SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Netilmicin 3 mg/ml eye drops, solution

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

1 ml of solution contains 3 mg of netilmicin (as netilmicin sulphate).

Excipients with known effects: benzalkonium chloride (0.05 mg/ml)

For the full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Eye drops, solution

Clear, colourless or pale-yellow solution, practically free from particles.

pH: 6.5 - 7.5

Osmolality: 0.274 – 0.306 Osmol/kg

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Netilmicin is indicated for the topical treatment of external infections of the eye and its adnexa caused by netilmicin sensitive bacteria.

Consideration should be given to official guidance on the appropriate use of antibacterial agents

4.2 Posology and method of administration

Posology

Instil 1 or 2 drops into the conjunctival sac of the affected eye(s) 3 times daily, or according to medical prescription.

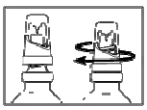
Paediatric population

The safety and efficacy of Netilmicin 3 mg/ml eye drops, solution in children aged 3 to 12 years and in adolescents aged 12 to 18 years have not been established.

Method of administration

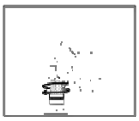
1. Wash/cleanse your hands thoroughly.

2. Screw the cap down tightly in order to pierce the tip of the bottle.



3. Unscrew the cap, invert the bottle and squeeze it gently so that a single drop falls into the affected eye(s). Do not allow the tip of the bottle to touch your eye, eyelids or any other surface in order to avoid contamination.

4. Replace and tighten the cap on the dropper bottle.



Precautions to be taken before handling or administering the medicinal product

If contact lenses are worn, these should be removed prior to eye drops instillation and may be reinserted after 15 minutes (see section 4.4).

Systemic absorption may be reduced by compressing the lacrimal sac at the medial canthus for a minute during and following the instillation of the drops. (This blocks the passage of drops via the naso-lacrimal duct to the wide absorptive area of the nasal and pharyngeal mucosa).

Duration of treatment

The usual duration of treatment is 5 days. The doctor may recommend a longer treatment in the case of refractory or complicated infections.

4.3 Contraindications

Hypersensitivity to the active substance, to aminoglycoside antibiotics or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Serious adverse reactions including neurotoxicity, ototoxicity and nephrotoxicity have occurred in patients receiving systemic aminoglycoside therapy. Caution is advised when used concomitantly (see section 4.5).

Prolonged use of topical antibiotics may determine overgrowth of resistant micro-organisms. If there is no clinical improvement reported within a relatively short period of time or should any irritation or sensitisation phenomena occur, it is necessary to discontinue therapy and start an appropriate treatment.

Netilmicin is not injectable, therefore it must not be injected subconjunctivally or introduced in the anterior chamber.

Contact lenses

Netilmicin 3 mg/ml eye drops, solution in multidose container contains benzalkonium chloride, which is commonly used as a preservative in ophthalmic products. Benzalkonium chloride may be absorbed by soft contact lenses and discolour them, therefore patients should be instructed to remove contact lenses prior to administration of the eye drop and wait at least 15 minutes after instillation before re-inserting contact lenses (see section 4.2 Posology and Method of Administration).

Benzalkonium chloride has been reported to cause eye irritation, symptoms of dry eyes and may affect the tear film and corneal surface. Should be used with caution in dry eye patients and in patients where the cornea may be compromised.

Patients should be monitored in case of prolonged use.

Close monitoring is required while using Netilmicin in patients with conditions where the cornea is compromised, or either the use of Netilmicin 3 mg/ml eye drops, solution in single-dose presentation, preservative free should be recommended.

During a superficial eye infection, the usage of contact lenses is strongly discouraged.

Paediatric population

Netilmicin is not recommended for use in children and adolescents (see section 4.2).

4.5 Interaction with other medicinal products and other forms of interaction

No significant pharmacological interactions have ever been reported with the use of Netilmicin.

Concomitant administration, even topical and particularly intracavitary, of other potentially nephro- and ototoxic antibiotics may increase the risk of such effects.

Concurrent or sequential use of the following nephrotoxic drugs with aminoglycosides may increase the potential for nephrotoxicity and concomitant use should be avoided: cisplatin, polymyxin B, colistin, viomycin, streptomycin, vancomycin, other aminoglycosides and some cephalosporins (cephaloridin) or potent diuretics such as ethacrynic acid and furosemide for their effects on kidneys.

In vitro, the association of an aminoglycoside with a beta-lactam antibiotic (penicillins or cephalosporins) may cause a reciprocal and relevant inactivation. A reduction of half-life or plasma levels of aminoglycoside occurred in patients suffering from renal insufficiency and in some patients with normal renal activity, even if an aminoglycoside and a penicillin-like antibiotic were administered by two different routes.

Patients must be informed that if more than one ophthalmic medicinal product is being used, the medicines must be administered at least 5 minutes apart. Eye ointments should be administered last.

4.6 Fertility, pregnancy and lactation

Pregnancy

Although preclinical studies show no foetal toxicity with topical administration of netilmicin, because of low systemic absorption of the product, during pregnancy the product should be administered only after a careful benefit-risk assessment and under strict medical control.

Lactation

Administration of Netilmicin is not recommended during lactation since aminoglycosides are excreted in breast milk in small amounts.

Fertility

There are no available data on the effect of Netilmicin on human fertility.

4.7 Effects on ability to drive and use machines

The instillation of the eye drops may cause temporary blurred vision. If blurred vision occurs at instillation, the patient should wait until his/her vision clears before driving or using machinery.

4.8 Undesirable effects

The reported undesirable effects are listed below according to MedDRA System Organ classification. There is not enough data available to determine the frequency of the individual effects listed (frequency not known):

Eye disorders:

- eye irritation
- conjunctival hyperaemia
- eyelid rash
- eyelid oedema
- eye pruritus

Immune system disorders:

- hypersensitivity
- urticaria

Episodes of eye irritation and hypersensitivity caused by Netilmicin are mild and transient.

Benzalkonium chloride has been reported to cause eye irritation, symptoms of dry eyes and may affect the tear film and corneal surface.

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 the Yellow Card Scheme (Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store).

4.9 Overdose

Cases of overdose have never been reported.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antiinfectives, Antibiotics, ATC code: S01AA23

Netilmicin is a semi-synthetic, broad-spectrum aminoglycoside antibiotic. It has been shown to be effective, at low concentrations, against different pathogenic bacteria, Gram + and Gram -, including gentamicin-resistant strains. This antibiotic, unlike gentamicin, is not susceptible to the inactivating action of bacterial phosphorylating and adenylating enzymes.

Netilmicin has a rapid bactericidal effect by inducing mistranslation in the genetic code of mRNA and thus introducing wrong amino-acids in the growing polypeptidic chain.

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. The following information gives only an approximate guidance on probabilities whether bacteria will be susceptible to netilmicin in Netilmicin.

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, the breakpoint definitions may not be applicable. Most isolates that would be classed as resistant by systemic breakpoints are successfully treated topically.

he frequency of overall aminoglycoside resistance may be up to 50% of all staphylococci in some European countries.

Table 1 Species Related Clinical MIC Breakpoints for Netilmicin (EUCAST 2017)

Microorganism	**Clinical MIC breakpoints (mg/l)**		
	S (□)	**R (□)**	**ECOFF**
Enterobacteriaceae	2	4	2
Pseudomonas	4	4	4
Acinetobacter	4	4	NR
Staphylococcus	1	1	1
Staphylococcus, coagulase negative	1	1	NR

Enterococcus	IE	IE	NR
Streptococcus A, B, C and G	NR	NR	NR
Streptococcus pneumoniae	NR	NR	NR
Viridans Streptococci	NR	NR	NR
Haemophilus influenzae	IE	IE	NR
Moraxella catarrhalis	IE	IE	NR
Neisseria gonorrhea	NR	NR	NR
Neisseria meningitidis	NR	NR	NR
Gram-positive anaerobes except *Clostridium difficile*	NR	NR	NR
Gram-negative anaerobes	NR	NR	NR
Breakpoint non specie-correlati	2	4	NR
Note: S = Sensitive. R = Resistant. ECOFF = Common epidemiological cut-off value for surveillance of resistance. IE = There is insufficient evidence that the species in question s a good target for therapy with tis drug. NR = Not Reported.			

In vitro studies have shown netilmicin to be active against most strains of common ocular pathogens and common skin flora bacteria. Table 2 provides a listing of susceptibility levels to netilmicin for a total of 767 bacterial isolates from clinical ocular samples, collected from France (FR), Germany (DE), Italy (IT), Poland (PL), the Slovak Republic (SK), Spain (ES), and the United Kingdom (UK), demonstrating the overall level of susceptibility of common ocular flora to the antibiotic.

Table 2 *In vitro* common susceptibility data to netilmicin from EU isolates

	Susceptible		**Intermediate**		**Resistant**		**MIC_{50} (µg/ml)**	**MIC_{90} (µg/ml)**
Organism	**[n]**	**[%]**	**[n]**	**[%]**	**[n]**	**[%]**		
S.aureus	252	100	0	0	0	0	0.25	0.5
S. aureus (coagulase negative)	302	96.5	10	3.2	1	0.3	0.06	4
S. epidermidis	216	95.6	9	4	1	0.4	0.05	4
S. pneumoniae							4	8
H. influenzae							0.25	0.5
Ps. Aeruginosa	39	100	0	0	0	0	4	4

Other information:

Cross-resistance between aminoglycosides (e.g. gentamicin, tobramycin and netilmicin) 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

Poor topic and systemic absorption is expected further to administration of Netilmicin into the conjunctival sac.

Peak plasma concentrations of 5 mg/ml of netilmicin are reached within 30-60 minutes further to intramuscular injection of 2 mg/ml. An intravenous infusion given over a 60-minute period results in a peak plasma concentration of approximately 11 mg/ml. The half-life is usually 2.0 to 2.5 hours in adults and increases with renal insufficiency.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on relevant studies conducted in rats, dogs, guinea pigs, cats, rabbits and monkeys.

The LD50 per intramuscular and intraperitoneal administration is 142 and 186 mg/kg respectively in mice, 166 and 266 mg/kg in rats and 160 < LD50 < 200 i.m. and 40 < LD50 < 72 i.v. in dogs.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium chloride

Benzalkonium chloride

Sodium hydroxide (for pH adjustment)

Purified water

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Unopened: 36 months.

After first opening: 28 days.

6.4 Special precautions for storage

Do not store above 25°C.

Keep the bottle in the outer box in order to protect from light.

6.5 Nature and contents of container

Low density polyethylene screw-cap bottle, containing 5 ml of eye drops.

6.6 Special precautions for disposal

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

7 MARKETING AUTHORISATION HOLDER

NewLine Pharma S.L.

Tarragona 151-157, 11th floor, block A

08014 Barcelona

Spain

8 MARKETING AUTHORISATION NUMBER(S)

PL 35412/0016

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

24/12/2019

10 DATE OF REVISION OF THE TEXT

24/12/2019