SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Netildex 3 mg/ml + 1 mg/ml eye drops, solution

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.

Excipients with known effect: Benzalkonium chloride 0.05 mg, 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.

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.

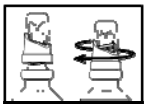
The product should be administered in paediatric patients only after a careful benefit-risk assessment and strict medical control.

Method of administration

Make sure the bottle is intact before use.

1. Wash your hands and sit comfortably.

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



3. Tilt the head back.

4. Use your finger to gently pull down the lower eyelid of your affected eye.

5. Invert the bottle and place the tip of the bottle close to, but not touching your eye.

Do not touch your eye or eyelid with the dropper tip.

6. Squeeze the bottle gently in order to administrate only one drop, then release the lower eyelid.

7. Close your eye and press a finger against the corner by the nose of the affected eye. Hold for 2 minutes.

8. Repeat in your other eye according to medical prescription.

9. Put the cap back on the bottle.

Precautions to be taken before handling or administering the medicinal product

Contact lenses should not be worn during treatment with corticosteroid eye drops due to increased risk of infection. If contact lenses are worn, these should be removed before instillation of the eye drops and may be reinserted after 15 minutes (see section 4.4). 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.

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.

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.

Contact lenses

Netildex eye drops 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 may change the colour of the contact lenses, 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. Netildex eye drops in multidose container should be used with caution in dry eye patients and in patients where the cornea may be compromised.

Close monitoring is required in case of frequent or prolonged use, and in patients with conditions where the cornea is compromised. Alternatively, the use of Netildex eye drops in single-dose container, which is preservative-free, should be recommended.

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 are 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 breastfeeding.

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 hypereamia, 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.

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

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.

Undesirable effects may occur if the whole content of one multidose container (containing dexamethasone 5 mg) is ingested. In such an event, medical advice should be sought immediately.

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 (≤)	**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 is 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**		**MIC50 (µg/ml)**	**MIC90 (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

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 lipophylic, 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,
Benzalkonium chloride,
Purified water.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Unopened: 2 years.
After first opening, use within 28 days.

6.4 Special precautions for storage

Store below 30°C.
For storage conditions after first opening of the medicinal product, see section 6.3.

6.5 Nature and contents of container

Box with 1 low density polyethylene screw-cap bottle, containing 5 ml of eye drops.

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 53941/0017

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

08/11/2024

10 DATE OF REVISION OF THE TEXT

08/11/2024