

PRODUCT MONOGRAPH

Pr FLAREX®

Fluorometholone Acetate Ophthalmic Suspension

0.1%

Corticosteroid

:

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**ACTION**

Adrenocorticoids suppress the inflammatory response (edema, fibrin deposition, capillary dilation, leukocyte migration, capillary proliferation, deposition of collagen and scar formation), to chemical, immunological, or mechanical irritants. Adrenocorticoids may cause a rise in intraocular pressure in susceptible individuals. They are absorbed into aqueous humor, cornea, iris, choroid, ciliary body and retina. Systemic absorption occurs but may be significant only at higher doses than recommended.

**INDICATIONS**

FLAREX® (Fluorometholone Acetate Ophthalmic Suspension) is indicated for the treatment of allergic and other steroid-responsive inflammatory conditions of the palpebral and bulbar conjunctiva, cornea and anterior segment of the eye.

**CONTRAINDICATIONS**

FLAREX® (Fluorometholone Acetate Ophthalmic Suspension) is contraindicated in acute superficial herpes simplex keratitis, vaccinia, varicella, and most viral diseases of cornea and conjunctiva; tuberculosis of the eye; fungal diseases of the eye; acute purulent untreated infections of the eye which, like other diseases caused by microorganisms, may be masked or enhanced by the presence of the steroid; and in those persons who have a known hypersensitivity to any component of this preparation.

## WARNINGS

Fluorometholone Acetate Ophthalmic Suspension is not for injection.

Use of topical corticosteroid may cause increased intraocular pressure. It is necessary that the intraocular pressure be checked frequently and particularly in patients with a history of glaucoma or with a family history of glaucoma. Prolonged use may result in glaucoma, damage to the optic nerve, defects in visual acuity and visual field, posterior subcapsular cataract formation, and/or may aid in the establishment of secondary ocular infections from pathogens due to suppression of host response. Acute purulent infections of the eye may be masked or exacerbated by the presence of steroid medications. In those diseases causing thinning of the cornea or sclera, perforation has been known to occur with the chronic use of topical steroids.

If sensitivity or other untoward reactions occur, discontinue the medication.

### **Pregnancy:**

Animal reproduction studies have not been conducted with FLAREX® (Fluorometholone Acetate Ophthalmic Suspension). However, it has been reported that studies with fluorometholone (alcohol) applied ocularly to pregnant rabbits at approximate human doses and above resulted in a significant dose-related increase in fetal abnormalities and in fetal loss. It is not known whether FLAREX® Ophthalmic Suspension can cause fetal harm when administered to a pregnant woman. FLAREX® Ophthalmic Suspension should be used in pregnancy only if the potential benefit outweighs the potential risk to the fetus.

## PRECAUTIONS

### General:

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 or is in use.

It is advisable to check intraocular pressure in some individuals (see WARNINGS). In diseases due to microorganisms, the infection may be masked, enhanced or activated by corticosteroids. Whenever there is a possibility of infection, supplemental therapy with suitable antibiotic agents should be considered.

Patients should be advised to inform their physicians of any prior use of corticosteroids.

### Nursing Mothers:

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Fluorometholone Acetate Ophthalmic Suspension is administered to a nursing woman.

### Pediatric Use:

Safety and effectiveness in children have not been established.

## ADVERSE REACTIONS

Glaucoma with optic nerve damage, visual acuity and field defects, cataract formation, and secondary ocular infection following suppression of host response may occur. Extended ophthalmic use of corticosteroid drugs may cause increased intraocular pressure in certain individuals and in those diseases causing thinning of the cornea, perforation has been known to occur. Rarely, filtering blebs have been reported when topical steroids have been used following cataract surgery. Occasionally stinging or burning may occur.

### **SYMPTOMS AND TREATMENT OF OVERDOSE**

Overdosage in the use of topical ophthalmic corticosteroids is a remote possibility. Discontinue medication when heavy or protracted use is suspected.

### **DOSAGE AND ADMINISTRATION**

One to two drops instilled into the conjunctival sac two to four times daily. During the initial 24 to 48 hours, the dosage may be safely increased to two drops every two hours. Care should be taken not to discontinue therapy prematurely.

#### **Special Instructions:**

Patients should be instructed to shake well before using and to avoid contamination of the dropper tip.

### **AVAILABILITY**

Pr FLAREX® Ophthalmic Suspension is available as a sterile ophthalmic suspension of fluorometholone acetate 0.1% in DROP-TAINER® dispensers of 5 mL. The suspension is preserved with benzalkonium chloride 0.01%.

Fluorometholone acetate is a Schedule F (prescription) drug.

#### **Stability and Storage Recommendations:**

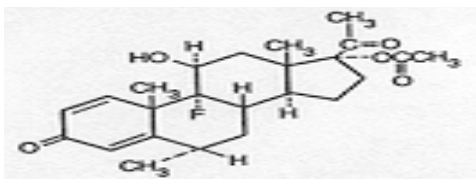
Protect from freezing and store upright at room temperature.

**PHARMACEUTICAL INFORMATION**Drug Substance:

Proper Name: Fluorometholone acetate

Chemical Name: 9-fluoro-11 $\beta$ ,-17-dihydroxy -6 $\alpha$ -methylpregna-1,4-diene-3,20-dione,  
17-acetate.

Structural Formula:



Molecular Formula: C<sub>24</sub>H<sub>31</sub>FO<sub>5</sub>

Molecular Weight: 418.5

Description: White to creamy white powder.

Solubility: Freely soluble in chloroform and acetone, soluble in ethanol,  
very slightly soluble in water.

Melting Point: approximately 230°C

Specific Rotation: + 28° in chloroform.

**Composition:**

FLAREX® (Fluorometholone Acetate Ophthalmic Suspension) is a sterile, suspension of fluorometholone acetate 0.1% with benzalkonium chloride 0.01% (as preservative), sodium chloride, monobasic sodium phosphate, edetate disodium, hydroxyethyl cellulose, tyloxapol, sodium hydroxide and/or hydrochloric acid (to adjust pH) and purified water.

## PHARMACOLOGY

### **Animal:**

Past experience demonstrates that one may alter, by derivatization, the bioavailability and consequently, the potency and efficacy of topical ocular steroids. It is known that ocular tissues contain enzymes capable of hydrolysing esters, especially acetate esters of steroids. The acetate group may confer a change in the lipophilicity of the steroid which in turn may alter its rate of passage through the cornea. It is believed that the acetate group is removed from the molecule through hydrolysis by the ocular enzymes.

To determine whether or not the 17-acetate ester of fluorometholone retains adequate anti-inflammatory activity in the eye, its efficacy in comparison to other steroids was studied using an immunogenic uveitis model in albino rabbits. Fluorometholone acetate exhibited anti-inflammatory efficacy in each of six uveitis experiments. In this series of experiments, fluorometholone acetate and fluorometholone alcohol (both at 0.1%) were equally potent anti-inflammatory agents. As these studies were not designed to give a complete dose response comparison, it cannot be concluded that the two compounds are precisely equivalent.

The effect of 0.1% Fluorometholone Acetate Ophthalmic Suspension has been studied in the rabbit using a keratitis model in which the invasion of the cornea by polymorphonuclear leukocytes was measured. Hourly topical administration of the drug suspension produced an average reduction of 46.8% in the polymorphonuclear leukocytes invading the corneal stroma. According to a similar experimental protocol, 0.1% Fluorometholone Alcohol Ophthalmic Suspension was shown to produce a mean decrease of 30.8% in corneal inflammatory activity as measured by leukocyte invasion. Thus, in the cornea, fluorometholone acetate appears to have a greater efficacy, as compared to fluorometholone alcohol, for reducing the number of leukocytes invading that tissue following an inflammatory stimulus.

**Clinical:**

The efficacy of corticosteroids for the treatment of inflammatory conditions in the eye is well established. Various steroids such as dexamethasone alcohol or phosphate, prednisolone acetate or phosphate, and fluorometholone alcohol are marketed for this purpose. The anti-inflammatory effects of the steroids reduce the severity of the signs and symptoms of ocular inflammation and may avert permanent structural changes which can affect the vision.

The intrinsic anti-inflammatory activity of the corticosteroid and its ability to penetrate the cornea, which is the primary route of absorption of topically applied drugs into the aqueous humor, determine not only its efficacy but also the propensity of the compound to provoke side effects. Some physicochemical properties of the steroid esters may vary from those of the parent alcohols. Properties such as solubility and partitioning between aqueous and nonaqueous solvents may affect the bioavailability of molecules in the eye.

Double masked randomized studies have shown that FLAREX was significantly ( $p = 0.03$ ) more effective than Fluorometholone Alcohol and equally effective as Prednisolone Acetate in the treatment of external ocular inflammation of non-microbial origin. All three steroids were essentially equally effective in the treatment of anterior uveal inflammation.

The elevation of intraocular pressure with prolonged use is perhaps the most serious effect of topical ophthalmic use of corticosteroids. The liability of provoking this effect varies among the currently marketed drugs, with the available evidence indicating that fluorometholone alcohol has less propensity to raise intraocular pressure in susceptible individuals compared to other steroids such as dexamethasone, prednisolone and their derivatives.

Fluorometholone acetate is the 17-acetate ester of fluorometholone. It is probable that this compound is hydrolysed *in vivo* to regenerate fluorometholone alcohol. Thus, fluorometholone acetate should share the same low propensity for raising IOP as fluorometholone.

In healthy volunteers, dosed with two drops of FLAREX four times per day for 15 days, the IOP was elevated in only 3 of the 20 individuals. In a double masked crossover study with Dexamethasone Phosphate 0.1%, FLAREX demonstrated a significantly lower propensity to raise IOP.

**TOXICOLOGY**

Fluorometholone Ophthalmic Suspension 0.1% has been marketed over the last decade in the United States, Canada and other countries as an ophthalmic corticosteroid. Animal toxicity studies of fluorometholone, including acute intraperitoneal LD<sub>50</sub>s in mice and rats, subacute oral toxicity in rats and dogs, and subacute topical ocular toxicity in rabbits have demonstrated the safety of this drug for human use.

Toxicology studies conducted with fluorometholone acetate are summarized in the following table:

<b>Test</b>	<b>Dosage (mg/kg)</b>	<b>Drug Related Findings</b>
<b>Acute Toxicity</b>		<b>LD<sub>50</sub> (mg/kg)</b>
Mouse: i.p.	750, 1000, 1500, 2000	1890.7 (female); >2000 (male)
Rat: i.p.	62.5, 125, 200, 500, 750, 1000	> 1000
Rabbit: Ocular irritation	1.8 mg/eye over 6 hours	minimal-moderate conjunctival congestion, minimal conjunctival swelling and discharge
<b>Long Term Toxicity</b>		
Mouse: 30 day	18 (p.o.)	Suppression of weight gain
Rat: 30 day	18 (p.o.)	Suppression of weight gain
Dog: 30 day	9 (p.o.)	Moderate fatty changes in liver
Dog: 5 day	3 (p.o.)	Increased glycogen deposition in liver; decreased adrenal weights
Rabbit: 5 day ocular irritation	0.5 mg/eye/day	Minimal conjunctival congestion
Rabbit: 45 day ocular irritation	0.5 mg/eye/day for 38 days	minimal-moderate conjunctival congestion; systemic steroid toxicity; 50% mortality rate at day 39
Rabbit: 30 day ocular irritation	0.8 mg/eye/day for 2 days; 0.5 mg/eye/day for 29 days	minimal-moderate conjunctival congestion; transient ocular discharge; transient diarrhea, loose stools and nasal discharge; suppression of weight gain

Although reproduction studies have not been carried out with FLAREX Ophthalmic Suspension, fluorometholone alcohol has been reported to be teratogenic and embryocidal when applied to both eyes of rabbits on days 6 to 18 of gestation. Cortisone, hydrocortisone and dexamethasone administered ocularly have also been reported to cause fetal anomalies in animal studies.

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