed trademark: Lotemax

Sponsor: Pharmos Corporation
33 Wood Ave, South, Suite 466
Iselin, NJ 08830

Agent: Bausch & Lomb Pharmaceuticals
8500 Hidden River Parkway
Tampa, FL 33637
(813) 975-7727

Pharmacologic Category: Steroid

Proposed Indication(s): Treatment of steroid responsive inflammatory conditions of the palpebral and bulbar conjunctiva, cornea and anterior segment of the eye.

Dosage Form and Route of Administration: Ophthalmic suspension for topical ocular administration

NDA Drug Classification: 1S

Labeling Review

Reviewer recommended additions are identified by shading. Reviewer recommended additions are identified by underlining and deletions are identified by ~~a strikeout line.~~ This review incorporates requested indications from NDA 20-583 as well as those from NDA 20-841.

This review is based on discussions with the applicant, with the understanding that the Office of Drug Evaluation V has not yet commented on the labeling and will have the final authority over the labeling.

Related Reviews: Pharm/Tox Review dated 4/25/97
Chemistry/Manufacturing Review dated 2/98

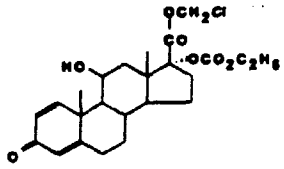
Labeling:

LOTEMAX™
loteprednol etabonate ophthalmic suspension, 0.5%

STERILE OPHTHALMIC SUSPENSION

DESCRIPTION:
LOTEMAX™ (loteprednol etabonate ophthalmic suspension) contains a sterile, topical anti-inflammatory corticosteroid for ophthalmic use. Loteprednol etabonate is a white to off-white powder.

Loteprednol etabonate is represented by the following structural formula:



$C_{24}H_{31}ClO_7$ Mol. Wt. 466.96

Chemical name: chloromethyl 17α-[(ethoxycarbonyl)oxy]-11β-hydroxy-3-oxoandrosta-1,4-diene-17β-carboxylate

Each mL contains:
ACTIVE: Loteprednol Etabonate 5 mg (0.5%);
INACTIVES: Glycerin, Povidone, Tyloxapol, Edetate Disodium and Purified Water. Hydrochloric Acid and/or Sodium Hydroxide may be added to adjust the pH to 5.3-5.6. The suspension is essentially isotonic with a tonicity of 250 to 310 mOsmol/kg.
PRESERVATIVE ADDED: Benzalkonium Chloride 0.01%.

CLINICAL PHARMACOLOGY:
Corticosteroids inhibit the inflammatory response to a variety of inciting agents and probably delay or slow healing. They inhibit the edema, fibrin deposition, capillary dilation, leukocyte migration, capillary proliferation, fibroblast proliferation, deposition of collagen, and scar formation associated with inflammation. There is no generally accepted explanation for the mechanism of action of ocular corticosteroids. However, corticosteroids are thought to act by the induction of phospholipase A_2 inhibitory proteins, collectively called lipocortins. It is postulated that these proteins control the biosynthesis of potent mediators of inflammation such as prostaglandins and leukotrienes by inhibiting the release of their common precursor arachidonic acid. Arachidonic acid is released from membrane phospholipids by phospholipase A_2. Corticosteroids are capable of producing a rise in intraocular pressure.

Loteprednol etabonate is structurally similar to other corticosteroids. However, the number 20 position ketone group is absent. It is highly lipid soluble which enhances its penetration into cells. Loteprednol etabonate is synthesized through structural modifications of prednisolone-related compounds so that it will undergo a predictable transformation to an inactive metabolite. Based upon *in vivo* and *in vitro* preclinical metabolism studies, loteprednol etabonate undergoes extensive metabolism to inactive carboxylic acid metabolites.

Results from a bioavailability study in normal volunteers established that plasma levels of loteprednol etabonate and Δ^1 cortienic acid etabonate (PJ 91), its primary, inactive metabolite, were below the limit of quantitation (1 ng/mL) at all sampling times. The results were obtained following the ocular administration of one drop in each eye of 0.5% loteprednol etabonate 8 times daily for 2 days or 4 times daily for 42 days. This study suggests that limited (<1 ng/mL) systemic absorption occurs with LOTEMAX.

Clinical Studies:

Post-operative Inflammation: Placebo-controlled clinical studies demonstrated that LOTEMAX is effective for the treatment of anterior chamber inflammation as measured by cell and flare.

Uveitis: Controlled clinical studies of patients with uveitis demonstrated that LOTEMAX was less effective than prednisolone acetate 1%. Overall, 72% of patients treated with LOTEMAX experienced resolution of anterior chamber cell by day 28, compared to 87% of patients treated with 1% prednisolone acetate. The incidence of patients with clinically significant increases in IOP (≥10mmHg) was 1% with LOTEMAX and 6% with prednisolone acetate 1%.

Giant Papillary Conjunctivitis:

Placebo controlled clinical studies demonstrated that LOTEMAX was effective in reducing the signs and symptoms of giant papillary conjunctivitis after 1 week of treatment and continuing for up to 6 weeks while on treatment.

Seasonal Allergic Conjunctivitis: A placebo controlled clinical study demonstrated that LOTEMAX was effective in reducing the signs and symptoms of allergic conjunctivitis during peak periods of pollen exposure.

INDICATIONS AND USAGE:
LOTEMAX is indicated for the treatment of steroid responsive inflammatory conditions of the palpebral and bulbar conjunctiva, cornea, and anterior segment of the globe such as allergic conjunctivitis, acne rosacea, superficial punctate keratitis, herpes zoster keratitis, iritis, cyclitis, selected infective conjunctivitides, when the inherent hazard of steriod use is accepted to obtain an advisable diminution in edema and inflammation.

LOTEMAX was less effective than prednisolone acetate 1% in two 28-day controlled clinical studies in acute anterior uveitis, where 72% of patients with LOTEMAX experienced resolution of anterior chamber cells, compared to 87% of patients treated with prednisolone acetate 1%. The incidence of patients with clinically significant increases in IOP (≥10 mmHg) was 1% with LOTEMAX and 6% with prednisolone acetate 1%. LOTEMAX should not be used in patients who require a more potent corticosteroid for this indication.

LOTEMAX is also indicated for the treatment of post-operative inflammation following ocular surgery.

CONTRAINDICATIONS:
LOTEMAX, 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. LOTEMAX 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.

The use of steroids after cataract surgery may delay healing and increase the incidence of bleb formation.

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 even though it may be difficult in children and uncooperative patients (see WARNINGS).

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 pain develops, redness, itching or inflammation becomes aggravated, the patient should be advised to consult a physician. As with all ophthalmic preparations containing benzalkonium chloride, patients should be advised not to wear soft contact lenses when using LOTEMAX™.

Reviewer's Comments:

The following comments are from the Pharm/Tox review. This reviewer concurs with the Pharm/Tox review with the exception that the more appropriate comparison to human dosing is a comparison on the basis of mg/kg/day.

"During my review of the genotoxicity studies, I noted deficiencies in the Ames and mouse lymphoma L5178Y tests. The Ames assay was conducted one time, and the results were negative. Negative results should be verified by a repeat assay; however, the

sponsor did not repeat the Ames assay. In the case of the mouse lymphoma assay, negative results were obtained for the first assay. Although the sponsor repeated this assay to confirm the negative results, the second assay was unacceptable due to an inadequate response in the positive controls. Although the Ames and mouse lymphoma assays are deficient, the fact that negative results were obtained in both lends additional support to the sponsor's claim that loteprednol etabonate is nongenotoxic.

These recommendations for labeling apply to NDA 20-583 also."

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 the Ames test, the mouse lymphoma tk assay, or in a chromosome aberration test in human lymphocytes, three *in vitro* tests. *In vivo* evidence of genotoxicity, an increased frequency of micronucleated immature erythrocytes, was not observed in mice that received a single 4 gm/kg dose of loteprednol etabonate (50,000 times the maximum daily clinical dose). Treatment of male and female rats with up to 50 mg/kg/day and 25 mg/kg/day of loteprednol etabonate, respectively, (600 and 300 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 (35 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 (6 times the maximum daily clinical dose). Oral treatment of rats during organogenesis with 50 or 100 mg/kg/day (600 and 1,200 times the maximum clinical dose) resulted in embryotoxicity (increased post-implantation losses with 100 mg/kg/day, and decreased fetal body weight and skeletal ossification with 50 and 100 mg/kg/day); doses of 5 (60 times the maximum daily clinical dose), 50 and 100 mg/kg/day caused teratogenicity (absent innominate artery at all doses, and cleft palate and umbilical hernia at 50 and 100 mg/kg/day). Loteprednol etabonate was maternally toxic (significantly reduced body weight gain during treatment) when administered to pregnant rats during organogenesis at doses of 5 to 100 mg/kg/day, but not at 0.5 mg/kg/day. The NOELs for the embryotoxic and teratogenic effects in rats were 5 mg/kg/day and 0.5 mg/kg/day (60 and 6 times the maximum daily clinical dose) for embryotoxicity and teratogenicity, respectively.

Oral exposure of pregnant rats to 5 and 50 mg/kg/day of loteprednol etabonate during the fetal period, a maternally toxic treatment regimen (significantly decreased body weight gain), resulted in teratogenicity (umbilical herniation) and embryotoxicity (decreased fetal birth weight); the NOEL for these effects was 0.5 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.

Oral treatment of female rats with 25 mg/kg/day (300 times the maximum daily clinical dose) from prior to mating through parturition increased the duration of gestation.

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 LOTEMAX 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 controlled, randomized studies of individuals treated for 28 days or longer with loteprednol etabonate, the incidence of significant elevation of intraocular pressure ($\geq$ 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.

DOSAGE AND ADMINISTRATION:
SHAKE VIGOROUSLY BEFORE USING.

Steroid Responsive Disease Treatment: Apply one to two drops of LOTEMAX into the conjunctival sac of the affected eye(s) four times daily. During the initial treatment within the first week, the dosing may be increased, up to 1 drop every hour, if necessary. Care should be taken not to discontinue therapy prematurely. If signs and symptoms fail to improve after two days, the patient should be re-evaluated (See PRECAUTIONS).

Post-Operative Inflammation:
Apply one to two drops of LOTEMAX into the conjunctival sac of the operated eye(s) four times daily beginning 24 hours after surgery and continuing throughout the first 2 weeks of the postoperative period.

HOW SUPPLIED:
LOTEMAX™ (loteprednol etabonate ophthalmic suspension) is supplied in a plastic bottle with a controlled drop tip in the following sizes:

2.5 mL	(NDC 24208-299-25) - AB29904
5 mL	(NDC 24208-299-05) - AB29907
10 mL	(NDC 24208-299-10) - AB29909
15 mL	(NDC 24208-299-15) - AB29911

DO NOT USE IF NECKBAND IMPRINTED WITH "Protective Seal" and YELLOW *(mortar and pestle graphic)* IS NOT INTACT.

Storage: Store upright between 15° - 25°C (59° - 77°F). DO NOT FREEZE.

KEEP OUT OF REACH OF CHILDREN.

Caution: Federal law prohibits dispensing without prescription.

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

XO50317 (Folded)
XM10039 (Flat)
Rev. 12/97-7L

THIS SECTION WAS DETERMINED **NOT** TO BE RELEASABLE

3 pages

13 **Recommendations -**

NDAs 20-583 and 20-841 are recommended for approval for the treatment of steroid responsive disease and inflammation following cataract surgery with the labeling identified in this review and agreement by the applicant to:

1. Produce, place on stability and perform full testing including:

   identity and quantification of degradation products and other impurities,
   composition, quantification, and resuspendability of any observed aggregates,
   water loss,
   particle size distribution,

at baseline, 3, 6, 9, 12, 18, 24, 30 and 36 months on samples stored in an upright and inverted position at 25°C with 40% or less relative humidity. The testing of resuspendability should include differing degrees of shaking to ascertain the minimum amount of shaking necessary to resuspend all aggregates and should not include sample sonification.

2. Withdraw from the market any product in which the pH falls below 3.5.

A safety update should be submitted with the revised labeling.

MO

Wiley A. Chambers, M.D.
Medical Officer, Ophthalmology

cc: NDA 20-583
NDA 20-841
HFD-550
HFD-550/PM/LoBianco
HFD-830/CHEM/Fenselau
HFD-805/MICRO/Cooney
HFD-550/PHARM/Weir
HFD-550/MO/Chambers

Medical Officer's Review of NDA 20-583 & 20-841
Amendment & Safety Update

NDA #20-583
NDA #20-841
M.O. Review #6

Submit Date: 2/24/98
Review completed: 2/25/98

Generic name: Loteprednol etabonate ophthalmic suspension, 0.5%
Proposed trademark: Lotemax

Sponsor: Pharmos Corporation
33 Wood Ave, South, Suite 466
Iselin, NJ 08830

Agent: Bausch & Lomb Pharmaceuticals
8500 Hidden River Parkway
Tampa, FL 33637
(813) 975-7727

Pharmacologic Category: Steroid

Proposed Indication(s):

LOTEMAX is indicated for the treatment of steroid responsive inflammatory conditions of the palpebral and bulbar conjunctiva, cornea, and anterior segment of the globe such as allergic conjunctivitis, acne rosacea, superficial punctate keratitis, herpes zoster keratitis, iritis, cyclitis, selected infective conjunctivitides, when the inherent hazard of steroid use is accepted to obtain an advisable diminution in edema and inflammation.

LOTEMAX was less effective than prednisolone acetate 1% in two 28-day controlled clinical studies in acute anterior uveitis, where 72% of patients with LOTEMAX experienced resolution of anterior chamber cells, compared to 87% of patients treated with prednisolone acetate 1%. The incidence of patients with clinically significant increases in IOP (≥ 10 mmHg) was 1% with LOTEMAX and 6% with prednisolone acetate 1%. LOTEMAX should not be used in patients who require a more potent corticosteroid for this indication.

LOTEMAX is also indicated for the treatment of post-operative inflammation following ocular surgery.

Dosage Form and Route of Administration: Ophthalmic suspension for topical ocular administration

NDA Drug Classification: 1S

Submitted: Revised labeling, safety update and Phase 4 commitments.

Labeling Review

Reviewer recommended additions are identified by shading. Reviewer recommended additions are identified by redlining and deletions are identified by ~~a strikeout line~~. This review incorporates requested indications from NDA 20-583 as well as those from NDA 20-841.

This review is based on discussions with the applicant, with the understanding that the Office of Drug Evaluation V has not yet commented on the labeling and will have the final authority over the labeling.

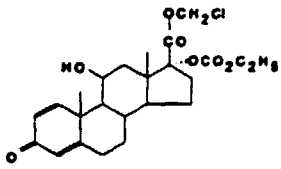
Related Reviews: Pharm/Tox Review dated 4/25/97
Chemistry/Manufacturing Review dated 2/98

LOTEMAX™
loteprednol etabonate ophthalmic suspension, 0.5%

STERILE OPHTHALMIC SUSPENSION

DESCRIPTION:
LOTEMAX™ (loteprednol etabonate ophthalmic suspension) contains a sterile, topical anti-inflammatory corticosteroid for ophthalmic use. Loteprednol etabonate is a white to off-white powder.

Loteprednol etabonate is represented by the following structural formula:



$C_{24}H_{31}ClO_7$ Mol. Wt. 466.96

Chemical name: chloromethyl 17α-[(ethoxycarbonyl)oxy]-11β-hydroxy-3-oxoandrosta-1,4-diene-17β-carboxylate

Each mL contains: ACTIVE: Loteprednol Etabonate 5 mg (0.5%);
INACTIVES: Edetate Disodium, Glycerin, Povidone, Purified Water and Tyloxapol. Hydrochloric Acid and/or Sodium Hydroxide may be added to adjust the pH to 5.3-5.6. The suspension is essentially isotonic with a tonicity of 250 to 310 mOsmol/kg.
PRESERVATIVE ADDED: Benzalkonium Chloride 0.01%.

CLINICAL PHARMACOLOGY:

Corticosteroids inhibit the inflammatory response to a variety of inciting agents and probably delay or slow healing. They inhibit the edema, fibrin deposition, capillary dilation, leukocyte migration, capillary proliferation, fibroblast proliferation, deposition of collagen, and scar formation associated with inflammation. There is no generally accepted explanation for the mechanism of action of ocular corticosteroids. However, corticosteroids are thought to act by the induction of phospholipase A_2 inhibitory proteins, collectively called lipocortins. It is postulated that these proteins control the biosynthesis of potent mediators of inflammation such as prostaglandins and leukotrienes by inhibiting the release of their common precursor arachidonic acid. Arachidonic acid is released from membrane phospholipids by phospholipase A_2. Corticosteroids are capable of producing a rise in intraocular pressure.

Loteprednol etabonate is structurally similar to other corticosteroids. However, the number 20 position ketone group is absent. It is highly lipid soluble which enhances its penetration into cells. Loteprednol etabonate is synthesized through structural modifications of prednisolone-related compounds so that it will undergo a predictable transformation to an inactive metabolite. Based upon *in vivo* and *in vitro* preclinical metabolism studies, loteprednol etabonate undergoes extensive metabolism to inactive carboxylic acid metabolites.

Results from a bioavailability study in normal volunteers established that plasma levels of loteprednol etabonate and Δ^1 cortienic acid etabonate (PJ 91), its primary, inactive metabolite, were below the limit of quantitation (1 ng/mL) at all sampling times. The results were obtained following the ocular administration of one drop in each eye of 0.5% loteprednol etabonate 8 times daily for 2 days or 4 times daily for 42 days. This study suggests that limited (<1 ng/mL) systemic absorption occurs with LOTEMAX.

Clinical Studies:

Post-operative Inflammation: Placebo-controlled clinical studies demonstrated that LOTEMAX is effective for the treatment of anterior chamber inflammation as measured by cell and flare.

Uveitis: Controlled clinical studies of patients with uveitis demonstrated that LOTEMAX was less effective than prednisolone acetate 1%. Overall, 72% of patients treated with LOTEMAX experienced resolution of anterior chamber cell by day 28, compared to 87% of patients treated with 1% prednisolone acetate. The incidence of patients with clinically significant increases in IOP (≥10mmHg) was 1% with LOTEMAX and 6% with ~~1%~~ prednisolone acetate 1%.

Giant Papillary Conjunctivitis:

Placebo-controlled clinical studies demonstrated that LOTEMAX was effective in reducing the signs and symptoms of giant papillary conjunctivitis after 1 week of treatment and continuing for up to 6 weeks while on treatment.

Seasonal Allergic Conjunctivitis: A placebo-controlled clinical study demonstrated that LOTEMAX was effective in reducing the signs and symptoms of allergic conjunctivitis during peak periods of pollen exposure.

INDICATIONS AND USAGE:
LOTEMAX is indicated for the treatment of steroid responsive inflammatory conditions of the palpebral and bulbar conjunctiva, cornea, and anterior segment of the globe such as allergic conjunctivitis, acne rosacea, superficial punctate keratitis, herpes zoster keratitis, iritis, cyclitis, selected infective conjunctivitides, when the inherent hazard of steriod use is accepted to obtain an advisable diminution in edema and inflammation.

LOTEMAX was less effective than prednisolone acetate 1% in two 28-day controlled clinical studies in acute anterior uveitis, where 72% of patients with LOTEMAX experienced resolution of anterior chamber cells, compared to 87% of patients treated with prednisolone acetate 1%. The incidence of patients with clinically significant increases in IOP (≥10 mmHg) was 1% with LOTEMAX and 6% with prednisolone acetate 1%. LOTEMAX should not be used in patients who require a more potent corticosteroid for this indication.

LOTEMAX is also indicated for the treatment of post-operative inflammation following ocular surgery.

CONTRAINDICATIONS:
LOTEMAX, 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. LOTEMAX 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.

The use of steroids after cataract surgery may delay healing and increase the incidence of bleb formation.

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 even though it may be difficult in children and uncooperative patients (see WARNINGS).

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 pain develops, redness, itching or inflammation becomes aggravated, the patient should be advised to consult a physician. As with all ophthalmic preparations containing benzalkonium chloride, patients should be advised not to wear soft contact lenses when using LOTEMAX™.

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 the Ames test, the mouse lymphoma tk assay, or in a chromosome aberration test in human lymphocytes, three *in vitro* tests. *In vivo* evidence of genotoxicity, an increased frequency of micronucleated immature erythrocytes, was not observed in mice that received a single 4 gm/kg dose of loteprednol etabonate (50,000 times the maximum daily clinical dose). Treatment of male and female rats with up to 50 mg/kg/day and 25 mg/kg/day of loteprednol etabonate, respectively, (600 and 300 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 menigiocele, abnormal left common carotid artery, and limb flexures) when administered orally to rabbits during organogenesis at a dose of 3 mg/kg/day (35 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 (6 times the maximum daily clinical dose). Oral treatment of rats during organogenesis with 50 or 100 mg/kg/day (600 and 1,200 times the maximum clinical dose) resulted in embryotoxicity (increased post-implantation losses with 100 mg/kg/day, and decreased fetal body weight and skeletal ossification with 50 and 100 mg/kg/day); doses of 5 (60 times the maximum daily clinical dose), 50 and 100 mg/kg/day caused teratogenicity (absent innominate artery at all doses, and cleft palate and umbilical hernia at 50 and 100 mg/kg/day). Loteprednol etabonate was maternally toxic (significantly reduced body weight gain during treatment) when administered to pregnant rats during organogenesis at doses of 5 to 100 mg/kg/day but not at 0.5 mg/kg/day. The NOELs for the embryotoxic and teratogenic effects in rats were 5 mg/kg/day and 0.5 mg/kg/day (60 and 6 times the maximum daily clinical dose) for embryotoxicity and teratogenicity, respectively.

Oral exposure of pregnant rats to 5 and 50 mg/kg/day of loteprednol etabonate during the fetal period, a maternally toxic treatment regimen (significantly decreased body weight gain), resulted in teratogenicity (umbilical herniation) and embyotoxicity (decreased fetal birth weight); the NOEL for these effects was 0.5 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.

Oral treatment of female rats with 25 mg/kg/day (300 times the maximum daily clinical dose) from prior to mating through parturition increased the duration of gestation.

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 LOTEMAX 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 controlled, randomized studies of individuals treated for 28 days or longer with loteprednol etabonate, the incidence of significant elevation of intraocular pressure ($\geq$ 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.

DOSAGE AND ADMINISTRATION:
SHAKE VIGOROUSLY BEFORE USING.

Steroid Responsive Disease Treatment: Apply one to two drops of LOTEMAX into the conjunctival sac of the affected eye(s) four times daily. During the initial treatment within the first week, the dosing may be increased, up to 1 drop every hour, if necessary. Care should be taken not to discontinue therapy prematurely. If signs and symptoms fail to improve after two days, the patient should be re-evaluated (See PRECAUTIONS).

Post-Operative Inflammation:
Apply one to two drops of LOTEMAX into the conjunctival sac of the operated eye(s) four times daily beginning 24 hours after surgery and continuing throughout the first 2 weeks of the postoperative period.

HOW SUPPLIED:
LOTEMAX™ (loteprednol etabonate ophthalmic suspension) is supplied in a plastic bottle with a controlled drop tip in the following sizes:

2.5 mL	(NDC 24208-299-25) - AB29904
5 mL	(NDC 24208-299-05) - AB29907
10 mL	(NDC 24208-299-10) - AB29909
15 mL	(NDC 24208-299-15) - AB29911

DO NOT USE IF NECKBAND IMPRINTED WITH "Protective Seal" and YELLOW (mortar and pestle graphic) IS NOT INTACT.

Storage: Store upright between 15° - 25°C (59° - 77°F). DO NOT FREEZE.

KEEP OUT OF REACH OF CHILDREN.

Rx only

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

XO50317 (Folded)
XM10039 (Flat)
Rev. 2/98-8B

Reviewer's Comments: *Acceptable.*

Package and Container Labeling- Submitted and consistent with Package Insert.

Reviewer's Comments: *Acceptable.*

Phase 4 Commitments:

"We therefore commit to the following:

Batches will be produced, placed on stability and full testing will be performed including:

LE content
Identity and quantification of degradation products and other impurities
Composition, quantification, and resuspendability of any observed aggregates
Water loss
Particle size distribution

Testing will be performed at baseline, 3, 6, 9, 12, 18, 24, 30 and 36 months on samples stored in an upright and inverted position at 25±2°C with 40±5% relative humidity.

The testing of resuspendability will include differing degrees of shaking to ascertain the minimum amount of shaking necessary to resuspend all aggregates and should not include sample sonification.

We will withdraw from the market any product in which the pH falls below 3.5."

Reviewer's Comments: *Acceptable.*

Safety update: No new safety information is available for this product.

Reviewer's Comments: *Acceptable.*

Recommendation:

NDA 20-583 and NDA 20-841, Lotemax (loteprednol etabonate ophthalmic suspension) 0.5% is recommended for approval.

m.d

Wiley A. Chambers, M.D.
Medical Officer, Ophthalmology

cc: NDA 20-583
NDA 20-841
HFD-550
HFD-550/PM/LoBianco
HFD-830/CHEM/Fenselau
HFD-805/MICRO/Cooney
HFD-550/PHARM/Weir
HFD-550/MO/Chambers

APPEARS THIS WAY
ON ORIGINAL