

PRODUCT MONOGRAPH

Pr **TOBREX® 0.3%**

(Tobramycin Ophthalmic Solution)

3 mg per mL

and

(Tobramycin Ophthalmic Ointment)

3 mg per gram

Antibiotic

ALCON CANADA INC.
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Mississauga, Ontario
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Date of Preparation
December 20, 1983

Control 8075A

PRODUCT MONOGRAPH

NAME OF DRUG

TOBREX®

(Tobramycin Ophthalmic Solution)

0.3%

and

(Tobramycin Ophthalmic Ointment)

0.3%

THERAPEUTIC OR PHARMACOLOGIC CLASSIFICATION

Antibiotic

ACTION

Like other aminoglycosides, the bactericidal activity of tobramycin is accomplished by specific inhibition of normal protein synthesis in susceptible bacteria, but at the present time, very little is known about this action. It is thought that inhibition of synthesis is due to an action on ribosomes that, in turn, causes bacterial misreading of messenger RNA.

INDICATIONS AND CLINICAL USE

TOBREX OPHTHALMIC SOLUTION (Tobramycin Ophthalmic Solution, USP) and TOBREX OPHTHALMIC OINTMENT (Tobramycin Ophthalmic Ointment, USP) are topical antibiotic preparations indicated in the treatment of external infections of the eye and its adnexa caused by susceptible bacteria. Appropriate monitoring of bacterial response to topical antibiotic therapy should accompany the use of TOBREX.

CONTRAINDICATIONS

TOBREX OPHTHALMIC SOLUTION and TOBREX OPHTHALMIC OINTMENT are contraindicated in patients with known hypersensitivity to any of the components. Partial cross-allergenicity to other aminoglycosides has been established.

WARNINGS

NOT FOR INJECTION INTO THE EYE.

Sensitivity to topically applied aminoglycosides may occur in some patients. If a sensitivity reaction to tobramycin occurs, discontinue use.

Pregnancy: Reproduction studies in three types of animals at doses up to thirty three times the normal human systemic dose have revealed no evidence of impaired fertility or harm to the fetus due to tobramycin. There are, however, no adequate and well controlled studies in pregnant women. Because animal studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers: Because of the potential for adverse reactions in nursing infants from tobramycin, a decision should be made whether to discontinue nursing the infant or to discontinue the drug, taking into consideration the importance of the drug to the mother.

PRECAUTIONS

As with other antibiotic preparations, prolonged use may result in overgrowth of nonsusceptible organisms, including fungi. If superinfection or drug resistance occurs, or irritation or sensitization to any of the components of these preparations develops, treatment with TOBREX OPHTHALMIC SOLUTION or TOBREX OPHTHALMIC OINTMENT should be discontinued and appropriate therapy should be initiated. The patient should be advised to consult a physician if improvement fails to occur, or if signs of superinfection should occur. The patient should also be advised to avoid contamination of the dropper tip by the eye, or other objects.

If TOBREX OPHTHALMIC SOLUTION or TOBREX OPHTHALMIC OINTMENT is administered concomitantly with systemic aminoglycoside antibiotics, care should be taken to monitor the total serum concentration.

ADVERSE REACTIONS

The most frequent adverse reactions to TOBREX OPHTHALMIC SOLUTION (Tobramycin Ophthalmic Solution, USP) and TOBREX OPHTHALMIC OINTMENT (Tobramycin Ophthalmic Ointment, USP) are localized ocular toxicity and hypersensitivity, including lid itching and swelling and conjunctival erythema. These reactions occur in approximately 3% of patients treated with TOBREX preparations. Other adverse reactions have not been reported from TOBREX therapy.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

Clinically apparent signs and symptoms of an overdose of TOBREX preparations (punctate keratitis, erythema, increased lacrimation, edema and lid itching) may be similar to adverse reaction effects in some patients. In case of dramatic systemic overdose, serum concentrations should be monitored and prolonged levels above 12 $\mu\text{g}/\text{mL}$ avoided. Hemodialysis will help remove tobramycin from the blood. Such reactions and the necessity for counter measures are not expected from the use of TOBREX OPHTHALMIC SOLUTION or TOBREX OPHTHALMIC OINTMENT.

DOSAGE AND ADMINISTRATION

Tobrex Ophthalmic Solution

In mild to moderate disease, instill one or two drops into the affected eye(s) every four hours. In severe infections, instill two drops into the eye(s) hourly until improvement, following which treatment should be reduced prior to discontinuation.

Tobrex Ophthalmic Ointment

In mild to moderate disease, instill a half inch ribbon into the conjunctival sac of the affected eye(s) two to three times per day. For severe infections, instill a half-inch ribbon into the conjunctival sac of the affected eye(s) every three to four hours until improvement is detected. Following improvement, treatment should be reduced prior to discontinuation.

AVAILABILITY

TOBREX OPHTHALMIC SOLUTION (Tobramycin Ophthalmic Solution, USP) is a sterile ophthalmic solution of tobramycin. Each mL contains: tobramycin 0.3% (3 mg), as active ingredient and benzalkonium chloride 0.01% as preservative. Inactive ingredients are: boric acid, sodium sulfate, sodium chloride, tyloxapol, sulfuric acid and/or sodium hydroxide (to adjust pH) and purified water.

Available as a sterile solution in 5mL Drop-tainer® dispenser, containing tobramycin 0.3% (3 mg/mL). The patient should be advised to avoid contamination of the dropper tip by avoiding contact with the eye, skin or other surfaces. Keep tightly closed.

TOBREX OPHTHALMIC OINTMENT (Tobramycin Ophthalmic Ointment, USP) is a sterile ophthalmic ointment containing the active ingredient tobramycin at a concentration of 3.0 mg/g and 0.5% chlorobutanol, as a preservative, in a mineral oil and petrolatum base.

The ointment is available in 3.5g metal ointment tube, which dispenses a ribbon of ointment.

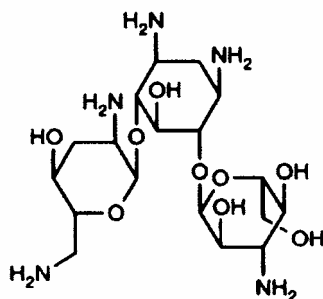
The patient should be advised to avoid contamination of the end of the tube by avoiding contact with the eye, skin or other surfaces. Keep tightly closed.

Tobramycin is a schedule F (prescription) drug.

PHARMACOLOGY

Structural Formula and Chemistry

Tobramycin



Chemical Name: 0-3-amino-3-deoxy- α -D-glucopyranosyl-(1 \rightarrow 4)-0-[2,6-diamino-2,3,6-trideoxy- α -D-ribohexopyranosyl-(1 \rightarrow 6)]-2-deoxy-L-streptamine.

Molecular Formula: $C_{18}H_{37}N_5O_9$

Molecular Weight: 467.54

Because the ocular concentrations of tobramycin achieved after topical application are higher than those which can be safely used in systemic therapy, standardized susceptibility tests may not be appropriate to predict the effectiveness of Tobramycin Ophthalmic Solution.

The gram positive bacteria against which Tobramycin Ophthalmic Solution is clinically effective include the coagulase-positive and coagulase-negative staphylococci, including penicillin-resistant strains, *Streptococcus pneumoniae*, other alpha-hemolytic streptococci, Group A beta-hemolytic and non-hemolytic streptococci. The gram-negative bacteria against which Tobramycin Ophthalmic Solution has been shown to have clinical effectiveness include most strains of *Pseudomonas aeruginosa*, *Escherichia coli*, *Klebsiella pneumoniae*, *Enterobacter aerogenes*, *Proteus mirabilis* (indole negative) and indole-positive *Proteus* species, as well as *Haemophilus* spp., *Moraxella* spp., and *Acinetobacter calcoaceticus* (*Herellea vaginocoli*). Bacterial susceptibility studies show that many microorganisms resistant to gentamicin retain susceptibility to tobramycin. A significant population resistant to tobramycin has not emerged; however, bacterial resistance may develop upon prolonged use.

MICROBIOLOGY

In vitro tests demonstrate that tobramycin is bactericidal and that it acts by inhibiting the synthesis of protein in bacterial cells.

Tobramycin is active against most strains of the following organisms:

Pseudomonas aeruginosa

Proteus sp. (indole-positive and indole-negative), including *Pr. mirabilis*,

Pr. morganii, *Pr. rettgeri* and *Pr. vulgaris*

Escherichia coli

Klebsiella-Enterobacter-Serratia sp.

Citrobacter sp.

Providencia sp.

Staphylococci, including *Staphylococcus aureus* (coagulase-positive and coagulase-negative)

Although most strains of group D streptococci demonstrate *in vitro* resistance, some strains in this group are susceptible. *In vitro* studies have shown that an aminoglycoside combined with an antibiotic which interferes with cell wall synthesis affects some group D streptococcal strains synergistically. The combination of penicillin G and tobramycin results in a synergistic bactericidal effect *in vitro* against certain strains of *Streptococcus faecalis*. However, this combination is not synergistic against other closely related organisms, e.g. *Str faecium*. Speciation of group D streptococci alone cannot be used to predict susceptibility. Susceptibility testing and tests for antibiotic synergism are required.

Susceptibility Plate Tests - If the Bauer-Kirby-Sherris-Turck method of disc susceptibility testing is used (Am J Clin Pathol 45:493, 1966), a disc containing 10 μ g tobramycin should give a zone of inhibition of at least 14 mm when tested against a tobramycin-susceptible bacterial strain and a zone of inhibition of 13 mm or less with resistant organisms.

The *in vitro* susceptibility of microorganisms to tobramycin is shown in the following chart.

In vitro Susceptibility of Microorganisms to Tobramycin
Cumulative Percent of Strains Inhibited in Broth or Agar Dilution Studies
MIC ($\mu\text{g/mL}$)

	# strains	<0.06	0.06-0.12	0.13-0.25	0.26-0.5	0.51-0.78	0.79-1.56	1.6-3.12	3.2-6.25	6.3-12.5	12.5-25
Citrobacter sp.	167		1	5	19	19	73	93	98	98	99
Enterobacter sp.	1126	1	4	15	36	39	81	91	97	99	99
Escherichia coli	2117		1	4	18	21	58	78	92	97	98
Herellea	206		4	8	25	26	76	91	97	99	100
Klebsiella sp.	1244	3	5	20	47	50	86	94	97	99	99
Klebsiella - Enterobacter	721		3	22	48	54	83	94	97	98	99
Paracolons	113			2	4	4	12	28	51	68	81
Proteus mirabilis (indole -)	1675			1	5	8	37	60	81	96	99
Proteus sp. (indole +)	1213		2	4	16	20	51	71	83	92	96
Pseudomonas	2880	6	18	40	63	70	91	96	97	98	99
Pseudomonas (gentamicin resistant)	153		12	18	27	30	35	46	59	71	80
Salmonella sp.	123			2	13	13	42	70	85	94	96
Serratia sp.	546				3	5	28	53	73	88	94
Shigella sp.	194				2	3	75	96	98	100	
Staphylococcus aureus	2013	11	28	42	70	73	87	93	96	99	99
Streptococcus faecalis	448			1	2	2	3	4	14	38	61
Streptococcus pyrogenes	177	7	13	15	18	18	27	43	65	87	95

* (Providencia, Bethesda-Ballerup, Arizona sp)

Data from published sources: 10^3 - 10^5 cells/mL inoculum in broth or agar dilution assays

TOXICOLOGY

Acute Toxicity:

The acute toxicity of parenterally administered tobramycin was related to immediate CNS effects. Death often occurred within a few minutes after an intravenous dose and 20 minutes to 2 hours after a subcutaneous administration. In a few rats and one guinea pig, delayed deaths were attributed to renal injury.

The intravenous LD₅₀ values ranged from 53 to 107 mg/kg for mice and 131 to 134 mg/kg for rats, while the subcutaneous LD₅₀ values were 416 to 484 mg/kg for mice and 928 to 1028 mg/kg for rats.

Tobramycin was no more toxic in the newborn rats than in rats 5 to 6 weeks of age, but it was slightly more toxic to 3 month old animals.

Two dogs were treated with subcutaneous doses of 100 and 200 mg/kg. No effect was observed with the 100 mg dose. Retching and tremors occurred after the administration of the 200 mg dose. The animals appeared normal after 3 hours. Two dogs tolerated single intravenous doses of 100 mg/kg with emesis as the only observed signs of toxicity.

Two cats received subcutaneous doses of 200 mg/kg of tobramycin which produced marked CNS effects that persisted for more than 5 hours. Both animals appeared normal on the following day.

An intravenous dose of 50 mg/kg in three cats produced a short-term ataxia. A dosage of 100 mg/kg caused convulsions and death.

Subacute Toxicity:

Rats: In a study using 10 animals/sex/dose, rats given 30 daily subcutaneous doses of 30, 60, or 120 mg/kg of tobramycin survived, with the exception of 1 of 20 of the 120 mg/kg dosage group. There were no significant changes in appearance or behaviour. The 120 mg/kg regimen caused a slight retardation of growth in the females. A slight renal toxicity was noted at all doses by

virtue of increases in SGOT, increased renal weights, and the histologic finding of a slight to moderate regeneration of renal cortical tubular epithelium. These effects were dose dependent.

In a similar study, rats tolerated 14 daily intravenous doses of 20-80 mg/kg of tobramycin with no adverse effects other than those associated with CNS effects after rapid injection. Six of the ten animals of the 80 mg/kg group died shortly after tobramycin administration. The hematologic and blood chemistry data of the surviving animals were unaffected. The relative renal weights of the tobramycin-dosed animals were significantly greater than control. The effect was dose dependent.

No drug-related tissue changes were noted in rats of the 20 mg/kg group. A slight regeneration of renal cortical tubular epithelium was detected in 1 of 20 animals given 40 mg/kg and most of those given 80 mg/kg. It was concluded that the only hazard in administration of tobramycin by the intravenous route rather than by the subcutaneous route is that a too rapid intravenous injection can cause convulsions and death.

Dogs: A study using 4 dogs for each daily intramuscular dose was carried out for 28 days. The appearance, behaviour, hematology, and blood chemistry were unaffected by doses of 3.75 to 15 mg/kg. Histologic examination of the tissue revealed that a slight renal injury, as evidenced by the finding of a mild regeneration of the cortical tubular epithelium, had occurred at the upper dose.

In a further study with 4 dogs, a daily dose of 30 mg/kg was tolerated for 2 weeks with no apparent ill effects; but thereafter, anorexia, weight loss, hypoactivity and a general CNS depression were noted. Two animals were killed during the fourth week because of morbidity. Renal tubular necrosis accompanied by regeneration of the tubular epithelium was noted in all animals of the 30 mg/kg group.

Dogs had a reduced tolerance for tobramycin dosage regimens of longer duration. In a study using 2 dogs/sex/dose for 90 days, a daily intramuscular dose of 3.75 or 7.5 mg/kg of tobramycin caused no changes in appearance, behaviour or body weight, but 2 of 4 dogs on the 7.5 mg/kg

dose had a mild degree of renal cortical tubular epithelial regeneration or a mild reparative nephrosis. A daily dose of 15 mg/kg of tobramycin was well tolerated by 2 of 4 dogs. The other 2 dogs of this group had marked appetite suppression, weight loss and marked elevations in BUN and SGOT. One of these dogs became deaf on Day 49. This dog also showed evidence of tobramycin accumulation. A mild to moderate reparative nephrosis and inflammatory reactions at the injection sites represented the only histologic evidence of injury.

The daily intravenous administration of 7.5, 15 or 30 mg/kg of tobramycin for 2 dogs/sex/dose over 14 days caused no changes in appearance or behaviour except for a single emetic episode in one dog of the 30 mg/kg group. Blood serum concentrations of tobramycin one hour after intravenous injection were similar to those found one hour after intramuscular administration. The hematologic and blood chemistry parameters were not altered significantly. A slight to moderate proteinuria was detected in one or two dogs of each dosage regimen, and a slight glucosuria occurred in one animal of the 15 mg/kg group. There was no histologic evidence of tissue injury. It seems probable, however, on the basis of the results of intramuscular administration of similar doses, that renal injury would occur with more prolonged intravenous dosage.

Cats: In a study using 2 animals/sex/dose, cats were given daily subcutaneous doses of 25 or 50 mg/kg. The 25 mg/kg dose was tolerated by 4 cats for 65 doses with no apparent vestibular injury. Hemorrhagic cystitis and urinary tract blockage due to urolithiasis in one male cat were considered unrelated to the drug, but co-existent renal cortical tubular necrosis with epithelial regeneration in the same cat were probably drug-related. One other cat had slight regeneration of renal cortical tubular epithelium. The 50 mg/kg/day dosage was poorly tolerated by all 4 cats. One cat was sacrificed after 25 doses, and another after 40 doses, because of poor physical condition. Tobramycin administration was terminated for the other 2 cats of this group on day 40. All 4 animals had severe vestibular injury. The 2 cats sacrificed during treatment had moderate renal tubular necrosis. A lack of histological evidence of renal injury in the 2 cats that were sacrificed 34 days after a 40 dose treatment, plus the finding of regenerative cortical tubular epithelium in animals killed during treatment suggested that moderate renal injury, occurring as the result of tobramycin administration may be reversible.

In a second study, 6 cats received tobramycin in a dosage of 35 mg/kg/day causing a marked reduction in post rotatory nystagmus (PRN) times in all 6 cats within 20 to 47 days.

Guinea Pigs: In a study using guinea pigs, a daily 50 mg/kg dose of tobramycin had no effect on growth or on auditory function in a 4-week period. A 100 mg/kg dose caused a 25% retardation of growth, as compared to controls. No hearing impairment was noted at 2 weeks, but some loss was detected at 4 weeks.

In a further study, daily doses of 150 to 200 mg/kg markedly depressed growth and was lethal to 40% of the animals within 6 weeks. Cochlear injury that occurred in 40% of the surviving animals was verified by electrophysiologic and histopathologic methods.

Teratology and Reproduction:

Daily subcutaneous administration of tobramycin given in 50 and 100 mg/kg doses to rats (30 animals/sex/dose) during all phases of the reproductive cycle, had no adverse effect on fertility or reproductive performance, nor did it affect the progeny.

In a further study, pregnant rats were given subcutaneous doses of 50 and 100 mg/kg of tobramycin from gestation days 14 through 20. Reparative nephrosis was detected in 6 of 25 of the 50 mg/kg group and 22 of 25 of the 100 mg/kg group at necropsy. There was no adverse effect on reproduction indices, nor on the growth of the progeny.

Daily subcutaneous doses of 20 or 40 mg/kg of tobramycin were given to pregnant rabbits (15 animals/dose) during organogenesis and early fetal development (gestation days 6-18). A marked anorexia and weight loss occurred in several animals; 3 of the 20 mg/kg group and 13 of the 40 mg/kg group died or aborted prior to gestation day 28. Drug-induced renal injury was evident in most of the animals that received the antibiotic. Fetal development appeared normal in all of the dams, including those that died or aborted. No drug-related abnormalities were detected in any of the progeny. It was concluded that daily subcutaneous doses as great as 40 mg/kg were not teratogenic in the rabbit, despite marked maternal toxicity.

Daily doses of tobramycin 100 mg/kg/day administered to pregnant guinea pigs in early gestation, from the beginning of the second week to the end of the fifth week, resulted in hearing loss and histologic damage to the six mothers. The litters born to these females, however, showed no hearing loss or damage to the inner ear. In contrast, when tobramycin was administered at 50 or 100 mg/kg daily to females in the terminal 4 weeks of gestation, 1 of 18 newborn animals had pinna reflex loss at 20,000 Hz and 4 of 38 had unilateral incomplete loss of outer hair cells at the basal end of the cochlea.

A 25 to 100 mg/kg daily dose of tobramycin to mice during the period of organogenesis produced no embryocidal or teratogenic effect.

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