

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Netilmicin 3 mg/ml eye drops, solution in single-dose container

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

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

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

The dose is 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 (under 12 years) and in adolescents (up to 18 years of age) have not been established.

Method of administration

- 1) Wash/cleanse your hands thoroughly before putting in the eye drops.
- 2) Open the aluminium sachet containing the single-dose containers.
- 3) Make sure the single-dose container is intact.



- 4) Detach one single-dose container from the strip and put the unopened containers back into the sachet.



- 5) Open by turning the flap of the container without pulling. Do not touch the tip after opening the container.



- 6) Squeeze the single-dose container gently so that a single drop falls into the affected eye(s). Do not allow the tip of the single-dose container to touch the eye or eyelids, or any other surface, so to avoid possible contamination.



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 microorganisms. 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.

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 their 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.

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.

The 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
<i>Enterobacteriaceae</i>	2	4	2
<i>Pseudomonas</i>	4	4	4
<i>Acinetobacter</i>	4	4	NR
<i>Staphylococcus</i>	1	1	1
<i>Staphylococcus</i> , coagulase negative	1	1	NR
<i>Enterococcus</i>	IE	IE	NR
<i>Streptococcus A, B, C and G</i>	NR	NR	NR
<i>Streptococcus pneumoniae</i>	NR	NR	NR
<i>Viridans Streptococci</i>	NR	NR	NR
<i>Haemophilus influenzae</i>	IE	IE	NR
<i>Moraxella catarrhalis</i>	IE	IE	NR
<i>Neisseria gonorrhea</i>	NR	NR	NR
<i>Neisseria meningitidis</i>	NR	NR	NR
Gram-positive anaerobes except <i>Clostridium difficile</i>	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 is a good target for therapy with this 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

Organism	Susceptible		Intermediate		Resistant		MIC ₅₀ (µg/ml)	MIC ₉₀ (µg/ml)
	[n]	[%]	[n]	[%]	[n]	[%]		
<i>S. aureus</i>	252	100	0	0	0	0	0.25	0.5
<i>S. aureus</i> (coagulase negative)	302	96.5	10	3.2	1	0.3	0.06	4
<i>S. epidermidis</i>	216	95.6	9	4	1	0.4	0.05	4
<i>S. pneumoniae</i>							4	8
<i>H. influenzae</i>							0.25	0.5
<i>Ps. Aeruginosa</i>	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, adenylyltransferase (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 topical 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 $160 < \text{LD50} < 200$ i.m. and $40 < \text{LD50} < 72$ i.v. in dogs.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium chloride

Sodium hydroxide (for pH adjustment)

Purified water

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Unopened: 24 months.

The single-dose containers must be used immediately after opening; any remaining contents must be discarded.

6.4 Special precautions for storage

Do not store above 25°C.

Keep the single-dose containers in the original aluminium sachet in order to protect from light.

6.5 Nature and contents of container

15 low density polyethylene single-dose containers filled with 0.3 ml of eye drops, solution.

20 low density polyethylene single-dose containers filled with 0.3 ml of eye drops, solution.

Each 5 single-dose containers are wrapped in an aluminium sachet.

Not all pack sizes may be marketed.

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 35412/0017

**9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE
AUTHORISATION**

24/12/2019

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24/12/2019