1. NAME OF THE MEDICINAL PRODUCT
Oftalmolosa® Cusi Gentamicin 0.3%

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
3 mg/g Ointment: 1 g ointment contains 5 mg gentamicin sulphate (equivalent to 3 mg gentamicin)

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM
Eye ointment: whitish, homogeneous soft ointment

4. CLINICAL PARTICULARS
4.1 Therapeutic indications
Infections of the anterior pole of the eye caused by germs sensitive to gentamicin; corneal ulcers and corneal bacterial abscesses. Conjunctivitis. Keratitis. Staphyloccocia. Blepharitis. Dacryocystitis. Preoperative sterilization of the conjunctiva.

4.2 Posology and method of administration
Normally two or three applications daily.
The number of daily applications and length of treatment can be modified in accordance with physician's criteria.

Paediatric population
Safety and effectiveness in the paediatric population have not been established**.**

<u>Correct administration procedure:</u>
Application to the inside of the eye:
Separate the eyelids from the eye and apply a small amount (approximately a grain of rice) of ointment into the conjunctival sac.

Application to the outside of the eye:
Soften and remove crusts with warm water, and apply the product directly onto the affected area.

Application of the ointment should be carried out under hygienic conditions. Do not touch the tube tip to any surface. Close tube after every application.

Method of administration
- For ocular use only.
- To prevent contamination of the dropper tip and solutions, care must be taken not to touch the eyelids, surrounding areas or other surfaces with the dropper tip of the bottle. Instruct patients to keep the bottle tightly closed when not in use.
- If more than one topical ophthalmic product is being used, the products must be administered at least 5 minutes apart. Eye ointments should be administered last.

4.3 Contraindications
Hypersensitivity to the active substance or to any of the excipients.

4.4 Special warnings and precautions for use

- Sensitivity to topically administered aminoglycosides may occur in some patients. Severity of hypersensitivity reactions may vary from local effects to generalized reactions such as erythema, itching, urticarial, skin rash, anaphylaxis, anaphylactoid reactions, or bullous reactions. If hypersensitivity develops during use of this medicine, treatment should be discontinued. (See Section 4.8)
- Cross-hypersensitivity to other aminoglycosides can occur, and the possibility that patients who become sensitized to topical gentamicin 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 or when applied topically to open wounds or damaged skin. Although these effects have not been reported following topical ocular use of gentamicin, caution is advised when used concomitantly.
- Prolonged use of OFTALMOLOSA® CUSÍ Gentamicin 0.3% may result in overgrowth of non-susceptible organisms, including fungi. If superinfection occurs, appropriate therapy should be initiated.

4.5 Interaction with other medicinal products and other forms of interaction
No clinically relevant interactions have been described.

4.6 6 Fertility, pregnancy and lactation
Fertility
Studies have not been performed to evaluate the effect of topical ocular administration of gentamicin on fertility.

Pregnancy
There are no or limited amount of data from the use of OFTALMOLOSA® CUSÍ Gentamicin 0.3% in pregnant women. Studies in animals have shown reproductive toxicity. (See Section 5.3).

Breast-feeding
Gentamicin is excreted in human milk following systemic administration. It is unknown whether gentamicin is excreted in human milk following topical ocular administration.

4.7 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 8 Undesirable effects
The following adverse reactions have been reported during clinical trials with OFTALMOLOSA® CUSÍ Gentamicin 0.3% 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). Within each frequency-grouping, adverse reactions are presented in order of decreasing seriousness.

System Organ Classification	**MedDRA Preferred Term (v.14.0)**
Eye disorders	*Common:* photophobia, eye pruritus, ocular discomfort, irritation, pain, stinging, burning ocular, hyperaemia *Uncommon:* keratitis
Immune system disorders	*Common:* hypersensitivity (ocular)

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. Consult physician or a Poison Control Center in the event of overdosage or accidental ingestion.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic Properties

Pharmacotherapeutic group: antibiotics

ATC code: S01AA11

Gentamicin is an aminoglycoside antibiotic and has a bactericidal action against many gram-negative aerobes and against some strains of staphylococci.

Mechanism of action

Aminoglycosides are taken up into sensitive bacterial cells by an active transport process which is inhibited in anaerobic, acidic, or hyperosmolar environments. Within the cell they bind to the 16S, 30S, and to some extent to the 50S, subunits of the bacterial ribosome, inhibiting protein synthesis and generating errors in the transcription of the genetic code. The manner in which cell death is brought about is imperfectly understood, and other mechanisms may contribute, including effects on membrane permeability.

Pharmacodynamic effects

COMMONLY SUSCEPTIBLE SPECIES

Many strains of Gram-negative bacteria including species of Brucella, Calymmatobacterium, Campylobacter, Citrobacter, Escherichia, Enterobacter, Francisella, Klebsiella, Proteus, Providencia, Pseudomonas, Serratia, Vibrio, and Yersinia. Some activity has been reported against isolates of Neisseria, although aminoglycosides are rarely used clinically in neisserial infections.

Among the Gram-positive organisms many strains of Staphylococcus aureus are highly sensitive to gentamicin. Listeria monocytogenes and some strains of Staph. Epidermidis may also be sensitive to gentamicin, but enterococci and streptococci are usually insensitive to gentamicin.

Some actinomycetes and mycoplasmas have been reported to be sensitive to gentamicin, but mycobacteria are insensitive at clinically achievable concentrations; anaerobic organisms, yeasts, and fungi are resistant.

INHERENTLY RESISTANT ORGANISMS

Resistance to the aminoglycosides may be acquired by three main mechanisms. The first is by mutation of ribosomal target sites leading to reduced affinity for binding; this type of resistance is generally only relevant for streptomycin and, even then, it appears to be rare in Gram-negative bacteria. Secondly, penetration of aminoglycosides into bacterial cells is by an oxygen-dependent active transport process and resistance may occur because of elimination or reduction of this uptake; when it occurs this generally results in cross-resistance to all aminoglycosides. Thirdly, and by far the most important cause of resistance to the aminoglycosides, is inactivation by enzymatic modification. Three main classes of enzyme conferring resistance have been found, operating by phosphorylation, acetylation, or addition of a nucleotide group, usually adenyl. Enzyme production is usually plasmid-determined and resistance can therefore be transferred between bacteria, even of different species. Resistance to other antibacterials may be transferred at the same time. In Staph. aureus, transfer of resistance is more likely when these drugs are used topically. Each type of enzyme produces characteristic patterns of resistance, but their overlapping and variable affinities for their substrates result in a wide range of permutations of cross-resistance to the different aminoglycosides. The different enzymes vary in their distribution and

prevalence in different locations, and at different times, presumably with variations in antibacterial usage, but relationships to the use of specific aminoglycosides are difficult to establish. These variations in drug sensitivity require local testing to determine resistance and establish susceptibility of bacteria to the aminoglycoside being used, but such local variations mean that estimates of the incidence of resistance are of limited value. In general, the occurrence of resistant pathogens seems to have been greater in southern than in northern Europe, and perhaps greater in the USA than in Europe. There has been particular concern over the increasing incidence of high-level gentamicin resistance among enterococci (in up to 50% of isolates from some centers), since they already possess inherent or acquired resistance to many drugs, including vancomycin in some cases. A similar problem exists with gentamicin resistance in meticillin-resistant strains of Staph. aureus. Such multiply-resistant strains pose a major therapeutic problem in those centers where they occur, since the usual synergistic combinations with other antibacterials are ineffective. However, results from some centers indicate that rational use of a wider range of aminoglycosides (including amikacin which is not affected by most of the aminoglycoside-degrading enzymes) has resulted in a modest decline in overall aminoglycoside resistance.

PK/PD relationship
See section 5.2.

Clinical efficacy and safety
Efficacy has been demonstrated in a clinical study and published literature. See Section 4.8. for safety information.

Paediatric population
Clinical trials have not been conducted in children.

5.2 Pharmacokinetic Properties

Absorption
Gentamicin was absorbed into aqueous humor and cornea but not in the vitreous humor after topical ocular dosing in patients undergoing cataract surgery. Systemic absorption after topical ocular administration was minimal with multiple dosing of 0.3% gentamicin every 2 hours.

Distribution
The apparent volume of distribution is approximately 120 – 200 mL/kg after systemic dosing. Gentamicin is 25-30% bound to serum proteins which is released when the drug is excreted.

Biotransformation
Gentamicin is not known to be metabolized.

Elimination
The half-life of gentamicin in serum after systemic dosing was 2-3 hours. Systemic elimination is principally renal excretion, mostly by glomerular filtration.

Linearity/non-linearity
Dose proportionality with topical ocular dosing is not known. After systemic dosing, dose proportionality was observed between doses of 1 and 2.5 mg/kg in man.

Pharmacokinetic/pharmacodynamic relationship-

No pharmacokinetic/pharmacodynamics relationships after topical ocular dosing have been established.

5.3 Preclinical Safety Data

Non-clinical data reveal no special hazard for humans administered gentamicin for local topical ocular or otic therapy based on conventional studies of safety pharmacology, genotoxicity, and carcinogenic potential.

Abnormal inner ear formation was observed when gentamicin was administered to pregnant rats and cats during organogenesis. Gentamicin administration during the second and third trimester of pregnancy can also result in auditory and vestibular nerve toxicity in the fetus if high enough doses are administered to the mother to become distributed into the circulation of the fetus. High doses of gentamicin (110 mg/kg/day SC) during gestation have also been shown to produce significant and persistent increases in the blood pressure, as well as nephrotoxicity, in the exposed rat offspring. Due to the low dose administered to the eye or ear from the prescribed use of this drug product, and the limited absorption of gentamicin, exposures sufficient to cause auditory or renal toxicity in the fetus are not anticipated to result from use of this product.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Ointment:

Cholesterol
Liquid paraffin
White soft paraffin

6.2 Incompatibilities

None specified.

6.3 Shelf-life

24 months. Use before the expiration date marked on the container and box.

6.4 Special precautions for storage

Store below 25°C

6.5 Nature and content of container

5 g aluminum tube with nozzle, white enamel, white screw cap

6.6 Instructions for Use and Handling <and Disposal>

No special requirements.

Any unused product or waste material should be disposed of in accordance with local requirements.

6.7 Manufacturer

See folding box

KEEP ALL MEDICATION OUT OF THE REACH OF CHILDREN

(Information issued: Feb 2016.SINv1)

Novartis Pharma AG, Basel, Switzerland