

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Netildex 3 mg /ml + 1 mg/ ml eye drops, solution in single-dose container.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml contains:

Netilmicin sulphate 4.55 mg, equivalent to Netilmicin 3 mg.

Dexamethasone disodium phosphate 1.32 mg, equivalent to Dexamethasone 1 mg.

Each single dose container contains:

Netilmicin sulphate 1.36 mg equivalent to Netilmicin 0.9 mg

Dexamethasone disodium phosphate 0.4 mg, equivalent to Dexamethasone 0.3 mg.

Excipients with known effect: Monobasic sodium phosphate monohydrate 1.47 mg, disodium phosphate dodecahydrate 10 mg.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Eye drops, solution in single-dose container.

Clear, colourless or slightly yellow solution.

pH: 6.7 - 7.7

Osmolality: 0.270 – 0.330 Osmol/kg

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Netildex is indicated for the treatment of inflammatory ocular conditions of the anterior segment of the eye, including post-operative cases, where bacterial infection or a risk of bacterial infection with netilmicin-susceptible microorganisms exists.

When prescribing Netildex, consideration should be given to official guidance on the appropriate use of antibacterial agents.

4.2 Posology and method of administration

Posology

For ophthalmic use only.

Adults (including the elderly)

Instill 1 drop into the conjunctival sac four times a day in each affected eye or according to medical prescription.

When using nasolacrimal occlusion or closing the eyelids for 2 minutes, systemic absorption is reduced. This may result in a decrease of systemic side effects and an increase in local activity.

Paediatric population

The safety and efficacy of Netildex in children and adolescents less than 18 years of age has not yet been established.

No data is available.

The product should be administered in paediatric patients only after a careful benefit-risk assessment and strict medical control.

Method of administration

Make sure the single-dose container is intact before use.

1. Wash your hands and sit comfortably.
2. Open the aluminium sachet containing the single-dose containers.
3. Separate one single-dose container from the strip and put the unopened containers back into the sachet.



4. Open by twisting the upper part without pulling. Do not touch the tip after opening the container.



5. Tilt the head back.
6. Use your finger to gently pull down the lower eyelid of your affected eye.
7. Invert the single-dose container and place the tip of the container close to, but not touching your eye. Do not touch your eye or eyelid with the container tip.



8. Squeeze the single-dose container in order to administrate only a drop, then release the lower eyelid.
9. Close your eye and press a finger against the corner by the nose of the affected eye. Hold for 2 minutes.
10. Repeat in the other eye according to medical prescription.
11. Discard the single dose container after use.

Netildex single-dose eye drops must be used immediately after opening.

After administration, the single-dose container and any unused content should be discarded.

Precautions to be taken before handling or administering the medicinal product

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

Patients should be advised that eye drops, if handled incorrectly, can become contaminated by bacteria, which may lead to eye infections. Serious ocular damage and subsequent loss of vision may result from using contaminated eye drops.

If more than one topical ophthalmic drug is being used, the drugs should be administered at least ten minutes apart. Eye ointments should be placed last.

Duration of treatment

The usual treatment duration can vary from 5 to 14 days.

4.3 Contraindications

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

The product contains corticosteroids therefore its use is contraindicated in patients affected by:

- 1) intraocular hypertension,
- 2) herpetic keratitis or other ocular infections caused by herpes simplex,
- 3) viral diseases of the cornea and of the conjunctiva,
- 4) ocular fungal diseases,
- 5) mycobacterial ocular infections.

4.4 Special warnings and precautions for use

Netildex is for ophthalmic use only and should not be orally administered nor should it be introduced into the anterior chamber of the eye.

Intraocular pressure should be routinely monitored in case of treatment lasting longer than 15 days.

Prolonged use may result in ocular hypertension/glaucoma with resultant damage to the optic nerve and defects in visual acuity and visual fields.

Prolonged use of corticosteroids may result in:

- 1) posterior subcapsular cataract formation,
- 2) delayed wound healing,
- 3) decrease of the host response and thus increased hazard of secondary ocular infections, in particular of fungal or viral nature.

In acute purulent infections of the eye, corticosteroids administration may mask or exacerbate infection. In those diseases causing thinning of the cornea or sclera, perforation has been reported with the use of topical steroids.

Sensitivity to topically applied aminoglycosides may occur in some patients. If sensitivity does occur, discontinue use.

This product contains dexamethasone and should be used cautiously in patients with glaucoma and should be considered carefully in patients with a family history of this disease.

Co-treatment with CYP3A inhibitors, including ritonavir and cobicistat-containing products, is expected to increase the risk of systemic side-effects. The combination should be avoided unless the benefit outweighs the increased risk of systemic corticosteroid side-effects, in which case patients should be monitored for systemic corticosteroid side-effects.

This product contains phosphates which may lead to corneal deposits or corneal opacity when topically administered. It should be used with caution in patients presenting with compromised cornea and in instances where the patient is receiving polypharmacy with other phosphate containing eye medications (see Section 4.5).

If significant clinical improvement is not reported within a few days, or should any irritation or sensitization phenomena occur, discontinue treatment and start an adequate therapy.

Visual disturbance

Visual disturbance may be reported with systemic and topical corticosteroid use. If a patient presents with symptoms such as blurred vision or other visual disturbances, the patient should be considered for referral to an ophthalmologist for evaluation of possible causes which may include cataract, glaucoma or rare diseases such as central serous chorioretinopathy (CSCR) which have been reported after use of systemic and topical corticosteroids

Paediatric population

Netildex 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 interaction studies have been performed with Netildex.

Information on each of the constituents is provided below:

Netilmicin:

Significant drug interactions with the use of netilmicin eye drops solution have not been reported.

Concomitant administration of other potentially nephrotoxic and ototoxic antibiotics (even topically, particularly if intracavitary) may increase the risk of these effects.

A potential increase of nephrotoxicity of some aminoglycosides has been reported following concomitant or subsequent administration of other potentially nephrotoxic substances, such as cisplatin, polymyxin B, colistin, viomycin, streptomycin, vancomycin, other aminoglycosides and some cephalosporins (cephaloridine) or potent diuretics such as ethacrynic acid and furosemide due to the effects on the kidney.

Concomitant or subsequent administration of these drugs with netilmicin should be avoided.

In vitro, the combination of an aminoglycoside with a beta-lactam antibiotic (penicillins or cephalosporins) may result in a significant mutual inactivation.

A decrease of half-life or plasma levels of aminoglycoside have been reported in patients with renal insufficiency and in some patients with normal renal function even when an aminoglycoside antibiotic and a similar penicillin have been administered through two different routes.

Dexamethasone:

The risk of increased intraocular pressure associated with prolonged corticosteroid therapy may be more likely to occur with concomitant use of anticholinergics, especially atropine and related compounds, in patients predisposed to acute angle closure.

CYP3A4 inhibitors (including ritonavir and cobicistat) may decrease dexamethasone clearance resulting in increased effects and adrenal suppression/Cushing's syndrome. The combination should be avoided unless the benefit outweighs the increased risk of systemic corticosteroid side-effects, in which case patients should be monitored for systemic corticosteroid effects.

The risk of corneal deposits or corneal opacity may be more likely to occur in patients presenting with compromised cornea and receiving polypharmacy with other phosphate containing eye medications.

4.6 Fertility, Pregnancy and lactation

Pregnancy

No clinical data is available referred to Netildex use in pregnant women.

Studies in animals have shown teratogen activity for dexamethasone.

It is preferable to avoid the use of Netildex during pregnancy.

Breastfeeding

There is insufficient information on the excretion of dexamethasone or netilmicin or their metabolites in human milk following ocular use.

A risk to the newborns/infants cannot be excluded.

Netildex should not be used during breast-feeding.

Fertility

There is no available data on the effect of Netildex on human fertility.

4.7 Effects on ability to drive and use machines

Netildex has moderate influence on the ability to drive and use machines.

Instillation of the eye drops may cause transient blurring of vision. Until this has resolved, patients should not drive or use machines.

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

- intraocular pressure increased (after 15-20 days of topical administration in susceptible or glaucomatous patients)
- posterior subcapsular cataract formation
- blurred vision
- occurrence or worsening of Herpes simplex or fungal infections
- impaired healing.

Immune system disorders

- ocular hypersensitivity: conjunctival hyperemia, burning, itching.

Endocrine Disorders

- Cushing's syndrome,
- adrenal suppression (see section 4.4).

Cases of corneal calcification have been reported very rarely in association with the use of phosphate containing eye drops in some patients with significantly damaged corneas.

Reporting of side effects

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 at 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: Anti-inflammatory agents and anti-infectives in combination, corticosteroids and anti-infectives in combination, ATC code: S01C A01

Netildex contains two active substances: dexamethasone and netilmicin.

Dexamethasone:

- Mechanism of action

Dexamethasone is a corticosteroid with a remarkable anti-inflammatory potency, 25 times higher than hydrocortisone. Like all corticosteroids, it acts mainly by inhibiting the release of arachidonic acid which is the precursor of the most important mediators of inflammation; i.e. prostaglandins and leukotrienes.

The efficacy of dexamethasone for the treatment of inflammatory conditions of the eye is well established.

- Pharmacodynamic effects

Corticosteroids achieve their anti-inflammatory effects through suppression of vascular endothelial cell adhesion molecules and cytokine expression. This 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 tissues.

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.

Netilmicin:

- Mechanism of action

Netilmicin 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 30S ribosomal sub-unit. Netilmicin in this combination provides antibacterial protection against susceptible bacteria.

- Pharmacodynamic effects

Table 1 provides MIC breakpoints, separating susceptible from intermediate susceptible organisms, and intermediate from resistant organisms, based on data from EUCAST.

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 netilmicin in Netildex.

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 (EUCAST 2012)

Microorganism	Clinical MIC breakpoints (mg/l)		
	S (\leq)	R (\geq)	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 gonorrhoea</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

Dexamethasone:

•Absorption:

Dexamethasone reaches intraocular therapeutic concentrations after instillation in the conjunctival sac. The maximum concentrations in the cornea and aqueous humour are attained within 1-2 hours. The plasma half-life of dexamethasone is approximately 3 hours.

• Distribution:

Systemic exposure is low following topical ocular administration of Netildex. Peak dexamethasone plasma levels after the last topical dose range from 220 to 888 picograms/ml (mean 555 ± 217 pg/ml) after administration of one drop of Netildex to each eye four times daily for two consecutive days.

•Metabolism:

After administration, dexamethasone sodium phosphate is subjected to a hydrolysis reaction, catalysed by enzymes in the tear film and cornea, and is partly converted into the lipid-soluble dexamethasone alcohol.

- Excretion:

Dexamethasone is eliminated extensively as metabolites.

Netilmicin:

- Absorption:

As with all aminoglycosides, netilmicin is scarcely lipophilic, therefore, after topical administration, it poorly penetrates the anterior chamber of the eye.

- Distribution:

Studies carried out in humans have revealed that after a single topical administration, the concentration of netilmicin in tears is typically 256 micrograms/ml after 5 minutes, 182 micrograms/ml after 10 minutes, 94 micrograms/ml after 20 minutes and 27 micrograms/ml after 1 hour.

- Metabolism:

Netilmicin is not metabolised following topical ocular use.

- Excretion:

As with other aminoglycoside antibiotics, netilmicin is primarily eliminated unchanged by the kidney.

5.3 Preclinical safety data

Non clinical safety data are derived mainly from published information.

Dexamethasone

Dexamethasone demonstrated to be well tolerated in laboratory animals (rabbits and rats) after local application for up to six months.

The toxicity symptoms of dexamethasone found in various animal species after oral administration are related to the adrenocorticosteroid effects and include the alteration of the adreno-pituitary axis and slight anemia.

Signs of toxicity were found in the stomach, liver, adrenal and pituitary glands, lungs and spleen of laboratory animals.

In the studies carried out following local administration, most of these conditions were absent or rare.

Present findings yield no indications of clinically relevant genotoxic properties of glucocorticoids.

In animal experiments, corticosteroids have been shown to produce foetal resorptions and cleft palate. In the rabbit corticosteroids have produced foetal resorptions and multiple abnormalities involving the head, ears, limbs and palate.

In addition, intrauterine growth inhibition and changes of functional development of the central nervous system have been reported.

Netilmicin

The aminoglycosides as a class of antibiotics are known to have the potential to cause significant nephrotoxic and ototoxic effects, some of which may be irreversible. Fertility, teratogenicity and postnatal studies of netilmicin in rats and rabbits have not provided any significant evidence of toxicity of netilmicin, particularly following ocular administration. In a study of ocular tolerance in rabbits no lesions at the conjunctival and corneal level or of the fundus were observed and ocular reflexes were not affected.

Fixed combination

Similar results to those summarised above for each active were found in studies in rabbits with the fixed combination

Environmental Risk Assessment

Calculation of the Predicted Environmental Concentration (PEC)_{Surface Water} for both dexamethasone and netilmicin has been based on a maximum human dose of eight drops of the drug product in a 24 hour period.

Each drop contains 0.05 mg dexamethasone and 0.15 mg netilmicin. The calculated PEC *Surface Water* values arising from the administration of the eye drops, for dexamethasone and netilmicin respectively, are 0.002 micrograms/l and 0.006 micrograms/l respectively. These values are lower than the 5% action limit (0.01 micrograms/l) and therefore the amount of dexamethasone and netilmicin dispensed in normal use is unlikely to represent a risk to the aquatic environment.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium citrate,
Monobasic sodium phosphate monohydrate,
Disodium phosphate dodecahydrate,
Purified water.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years.

The product does not contain preservatives.

Shelf-life after first opening: After administration the single-dose container should be discarded even if only partially used.

6.4 Special precautions for storage

Store below 30°C.

Store the single-dose containers in the sachet in order to protect from light and moisture.

For storage conditions after first opening of the medicinal product, see section 6.3.

6.5 Nature and contents of container

0.3 ml low density polyethylene (LDPE) single-dose containers wrapped in an aluminum sachet containing 5 single-dose containers.

Pack sizes of 15 or 20 single-dose containers.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

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

7 MARKETING AUTHORISATION HOLDER

SIFI Pharmaceuticals Limited

29/30 Fitzroy Square

London W1T 6LQ

United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

PLGB 53941/0018

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

08/11/2024

10 DATE OF REVISION OF THE TEXT

08/11/2024