NOVARTIS

FLUOROMETHOLONE

acetate

FLAREX®
1mg/mL (0.1%)
Sterile Ophthalmic Suspension
Corticosteroid

DESCRIPTION AND COMPOSITION

Pharmaceutical form

White to off white Sterile Ophthalmic Suspension. The reference monograph for this drug product is USP.

Active substance

Each mL of the suspension contains:
Fluorometholone Acetate, USP.....1.0 mg

Excipients

Sodium chloride, monobasic sodium phosphate (monohydrate), disodium edetate, hydroxyethylcellulose, tyloxapol, benzalkonium chloride, hydrochloric acid, sodium hydroxide, purified water.

INDICATIONS

Fluorometholone Acetate (Flarex®) Sterile Ophthalmic Suspension is indicated for the treatment of steroid-responsive, non-infectious inflammations of the eyes, such as inflammations of palpebral and bulbar conjunctiva, cornea, and anterior segment of the eye.

DOSAGE REGIMEN AND ADMINISTRATION

Dosage regimen

One or 2 drops in the conjunctival sac of the affected eye 4 times daily. During the initial 48 hours the dosage may be increased to 2 drops every 2 hours.

Special populations

Renal and hepatic impairment

No studies have been conducted with Fluorometholone Acetate (Flarex®) Sterile Ophthalmic Suspension in patients with hepatic or renal impairment.

Pediatric patients (below 3 years)

Safety and efficacy of Fluorometholone Acetate (Flarex®) Sterile Ophthalmic Suspension in children below 3 years has not been established.

Geriatric patients (65 years of age or above)

No dosage regimen adjustment is required in patients 65 years of age or above.

Method of administration

- For ocular use only.
- After cap is removed, if tamper evident snap collar is loose, remove the snap collar before using product.
- Eye drops are not for injection. They should never be injected subconjunctivally, nor should they be directly introduced into the anterior chamber of the eye.
- The bottle must be shaken well before use.
- To avoid contamination, the dropper tip should not touch any surface. The dropper tip should also not come into contact with the eye as this may cause injury to the eye.
- Either nasolacrimal occlusion or gently closing the eyelid(s) after administration is recommended. This may reduce the systemic absorption of medicinal products administered via ocular route and result in a decrease in systemic adverse reactions.
- It is advisable that the intraocular pressure be routinely monitored.
- Care must be taken not to discontinue therapy prematurely.
- Physician should be consulted if there is no improvement after 2 weeks.

CONTRAINDICATIONS

- Hypersensitivity to the active substance or to any of the excipients.
- Acute, untreated bacterial infections.
- Herpes simplex keratitis.
- Vaccinia, varicella, and other viral infection of cornea or conjunctiva.
- Fungal diseases of ocular structures.
- Mycobacterial ocular infections.

WARNINGS AND PRECAUTIONS

- Prolonged use of topical ophthalmic corticosteroids may result in ocular hypertension and/or glaucoma, with damage to the optic nerve, reduced visual acuity and visual field defects, and posterior subcapsular cataract formation. In patients receiving prolonged ophthalmic corticosteroid therapy, intraocular pressure should be checked routinely and frequently. This is especially important in pediatric patients, as the risk of corticosteroid-induced ocular hypertension may be greater in children and may occur earlier than in adults.
- The risk of corticosteroid-induced raised intraocular pressure and/or cataract formation is increased in predisposed patients (e.g. diabetes).
- 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, see section INTERACTIONS).

- Corticosteroids may reduce resistance to and aid in the establishment of bacterial, fungal or viral infections and mask the clinical signs of infection.
- Fungal infection should be suspected in patients with persistent corneal ulceration who have been or are receiving these drugs, and corticosteroids therapy should be discontinued if fungal infection occurs.
- Topical ophthalmic corticosteroids may slow corneal wound healing. Topical NSAIDs are also known to slow or delay healing. Concomitant use of topical NSAIDs and topical steroids may increase the potential for healing problems (see section INTERACTIONS).
- In those diseases causing thinning of the cornea or sclera, perforations have occurred with the use of topical corticosteroids.
- Fluorometholone Acetate (Flarex®) Sterile Ophthalmic Suspension contains benzalkonium chloride which may cause eye irritation and may possibly discolor soft contact lenses. Contact lenses must be removed before administration of eye drops and reinserted at least 15 minutes later.

ADVERSE DRUG REACTIONS

Adverse drug reactions from spontaneous reports and literature cases (frequency not known)

The following adverse drug reactions have been derived from post-marketing experience with Fluorometholone Acetate (Flarex®) Sterile Ophthalmic Suspension via spontaneous case reports and literature cases. Because these reactions are reported voluntarily from a population of uncertain size, it is not possible to reliably estimate their frequency which is therefore categorized as not known.

Adverse drug reactions are listed according to system organ classes in MedDRA. Within each system organ class, ADRs are presented in order of decreasing seriousness.

Table 1 Adverse drug reactions from spontaneous reports and literature (frequency not known)

System Organ Classification	Adverse drug reactions
Eye disorders	intraocular pressure increased, eye pain, eye irritation, ocular discomfort, foreign body sensation in eyes, vision blurred, ocular hyperaemia, lacrimation increased
Gastrointestinal disorders	dysgeusia

INTERACTIONS

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

- Co-treatment with CYP3A4 inhibitors, including ritonavir and cobicistat, may increase systemic exposure resulting in increased risk of systemic 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.

PREGNANCY, LACTATION, FEMALES AND MALES OF REPRODUCTIVE POTENTIAL

Pregnancy

Risk summary

There is limited data on the use of Fluorometholone Acetate (Flarex®) Sterile Ophthalmic Suspension in pregnant women. In rabbits, ocular instillation of fluorometholone below the therapeutic dose levels resulted in embryocidality, fetotoxicity and teratogenicity.

Fluorometholone Acetate (Flarex®) Sterile Ophthalmic Suspension is not recommended during pregnancy.

Animal data

An embryo-fetal development study was conducted in rabbits. Fluorometholone was ocularly instilled to both eyes at doses of 0.075, 0.15, 0.30 and 0.60 mg/day from gestation day 6 to 18, targeting the period of organogenesis. Maternal body weight gain increased during the first 4 days of treatment followed by a decrease until the end of the treatment at all dose levels. Dose related increase in the incidence of total litter losses (abortion and/or total resorption), higher fetal loss, lower litter size and lower litter and mean pup weights were noted. An increased incidence of minor anomalies and major malformations including cleft palate, deformed rib cage, anomalous limbs, encephalocele, craniorachischisis, and spina bifida occurred at all doses. The lowest dose (0.075 mg/rabbit) in this study corresponds to a dose ratio of about 0.1 (based on body surface area), when compared to the maximum recommended human ocular dose of 0.048 mg/kg/day.

Lactation

Risk summary

It is unknown whether fluorometholone/metabolites are transferred to human milk following topical ocular administration. Systemic corticosteroids are transferred to human milk and could suppress growth, interfere with endogenous corticosteroid production, or cause other untoward effects. A risk to the breastfeeding child cannot be excluded.

A decision must be made whether to discontinue breast-feeding or to discontinue / abstain from therapy taking into account the benefit of breastfeeding for the child and the benefit of therapy for the woman.

Females and males of reproductive potential

Infertility

There are no data regarding the effects of Fluorometholone Acetate (Flarex®) Sterile Ophthalmic Suspension on male or female fertility.

OVERDOSAGE

An ocular overdose of Fluorometholone Acetate (Flarex®) Sterile Ophthalmic Suspension is not likely to be associated with toxicity.

Accidental ingestion is also unlikely to be associated with toxicity.

CLINICAL PHARMACOLOGY

Fluorometholone is a synthetic corticosteroid (glucocorticoid), a derivative of desoxyprednisolone. It is a member of the group of universally known steroids used for the treatment of eye inflammation.

Mechanism of action (MOA)

There is no generally accepted explanation for the mechanism of action of ocular corticosteroids. It is believed they act by the induction of phospholipase A2 inhibitory proteins, collectively called lipocortins, which 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 A2.

Their primary target is the cytosolic glucocorticoid receptor. After binding the receptor, the newly formed receptor-ligand complex translocates itself into the cell nucleus, where it binds to many glucocorticoid response elements (GRE) in the promoter region of the target genes. The DNA bound receptor interacts with basic transcription factors, causing an increase in expression of target genes.

Pharmacodynamics (PD)

Corticosteroids such as fluorometholone inhibit the inflammatory response to a variety of inciting agents and are associated with a delay in healing. They inhibit the edema, fibrin deposition, capillary dilation, leukocyte migration, capillary proliferation, fibroblast proliferation, deposition of collagen, and scar formation associated with inflammation.

Pharmacokinetics (PK)

Absorption and distribution

Fluorometholone acetate 0.1% is absorbed rapidly into rabbit cornea after topical ocular administration with a maximum concentration of 2.95 ng/g at the earliest time point sampled (0.5 hour). The hydrolysis product, fluorometholone was observed in half the rabbit corneas at 2 hours. Fluorometholone acetate concentrations in aqueous humor similarly peaked at the earliest time point and its hydrolysis product, fluorometholone peaked at 1 hour in aqueous humor with similar concentration to that of topical ocular administered fluorometholone.

Biotransformation/metabolism

Fluorometholone acetate is an ester which is subject to rapid hydrolysis in ocular tissues as well as blood. The principal metabolite is fluorometholone which is likely to undergo further systemic metabolism as described above.

Elimination

The elimination pathway of topical ocular administered fluorometholone and its metabolites had not been reported. Most topical corticosteroids are metabolized in the liver and their metabolites excreted in urine and bile.

Linearity/non-linearity

Ocular uptake studies evaluating dose-proportionality of either fluorometholone or fluorometholone acetate have not been conducted.

PK/PD relationship

A specific PK/PD model has not been established for fluorometholone. Corticosteroids cause a rise in intraocular pressure in susceptible individuals. In a small study, Fluorometholone Acetate (Flarex®) Sterile Ophthalmic Suspension demonstrated a significantly longer average time to produce a rise in intraocular pressure than did dexamethasone phosphate; however, the ultimate magnitude of the rise was equivalent for both drugs and in a small percentage of individuals a significant rise in intraocular pressure occurred within 1 week. Published literature reports fluorometholone has a dose-dependent ocular hypertensive effect, particularly in steroid responders and children, although less-pronounced compared to dexamethasone.

Special populations

Hepatic Impairment, Renal Impairment and Geriatric Patients

Studies evaluating the pharmacokinetics with Fluorometholone Acetate (Flarex®) Sterile Ophthalmic Suspension in patients with hepatic and renal impairment or in geriatric patients have not been conducted.

Pediatric use (see sections DOSAGE REGIMEN AND ADMINISTRATION and WARNINGS AND PRECAUTIONS)

When fluorometholone is used in children, a lower frequency and shorter duration of usage is recommended. The ocular-hypertensive response in children occurs more frequently, more severely, and more rapidly than that reported in adults. Additionally, ocular corticosteroids including fluorometholone are associated with systemic activity which can cause temporary growth suppression in children.

Fluorometholone Acetate (Flarex®) Sterile Ophthalmic Suspension is not indicated in children under 3 years old. No specific studies have been conducted in this age group. Use of fluorometholone in children under the age of 3 is limited to a single published study (n=21). Transient ocular hypertension induced by fluorometholone could not be observed, however there were no sustained or long-term effects on optic nerve health, and a normal course of ocular growth was observed in these children.

NON-CLINICAL SAFETY DATA

No carcinogenesis, mutagenesis or impairment of fertility studies have been conducted in animals or in humans with fluorometholone. Non-clinical data from fluorometholone studies reveal systemic effects which are commonly associated with corticosteroids and include suppression of body weight gain; a decrease in lymphocyte count; atrophy of the lymphatic glands and adrenal gland; and for local effects, thinning of the skin.

No fertility, peri- and postnatal development, juvenile toxicity studies are available. For information on embryo-fetal development study, see section PREGNANCY, LACTATION, FEMALES AND MALES OF REPRODUCTIVE POTENTIAL.

INCOMPATIBILITIES

Not applicable

STORAGE

Store at temperatures not exceeding 25°C. SHAKE WELL BEFORE USING.

Discard one month after opening.

Fluorometholone Acetate (Flarex®) Sterile Ophthalmic Suspension should not be used after the date marked "EXP" on the pack.

Fluorometholone Acetate (Flarex®) Sterile Ophthalmic Suspension must be kept out of the reach and sight of children.

AVAILABILITY

5 mL plastic DROPTAINER® dispenser.

INSTRUCTIONS FOR USE AND HANDLING

No special requirements.

Special precautions for disposal

No special requirements.

CAUTION:

Foods, Drugs, Devices, and Cosmetics Act prohibits dispensing without prescription.

For suspected adverse drug reaction, report to the FDA: **www.fda.gov.ph**

The patient is advised to seek IMMEDIATE medical attention at the first sign of adverse drug reaction.

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® = registered trademark

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