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Global Drug Regulatory Affairs

Infectoflam

(fluorometholone and gentamicin sulphate)

Eye Drops and Eye Ointment

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1. NAME OF THE MEDICINAL PRODUCT

Infectoflam, 0.1% fluorometholone plus 0.3% gentamicin, eye drops.

Infectoflam, 0.1% fluorometholone plus 0.3% gentamicin, eye ointment.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Eye drops
1 ml of Infectoflam eye drops contains 1 mg fluorometholone and 5 mg of gentamicin sulphate equivalent to 3.0 mg of gentamicin.

Eye ointment
1 gm of Infectoflam ointment contains 1 mg fluorometholone and 5 mg of gentamicin sulphate equivalent to 3.0 mg of gentamicin.

Fluorometholone: 9-fluoro-11b,17-dihydroxy-6a-methylpregna -1,4-diene-3,20-dione.

Gentamicin sulfate occurs as a white to buff powder and is soluble in water and insoluble in alcohol. It is a mixture of three aminoglycoside derivatives C_1, C_2 and C_{1a}.

For excipients, see 6.1.

3. PHARMACEUTICAL FORM

Eye drops.
Sterile suspension.

Eye ointment.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment and prophylaxis of inflammatory conditions of the anterior segment of the eye, such as post-operative inflammation following eye surgery, where corticosteroid treatment is required and there is an increased risk or evidence of bacterial infection

4.2 Posology and method of administration

Eye drops

Bacterial infections
Dosage depends on the severity of the condition. Usually, one drop to be instilled into the conjunctival sac 5 times daily for one week. Following the first week of treatment, the dosage may be decreased. In severe cases, 1 drop per hour for the first couple of days.

Post-operative treatment
One drop to be instilled into the conjunctival sac 4 times daily for one week. Following the first week of treatment, the dosage may be decreased.

In combination with eye ointment
The eye ointment is particularly suitable as supportive therapy to treatment with eye drops. Apply an approximately 5 mm long ribbon of ointment in the conjunctival sac before going to sleep (5 mm ribbon of ointment corresponds to 0.027 mg gentamicin and 0.0088 mg fluorometholone). Instill one drop of Infectoflam eye drops into the conjunctival sac 3 times daily.

Eye ointment

Apply an approximately 5 mm long ribbon of ointment in the conjunctival sac 3-4 times daily. Following the first week of treatment, the dosage may be decreased.

Elderly: See dose for adults.

Pediatric Use: Safety and effectiveness in children have not been established.

Care should be taken not to discontinue therapy prematurely.

The physician treating the case determines the duration of administration. *Duration of use should usually not exceed 2 weeks.*

Shake the eye drops vigorously before use. The tip of the container should not come into contact with any surface including the eye, as this may contaminate the medicament. Replace the cap on the bottle immediately after use in order to avoid contamination of the ointment.

4.3 Contraindications

- Hypersensitivity to any of the active substances, to any of the excipients or to other corticosteroids. Cross sensitivity with other aminoglycoside antibiotics may occur.

- Fungal diseases (mycoses) of ocular structures and mycobacterial infections of the eye.

- Acute superficial herpes simplex keratitis (dentritic keratitis), vaccinia, varicella, and most other viral diseases of cornea and conjunctiva.

Corticosteroids decrease human resistance to bacterial, fungal and viral infections; application may exacerbate infections and encourage the development of new or secondary infections.

4.4 Special warnings and special precautions for use

- Although the risk is considerably less with fluorometholone than with other steroids, prolonged use of steroids may cause a pathological increase in intraocular pressure. In predisposed individuals and those known to have glaucoma, intraocular pressure must be monitored regularly, especially in cases of prolonged treatment.

- Caution should be exercised in patients with Diabetes mellitus. These patients may be predisposed toward increases in intraocular pressure and/or cataract formation.

- In those diseases causing thinning of the cornea or sclera, perforation has been known to occur with chronic use of topical steroids.

- Intensive long-term therapy may possibly contribute to the formation or exacerbation of posterior sub-capsular cataracts.

- Prolonged use may suppress the host immune response and thus increase the hazard of secondary ocular infections. Fungal infections of the cornea are particularly prone to develop coincidentally

with long-term local steroid or antibiotic application. Fungus invasion must be considered in any persistent corneal ulceration where a steroid has been used or is in use.

- Prolonged use may lead to skin sensitisation, the emergence of resistant organisms and overgrowth of non-susceptible organisms including fungi. If there is no improvement after 7-8 days, treatment should discontinue and the patients' condition reassessed.

- The use of steroids immediately after cataract surgery, may delay healing and increase the incidence of bleb formation.

- At high concentrations, gentamicin may retard healing of the corneal epithelium.

- Gentamicin is not effective in viral and fungal infections.

- In chronic conditions and after long-term use withdrawal of treatment should be carried out by gradually decreasing the frequency of applications.

- 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 Infectoflam eye drops contain benzalkonium chloride as a preservative. Therefore, the medicament should not be used while wearing soft contact lenses. The lenses should be removed before application of the drops and not reinserted earlier than 15 minutes after use.

4.5 Interaction with other medicinal products and other forms of interaction

- *Antiglaucoma agents. Chronic or intensive use of ophthalmic corticosteroids in susceptible individuals may increase intraocular pressure and decrease the efficacy of antiglaucoma agents .*

- *Anticholinergics, especially atropine and related compounds. The risk of intraocular hypertension may be increased with prolonged corticosteroid therapy; this may be more likely to occur during use of cycloplegic/mydriatic agents in patients predisposed to acute angle closure.*

- If a supplementary ophthalmic medication is used, there must be an interval of at least five minutes between the administration of the two products.

- The concurrent administration of gentamicin with topically administered amphoterecin B, heparin, sulphadiazine, cephalothin, methylprednisolone or cloxacillin may lead to visible deposits in the conjunctival sac.

4.6 Pregnancy and lactation

Animal studies with corticosteroids have revealed that fluoromethalone is teratogenic and embryocidal when administered to the eyes of pregnant rabbits on days 6-18 of gestation. Gentamicin has been shown to depress body weights, kidney weights and median glomerular counts in newborn rats when administered systemically to pregnant rats in doses approximately 500 times the maximum recommended ophthalmic human dose. No controlled studies are available in pregnant women. For this reason Infectoflam should only be administered if the expected maternal benefit outweighs the potential risk to the fetus or the newborn infant.

It is not known whether topical ophthalmic administration of corticosteroids could result in sufficient systemic absorption to produce detectable quantities in human 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, a decision should be made whether to discontinue nursing or to continue the drug, taking into account the importance of the drug to the mother.

4.7 Effects on ability to drive and use machines

Patients should be advised that the use of this product might cause transient blurring of vision. If affected, patients should not drive or operate machinery until vision has cleared.

4.8 Undesirable effects

The most frequently reported adverse reactions are those indicative of hypersensitivity reactions (itching, redness, swelling, foreign body sensation, or other sign of irritation not present before therapy). Ocular burning or stinging upon drug instillation and blurred vision have also been reported. Punctate keratitis has been reported following treatment with gentamicin ophthalmic products.

Adverse effects associated with topical steroid therapy include elevation of intraocular pressure with possible development of glaucoma with optic nerve damage, visual acuity and field defects, posterior subcapsular cataract formation, ocular hypertension, secondary ocular infection following suppression of host response, delayed wound healing and corneal thinning and/or perforation of the globe may occur. Ptosis, and mydriasis have also been related to the use of topical steroids.

Although systemic effects are uncommon, there have been some cases of systemic hypercorticoidism after topical administration of corticosteroids

4.9 Overdose

The oral ingestion of the contents of one bottle is unlikely to cause any adverse effect as gentamicin is very poorly absorbed from the gastrointestinal tract and as fluorometholone is unlikely to have adverse effects in acute overdose.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: corticosteroid and antiinfective in combination, ATC code: S01C A07

Gentamicin
Gentamicin sulfate is a water soluble antibiotic of the aminoglycoside group. It is obtained from cultures of *Micromonospora purpurea* and is a mixture of the sulfate salts of three closely related forms, gentamicin C_1, C_2 and C_{1a}. All three components appear to have similar antimicrobial activities.

Unlike the majority of antibiotics, aminoglycosides are bactericidal and act by inhibiting protein synthesis. Aminoglycosides bind to specific receptors on the 30 S subunit of bacterial ribosomes inhibiting protein synthesis.

Gentamicin sulfate is active *in vitro* against many strains of the following microorganisms: *Staphylococcus aureus. Enterobacter aerogenes, Escherichia coli, Haemophilus influenzae, Klebsiella pneumoniae, Neisseria gonorrhoeae,and Pseudomonas aeruginosa*. Gentamicin is only minimally active against some streptococci and inactive against most anaerobic bacteria.

The principal bacteria responsible for infections of the anterior segment of the eye i.e. Staphylococci, *Pseudomonas aeruginosa* and Proteus can be successfully treated with topical gentamicin.

A good therapeutic effect has been recorded with gentamicin in experimentally-induced Pseudomonas or *S. aureus* keratitis.
Natural and acquired resistance to gentamicin has been observed. Gentamicin resistance may occur due to a decrease in the permeability of the drug through the bacterial cell wall, mutation of ribosomal target sites leading to reduced affinity for binding, or the presence of a plasmid-mediated resistance factor. There is partial cross-resistance between gentamicin and other aminoglycosides.

Gentamicin shows the following in vitro activity:

	MIC_{90} of gentamicin (in µg/ml)
Susceptible bacteria	
Staphylococcus aureus	*1*
Escherichia coli	*0.5*
Enterobacter	*0.5*
Listeria monocytogenes	*0.5*
Klebsiella spp.	*0.25*
Shigella spp.	*1*
Haemophilus influenzae	*3.4*
Neisseria gonorrhoeae	*1.5-6*
Salmonella spp.	*0.25-1*
Proteus	*2*
Moderately sensitive bacteria	
Staphylococci. spp (excluding Staph. epidermidis)	*8*
Streptococci pneumoniae	*7*
Streptococci pyogenes	*8*
Pseudomonas aeruginosa	*8*
Slightly sensitive or resistant bacteria	
Streph. faecalis	*16*
Staph. epidermidis	*32*
a,b-haemolytic Strep.	*resistant*
K. pneumoniae	*64*
Serratia marcescens	*>128*

Fluorometholone
Fluorometholone is a synthetic fluorinated corticosteroid with anti-inflammatory properties. Corticosteroids diffuse across cell membranes and complex with specific cytoplasmic receptors. These complexes then enter the cell nucleus, bind to DNA, and stimulate transcription of mRNA and subsequent protein synthesis of enzymes ultimately responsible for anti-inflammatory effects of topical application of corticosteroids to the eye.

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

There is no generally accepted explanation for the mechanism of action of ocular corticosteroids. However, corticosteroids are thought to act by the induction of phospolipase A2 inhibitory proteins collectively called lipocortins. It is postulated that these proteins 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.
Corticosteroids are capable of producing a rise in intraocular pressure. Fluorometholone has a lower propensity to increase intraocular pressure than dexamethasone.

Combination
Local tolerability
Infectoflam is well tolerated.

The combination of the two substances provides bacterial treatment or prophylaxis with an anti-inflammatory action.

5.2 Pharmacokinetic properties

Gentamicin
Following topical administration, bactericidal concentrations are obtained in the conjunctiva and cornea as a function of the dosage frequency. Therapeutic concentrations may also be achieved in the anterior chamber of the inflamed eye with frequent instillations.

Fluorometholone
Penetration of fluorometholone through the intact cornea is better than that of other steroids and only minimal changes are observed when the epithelium is removed. Thirty minutes after instillation of a 0.1% fluorometholone suspension, maximum tissue concentrations between 1.5-1.9 µg/g in the cornea and 0.14 µg /g in the anterior chamber of the eye were detected.

Fluorometholone is rapidly metabolized after crossing the cornea. The half-life of fluorometholone in the aqueous humour is 54 minutes.

Combination
There is no known pharmacokinetic interaction between the two components.

5.3 Preclinical safety data

Local toxicity
Application of 50 µl of fluorometholone-gentamicin eye drops 8 times a day over a period of 6 weeks in the eyes of dogs did not lead to any persistent changes or systemic signs and symptoms, nor did a 14-day study with 50 mg fluorometholone-gentamicin eye ointment 3 times a day show either local or systemic toxic effects.

Carcinogenic, mutagenic and impairement of fertility studies
No studies have been conducted in animals or in humans to evaluate the carcinogenic or mutagenic potential of fluorometholone.

There are no published carcinogenicity or impairment of fertility studies on gentamicin. Aminoglycosides have been found to be non-mutagenic.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Eye drops:
benzalkonium chloride,

boric acid,
borax,
disodium edetate,
conc. α-tocopherol acetate,
sodium chloride,
aluminum hydroxide gel,
methylhydroxypropyl-cellulose,
water for injection.

Eye ointment:
wool fat,
liquid paraffin,
cetystearyl alcohol,
white petrolatum,
water for injection

6.2 Incompatibilities

None relevant to topical use.

6.3 Shelf life

Eye drops:
Unopened: 3 years.

Eye ointment
Unopened: 5 years

6.4 Special precautions for storage

Do not store above 25°C.

6.5 Nature and contents of container

Eye drops:
Infectoflam eye drops in 5 ml LDPE bottles with LDPE droppers and HDPE closure.

Eye ointment
Infectoflam eye ointment in aluminium tubes containing 4 g and a HDPE closure.

Combi pack
Contains one 5 ml bottle and one 4 g tube.

6.6 Instructions for use and handling

None.

7. DATE OF REVISION OF THE TEXT

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