



NDA 50-612/S-014

Allergan, Inc.
Attention: Elizabeth Bancroft
Senior Director, Regulatory Affairs
2525 Dupont Drive
P.O. Box 19534
Irvine, California 92623-9534

Dear Ms. Bancroft:

Please refer to your supplemental new drug application dated August 20, 2001, received August 22, 2001, submitted under the Federal Food, Drug, and Cosmetic Act for Pred-G (gentamicin and prednisolone acetate ophthalmic ointment, USP) 0.3%/0.6%.

This application is subject to the exemption provisions contained in section 125(d)(2) of Title I of the FDA Modernization Act of 1997.

We acknowledge receipt of your submissions dated April 24 and October 6, 2003. Your submission of April 24, 2003, constituted a complete response to our February 22, 2002, action letter.

This supplemental new drug application provides for a change in manufacturing site from Hormigueros, Puerto Rico, to Waco, Texas, and for revised labeling.

We completed our review of this application, as amended. This application is approved, effective on the date of this letter, for use as recommended in the agreed-upon labeling text.

The final printed labeling (FPL) must be identical to the enclosed labeling text for the package insert and immediate container labels submitted October 6, 2003.

Please submit the FPL electronically according to the guidance for industry titled Providing Regulatory Submissions in Electronic Format – NDA. Alternatively, you may submit 20 paper copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount 15 of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FPL for approved supplement NDA 50-612/S-014" Approval of this submission by FDA is not required before the labeling is used.

We remind you that you must submit patent information on form FDA 3542, *Patent Information Submitted Upon and After Approval of an NDA or Supplement*, within 30 days of the date of this letter as required by 21 CFR 314.53(c)(2)(ii) and 314.53(d)(2) at the address provided by 21 CFR 314.53(d)(4). The form may be obtained at <http://www.fda.gov/opacom/morechoices/fdaforms/cder.html>. To expedite review of this patent declaration form, we request you submit an additional copy of the form to this application and to the Center for Drug Evaluation and Research "Orange Book" staff at

Food and Drug Administration
Office of Generic Drugs, HFD-610
Orange Book Staff
7500 Standish Place
Metro Park North II
Rockville, MD 20855-2773

If you issue a letter communicating important information about this drug product (i.e., a "Dear Health Care Professional" letter), we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HFD-410
FDA
5600 Fishers Lane
Rockville, MD 20857

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Raphael R. Rodriguez, Regulatory Project Manager, at (301) 827-2090.

Sincerely,

{See appended electronic signature page}

Linda L. Ng, Ph.D.
Chemistry Team Leader for the
Division of Anti-Inflammatory, Analgesic
and Ophthalmic Drug Products, HFD-550
DNDC III, Office of New Drug Chemistry
Center for Drug Evaluation and Research

Enclosure

ALLERGAN

PRED-G®

(gentamicin and prednisolone acetate ophthalmic ointment, USP) 0.3%/0.6%
sterile

DESCRIPTION

Pred-G® sterile ophthalmic ointment is a topical anti-inflammatory/anti-infective combination product for ophthalmic use.

Structural Formulas:

[Structure]

prednisolone acetate

$C_{23}H_{20}O_6$

[Structure]

gentamicin sulfate

Chemical Names: Prednisolone acetate: 11β , 17,21-Trihydroxypregna-1,4-diene-3,20-dione 21-acetate.

Gentamicin sulfate is the sulfate salt of gentamicin C₁, gentamicin C₂, and gentamicin C_{1A} which are produced by the growth of *Micromonospora purpurea*.

Contains: Actives: gentamicin sulfate equivalent to 0.3% gentamicin base, prednisolone acetate 0.6%; **Preservative:** chlorobutanol (chloral derivative) 0.5%; **Inactives:** mineral oil; petrolatum (and) lanolin alcohol; purified water; and white petrolatum.

CLINICAL PHARMACOLOGY

Corticosteroids suppress the inflammatory response to a variety of agents and they probably delay or slow healing. Since corticosteroids may inhibit the body's defense mechanism against infection, a concomitant antimicrobial drug may be used when this inhibition is considered to be clinically significant in a particular case.

The anti-infective component in Pred-G® ophthalmic ointment is included to provide action against specific organisms susceptible to it. Gentamicin sulfate is active in vitro against susceptible strains of the following microorganisms: *Staphylococcus aureus*, *Streptococcus pyogenes*, *Streptococcus pneumoniae*, *Enterobacter aerogenes*, *Escherichia coli*, *Haemophilus influenzae*, *Klebsiella pneumoniae*, *Neisseria gonorrhoeae*, *Pseudomonas aeruginosa*, and *Serratia marcescens*.

When a decision to administer both a corticosteroid and an antimicrobial is made, the administration of such drugs in combination has the advantage of greater patient compliance and convenience, with the added assurance that the appropriate dosage of both drugs is administered. When both types of drugs are in the same formulation, compatibility of ingredients is assured and the correct volume of drug is delivered and retained.

The relative potency of corticosteroids depends on the molecular structure, concentration, and release from the vehicle.

INDICATIONS AND USAGE

Pred-G ophthalmic ointment is indicated for steroid-responsive inflammatory ocular conditions for which a corticosteroid is indicated and where superficial bacterial ocular infection or a risk of bacterial ocular infection exists.

Ocular steroids are indicated in inflammatory conditions of the palpebral and bulbar conjunctiva, cornea, and anterior segment of the globe where the inherent risk of steroid use in certain infective conjunctivitis is accepted to obtain a diminution in edema and inflammation. They are also indicated in chronic anterior uveitis and corneal injury from chemical, radiation, or thermal burns or penetration of foreign bodies.

The use of a combination drug with an anti-infective component is indicated where the risk of superficial ocular infection is high or where there is an expectation that potentially dangerous numbers of bacteria will be present in the eye.

The particular anti-infective drug in this product is active against the following common bacterial eye pathogens: *Staphylococcus aureus*, *Streptococcus pyogenes*, *Streptococcus pneumoniae*, *Enterobacter aerogenes*, *Escherichia coli*, *Haemophilus influenzae*, *Klebsiella pneumoniae*, *Neisseria gonorrhoeae*, *Pseudomonas aeruginosa*, and *Serratia marcescens*.

CONTRAINDICATIONS

Pred-G ophthalmic ointment 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. Pred G ointment is also contraindicated in individuals with known or suspected hypersensitivity to any of the ingredients of this preparation or 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. Prolonged use of corticosteroids may suppress the host immune response and thus increase the hazard of secondary ocular infections. Various ocular diseases and long term use of topical corticosteroids have been known to cause corneal and scleral thinning. Use of topical corticosteroids in the presence of thin corneal or scleral tissue may lead to perforation. Acute purulent infections of the eye may be masked or enhanced by the presence of corticosteroid medication.

If these products are used for 10 days or longer, intraocular pressure should be routinely monitored even though it may be difficult in children and uncooperative patients. Steroids should be used with caution in the presence of glaucoma. Intraocular pressure should be checked frequently.

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

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, frequent slit lamp microscopy is recommended.

PRECAUTIONS

General: Ocular irritation and punctate keratitis have been associated with the use of PRED-G® ophthalmic ointment. The initial prescription and renewal of the medication order beyond 8 grams should be made by a physician only after examination of the patient's intraocular pressure, examination of the patient with the aid of magnification such as slit lamp biomicroscopy and, where appropriate, fluorescein staining.

As fungal infections of the cornea are particularly prone to develop coincidentally with long term corticosteroid applications, fungal invasion should be suspected in any persistent corneal ulceration where a corticosteroid has been used or is in use. Fungal cultures should be taken when appropriate.

Information for Patients: If inflammation or pain persists longer than 48 hours or becomes aggravated the patient should be advised to discontinue use of the medication and consult a physician.

This product is sterile when packaged. To prevent contamination care should be taken to avoid touching the tip of the tube to eyelids or to any other surface. The use of this tube by more than one person may spread infection. Keep out of reach of children

Carcinogenesis, mutagenesis, impairment of fertility: There are no published carcinogenicity or impairment of fertility studies on gentamicin. Aminoglycoside antibiotics have been found to be non-mutagenic.

There are no published mutagenicity or impairment of fertility studies on prednisolone. Prednisolone has been reported to be non-carcinogenic.

Pregnancy: Pregnancy Category C. Gentamicin has been shown to depress newborn body weights, kidney weights and median glomerular counts in newborn rats when administered systemically to pregnant rats in daily doses of approximately 500 times the maximum recommended ophthalmic dose in humans. There are no adequate and well controlled studies in pregnant women. Gentamicin should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Prednisolone has been shown to be teratogenic in mice when given in doses 1-10 times the human ocular dose. Dexamethasone, hydrocortisone and prednisolone were ocularly applied to both eyes of pregnant mice five times per day on days 10 through 13 of gestation. A significant increase in the incidence of cleft palate was observed in the fetuses of the treated mice. There are no adequate well-controlled studies in pregnant women. PRED-G® ophthalmic ointment 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 administration of corticosteroids could result in sufficient systemic absorption to produce detectable quantities in breast milk. Systemically administered corticosteroids appear in breast milk and could suppress growth, interfere with endogenous corticosteroid production, or cause untoward effects. Because of the potential for serious adverse reactions in nursing infants from PRED-G®, a decision should be made whether to discontinue nursing while the drug is being administered or to discontinue the medication.

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

Geriatric Use: No overall differences in safety or effectiveness have been observed between elderly and young patients.

ADVERSE REACTIONS

Adverse reactions have occurred with steroid/anti-infective combination drugs which can be attributed to the steroid component, the anti-infective component, or the combination. Exact incidence figures are not available since no denominator of treated patients is available.

The most frequent reactions observed include ocular discomfort, irritation upon installation of the medication and punctate keratitis. These reactions have resolved upon discontinuation of the medication.

Reactions occurring most often from the presence of the anti-infective ingredient are allergic sensitizations. The reactions due to the steroid component in decreasing order of frequency are: elevation of intraocular pressure (IOP) with possible development of glaucoma, and infrequent optic nerve damage; posterior subcapsular cataract formation; and delayed wound healing.

Secondary infections: The development of secondary ocular infection has occurred after use of combinations containing steroids and antimicrobials. Fungal and viral infections of the cornea are particularly prone to develop coincidentally with long-term applications of steroid. The possibility of fungal invasion should be considered in any persistent corneal ulceration where steroid treatment has been used. (See **WARNINGS**) Secondary bacterial ocular infection following suppression of host responses also occurs.

DOSAGE AND ADMINISTRATION

A small amount (1/2 inch ribbon) of ointment should be applied in the conjunctival sac one to three times daily. Care should be taken not to discontinue therapy prematurely.

Not more than 8 grams should be prescribed initially, and the prescription should not be refilled without further evaluation as outlined in **PRECAUTIONS** above.

If signs and symptoms fail to improve after two days, the patient should be re-evaluated (see **PRECAUTIONS**).

HOW SUPPLIED

Pred-G® (gentamicin and prednisolone acetate ophthalmic ointment, USP) 0.3%/0.6% is supplied sterile in collapsible aluminum tubes with epoxy-phenolic liners with tips with black LDPE caps of the following size:

3.5g-NDC 0023-0066-04

Note: Store at 15°-25°C (59°-77°F).

Rx only.

Revised April 2003

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Irvine, California 92612 U.S.A.

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7228X

3.5 gm Pred-G Tube Label

<p>NDC 0023-0066-04 PRED-G® (gentamicin and prednisolone acetate ophthalmic ointment, USP) 0.3%/0.6% Contains: Actives: gentamicin sulfate equivalent to 0.3% gentamicin base; prednisolone acetate 0.6%. Preservative: chlorobutanol (chloral derivative) 0.5% Inactives: mineral oil; petrolatum (and) lanolin alcohol; purified water; and white petrolatum. USUAL DOSAGE: Refer to package insert. Note: Store at 15°-25°C (59°-77°F).</p>	<p>3.5 g sterile ALLERGAN Rx only</p> <p>© 2003 Allergan Inc. Irvine, California 92612 U.S.A. ®Registered trademarks of Allergan, Inc. 7228X</p>
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/s/

Linda Ng
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