SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT
DEXANETIL 0.1% + 0.3% eye drops, solution
Sterile

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
Each 1 mL contains:
Active substances:
Dexamethasone sodium phosphate ..... 1.32 mg (equivalent to 1 mg dexamethasone)
Netilmicin sulfate ..... 4.55 mg (equivalent to 3 mg netilmicin)

Excipients:
Benzalkonium chloride ..... 0.05 mg
Disodium phosphate (anhydrous) ..... 3.96 mg
Sodium dihydrogen phosphate dihydrate ..... 1.66 mg
For excipients, see section 6.1.

3. PHARMACEUTICAL FORM
Eye drops, solution
Clear, colorless, sterile solution free from visible particles.

4. CLINICAL PARTICULARS
4.1 Therapeutic indications
DEXANETIL 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 DEXANETIL, consideration should be given to official guidance on the appropriate use of antibacterial agents.

4.2. Posology and method of administration
Posology/frequency and duration of administration:
For ophthalmic use only.
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.
The usual treatment duration can vary from 5 to 14 days.

Method of administration
DEXANETIL,
- For ophthalmic use only.
- Administered to the eye.
- To pierce the plastic bottle, turn the cap towards the pointed tip. Close the bottle by turning the pointed tip.
- Avoid touching the tip of the container to the eye, hands, or any other surface while applying the medicine.
- Ensure that the packaging is intact before use.

Once the bottle is opened, use it within 28 days.

Precautions to be taken before administering this 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.

Additional information on special populations:
Renal/Hepatic impairment:
No special dose adjustment is required for patients with renal or hepatic impairment.

Pediatric population:
The safety and efficacy of DEXANETIL in children and adolescents under 18 years of age have not yet been established. This product should be administered in paediatric patients only after a careful benefitrisk assessment and strict medical control.

Geriatric population:
No special dose adjustment is required for elderly patients.

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

This 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
DEXANETIL is for ophthalmic use only; it should not be administered orally or applied into the anterior chamber of the eye.

For treatments lasting longer than 15 days, intraocular pressure should be routinely monitored.

Prolonged use may cause ocular hypertension/glaucoma, leading to optic nerve damage and defects in visual acuity/visual fields.
Long-term corticosteroid use may result in:
1) Formation of posterior subcapsular cataract,
2) Delayed wound healing,

3) Reduced host response and, consequently, an increased risk of secondary ocular infections, particularly fungal or viral.

In acute purulent eye infections, corticosteroid application may mask or exacerbate the infection. Perforation has been reported with topical corticosteroid use in diseases that cause corneal or scleral thinning.

Some patients may develop hypersensitivity to topically applied aminoglycosides. If hypersensitivity occurs, use should be discontinued.

This medicine contains dexamethasone; therefore, it should be used with caution in patients diagnosed with glaucoma and carefully evaluated in those with a family history of this disease.

Concomitant 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 of treatment outweighs the increased risk of systemic corticosteroid side effects. If treatment is initiated, patients should be monitored for systemic corticosteroid-related side effects.

Visual impairment
Visual disturbance may be reported following 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.

Contact lenses
This medication contains 0.05 mg of benzalkonium chloride per 1 mL. Benzalkonium chloride may be absorbed by soft contact lenses and cause discoloration. Contact lenses should be removed before using this medication and reinserted 15 minutes afterward (see Section 4.2).

Benzalkonium chloride may cause eye irritation, particularly in individuals with dry eye syndrome or corneal (the transparent layer at the front of the eye) disorders. Abnormal sensations, stinging, or pain in the eye may be experienced after use.

This medication contains 3.66 mg of phosphate per 1 mL as excipient.

If there is severe damage to the transparent layer at the front of the eye (cornea), phosphates may, in rare cases, cause cloudy deposits due to calcium accumulation during treatment.

4.5. Interaction with other medicinal products and other forms of interaction
No interaction studies have been conducted with DEXANETIL. Information on each of the constituents is provided below.

Netilmicin:
No significant drug interactions have been reported with the use of netilmicin eye drops solution. The concurrent 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. The concomitant or sequential use of these drugs with netilmicin should be avoided.
In vitro, the combination of aminoglycosides and beta-lactam antibiotics (penicillins or cephalosporins) may lead to significant mutual inactivation.
In patients with renal impairment and some patients with normal renal function, even when aminoglycoside antibiotics and similar penicillins are administered via different routes, a reduction in the aminoglycoside's half-life or plasma levels has been reported.

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 reduce dexamethasone clearance, leading to increased effects and the potential for adrenal suppression/Cushing's syndrome. The combination should be avoided unless the benefits outweigh the increased risk of systemic corticosteroid side effects. If used together, patients should be monitored for systemic corticosteroid effects.
In patients presenting with corneal disorders who are on multiple eye medications containing phosphates, the risk of corneal deposits or corneal opacity may be higher.

Additional information on special populations
No interaction studies have been conducted.

Pediatric population:
No interaction studies have been conducted.

4.6. Fertility, pregnancy and lactation
General recommendation
Pregnancy category: C

Women of childbearing potential / Birth control (Contraception)
There is insufficient data regarding the use of the product in women of childbearing potential. No specific precautions have been identified for women of childbearing potential who are not using any form of contraception.

Pregnancy
There is no clinical data on the safety of netilmicin during pregnancy. Animal studies have shown no direct or indirect effects on pregnancy, embryonal and postnatal development, or birth (see Section 5.3).

Regarding dexamethasone safety during pregnancy; animal studies have demonstrated that corticosteroids cause fetal resorptions and cleft palate. In rabbits, corticosteroids have led to fetal resorptions and multiple abnormalities affecting the head, ears, limbs, and palate (see Section 5.3). DEXANETIL should only be used if the benefit is considered to outweigh the risk.

Animal studies are insufficient to determine the effects of the drug on pregnancy/and-or/embryonal/fetal development/and-or/birth/and-or/postnatal development (see Section 5.3). The potential risk to humans is unknown.

Lactation
There is insufficient information regarding the excretion of dexamethasone, netilmicin, or their metabolites into human breast milk following ocular use. The risk to newborns/infants cannot be excluded. DEXANETIL should not be used during breastfeeding.

Reproductive ability/Fertility
There is insufficient data on the effects of the drug on fertility.

4.7. Effects on the ability to drive and use machines
It may cause a mild effect on the ability to drive and operate machinery. Instillation of the eye drops may cause temporary blurred vision. Patients should not drive or operate machinery until this effect has resolved.

4.8. Undesirable effects
The reported undesirable effects are listed below according to MedDRA System Organ Classification, along with the following frequency categories. 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), very rare (<1/10,000), not known (cannot be estimated from the available data).

Immune system disorders
Not known: ocular hypersensitivity: conjunctival hyperemia, burning, itching.

Endocrine disorders
Not known:
- Cushing's syndrome,
- Adrenal suppression (see Section 4.4).

Eye disorders
Not known:
- Increased intraocular pressure (after 15-20 days of topical use in predisposed or glaucomatous patients)
- Posterior subcapsular cataract formation
- Blurred vision
- Onset or worsening of Herpes simplex or fungal infections
- Delayed healing

In some patients with severely damaged corneas, very rare cases of corneal calcification have been reported with the use of phosphate-containing eye drops.

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

Reporting of suspected adverse reactions:
Reporting suspected adverse reactions after authorization 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 national reporting system.

4.9. Overdose and treatment
No cases of overdose have been reported.
If the entire content of DEXANETIL 0.1% + 0.3% eye drops solution (5 mg dexamethasone) is ingested orally, undesirable effects may occur. In such cases, medical attention 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: S01CA01

Mechanism of Action:
DEXANETIL contains two active substances: dexamethasone and netilmicin.

Dexamethasone
Mechanism of action
Dexamethasone is a corticosteroid with significant 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 effectiveness of dexamethasone in treating inflammatory eye diseases is well established.

Pharmacodynamic effects
Corticosteroids exert their anti-inflammatory effects by suppressing the expression of vascular endothelial adhesion molecules and cytokines. This leads to a decrease in pro-inflammatory mediator expression and inhibition of leukocyte adhesion to vascular endothelium, thereby preventing their migration into inflamed ocular tissues.
Dexamethasone is one of the most potent anti-inflammatory agents, demonstrating significant anti-inflammatory activity with reduced mineralocorticoid effects compared to some other steroids.

Netilmicin
Mechanism of action:
Netilmicin is a potent, broad-spectrum aminoglycoside antibiotic with a rapid bactericidal effect. Its primary action on bacterial cells is through inhibition of peptide bonding and synthesis at the 30S ribosomal subunit. In this combination, netilmicin provides antibacterial protection against susceptible bacteria.

Pharmacodynamic effects
Table 1 shows the 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 over time for selected species, and it is particularly important to have local resistance data when treating severe infections. When

necessary, expert advice should be sought regarding local resistance prevalence, especially in cases where the effectiveness of the active substance for certain infections is questionable. The following information serves only as a general guideline regarding the likelihood of bacterial susceptibility to netilmicin in DEXANETIL.

Breakpoints defining isolates as susceptible or resistant are useful in predicting the clinical efficacy of systemically administered antibiotics. However, when an antibiotic is applied topically in very high concentrations directly to the site of infection, these breakpoints may not be applicable. Many isolates classified as resistant based on systemic breakpoints can, in fact, be successfully treated with topical administration.

The frequency of general aminoglycoside resistance can reach 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
Species-irrelevant breakpoints	2	4	NR
Note: S = Sensitive. R = Resistant. ECOFF = Common epidemiological cut-off value for monitoring resistance. IE = There is insufficient evidence to suggest that the species is a good target for treatment with this drug. NR = Not reported.			

In vitro studies have shown that netilmicin is 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, Germany, Italy, Poland, the Slovak Republic, Spain, and the United Kingdom, 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

	Sensitive	**Intermediate**	**Resistant**	**MIC_{50} (mcg/**	**MIC_{90} (mcg/**

Organism	[n]	[%]	[n]	[%]	[n]	[%]	mL)	mL)
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 among aminoglycosides (e.g., gentamicin, tobramycin, and netilmicin) is dependent on enzyme modifications, specifically adenyltransferase (ANT) and acetyltransferase (ACC). However, due to the varying specificities of different modifying enzymes, cross-resistance among aminoglycoside antibiotics can differ. The most common mechanism of acquired resistance to aminoglycosides is antibiotic inactivation by plasmid and transposon-encoded modifying enzymes.

5.2. Pharmacokinetic properties
General properties
Dexamethasone:
Absorption:
After instillation into the conjunctival sac, dexamethasone reaches intraocular therapeutic concentrations. Maximum concentrations in the cornea and aqueous humor are reached within 1-2 hours. The plasma half-life of dexamethasone is approximately 3 hours.

Distribution:
Systemic exposure is low after the topical ocular dexamethasone-netilmicin combination application.
After applying one drop of the dexamethasone-netilmicin combination to each eye four times a day for two consecutive days, the peak plasma dexamethasone levels after the last topical dose range from 220 to 888 picograms/mL (mean 555 ± 217 pg/mL).

Metabolism:
After the application of dexamethasone sodium phosphate, it undergoes a hydrolysis reaction, catalyzed by enzymes in the tear film and cornea, and converting partially into the lipid-soluble dexamethasone alcohol.

Elimination:
Dexamethasone is predominantly eliminated as metabolites.

Netilmicin:
Absorption:
Like all aminoglycosides, netilmicin is scarcely lipophylic, therefore, after topical administration, it poorly penetrates the anterior chamber of the eye.

Distribution:
Studies in humans show that after a single topical administration, netilmicin concentration in the 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 metabolized after topical ocular use.

Elimination:
Like other aminoglycoside antibiotics, netilmicin is predominantly eliminated unchanged by the kidneys.

5.3. Preclinical safety data
Preclinical safety data is primarily derived from published information.

Dexamethasone
Dexamethasone has been shown to be well tolerated in laboratory animals (rabbits and rats) after local application for up to six months.
The symptoms of dexamethasone toxicity observed in various animal species following oral administration are associated with adrenal corticosteroid effects and include changes in the adreno-pituitary axis and mild anemia.
Toxicity signs were observed in the stomach, liver, adrenal and pituitary glands, lungs, and spleen of laboratory animals.
In studies following local application, most of these conditions were absent or rare. Current findings do not indicate any clinically significant genotoxic properties of glucocorticoids.
In animal experiments, corticosteroids have been shown to cause fetal resorptions and cleft palate. In rabbits, corticosteroids caused fetal resorptions and multiple abnormalities including in the head, ears, limbs, and palate.
Additionally, intrauterine growth inhibition and functional changes in the development of the central nervous system have been reported.

Netilmicin
Some aminoglycosides, as a class of antibiotics, are known to have potentially cause significant nephrotoxic and ototoxic effects, which can 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
In studies examining the fixed combination in rabbits, similar findings to those summarized above for each active substance were observed.

Environmental Risk Assessment
The Predicted Environmental Concentration (PEC) Surface Water for both dexamethasone and netilmicin has been calculated based on the maximum human dose of eight drops within a 24-hour period.
Each drop contains 0.05 mg of dexamethasone and 0.15 mg of netilmicin. The calculated PEC Surface Water values for dexamethasone and netilmicin, resulting from the application of the eye drops, are 0.002 micrograms/L and 0.006 micrograms/L, respectively. These values are below the 5% action limit (0.01 micrograms/L), and therefore, the amounts 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

Benzalkonium chloride
Disodium phosphate (anhydrous)
Sodium dihydrogen phosphate dihydrate
Sodium citrate (anhydrous)
Water for injection

6.2. Incompatibilities

There are no known incompatibilities.

6.3. Shelf life

24 months
After opening, it should be used within 28 days when stored below 25°C.

6.4. Special precautions for storage

Should be stored at room temperature below 25°C and in its packaging.

6.5. Nature and contents of container

It is available in a 5 mL opaque, white colored, low density polyethylene bottle with a low density polyethylene dropper and a twist-off white polyethylene cap, along with instructions for use inside a cardboard box.

6.6. Special precautions for disposal and other handling

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

7. MARKETING AUTHORIZATION HOLDER

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2020/8

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Date of latest renewal:

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