1. NAME OF THE MEDICINAL PRODUCT

Tobrasone
Tobramycin & Dexamethasone Ophthalmic Ointment USP

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Composition:
Tobramycin Sulphate USP
Eq. to Tobramycin 0.3%w/w
Dexamethasone USP 0.1%w/w
Sterile ointment base q.s

Batch Size :- 100Ltr.
Formula :-

Sr. No.	Raw Materials	Standards	Quantity/ml (mg)	Batch Qty.(kg)	Overages	Use
1	Tobramycin Sulphate	USP	6.0	0.600 kg	20.0%	Active
2	Dexamethasone	USP	1.10	0.110kg	10.0%	Active
3	Glycerin	USP	50	5.000kg	--	Solubilizer
4	Liquid paraffin	BP	100	10.000kg	--	Ointment base
5	Propylene Glycol	BP	100	10.000 kg	--	Solubilizer

Note:- Quantity of active ingredients to be taken by consideration of their Assay and water content

3. PHARMACEUTICAL FORM

Ophthalmic Ointment

4. Clinical particulars

4.1 Therapeutic indications

This medication is used to treat or prevent eye infections. This medication contains two drugs. Tobramycin belongs to a class of drugs called aminoglycoside antibiotics. It works by stopping the growth of bacteria. Dexamethasone belongs to a class of drugs called corticosteroids. It works by reducing swelling.

This medication treats/prevents only bacterial eye infections. It will not work for other types of eye infections. Unnecessary use or overuse of any antibiotic can lead to its decreased effectiveness.

4.2 Posology and method of administration

Do not use while wearing soft contact lenses. A preservative in this medicine could permanently stain the lenses.
Use the medicine at least 15 minutes before inserting your contact lenses.
Wash your hands before using eye medication.
Shake the eye drops well just before each use.
To use the eye drops: Tilt your head back slightly and pull down your lower eyelid to create a small pocket. Hold the dropper above the eye and squeeze a drop into this pocket. Close your eyes for 1 or 2 minutes.
Use only the number of drops your doctor has prescribed.
To apply the ointment: Tilt your head back slightly and pull down your lower eyelid to create a small pocket. Squeeze a ribbon of ointment from the tube into this pocket. Blink your eye gently and then keep it closed for 1 or 2 minutes. Wipe excess ointment from your eyelashes using a clean tissue.
Do not touch the tip of the eye dropper or ointment tube or place it directly on your eye. A contaminated tip can infect your eye, which could lead to serious vision problems.
If you use this medicine for longer than 10 days, you may need frequent vision tests to check the pressure inside your eyes.
Call your doctor if your symptoms do not improve after 2 days of treatment.
You should not stop using this medicine suddenly. Follow your doctor's instructions about tapering your dose.
Store this medicine at room temperature. Do not freeze. Keep the tube tightly closed when not in use. Store the eye drops in an upright position.

4.3 Contraindications

You should not use this medicine if you are allergic to dexamethasone or tobramycin, or if you have a fungal or viral infection in your eyes (including herpes simplex).

Tell your doctor if you have ever had:

- Glaucoma; or
- Cataracts, or if you need cataract surgery.

It is not known whether this medicine will harm an unborn baby. Tell your doctor if you are pregnant.

It may not be safe to breast-feed while using this medicine. Ask your doctor about any risk.

4.4 Special warnings and precautions for use

Before using tobramycin with dexamethasone, tell your doctor or pharmacist if you are allergic to either drug; or to other aminoglycoside antibiotics (e.g., gentamicin); or if you have any other allergies. This product may contain inactive ingredients, which can cause allergic reactions or other problems. Talk to your pharmacist for more details.

Before using this medication, tell your doctor or pharmacist your medical history, especially of: other eye problems (e.g., glaucoma)

Your vision may be temporarily blurred or unstable after applying this drug. Do not drive, use machinery, or do any activity that requires clear vision until you are sure you can perform such activities safely.

This medication should be used only when clearly needed during pregnancy. Discuss the risks and benefits with your doctor.

It is not known if this medication passes into breast milk. Consult your doctor before breast-feeding.

4.5 Interaction with other medicinal products and other forms of interaction

Interactions are not expected. Do not use any other eye products without telling your doctor or health care professional.

This list may not describe all possible interactions. Give your health care provider a list of all the medicines, herbs, non-prescription drugs, or dietary supplements you use. Also tell them if you smoke, drink alcohol, or use illegal drugs. Some items may interact with your medicine.

4.6 Pregnancy and Lactation

Pregnancy:

There are no or limited amount of data from the topical ocular use of tobramycin and dexamethasone in pregnant women. Tobramycin does cross the placenta into the fetus after intravenous dosing in pregnant women. Tobramycin is not expected to cause ototoxicity from in utero exposure. Prolonged or repeated corticoid use during pregnancy has been associated with an increased risk of intra-uterine growth retardation. Infants born of mothers who have received substantial doses of corticosteroids during pregnancy should be observed carefully for signs of hypoadrenalism.

Studies in animals have shown reproductive toxicity after systemic administration of tobramycin and dexamethasone. These effects were observed at exposures considered sufficiently in excess of the maximum human ocular dosage delivered from the maternal use of the product.

TOBRASONE is not recommended during pregnancy.

Breast-feeding

Tobramycin is excreted in human milk after systemic administration. No data is available on the passage of dexamethasone into human breast milk. It is unknown whether tobramycin and dexamethasone are excreted in human milk following topical ocular administration. It is not likely that the amount of Tobramycin and Dexamethasone would be detectable in human milk or be capable of producing clinical effects in the infant following topical use of the product.

A risk to the suckling child cannot be excluded. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from therapy taking into account the benefit of breast feeding for the child and the benefit of therapy for the woman.

Fertility

Studies have not been performed to evaluate the effect of tobramycin on human or animal fertility. There is limited clinical data to evaluate the effect of dexamethasone on male or female fertility.

4.6 Effects on ability to drive and use machines

TOBRASONE has no or negligible influence on the ability to drive and use machines.

No studies on the effects on the ability to drive and use machines have been performed. As with any eye drop, temporarily blurred vision or other visual disturbances may affect the ability to drive or use machines. If blurred vision occurs, the patient must wait until the vision is clear before driving or using machines.

4.7 Undesirable effects

Temporary blurred vision, eye redness, eye discomfort, and eyelid itching/swelling may occur. If any of these effects persist or worsen, notify your doctor or pharmacist promptly.

Remember that your doctor has prescribed this medication because he or she has judged that the benefit to you is greater than the risk of side effects. Many people using this medication do not have serious side effects.

Use of this medication for prolonged/repeated periods may result in a new fungal eye infection and may increase your risk for other eye problems (e.g., glaucoma, cataracts). Do not use this medication for longer than prescribed. Tell your doctor right away if you notice any of the following:

- New or worsening eye symptoms (e.g., discharge, swelling)
- Vision changes
- Eye pain

A very serious allergic reaction to this drug is unlikely, but seek immediate medical attention if it occurs. Symptoms of a serious allergic reaction may include:

- Rash
- Itching/swelling (especially of the face/tongue/throat)
- Severe dizziness
- Trouble breathing

This is not a complete list of possible side effects. If you notice other effects not listed above, contact your doctor or pharmacist.

4.8 Overdose

Due to the characteristics of this preparation, no toxic effects are to be expected with an ocular overdose of this product, or in the event of accidental ingestion of the contents of one bottle or tube.

A topical overdose of TOBRASONE may be flushed from the eye(s) with lukewarm tap water.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamics properties

Pharmacotherapeutic group: Anti-inflammatory agents and anti-infectives in combination, corticosteroids and anti-infectives in combination.

ATC code: S01C A01.

Dexamethasone:

The efficacy of corticosteroids for the treatment of inflammatory conditions of the eye is well established. Corticosteroids achieve their anti-inflammatory effects through suppression of vascular endothelial cell adhesion molecules, cyclooxygenase I or II, and cytokine expression. This action 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 tissue. 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.

Tobramycin:

Tobramycin 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 ribosome. Tobramycin in this combination provides antibacterial protection against susceptible bacteria.

The following MIC breakpoints, separating susceptible from intermediate susceptible organisms, and intermediate susceptible from resistant organisms, are suggested: S ($\leq$ 4 µg/ml, R ($\geq$ 8 µg/ml). 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 tobramycin in TOBRASONE.

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

Paediatric Population

The safety and efficacy of TOBRASONE in children have been established by broad clinical experience, but only limited data are available. In a clinical study of TOBRASONE suspension for the treatment of bacterial conjunctivitis, 29 paediatric patients, ranging in age from 1 to 17 years, were treated with 1 or 2 drops of TOBRASONE every 4 or 6 hours for 5 or 7 days. In this study, differences in the safety profile between adult and paediatric patients were not observed.

Other information

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

Tobramycin:

Animal studies have shown that tobramycin is absorbed into the cornea following ocular administration. Following systemic administration to patients with normal renal function, a plasma half-life of approximately 2 hours has been observed. Tobramycin is eliminated almost exclusively by glomerular filtration with little if any biotransformation. Plasma concentrations of tobramycin following the 2-day topical ocular regimen of TOBRASONE were below the limit of quantification in most subjects or low (≤0.25 microgram/ml).

Dexamethasone:

Following ocular administration, dexamethasone is absorbed into the eye with maximum concentrations in the cornea and aqueous humour attained within 1-2 hours. The plasma half-life of dexamethasone is approximately 3 hours. Dexamethasone is eliminated extensively as metabolites. Systemic exposure to dexamethasone is low following topical ocular administration of TOBRASONE. Peak dexamethasone plasma levels after the last topical dose ranged from 220 to 888pg/ml (mean 555 ± 217pg/ml) after administration of one drop of TOBRASONE to each eye four times per day for two consecutive days.

5.3 Preclinical safety data

Non-clinical data revealed no special hazard for humans from topical ocular exposure to tobramycin or dexamethasone based on conventional repeated-dose topical ocular toxicity studies, genotoxicity or carcinogenicity studies. Effects in non-clinical reproductive and developmental studies with tobramycin and dexamethasone were observed only at exposures considered sufficiently in excess of the maximum human ocular dosage indicating little relevance to clinical use for low-dose short-term courses of therapy.

Tobramycin has not been shown to induce teratogenicity in rats or rabbits. The ocular administration of 0.1% dexamethasone resulted in fetal anomalies in rabbits. Dexamethasone had no adverse effects on female fertility in a chorionic gonadotropin primed rat model.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Glycerin USP
Liquid paraffin BP
Propylene Glycol BP

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years.

6.4 Special precautions for storage

Do not store above 30°C.

Keep in a cool & dry place.

6.5 Nature and contents of container <and special equipment for use, administration or implantation>

5 gm Aluminum collapsible liquor coating tube sealed with HDPE screw cap with the pack insert is packed in Primary Carton.

6.6 Special precautions for disposal <and other handling>

No special requirements.

7. <APPLICANT/MANUFACTURER>

Hanuchem Laboratories
1317 – 20, Manpura, Baddi, Dist. Solan (HP.)
173205. India.