# SUMMARY OF PRODUCT CHARACTERISTICS

## 1. Name of the medicinal product

LOFOTO (Tobramycin and Dexamethasone) 3mg/ml/1mg/ml Eye Drops, Suspension

## 2. Qualitative and quantitative composition

Each ml contains: Tobramycin 3mg Dexamethasone 1mg

For full list of excipients, see section 6.1

## 3. Pharmaceutical form

Eye Drops, Suspension

## 4. Clinical particulars

### 4.1 Therapeutic indications

Prevention and treatment of inflammation and prevention of infection associated with cataract surgery in adults and children aged 2 years and older.

### 4.2 Posology and method of administration

Adults:

One drop instilled into the conjunctival sac(s) every 4 to 6 hours while the patient is awake. During the initial 24 to 48 hours, the dosage may be increased to one drop every two hours while the patient is awake. Dosing should continue for 14 days not to exceed a maximum of 24 days. Frequency should be decreased gradually as warranted by improvement in clinical signs. Care should be taken not to discontinue therapy prematurely.

Use in the Elderly:

Clinical studies have indicated dosage modifications are not required for use in the elderly.

Paediatric population:

LOFOTO may be used in children 2 years of age and older at the same dose as in adults. Currently available data is described in section 5.1.

The safety and efficacy in children younger than 2 years of age have not been established, and no data is available.

Shake the bottle well before use. To prevent contamination of the dropper tip and suspension, care should be taken not to touch the eyelids, surrounding areas, or other surfaces with the dropper tip of the bottle. Keep the bottle tightly closed when not in use.

In case of concomitant therapy with other topical ophthalmic medicinal products, an interval of 5 minutes should be allowed between successive applications. Eye ointments should be administered last.

**4.3 Contraindications**

• Hypersensitivity to tobramycin or dexamethasone or to any of the excipients listed in section 6.1

• Herpes simplex keratitis

• Vaccinia, varicella and other viral disease of the cornea and conjunctiva

• Mycobacterial infections of the eye caused by, but not limited to, acid-fast bacilli such as *Mycobacterium tuberculosis, Mycobacterium leprae,* or *Mycobacterium avium*.

• Fungal diseases of ocular structures.

• Untreated purulent infection of the eye.

**4.4 Special warnings and precautions for use**

LOFOTO is for topical use only and not for injection or oral use. Prolonged use of topical ophthalmic corticosteroids (i.e., longer than the maximum duration used in clinical trials [24 days]) may result in ocular hypertension/glaucoma with resultant damage to the optic nerve and reduced visual acuity and visual fields defects and may also result in posterior subcapsular cataract formation. It is advisable that the intraocular pressure be checked frequently. This is especially important in paediatric patients receiving dexamethasone-containing products, as the risk of steroid-induced ocular hypertension may be greater in children below 6 years of age and may occur earlier than a steroid response in adults. The frequency and duration of treatment should be carefully considered, and the intraocular pressure should be monitored from the outset of treatment, recognizing the risk for earlier and greater steroid-induced intraocular pressure increases in the paediatric patients. Prolonged use may also result in secondary ocular infections due to suppression of host response. Corticosteroids may reduce resistance to and aid in the establishment of bacterial, viral or fungal infections and mask the clinical signs of infection. Sensitivity to topically administered aminoglycosides may occur in some patients. If hypersensitivity develops during use of this medicine, treatment should be discontinued. Cross-hypersensitivity to other aminoglycosides can occur, and the possibility that patients

who become sensitized to topical tobramycin may also be sensitive to other topical and/or systemic aminoglycosides should be considered. Serious adverse reactions including neurotoxicity, ototoxicity and nephrotoxicity have occurred in patients receiving systemic aminoglycoside therapy. Caution is advised when used concomitantly. Fungal infection should be suspected in patients with persistent corneal ulceration. If fungal infection occurs, corticosteroids therapy should be discontinued. Prolonged use of antibiotics such as tobramycin may result in overgrowth of non-susceptible organisms, including fungi. If superinfection occurs, appropriate therapy should be initiated. Topical ophthalmic corticosteroids may slow corneal wound healing. In those diseases causing thinning of the cornea or sclera, perforations have been known to occur with the use of topical corticosteroids Benzalkonium chloride, used as a preservative in this product, has been reported to cause punctate keratopathy and/or toxic ulcerative keratopathy. Benzalkonium chloride may cause eye irritation and discolour soft contact lenses. Avoid contact with soft contact lenses. Contact lens wear is not recommended during treatment of an ocular infection or inflammation. If patients are allowed to wear contact lenses, they must be instructed to remove lenses prior to application of LOFOTO and wait at least 15 minutes before reinsertion.

**4.5 Interaction with other medicinal products and other forms of interaction**

No clinically relevant interactions have been described with topical ocular dosing.

**4.6 Fertility pregnancy and lactation**

Pregnancy:

There are no adequate data from the use of LOFOTO in pregnant women. Animal studies with subcutaneous administration of tobramycin have not revealed any teratogenic effects. High systemic doses of aminoglycoside antibiotics have been associated with ototoxicity. However, after ocular, topical administration, systemic levels are expected to be very low and tobramycin is not expected to cause direct or indirect harmful effects on reproduction. Topical administration ofcorticosteroids to pregnant animals can cause abnormalities in foetal development, including cleft palate. The clinical relevance is not known. Further, animal and clinical data indicate that administration of pharmacological doses of glucocorticoids during pregnancy may increase the risk for intrauterine growth retardation, adult cardiovascular and/or metabolic disease and/or impaired neurobehavioral development. Treatment during pregnancy, and especially during the first three months, should only take place after a careful benefit-risk assessment. Therefore, women should inform their physician if pregnancy occurs. So far, use in humans has not generated any suspicion of embryotoxic effects. However, during long-term treatment growth disorders in the unborn child cannot be ruled out. Treatment towards the end of pregnancy may inhibit the body's own production of glucocorticoids necessitating treatment after birth.

Therefore, during pregnancy, LOFOTO should only be used when the potential benefit justifies the potential risks.

Lactation:

Systemically administered corticosteroids appear in human milk and could suppress growth, interfere with endogenous corticosteroid production, or cause other untoward effects. It is not known whether topical administration of corticosteroids could result in sufficient systemic absorption to product detectable quantities in human milk. LOFOTO should not be used during breast-feeding unless the potential benefit outweighs the potential risk.

Fertility

Studies have not been performed to evaluate the effect of topical ocular administration of LOFOTO on human fertility**.**

**4.7 Effects on ability to drive and use machines**

LOFOTO has no or negligible influence on the ability to drive and use machines.No studies on the effects on the ability to drive and use machines have been performed. As with any eye drop, temporarily blurred vision or other visual disturbances may affect the ability to drive or use machines. If blurred vision occurs, the patient must wait until the vision is clear before driving or using machines.

**4.8 Undesirable effects**

Summary of the safety profile

In clinical studies involving over 1600 patients, TOBRADEX was administered up to six times daily. No serious ophthalmic or systemic adverse reactions related to TOBRADEX or components of the combination were reported in clinical studies. The most frequently reported adverse reactions with TOBRADEX were eye pain, intraocular pressure increased, eye irritation (burning upon instillation) and eye pruritus occurring in less than 1% of patients.

Tabulated list of adverse reactions.

The following adverse reactions have been reported with TOBRADEX during clinical trials or during post marketing experience and are classified according to the subsequent convention: very common (≥ 1/10), common (≥ 1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000) and very rare (<1/10,000), and not known (cannot be estimated from the available data). Within

each frequency-grouping, adverse reactions are presented in order of decreasing seriousness.

| System organ classification | Frequency | Adverse reaction |
|---|---|---|
| Immune system disorders | Not known | hypersensitivity |
| Nervous system disorders | Uncommon<br>Not known | headache<br>dizziness |
| Eye disorders | Uncommon<br><br>Rare<br><br><br>Not known | eye pain, eye pruritus, ocular discomfort, ocular hypertension, conjunctival oedema, increased intraocular pressure, eye irritation<br>keratitis, eye allergy, blurred vision, dry eye, ocular hyperaemia<br>eyelid oedema, erythema of the eyelid , mydriasis, lacrimation increased |
| Respiratory, thoracic, and mediastinal disorders | Uncommon | Rhinorrhoea, laryngospasm |
| Gastrointestinal disorders | Rare<br>Not known | dysgeusia<br>nausea, abdominal discomfort |
| Skin and subcutaneous tissue disorders | Not known | rash, swelling face, pruritus |

**Description of selected adverse reactions**

The following adverse reactions have been observed following use with Dexamethasone ophthalmic suspension:

| System organ classification | Frequency | Adverse reaction |
|---|---|---|
| Nervous system disorders | Common | headache |
| Eye disorders | Common | eye irritation,* ocular hyperaemia,* erythema of eyelid, abnormal sensation in eye* |
| Respiratory, thoracic, and mediastinal disorders | Common | Post nasal drip |

The following adverse reactions have been observed following use with Tobramycin ophthalmic solution:

| System organ classification | Frequency | Adverse reaction |
|---|---|---|
| Eye disorders | Common<br>Uncommon | ocular hyperaemia,* eye pain*<br>eye pruritus,* ocular discomfort,* eye allergy, eyelid oedema,* conjunctivitis,* glare, increased lacrimation,* keratitis* |

* These adverse reactions were also observed with TOBRAMYCIN+DEXAMETHASONE EYE DROPS.SUSP during post marketing.

Prolonged use of topical ophthalmic corticosteroids may result in increased intraocular pressure with damage to the optic nerve, reduced visual acuity and visual field defects, posterior subcapsular cataract formation and delayed wound healing. Due to the corticosteroid component, in diseases causing thinning of the cornea or sclera there is a higher risk for perforation especially after long treatments (See Section 4.4). The development of secondary infection has occurred after the use of combinations containing corticosteroids and antimicrobials. Fungal infections of the cornea are particularly prone to develop coincidentally with long term applications of steroids. Serious adverse reactions including neurotoxicity, ototoxicity and nephrotoxicity have occurred in patients receiving systemic tobramycin therapy (See Section 4.4). Sensitivity to topically administered aminoglycosides may occur in some patients (See Section 4.4).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via EFDA yellow Card Scheme, online at https://primaryreporting.who-umc.org/ET or toll free call 8482 to Ethiopian food and drug authority (EFDA).

### 4.9 Overdose

Due to the characteristics of this preparation, no toxic effects are to be expected with an ocular overdose of this product, or in the event of accidental ingestion of the contents of one bottle or tube.

A topical overdose of LOFOTO may be flushed from the eye(s) with lukewarm tap water.

## 5. Pharmacological properties

## 5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Anti-inflammatory agents and anti-infectives in combination, corticosteroids and anti-infectives in combination

ATC code: S01C A01

Dexamethasone:

The efficacy of corticosteroids for the treatment of inflammatory conditions of the eye is well established. Corticosteroids achieve their anti-inflammatory effects through suppression of vascular endothelial cell adhesion molecules, cyclooxygenase I or II, and cytokine expression. This action culminates in a reduced expression of pro-inflammatory mediators and the suppression of adhesion of circulating leukocytes to the vascular endothelium, thereby preventing their migration into inflamed ocular tissue. Dexamethasone has marked anti-inflammatory activity with reduced mineralocorticoid activity compared with some other steroids, and is one of the most potent anti-inflammatory agents.

Tobramycin:

Tobramycin is a potent, broad-spectrum, rapidly bactericidal aminoglycoside antibiotic. It exerts its primary effect on bacterial cells by inhibiting polypeptide assembly and synthesis on the ribosome. Tobramycin in this combination provides antibacterial protection against susceptible bacteria.

The following MIC breakpoints, separating susceptible from intermediate susceptible organisms, and intermediate susceptible from resistant organisms, are suggested: S ( < 4 μg/ml, R (> 8 μg/ml). The prevalence of resistance may vary geographically and with time for selected species and local information on resistance is desirable, particularly when treating severe infections. As necessary, expert advice should be sought when the local prevalence of resistance is such that the utility of the agent in at least some types of infections is questionable. The following information gives only an approximate guidance on probabilities whether bacteria will be susceptible to tobramycin in TOBRAMYCIN+DEXAMETHASONE EYE DROPS.SUSP.

The breakpoint definitions classifying isolates as susceptible or resistant are useful in predicting clinical efficacy of antibiotics that are administered systemically. However, when the antibiotic is administered in very high concentrations topically directly on the site of infection, these breakpoint definitions may not be applicable. Most isolates that would be classified as resistant by systemic breakpoints are indeed successfully treated topically.

In vitro studies have shown tobramycin to be active against most strains of common ocular pathogens and common skin flora bacteria as listed in the Table below:

| Categories | Frequency of Acquired Resistance in Europe |
|---|---|
| SENSITIVE SPECIES | |
| Aerobic Gram-Positive Microorganisms | |
| Corynebacterium species | 0-3% |
| Staphylococcus aureus Methicillin -S [a] | 0-3% |
| Staphylococcus epidermidis Methicillin -S [a] | 0-28% |
| Other Coagulase-negative Staphylococci | 0-40% |
| Aerobic Gram-Negative Microorganisms | |
| Acinetobacter species | 0% |
| Citrobacter species | 0% |
| Escherichia coli | 0% |
| Enterobacter species | 0% |
| Haemophilus influenzae | 0% |
| Klebsiella species | 0 % |
| Moraxella species | 0% |
| Proteus species | 0% |
| Pseudomonas aeruginosa | 0% |
| MODERATELY SUSCEPTIBLE SPECIES | |
| (in vitro, intermediate susceptibility) | |
| Aerobic Gram-Negative Microorganisms | |
| Serratia marcescens | |
| INHERENTLY RESISTANT SPECIES | |
| Aerobic Gram-Positive Microorganisms | |
| Enterococcus species | |

| | |
|---|---|
| Staphylococcus aureus Methicillin –R [a]<br>Staphylococcus epidermidis Methicillin –R [a]<br>Streptococcus pneumoniae<br>Streptococcus species | 50 – 70%<br>30 – 40% |
| Aerobic Gram-negative microorganisms<br>Burkholderia cepacia<br>Stenotrophomonas maltophilia | |
| Anaerobic microorganisms<br>Strict anaerobic bacteria | |
| Others<br>Chlamydia species<br>Mycoplasma species<br>Rickettsia species | |

[a] Methicillin-susceptible (S), Methicillin-resistant (R). The beta-lactam (i.e., methicillin; penicillin) resistance phenotype is unrelated to the aminoglycoside resistance phenotype and both are unrelated to the virulence phenotypes. Some methicillin-resistant (R) S. aureus strains (MRSA) are susceptible to tobramycin (MIC: S ≤4); conversely some strains of methicillin–susceptible (S) S. aureus (MSSA) are resistant to tobramycin (MIC: S ≥8)

The frequency of methicillin resistance (R) may be up to 50 % of all staphylococci in some European countries

Paediatric Population

The safety and efficacy of TOBRAMYCIN+DEXAMETHASONE EYE DROPS.SUSP in children have been established by broad clinical experience, but only limited data are available. In a clinical study of TOBRAMYCIN+DEXAMETHASONE EYE DROPS.SUSP for the treatment of bacterial conjunctivitis, 29 paediatric patients, ranging in age from 1 to 17 years, were treated with 1 or 2 drops of TOBRAMYCIN+DEXAMETHASONE EYE DROPS.SUSP every 4 or 6 hours for 5 or 7 days. In this study, differences in the safety profile between adult and paediatric patients were not observed.

Other information

Cross-resistance between aminoglycosides (e.g., gentamicin and tobramycin) is due to the specificity of the enzyme modifications, Adenyltransferase (ANT) and Acetyltransferase (ACC). However, cross-resistance varies between the aminoglycoside antibiotics due to the differing specificity of the various modifying enzymes. The most common mechanism of acquired resistance to aminoglycosides is antibiotic inactivation by plasmid and transposon-encoded modifying enzymes.

## 5.2 Pharmacokinetic properties

Tobramycin:

Animal studies have shown that tobramycin is absorbed into the cornea following ocular administration. Following systemic administration to patients with normal renal function, a plasma half-life of approximately 2 hours has been observed. Tobramycin is eliminated almost exclusively by glomerular filtration with little if any biotransformation. Plasma concentrations of tobramycin following the 2-day topical ocular regimen of TOBRAMYCIN+DEXAMETHASONE EYE DROPS.SUSP were below the limit of quantification in most subjects or low (≤0.25 microgram/ml).

Dexamethasone:

Following ocular administration, dexamethasone is absorbed into the eye with maximum concentrations in the cornea and aqueous humour attained within 1-2 hours. The plasma half-life of dexamethasone is approximately 3 hours. Dexamethasone is eliminated extensively as metabolites. Systemic exposure to dexamethasone is low following topical ocular administration of TOBRAMYCIN+DEXAMETHASONE EYE DROPS.SUSP. Peak dexamethasone plasma levels after the last topical dose ranged from 220 to 888pg/ml (mean 555 ± 217pg/ml) after administration of one drop of TOBRAMYCIN+DEXAMETHASONE EYE DROPS.SUSP to each eye four times per day for two consecutive days.

## 5.3 Preclinical safety data

The systemic toxicity profile of the individual actives is well established. Preclinical effects of tobramycin and dexamethasone were observed only at exposures considered sufficiently in excess of the maximum human exposure indicating little relevance to human use.

# 6. Pharmaceutical particulars

## 6.1 List of excipients

Disodium edetate

Hydroxyethylcellulose

Benzalkonium chloride

Sodium chloride

Sodium sulphate

Sulphuric acid

Sodium hydroxide

Tyloxapol

Water for injections

**6.2 Incompatibilities**

Not applicable

**6.3 Shelf life**

2 years

After the first opening of the container, the sterile ophthalmic suspension should not be used longer than four weeks.

**6.4 Special precautions for storage**

No special precautions for storage

**6.5 Nature and contents of container**

LOFOTO is a white, homogenous, sterile water suspension, in a white plastic bottle of 5 ml, with a white cap and white filler block

**6.6 Special precautions for disposal and other handling**

No special requirements

**7. Marketing authorisation holder**

RAFARM SA,
*12 Korinthou Street, Neo Psihico, 15451, Attiki, Greece*

**8. Marketing authorisation number(s)**

Registration No :04868/6609/NMR/2018

**9. Date of first authorisation/renewal of the authorisation**

Approval date :26-12-2019

**10. Date of revision of the text**

July 2024