PRODUCT MONOGRAPH

Pr FLAREX®

Fluorometholone Acetate Ophthalmic Suspension

0.1% w/v

Corticosteroid

Novartis Pharmaceuticals Canada Inc.
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Fluorometholone Acetate Ophthalmic Suspension

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
Topical ophthalmic	Ophthalmic suspension/ fluorometholone acetate 0.1% w/v	Benzalkonium chloride as preservative. *For a complete listing see Dosage Forms, Composition and Packaging section.*

INDICATIONS AND CLINICAL USE

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.

Geriatrics (> 65 years of age):
FLAREX is not recommended for use in the elderly as the safety and efficacy of FLAREX has not been established in this population.

Pediatrics (< 18 years of age):
FLAREX is not recommended for use in children or adolescents as the safety and efficacy of FLAREX has not been established in this population.

CONTRAINDICATIONS

FLAREX is contraindicated in patients with:

- Hypersensivity to fluorometholone or to any ingredient in the formulation or component of the container. For a complete listing, see the DOSAGE FORMS, COMPOSITION AND PACKAGING section of the product monograph.
- Hypersensitivity to corticosteroids.
- Acute superficial herpes simplex keratitis, vaccinia, varicella, and most viral diseases of the cornea and conjunctiva.
- Mycobacterial infections, including tuberculosis of the eye.
- Fungal diseases of the eye.

- Acute untreated infections of the eye that like other diseases caused by microorganisms, may be masked or enhanced by the presence of the steroid.

WARNINGS AND PRECAUTIONS

General

Not for injection.

The initial prescription and renewal of FLAREX should be made only after appropriate ophthalmologic examination (including but not limited to intraocular pressure assessment and slit lamp biomicroscopy). If signs and symptoms fail to improve after two days, the patient should be re-evaluated. FLAREX should not be used beyond 10 days, unless absolutely necessary, and only under ophthalmologic monitoring.

Acute infections of the eye may be masked or exacerbated by the presence of steroid medications. Prolonged use may increase the risk of secondary ocular infections from pathogens due to suppression of the host response.

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. FLAREX therapy should be discontinued if fungal infection occurs.

In disease 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. If sensitivity or other untoward reactions occur, the patient should be advised to discontinue the medication.

Endocrine and Metabolism

Systemic corticosteroid side-effects may occur after intensive or long-term continuous ophthalmic corticosteroid therapy in predisposed patients, including children and patients treated with CYP3A4 inhibitors (e.g. ritonavir and cobicistat).

Ophthalmologic

Use of topical ophthalmic corticosteroids may cause increased intraocular pressure (IOP). It is necessary that IOP be checked frequently, particularly in patients with a history or family history of glaucoma. Prolonged use may result in glaucoma, damaged to the optic nerve, defects in visual acuity and visual field, and/or posterior subcapsular cataract formation.

The risk of corticosteroid-induced elevation of IOP and/or cataract formation is increased in predisposed patients (e.g. diabetes).

Topical ophthalmic corticosteroids may slow corneal wound healing. In those diseases causing

thinning of the cornea or sclera, perforation has been known to occur with the chronic use of topical steroids. Topical nonsteroidal anti-inflammatory drugs (NSAIDs) are also known to slow or delay healing; therefore, concomitant use of topical NSAIDs and topical steroids may increase the potential for healing problems.
The wearing of contact lenses is discouraged during treatment of an ocular inflammation. If patients do wear contact lenses during treatment, FLAREX should not be used while the patient is wearing soft contact lenses. FLAREX contains benzalkonium chloride, which is known to discolour soft contact lenses. Patients must be instructed to remove their contact lenses prior to application of FLAREX and wait at least 15 minutes before re-insertion.

Temporary blurred vision or other visual disturbances may affect the ability to drive or use machines. If blurred vision occurs at instillation, the patient must wait until the vision clears before driving or using machinery.

Special Populations
Pregnant Women: FLAREX is not recommended for use in pregnant women. The safety of FLAREX during pregnancy has not been evaluated in adequate and well controlled clinical studies in humans. Animal studies have shown that fluorometholone can be embryocidal, fetotoxic, and teratogenic in rabbits when administered by ocular instillation (see TOXICOLOGY).

Nursing Women: It is unknown whether FLAREX is excreted in human milk. Caution is advised if FLAREX is administered to a nursing woman.

Geriatrics (> 65 years of age):
FLAREX is not recommended for use in the elderly.

Pediatrics (< 18 years of age):
FLAREX is not recommended for use in children or adolescents.

ADVERSE REACTIONS

Adverse Drug Reaction Overview
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.

Post-Market Adverse Drug Reactions
Eye disorders: Intraocular pressure increased, eye pain, eye irritation, ocular discomfort, foreign body sensation in eyes, vision blurred, ocular hyperemia, lacrimation increased;
Others: dysgeusia.

DRUG INTERACTIONS

Overview

Specific drug interaction studies have not been performed with fluorometholone acetate. Concomitant use of topical nonsteroidal anti-inflammatory drugs (NSAIDs) and topical steroids may further delay wound healing (see WARNINGS AND PRECAUTIONS, Ophthalmologic).

Co-treatment with CYP3A4 inhibitors, including ritonavir and cobicistat, may increase systemic exposure resulting in increased risk of systematic side-effects. The combination should be avoided unless the benefit outweighs the increased risk of systemic corticosteroid side-effects, in which case patients should be monitored for systemic corticosteroid side-effects.

DOSAGE AND ADMINISTRATION

Recommended Dose and Dosage Adjustment

Adults: One to two drops instilled in the conjunctival sac of the affected eye(s) 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.
If signs and symptoms fail to improve after 2 days, the patient should be re-evaluated.

Missed Dose

If a dose is missed, the missed dose should be administered as soon as possible. Treatment should then be continued with the next dose as planned.

Administration

Patients should be instructed to shake the bottle well before each use and not to touch the dropper tip to their eye, eyelid, or any other surface to avoid potentially harmful contamination of the dropper tip and medicine.
After cap is removed, if the tamper evident snap collar is loose, instruct patients to remove it before using the product.

OVERDOSAGE

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

For management of a suspected drug overdose, contact your regional Poison Control Centre.

ACTION AND CLINICAL PHARMACOLOGY

Corticosteroids suppress the inflammatory response (i.e., edema, fibrin deposition, capillary

dilation, leukocyte migration, capillary proliferation, deposition of collage, and scar formation) to chemical, immunological, or mechanical irritants. Corticosteroids may cause a rise in intraocular pressure in susceptible individuals. They are absorbed into aqueous humour, cornea, iris, choroid, ciliary body and retina. Systemic absorption occurs but may be significant only at higher doses than recommended.

STORAGE AND STABILITY

Protect from freezing. Store upright at room temperature. Keep out of the reach and sight of children.

DOSAGE FORMS, COMPOSITION AND PACKAGING

FLAREX is a sterile, suspension containing the following:
Medicinal ingredient: fluorometholone acetate 0.1% w/v
Preservative: benzalkonium chloride 0.01% w/v
Non-medicinal ingredients: sodium chloride, monobasic sodium phosphate, edetate disodium, hydroxyethyl cellulose, tyloxapol, sodium hydroxide and/or hydrochloric acid (to adjust pH) and purified water.

FLAREX is available in 5 mL dispensers.

Tamper evidence is provided by a closure with an extended skirt that locks to the bottle finish on application and breaks away from the closure on opening.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

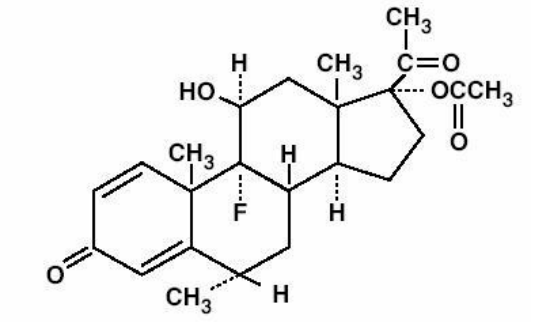
Drug Substance

Proper name: fluorometholone acetate

Chemical name: 9-fluoro-11β,-17-dihydroxy -6α-methylpregna-1,4-diene-3,20-dione, 17-acetate.

Molecular formula and molecular mass: $C_{24}H_{31}FO_5$; 418.5

Structural formula:



Physicochemical properties:

Description:	white to creamy white powder
Solubility:	freely soluble in chloroform and acetate; soluble in ethanol; very slightly soluble in water
Melting Point:	approximately 230°C
Specific Rotation:	+ 28° in chloroform

CLINICAL TRIALS

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 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 humour, determine not only its efficacy but also the propensity of the compound to provoke side effects. Some physiochemical 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 (IOP) 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 IOP 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 probably that this compound is hydrolysed *in vivo* to regenerate fluorometholone alcohol. This, fluorometholone acetate should share the same low propensity for raising IOP as fluorometholone.
In healthy volunteers dosed with two drops of FLAREX four times a day for 15 days, 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.

DETAILED PHARMACOLOGY

Animal Studies

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 experiements, 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 decreased of 30.8% in corneal inflammatory activity as measured by leukocyte invasion. Thus, fluorometholone acetate appears to have a greater efficacy, as compared to fluorometholone alcohol, for reducing the number of leukocytes invading the cornea following an inflammatory stimulus.

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_{50}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:

Table 1: Summary of Toxicology Studies Conducted with Fluorometholone Acetate

Test	**Dosage (mg/kg)**	**Drug Related Findings LD_{50} (mg/kg)**
Acute Toxicity		
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 to moderate conjunctival congestion; minimal conjunctival swelling and discharge
Long Term Toxicity		
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 to 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 to moderate conjunctival congestion; transient ocular discharge; transient diarrhea, loose stools and nasal discharge; suppression of weight gain

In reproduction studies, fluorometholone alcohol has been reported to be teratogenic and embryocidal when applied to both eyes of rabbits on days 6 to 18 of gestation, with dose-related fetal loss and fetal abnormalities, such as encephalocele, craniorachischisis, and spina bifida. Cortisone, hydrocortisone, and dexamethasone administered ocularly have also been reported to cause fetal anomalies in animal studies.

No studies have been conducted to evaluate the carcinogenicity or mutagenicity of fluorometholone.

REFERENCES

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5. Mindel JS, Tavitian HO et al. Comparative ocular pressure elevation by medrysone, fluorometholone, and dexamethasone phosphate. Arch Ophthal 1980; 98: 1577-1578.

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PART III: CONSUMER INFORMATION

Pr FLAREX®
Fluorometholone Acetate Ophthalmic Suspension

This leaflet is part III of a three-part "Product Monograph" published when FLAREX® was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about FLAREX. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:
FLAREX is used to treat eye allergies and eye inflammation.

What it does:
FLAREX contains a corticosteroid, fluorometholone acetate, that works by blocking the inflammatory response.

When it should not be used:
Do not use FLAREX if you:

- Are allergic (*hypersensitive*) to fluorometholone acetate or any of the other ingredients in FLAREX and its container (see What the important non-medicinal ingredients are).
- Are allergic to other corticosteroids.
- Have herpes simplex keratitis (inflamed cornea of the eye caused by the herpes simplex virus), smallpox, chickenpox, or any other viral infection of the eye.
- Have a mycobacterial infection of the eye, including tuberculosis.
- Have a fungal infection of the eye.
- Have an untreated bacterial eye infection.

What the medicinal ingredient is:
Fluorometholone acetate, 0.1% w/v

What the important nonmedicinal ingredients are:
Preservative: benzalkonium chloride
Others: edetate disodium, hydroxyethyl cellulose, monobasic sodium phosphate, sodium chloride, tyloxapol, sodium hydroxide and/or hydrochloric acid (to adjust pH), and purified water.

What dosage forms it comes in:
Eye drop suspension in 5 mL bottle

WARNINGS AND PRECAUTIONS

BEFORE you use FLAREX talk to your doctor or pharmacist if you:

- Have glaucoma (high pressure in the eyes) or family history of glaucoma. Your doctor needs to check the pressure in your eyes (*intraocular pressure*) regularly.
- Have diabetes. You may be at a higher risk of developing high pressure in the eyes or cataracts (clouding of the lens of the eye).
- Have a disease that causes thinning of the eye. Small tears (*perforations*) have occurred.
- Are taking a class of drugs known as nonsteroidal anti-inflammatory drugs (NSAIDs). Taking FLAREX with NSAIDs may slow healing of the eye.
- Have taken another corticosteroid drug before.
- Are over 65 years old.
- Are under 18 years old.

STOP taking FLAREX if you:

- Develop an allergic reaction.
- Develop an eye infection.

Talk to your doctor if your eye symptoms do not improve after 2 days of treatment with FLAREX. Do not take FLAREX for longer than 10 days unless your doctor tells you to. If you must take FLAREX past 10 days, it should be under your doctor's watch.

While taking FLAREX
If you use FLAREX* for a long time:

- Your doctor should check the pressure in your eyes regularly. This is especially important for individuals with glaucoma, a family history of glaucoma or diabetes. Taking FLAREX for an extended time increases the risk of developing increased pressure in the eyes, glaucoma, vision problems, and cataracts.

You may also be at risk for developing an eye infection.

Side effects of corticosteroids include swelling around the trunk and in the face area with weight gain. These may happen when a corticosteroid such as FLAREX is absorbed into your blood. Side effects may happen after intense or constant long-term treatment with FLAREX. The side effects may happen in predisposed patients such as children, and patients treated with medicines that contain ritonavir or cobicistat. Talk to your doctor if you experience swelling around the trunk and in the face area with weight gain.

Contact lenses
You should not wear contact lenses when you have eye inflammation.

If you must wear contact lenses, do not wear them while using FLAREX. FLAREX contains a preservative (*benzalkonium chloride*), which is known to discolour soft contact lenses. Avoid contact with soft contact lenses.

Remove your contact lenses before applying FLAREX and wait at least 15 minutes before putting your lenses back in.

Driving and using machinery
Your vision may become temporarily blurry after using FLAREX. If this occurs, wait until your vision clears before driving or using machinery.

Pregnancy and Breastfeeding
If you are pregnant, may be pregnant or planning to become pregnant, talk to your doctor or pharmacist before using FLAREX.

It is not known whether FLAREX is present in breastmilk. Talk to your doctor or pharmacist if you are breastfeeding or planning to breast-feed.

INTERACTIONS WITH THIS MEDICATION

Tell your doctor or pharmacist about all the medicines you are taking, recently took or are planning to take, including those without a prescription.

Taking FLAREX at the same time as an NSAID may slow healing of the eye.

Tell your doctor if you are using medicines that contain ritonavir or cobicistat. This may increase the amount of fluorometholone in the blood.

PROPER USE OF THIS MEDICATION

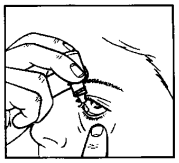
SHAKE WELL BEFORE USE.

After removing the cap: if the security snap collar is loose, remove the snap collar before using FLAREX.

Usual adult dose:
1 to 2 drops in the affected eye(s) 2 to 4 times a day.

During the first 24 to 48 hours (1 to 2 days), you may apply as much as 2 drops every 2 hours.

How to use:



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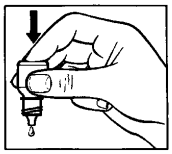

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1. Get the FLAREX bottle and a mirror.
2. Shake well before use.
3. Hold the bottle, pointing down, between your thumb and fingers.
4. Tilt your head back.
5. Pull down your lower eyelid with a clean finger until there is a 'v' pocket between your eyelid and your eye. The drop will go in here (picture 1).
6. Bring the bottle tip close to the eye. Do this in front of a mirror if it helps.
7. Do not touch your eye, eyelid, surrounding areas or other surfaces with the dropper to avoid contaminating the suspension.
8. Gently press on the base of the bottle to release one drop at a time. Do not squeeze the bottle. It is designed so that a gentle press on the bottle is all that it needs (picture 2).
9. If you miss, try again.
10. If you apply FLAREX to both eyes, repeat the steps for your other eye.
11. Close the bottle immediately after use.

If you are using other eye drop or eye ointment medicines, leave at least 5 minutes between each medicine. Eye ointments should be used last.

Overdose:
If you use more FLAREX than you should, rinse it out with lukewarm water. Do not apply more FLAREX until it is time for your next regular dose.

In case of drug overdose, contact a health care practitioner, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

Missed Dose:
If you forget to apply a dose of FLAREX, apply it as soon as you remember. However, if it is close to your next regular dose, skip the missed dose and continue with your usual schedule. **Do not** double dose to make up for a skipped dose.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Like all medicines, FLAREX may cause side effects, although not everybody gets them.

Side effects that may occur include: increased pressure in the eyes (*intraocular pressure*), eye pain, eye irritation, eye discomfort, such as burning or stinging, foreign sensation in the eye, blurred vision, eye redness, increased tearing, and bad taste in the mouth.

This is not a complete list of side effects. For any unexpected effects while taking FLAREX, contact your doctor or pharmacist.

HOW TO STORE IT

Store at room temperature in an upright position. Protect from heat and freezing. Keep out of the reach and sight of children.

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- **Report online at www.healthcanada.gc.ca/medeffect**
- **Call toll-free at 1-866-234-2345**
- **Complete a Canada Vigilance Reporting Form and:**
  - **Fax toll-free to 1-866-678-6789, or**
  - **Mail to: Canada Vigilance Program**
    Health Canada
    Postal Locator 1908C
    Ottawa, Ontario
    K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at www.healthcanada.gc.ca/medeffect.

NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be found at:
www.novartis.ca
or by contacting the sponsor, Novartis Pharmaceuticals Canada Inc., at:
1-800-363-8883

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