# PRODUCT MONOGRAPH

# Pr**FML®**

Fluorometholone Ophthalmic Suspension 0.1% w/v

Corticosteroid Anti-Inflammatory

Allergan Inc.
Markham, ON
L6G 0B5

Date of Preparation:
October 30, 1972

Date of Revision:
May 2, 2018

Submission Control No: 214474

## NAME OF DRUG

**Pr FML®**
Fluorometholone Ophthalmic Suspension 0.1% w/v

## THERAPEUTIC CLASSIFICATION

Topical corticosteroid

## ACTIONS

Corticosteroids inhibit the inflammatory response to a variety of inciting agents of a mechanical, chemical and immunological nature. They inhibit edema, fibrin deposition, capillary dilation, leukocyte migration, phagocytic activity, capillary proliferation, fibroblast proliferation, deposition of collagen and scar formation associated with inflammation. Corticosteroids are thought to act by controlling the rate of synthesis of proteins. Corticosteroids and their derivatives are capable of producing a rise in intraocular pressure.

## INDICATIONS

FML® (fluorometholone ophthalmic suspension 0.1% w/v) is indicated for the treatment of steroid-responsive inflammation of the palpebral and bulbar conjunctiva, cornea, and anterior segment of the globe.

## CONTRAINDICATIONS

FML® is contraindicated in:

- Superficial (or epithelial) herpes simplex keratitis (dendritic keratitis), vaccinia, varicella, and other viral diseases of the cornea and conjunctiva.
- Fungal diseases of ocular structures.
- Mycobacterial infections of the eye (e.g., Tuberculosis of the eye).
- Acute untreated infections of the eye.
- Hypersensitivity to the constituents of this medication (for a listing of ingredients, see PHARMACEUTICAL INFORMATION), or hypersensitivity to other corticosteroids.

## WARNINGS

Use of topical corticosteroids may cause increased intraocular pressure (IOP) in certain individuals. It is necessary that the IOP be checked frequently in patients with a history of glaucoma.

Use of corticosteroids may prolong the course and may exacerbate the severity of many viral eye infections (including herpes simplex). Use of corticosteroids in the treatment of patients with a history of herpes simplex requires great caution; frequent slit lamp microscopy is recommended.

Prolonged use of FML® (beyond 10 days) may result in glaucoma in susceptible individuals, with damage to the optic nerve, defects in visual acuity and fields of vision. Prolonged use may result in posterior subcapsular cataract formation, and may also suppress the host immune response, and thus increase the hazard of secondary ocular infections (See PRECAUTIONS section).

Visual disturbance may be reported with systemic and topical corticosteroid use. If a patient presents with symptoms such as blurred vision or other visual disturbances, consider evaluating for possible causes which may include cataract, glaucoma or rare diseases such as central serous chorioretinopathy (CSCR) which have been reported after use of systemic and topical corticosteroids.

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 use of topical steroids.

Concomitant use of topical NSAIDs and topical steroids may increase the potential for healing problems.

Although the systemic exposure is expected to be low with topical ophthalmic corticosteriod administration, co-treatment with CYP3A inhibitors may increase the risk of systemic corticosteroid-related side-effects.

Acute untreated infections of the eye may be masked or activity enhanced by the presence of steroid medication.

As with any ocular medication, if transient blurred vision occurs at instillation, the patient should wait until the vision clears before driving or using machinery.

## PRECAUTIONS

The initial prescription and renewal of FML® should be made only after appropriate ophthalmologic examination (including but not limited to IOP assessment and slit lamp biomicroscopy). If signs and symptoms fail to improve after two days, the patient should be re-evaluated.

Given the risks of serious adverse outcomes, FML® should not be used beyond 10 days, unless absolutely necessary, and only under strict ophthalmologic monitoring, including but not limited to tonometry and slit-lamp examination. Prolonged use of topical steroids increases the risk of raised IOP,

glaucoma, and subcapsular cataract formation (See WARNINGS section).

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

The preservative in FML®, benzalkonium chloride, may be absorbed by soft contact lenses and cause their discoloration. Patients wearing soft contact lenses should be instructed to remove contact lenses prior to administration of the suspension and wait at least 15 minutes after instilling FML® before reinserting soft contact lenses.

Pediatric
Safety and effectiveness have not been demonstrated in children of the age group 2 years or below.

Use in pregnancy
FML® should not be used during pregnancy, unless the potential benefits to the mother clearly outweigh the risks to the fetus. Safety of the use of topical steroids in humans during pregnancy has not been established. Fluorometholone has been shown to be embryocidal, fetotoxic, and teratogenic in pregnant rabbits when administered by ocular instillation (See TOXICOLOGY section).

Nursing women
It is not known whether topical ophthalmic administration of FML® could result in detectable quantities in human breast milk. Systemically administered corticosteroids appear in human milk and could suppress growth, interfere with endogenous corticosteroid production, or cause other untoward effects. Because of the potential for serious adverse reactions in nursing infants from fluorometholone, FML® is not recommended in nursing women, unless the benefit to the mother clearly outweighs the risks to the nursing infant.

Carcinogenesis, Mutagenesis, Impairment of Fertility
No studies have been conducted in animals or in humans to evaluate the potential of these effects with fluorometholone.

Patient Monitoring
Ophthalmologic examinations, especially tonometry and slit-lamp examination, are required at periodic intervals for patients on FML® therapy for more than several weeks, since chronic therapy may cause posterior subcapsular cataracts, increased IOP and glaucoma and may enhance the establishement of ocular infections. Other tests may be warranted in some patients depending on condition.

## ADVERSE REACTIONS

Ocular adverse reactions associated with ophthalmic steroids may include elevated intraocular pressure (IOP), which may be associated with optic nerve damage, loss of visual acuity and field of vison defects, posterior subcapsular cataract formation, secondary ocular infection, delayed wound healing (including perforation of the globe where there is thinning of the cornea or sclera).

**Eye disorders:** posterior subcapsular cataract formation, secondary ocular infection from pathogens

liberated from ocular tissues, and perforations of the globe

Post-Market Adverse Drug Reactions
The following adverse reactions have been identified during postmarketing use of FML® in clinical practice. Because they are reported voluntarily from a population of unknown size, estimates of frequency cannot be made.

**Eye disorders:** eye irritation, conjunctival/ocular hyperemia, visual disturbance, foreign body sensation, eyelid edema, blurred vision, eye discharge, eye pruritis, lacrimation increased, eye edema/eye swelling, mydriasis, ulcerative keratitis, ocular infection (including bacterial, fungal, and viral infections), visual field defect, punctate keratitis
**Immune system disorders:** hypersensitivity and allergic reactions
**Nervous system disorders:** dysgeusia
**Skin and subcutaneous tissue disorders:** rash

## SYMPTOMS AND TREATMENT OF OVERDOSAGE

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

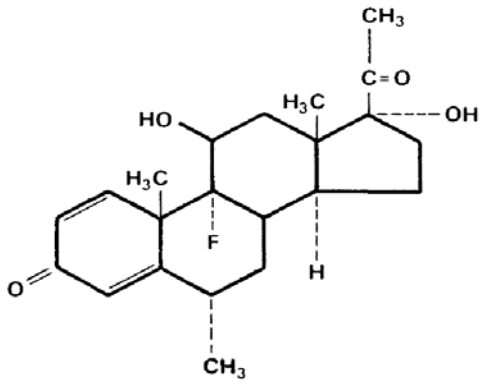
There is no known treatment of overdosage. If accidental overdosage occurs in the eye, flush the eye with water or normal saline. Discontinue medication when heavy or protracted use is suspected.

## PHARMACEUTICAL INFORMATION

Description
Fluorometholone is an odorless, white to slightly yellow-white powder with a melting point of about 280°C with some decomposition, an empirical formula of $C_{22}H_{29}FO_4$, and a molecular weight of 376.47. It has a characteristic ultraviolet absorption maximum in methanol at 239 millimicrons.

Chemical name 9-Fluoro-llß, 17-dihydroxy-6α-methylpregna-l, 4-diene-3, 20-dione.

Structural formula




Empirical Formula: $C_{22}H_{29}FO_4$ Molecular Weight: 376.47

Composition:
FML® contains fluorometholone 0.1% w/v as the active ingredient, with benzalkonium chloride 0.0046% w/v as the preservative. Inactive ingredients in the preserved multi dose bottles are polyvinyl alcohol, edetate disodium, sodium chloride, sodium phosphate monobasic monohydrate, sodium phosphate dibasic heptahydrate, polysorbate 80, sodium hydroxide to adjust pH, and purified water. Product is supplied sterile.

## DOSAGE AND ADMINISTRATION

Recommended Dose and Dosage Adjustment
FML® is for topical ophthalmic use only. Shake fluorometholone ophthalmic suspensions well before use.

Instill 1 to 2 drops into the conjunctival sac two to four times daily. During the initial 24 to 48 hours, the dosage may be safely increased to 2 drops every 4 hours. 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.

The dosing of fluorometholone ophthalmic suspension 0.1% may be reduced, but care should be taken not to discontinue therapy prematurely. If FML® is used for longer than 10 days (see WARNINGS), withdrawal of treatment should be carried out by gradually decreasing the frequency of applications.

Missed Dose
If you forget to apply your eye drops at your normal time, simply apply them as soon as you remember. Then go back to the original schedule as directed by your doctor. **Don't try to catch up on missed drops by applying more than one dose at a time.**

Administration
To prevent eye injury or contamination, care should be taken to avoid touching the bottle to the eye, the eyelids or to any other surface. The use of the bottle by more than one person may spread infection.

## STORAGE AND STABILITY

Store in an upright position at 15ºC - 25ºC. Protect from freezing. Keep bottle tightly closed when not in use.

Discard any unused product 1 month after first opening.

The product should be discarded after the expiration date. Any unused product or waste material should be disposed of in accordance with local requirements.

## DOSAGE FORMS AND AVAILABILITY

FML® is available as a sterile topical ophthalmic suspension in an opaque low density polyethylene (LDPE) bottles with dropper tips and high impact polystyrene (HIPS) caps in the following sizes: 5mL and 10mL. On prescription only.

## PHARMACOLOGY

In comparison with hydrocortisone, fluorometholone was found two to three times as effective in tests of catabolic effects in monkeys. It was, however, 131 times as effective in anti-inflammatory effect (using rat granuloma pouch techniques) and approximately 40 times as effective in a variety of other test models. Fluorometholone and prednisolone were evaluated for anti-inflammatory potency in a system employing the eyes of albino rabbits. The results of the study showed fluorometholone to be forty (40) times as effective as hydrocortisone in comparison to prednisolone which was found to be two (2) times as effective as hydrocortisone. These results are in accord with published data on topical anti-inflammatory corticosteroids. In a study on adult female rabbits, fluorometholone was found qualitatively to penetrate the intact eye into the aqueous humor. These results are in accord with published data on dexamethasone and prednisolone.

Glucocorticoids inhibit both the early inflammatory activities such as edema, fibrin deposition, capillary dilatation, and migration of phagocytes as well as the later manifestations such as capillary proliferation, fibroblast proliferation, collagen deposition and cicatrization.

These drugs are believed to block the progression of inflammation by increasing the resistance of cells to cytotoxic breakdown products in the inflammatory zone. There is evidence to indicate that glucocorticoids inhibit inflammation and its spread by stabilizing membranes, especially those of the lysosomes.

## TOXICOLOGY

The recommended maximum human dosage of 0.1% fluorometholone (2 drops 4 times per day per 50 kg of body weight) is capable of causing systemic effects in animals when administered orally. Dosages of twenty (20) and thirty (30) times human equivalent dosages were administered to dogs and rats during both 90-day oral subacute toxicity studies. Systemic effects typical of glucocorticoids were noted, such as decreases in body weight gain, leukopenia, heterophilia, lymphocytopenia and liver malfunction. This was an unexpected finding as considerable data were available to Allergan Pharmaceuticals concerning subacute oral administration to humans that indicated no effect with three (3) times the human dosage when administered orally (2.5 mg per day vs. 0.8 mg for maximum ophthalmic exposure). The male rats were less affected at the thirty (30) times human equivalent dosage than the low-dosage females. By the 60th day of treatment, the eyes in all the female rats in the 0.16 mg/kg/day dosage level unexpectedly appeared partially buphthalmic and nebulous, lacking the pink color which results from the capillary bed.

The oral administration of a drug is bound to result in a greater systemic absorption than an ophthalmic application; however, the degree of difference is not known.

Draize eye irritation studies have been successfully completed using 0.1% and 0.25% fluorometholone. Nine (9) albino rabbits were utilized to test the toxicity of both 0.1% and 0.25% fluorometholone formulation on the eye mucosa. In addition to the routine observations during the twenty (20) day instillation period, each rabbit was observed for a seven (7) day post instillation period for possible delayed changes or lesions. Two percent fluorescein was instilled to determine if there was any corneal damage resulting from the treatment. One (1) animal was sacrificed on the last day of the observation period and subjected to a histological examination.

Upon examination, there were no histological differences observed between the treated and the control eyes. Thus, both concentrations (0.1% and 0.25%) were found to be free from any irritating effects.

Due to the maximum human dosage (3 drops 4 times per day) administered to young 2 kg rabbits for a twenty (20) day period, it was not surprising that some of the animals did suffer from symptoms of glucocorticoid excess and eventually died from treatment.

A Draize eye irritation test has been successfully completed with FML-NEO (0.1% fluorometholone-0.5% neomycin sulfate) Liquifilm Ophthalmic Suspension, a similar formulation in that fluorometholone is a component of the combination product.

Nine (9) albino rabbits were utilized to test the toxicity of fluorometholone-neomycin sulfate formulation on the eye mucosa. In addition to the routine observations for possible delayed ocular changes or lesions during the 90-day instillation period, the animals were sacrificed on the last day of the observation period and subjected to a histological examination. Upon examination, there were no histological differences between the treated and the control eyes.
During the fifth (5th) week of study it was noted that the animals in the higher dose level (l0x and 20x human dose) unexpectedly appeared to have protruded eyes, a buphthalmos-like condition, which persisted throughout the remainder of the study.
Systemic effects typical of glucocorticoids were noted, such as decreases in body weight gain, leukopenia, heterophilia, lymphocytopenia and liver malfunction.

When Fluorometholone was applied ocularly daily to rabbits on days 6-18 of gestation, dose-related fetal loss and fetal abnormalities including cleft palate, deformed rib cage, anomalous limbs and neural abnormalities such as encephalocele, craniorachischisis, and spina bifida were observed.

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

## REFERENCES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**INFORMATION FOR THE CONSUMER**

**PrFML®**
**Fluorometholone**
**Ophthalmic suspension 0.1% w/v**

**This leaflet is part of the "Product Monograph" and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about FML®. Contact your doctor or pharmacist if you have any questions about the drug.**

## ABOUT THIS MEDICATION

**What the medication is used for:**
**FML®** is used to treat inflammation of the eye.

**What it does:**
**FML®** is an eye drop which contains the steroid fluorometholone, which reduces the production of substances linked to inflammation. By reducing these substances, the inflammation and pain are reduced in the eye.

**When it should not be used:**
Do not use **FML®**:
- if you are allergic (hypersensitive) to fluorometholone, benzalkonium chloride, or any of the other ingredients in **FML®**. (See **What the important nonmedicinal ingredients are**), or if you are allergic to other corticosteroids
- if you have (or think you have) an infection of the eye, including a bacterial infection, a viral infection (such as herpes simplex keratitis, vaccinia, varicella), or a fungal infection or if you have tuberculosis of the eye

**What the medicinal ingredient is:**
Fluorometholone

**What the important nonmedicinal ingredients are:**
Benzalkonium chloride 0.0046% w/v (as preservative), polyvinyl alcohol, edetate disodium, sodium chloride, sodium phosphate monobasic monohydrate, sodium phosphate dibasic heptahydrate, polysorbate 80, sodium hydroxide to adjust pH, and purified water.

**What dosage forms it comes in:**
Sterile ophthalmic suspension, fluorometholone 0.1% w/v

## WARNINGS AND PRECAUTIONS

This product should be used with caution in patients with a history of glaucoma .

Prolonged use may cause the pressure inside your eye (intraocular pressure) to increase.

**FML®** may slow healing after surgery or a wound. Contact your doctor right away if you develop further symptoms such as: eye redness, itching, tearing, discharge, feeling something in your eye, seeing floating spots or sensitivity to light.

Your sight may become blurred for a short time just after using **FML®**. You should not drive or use machines until your sight is clear again.

BEFORE you use **FML®** talk to your doctor or pharmacist if:
- you have or have ever had glaucoma (increased pressure in the eye that can lead to gradual loss of vision). **FML®** ophthalmic emulsion may increase the risk of glaucoma, especially when it is used for more than 10 days. Your doctor may monitor the pressure in your eyes
- you are pregnant or intend to become pregnant
- you are breastfeeding or plan to breastfeed. You should not use **FML®** unless your doctor determines it is appropriate for your infant as there may be a risk of harming the nursing baby
- you have an eye infection or any other eye condition
- you are allergic to fluorometholone, to any of the other ingredients, such as benzalkonium chloride, or to any of the parts of the container
- you wear contact lenses. The preservative in **FML®** (benzalkonium chloride) may be absorbed by and discolour soft contact lenses. Lenses should be removed prior to application of **FML®** and kept out for 15 minutes after use

While taking **FML®**
If pain and inflammation fail to improve after two days of using **FML®**, or if other new or worsening symptoms occur, consult your doctor.

## INTERACTIONS WITH THIS MEDICATION

Tell your doctor about all the medicines you are taking including those without a prescription, vitamins, minerals and herbal products.

No drug interaction studies have been done with **FML®**.

## PROPER USE OF THIS MEDICATION

**Usual adult dose and dose for children above the age of 2:**
Apply 1-2 drops into the conjunctival sac (a space between the lower eyelid and eye- see pictogram) two to four times daily. During the first 24 to 48 hours, the dosage may be safely increased to 2 drops every 4 hours. Use **FML®** for as long as your doctor tells you. Do not stop treatment early.

**How to Use:**
The proper application of your eye drops is very important. If you have any questions ask your doctor or pharmacist.

1. Shake the bottle before use. Wash your hands. Tilt your head back and look at the ceiling.

1.


2. Gently pull the lower eyelid down until there is a small pocket.

2.


3. Turn the bottle upside down and squeeze it to release one or two drops into each eye that needs treatment.

3.


4. Let go of the lower lid, and close your eye for 30 seconds.

4.


5. If a drop misses your eye, try again.

6. Close the cap immediately after use.

7. Wipe the excess liquid from your face.

8. Wash your hands to remove any medication

To help prevent infections, do not let the tip of the bottle touch your eye, eyelid or anything else.

This bottle should be used by only one person, as the use by more than one person may spread infection.

If signs and symptoms fail to improve after two days of using **FML®**, consult your doctor.

If you develop an eye infection or other new or worsening symptoms, contact your doctor or pharmacist.

If you are using any other medication in the eye, wait at least 15 minutes before applying.

**Overdose:**

| |
|---|
| In case of accidental oral ingestion or overdose, contact your doctor, regional poison control centre immediately or hospital emergency department, even if there are no symptoms. |

**If you accidentally use too many drops, just go back to your regular once a day dosing the next day.**

**Missed Dose:**
If you forget to apply **FML®** at your normal time, simply apply them as soon as you remember. Then go back to the original schedule as directed by your doctor. **Don't try to catch up on missed drops by applying more than one dose at a time.**

## SIDE EFFECTS AND WHAT TO DO ABOUT THEM

You should contact your doctor if any of the following less serious side effects become bothersome: eye irritation, redness, blurred vision, itching, tearing, taste disorder.

If an allergic (hypersensitivity) reaction occurs, with symptoms such as rash, hives, swelling of the face, lips, tongue or throat, difficulty breathing, contact your doctor.

You should see your doctor if any of the following side effects that affect the eye(s) prove troublesome or if they are long lasting:

- increased pressure inside your eye and/or glaucoma
- cataract (a loss of transparency of the lens of the eye with partial or complete loss of vision)
- new or worsening pain and/or redness of the eye
- difficulty seeing clearly
- secondary infection in the eye
- break of the eye globe

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

## SERIOUS SIDE EFFECTS AND WHAT TO DO ABOUT THEM

| Symptom / effect | | Talk with your doctor or pharmacist | | Stop taking drug and call your doctor or pharmacist |
|---|---|---|---|---|
| | | Only if severe | In all cases | |
| Vision changes | Blurred vision; eye swelling; eye pain; eye discharge; foreign body sensation | ✓ | | ✓ |
| New eye infection | Eye redness, eye swelling, eye crusting, weeping eyes | | ✓ | ✓ |

## HOW TO STORE IT

**FML®** should be stored between 15ºC - 25ºC. Protect from freezing.

Store it in a safe place where children cannot reach it or see it.

**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 0701E**
  **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 obtained by contacting the sponsor, Allergan Inc. at: 1-800-668-6424.

This leaflet was prepared by Allergan Inc.

Last revised: May 2, 2018