1 NAME OF THE MEDICINAL PRODUCT

FLAREX

FLUCON

AFLAREX SUSPENSION

FLAREX OPHTHALMIC SUSPENSION, 0.1%

FLAREX Eye Drops, Suspension

Flarex 1 mg/ml Eye Drops, Suspension

* *Alternative names may be applicable. Refer to the currently approved product labeling.*

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Active ingredient for Flucon is Fluorometholone 0.1%

Active ingredient for Flarex is Fluorometholone acetate 0.1%.

For excipients, see section 6.1.

**Refer to the currently approved product labeling.*

3 PHARMACEUTICAL FORM

Eye Drops, Suspension

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

[Flucon Eye Drops, suspension and Flarex Eye Drops, suspension] for ophthalmic use are indicated for:

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.

* *Refer to the currently approved product labeling. Indication and patient population are per national approval.*

4.2 Posology and Method of Administration

Posology

Use in subjects 3years and older (including the elderly)

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.

Pediatric population

Safety and efficacy of Flucon Eye Drops, Suspension and Flarex Eye Drops, Suspension in children below 3 years have not been established.

Method of administration

For ocular use only.

After cap is removed, if tamper evident snap collar is loose, remove before using product. *[Only applicable for eye drops containing a snap collar]*

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 prevent contamination of the dropper tip and suspension, care must be taken not to touch the eyelids, surrounding areas, or other surfaces with the dropper tip of the bottle.

It is advisable that the intraocular pressure be routinely monitored

Care must be taken not to discontinue therapy prematurely

If not improvement after 2 weeks, consult physician.

* *Refer to the currently approved product labeling. Posology and patient population are per national approval.*

4.3 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.

4.4 Special Warnings and Precautions for Use

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. *[FOR COUNTRIES THAT HAVE PAEDIATRIC USE INCLUDED OR APPROVED IN THE LOCAL LABEL:]* <This is especially important in paediatric patients, as the risk of corticosteroid-induced ocular hypertension may be greater in children and may occur earlier than in adults>. *[FOR COUNTRIES THAT HAVE PAEDIATRIC USE EXCLUDED OR CONTRA-INDICATED IN THE LOCAL LABEL:]* <This is especially important in paediatric patients, as the risk of corticosteroid-induced ocular hypertension may be greater in children and may occur earlier than in adults. *[BRANDNAME]* is not approved for use in paediatric patients>.

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).

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 4.5).

In those diseases causing thinning of the cornea or sclera, perforations have been known to occur with the use of topical corticosteroids.

The wearing of contact lenses is discouraged during treatment of an ocular inflammation. [Flucon Eye Drops, Suspension] and [Flarex Eye Drops, Suspension] contain benzalkonium chloride which may cause eye irritation and is known to discolour soft contact lenses. Avoid contact with soft contact lenses. In case patients are allowed to wear contact lenses, they must be instructed to remove contact lenses prior to application of [Flucon Eye Drops, Suspension] and [Flarex Eye Drops, Suspension] and wait at least 15 minutes before reinsertion. *[Only for products containing benzalkonium chloride]*.

4.5 Interaction with other Medicinal Products and Other Forms of Interaction

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 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.

4.6 Pregnancy and Lactation

Fertility

There are no data regarding the effects of [Flucon Eye Drops, suspension] and [Flarex Eye Drops, suspension] on male or female fertility.

Pregnancy

There are no or limited amount of data from the use of [Flucon Eye Drops, suspension] and [Flarex Eye Drops, suspension] in pregnant women. Studies in animals with corticosteroids have shown reproductive toxicity.*

Breast-feeding

It is unknown whether fluorometholone/metabolites are excreted in human milk following topical ocular administration. Systemic corticosteroids are excreted in human milk. A risk to the suckling child cannot be excluded.*

**Refer to Regional Guidelines on Pregnancy and Lactation for appropriate recommendation statements.*

4.7 Effects on Ability to Drive and Use Machines

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

4.8 Undesirable Effects

The following adverse reactions have been identified from post-marketing surveillance following administration of [Flucon Eye Drops, suspension] and [Flarex Eye Drops, suspension]. Frequencies cannot be estimated from the available data. Within each System Organ Class adverse reactions are presented in order of decreasing seriousness.

System Organ Classification	**Adverse reactions** [MedDRA Term (v.15.1)]

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

4.9 Overdose

An ocular overdose of [Flucon Eye Drops, Suspension] and [Flarex Eye Drops, Suspension] is not likely to be associated with toxicity.

Accidental ingestion is also unlikely to be associated with toxicity.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic Properties

Pharmacotherapeutic group: ophthalmological; anti-inflammatory agents; corticosteroids, plain

ATC code: S01B A07

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.

Pharmacodynamic effects

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.

Mechanism of action

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.

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, Flucon Eye Drops, Suspension and Flarex Eye Drops, 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.

Pediatric use (See sections 4.2. and 4.4)

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.

Flucon Eye Drops, Suspension and Flarex Eye Drops, Suspension are 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.

Data from clinical studies

Flucon Eye Drops, Suspension and Flarex Eye Drops, Suspension demonstrated efficacy in the treatment of ocular inflammation of noninfectious origin in 3 well-controlled clinical trials and 12 published studies.

** Refer to the currently approved product labeling. Indication and patient population as per national approval*

5.2 Pharmacokinetic Properties

Fluorometholone

Absorption and Distribution

Following topical ocular administration of 0.1% fluorometholone in 22 adult patients undergoing cataract surgery, the maximum fluorometholone concentration of 5.1 ng/mL in aqueous humor was observed at 0.5-1 hour post dose.

Following topical ocular administration of a single 0.1% dose of fluorometholone to rabbits, the drug was absorbed into the eye. Maximal cornea concentrations of 0.029 µg/g were observed 2 hours after topical ocular administration and maximum aqueous humor concentrations (0.013 µg/ml) were observed at the first sampling time point of 0.5 hours

Biotransformation

Fluorometholone is metabolized in humans by reduction of the 6,7 alkane bond to form 6,7-dehydro-fluorometholone as well as hydroxylation to form 6-hydroxy-fluorometholone.

These two metabolites undergo further oxidation to form 6,7-dehydro-20-hydroxy-fluorometholone and 6,20 dehydroxy-fluorometholone, respectively.

Fluorometholone Acetate

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 timepoint 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 timepoint and its hydrolysis product, fluorometholone peaked at 1 hour in aqueous humor with similar concentration to that of topical ocular administered fluorometholone.

Biotransformation

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.

Fluorometholone and Fluorometholone Acetate

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.

Hepatic Impairment, Renal Impairment and Geriatric Patients

Studies evaluating the pharmacokinetics with Flucon or Flarex eye drop suspensions in patients with hepatic and renal impairment or in geriatric patients have not been conducted.

5.3 Preclinical Safety Data

No carcinogenesis, mutagenesis or impartment 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.

Non-clinical reproductive and developmental toxicity studies with other corticosteroids have demonstrated exaggerated systemic pharmacology at exposures considered sufficiently in excess of the maximum human exposure, indicating little relevance to clinical use.

6 PHARMACEUTICAL PARTICULARS

6.1 List of Excipients

Flarex:

Benzalkonium chloride

Edetate disodium (dehydrate)

Hydrochloric acid

Hydroxyethyl cellulose

Monobasic sodium phosphate (monohydrate)

Purified water

Sodium chloride

Sodium hydroxide

Tyloxapol

Flucon:

Sodium dihydrogen phosphate monohydrate

Disodium phosphate anhydrous

Polysorbate 80

Sodium chloride

Benzalkonium chloride

Disodium edetate

Polyvinyl alcohol

Hypromellose

Hydrochloric acid

Sodium hydroxide

Purified water

** Information might differ in some countries. Refer local labeling.*

6.2 Incompatibilities

Not applicable

** Information might differ in some countries. Refer local labeling.*

6.3 Shelf Life

Flarex:

Up to 36 months

Flucon:

Up to 36 months

** Information might differ in some countries. Refer local labeling.*

6.4 Special Precautions for Storage

Flucon :

Do not store above 25°C.

Flarex:

Do not store above 30°C".

** Information might differ in some countries. Refer local labeling.*

6.5 Nature and Contents of Container

5 mL, 2.5 mL, 8 mL, 10 mL

Polyethylene (PE) bottle and plug, polypropylene (PP) plug
OR
PE Droptainer bottle
OR
Low-density PE bottle with PP closure

** Information might differ in some countries or for different fill sizes / presentations. Refer to local labeling.*

6.6 Instructions for Use and Handling <and Disposal>

No special requirements.

7 CHANGES FROM PREVIOUS VERSION

CDS Amendment – TDOC-0050386 v.2.0, standard implementation

The following information has been added to sections 4.4 and 4.5:

> Section 4.4: 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).
>
> Section 4.5: 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.

TDOC-0050386 v.1.0 New CCDS.The following changes have been made to the previous reference document (CCSI TDOC-0012241)

Amendment: TDOC-0012241 v3.0, January 2014:

The document is amended with the following information:

Section 4.4:

- The warning "The risk of corticosteroid-induced raised intraocular pressure and/or cataract formation is increased in predisposed patients (e.g. diabetes)" is added.
- The warning "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 4.5)." is added.

Section 4.5:

- The statement "Concomitant use of topical steroids and topical NSAIDs may increase the potential for corneal healing problems." is added and the statement "No clinically relevant interactions have been described" is removed.

TDOC-0012241 v2.0, April 2013:

The following changes have been made which do not reflect any new and potential important safety finding for the product:

The whole document has been adapted to CCSI templates.

Information has been restricted to core safety data. Information not considered minimum safety data or not properly justified has been removed from the document.

Document has been amended to be in line with the known safety data on corticosteroids.

The following sections have been updated taking into consideration the above premises:

- Section 4.3:

"Acute untreated purulent bacterial infections" modified to "Acute untreated bacterial infections".

"Acute epithelial herpes simplex keratitis" modified to "Herpes simplex keratitis".

"Vaccinia varicella and other viral infections of cornea and conjunctiva (except herpes zoster keratitis)" modified to exclude exception.

- Section 4.4:

  Warning on greater risk of corticosteroid-induced ocular hypertension in children added.

  Warning on resistance to infections updated to exclude text "preventing recognition of ineffectiveness of the antibiotic".

  Warning on stromal keratitis or uveitis caused by herpes simplex deleted.

  Warning on benzalkonium chloride and contact lens wearing modified as per current Alcon's CCSI standard.

- Section 4.6: The recommendations for use during pregnancy and breast-feeding were deleted from the document as per current standards and deferred to country level. Information about excretion in human milk from systemic use of corticosteroids was included. Stylistics changes were performed to adapt to current Guidelines.
- Section 4.8: No clinical trials data was incorporated. The terms dysgeusia and intraocular pressure increased were added to the tabulated list of ADRs as result of the review of the Post-Marketing Surveillance data.
- Section 4.9: Statement on treatment measures in case of accidental ingestion was removed from the CCSI as this was not considered minimum safety information.

TDOC-0012241 1.0 August 2010:

Not applicable. New CCSI.

8 APPENDICES

Not applicable.

9. REFERENCES

This version of the Core Data Sheet document is without references.