PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

[Pr] APO-TOBRAMYCIN

Tobramycin Ophthalmic Solution, USP

0.3% w/v

Antibacterial (ophthalmic)

APOTEX INC.
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Tobramycin Ophthalmic Solution, USP

0.3% w/v

Antibiotic

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of 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.

Clinical Pharmacology

Pharmacodynamics

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, and 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 calcoacetius* (*Herellea vaginicoli*). 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.

Pharmacokinetics

Tear film concentrations were studied in sixteen (16) healthy male and female subjects who were administered one drop of tobramycin ophthalmic solution (0.3% w/v) in each eye daily for nine (9) consecutive days. The area under the tobramycin tear fluid concentration versus time curve (AUC_I) of tobramycin ophthalmic solution (0.3% w/v) was 3494.27 minx: gxmL$^{-1.}$ The area within the tobramycin tear fluid concentration versus time curve, exceeding the minimal inhibitory concentration$_{90}$ (AUC over MIC_{90}) was obtained as 2282.47 minx: gxmL$^{-1.}$ following single administration of tobramycin ophthalmic solution (0.3% w/v). The duration of time over which the tobramycin tear fluid concentrations remained above MIC_{90} was 25.1 minutes after the single administration of tobramycin ophthalmic solution (0.3% w/v) (see PHARMACOLOGY Human

Pharmacokinetics).

INDICATIONS AND CLINICAL USE

APO-TOBRAMYCIN (Tobramycin Ophthalmic Solution, USP) is a topical antibiotic preparation 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 APO-TOBRAMYCIN.

To reduce the development of drug-resistant bacteria and maintain the effectiveness of APO-TOBRAMYCIN and other antibacterial drugs, APO-TOBRAMYCIN Ophthalmic Solution should be used only to treat infections that are proven or strongly suspected to be caused by susceptible bacteria.

CONTRAINDICATIONS

APO-TOBRAMYCIN (Tobramycin Ophthalmic Solution, USP) is contraindicated in:

- Patients who are hypersensitive to tobramycin or any ingredient in the formulation (see PHARMACEUTICAL INFORMATION).
- Patients with a known hypersensitivity to any aminoglycoside.

WARNINGS AND PRECAUTIONS

NOT FOR INJECTION INTO THE EYE.

Sensitivity to topically applied aminoglycosides may occur in some patients. The severity of hypersensitivity reactions may vary from local effects to generalized reactions, such as erythema, itching, urticaria, skin rash, anaphylaxis, anaphylactoid reactions, or bullous reactions. If a hypersensitivity reaction to tobramycin occurs, discontinue use.

Cross hypersensitivity to other aminoglycosides can occur, and the possibility that patients who become sensitized to topical ocular tobramycin may also be sensitive to other topical and/or systemic aminoglycosides should be considered.

Serious adverse reactions including neurotoxicity, ototoxicity and nephrotoxicity have occurred in patients receiving systemic aminoglycoside therapy, including tobramycin. Caution should be exercised if APO-TOBRAMYCIN is administered with systemic aminoglycosides or other drugs that have neurotoxic, ototoxic, or nephrotoxic effects, particularly in patients with known or suspected renal, auditory, vestibular, or neuromuscular dysfunction. If APO-TOBRAMYCIN is administered concomitantly with systemic aminoglycoside antibiotics, care should be taken to monitor the total aminoglycoside serum concentration.

Caution should be exercised when prescribing APO-TOBRAMYCIN to patients with known or suspected neuromuscular disorders such as myasthenia gravis or Parkinson’s disease. Aminoglycosides, including tobramycin, may aggravate muscle weakness because of their known effect on neuromuscular function and potential to produce neuromuscular blockade.

If irritation or sensitization to any of the other components of APO-TOBRAMYCIN develops, treatment should be discontinued and appropriate therapy should be initiated.

APO-TOBRAMYCIN is not approved for intraocular and/or subconjunctival use. Ocular side effects beyond the external eye, e.g. macular infarction/necrosis have been reported following administration of aminoglycosides, including tobramycin, by these routes.

Susceptibility/Resistance:

Development of Drug-Resistant Bacteria
Prescribing APO-TOBRAMYCIN in the absence of a proven or strongly suspected bacterial infection is unlikely to provide benefit to the patient and risks the development of drug-resistant bacteria.

Potential for Microbial Overgrowth
As with other antibiotic preparations, prolonged use may result in overgrowth of non-susceptible organisms, including fungi. If superinfection or drug resistance occurs, treatment with APO-TOBRAMYCIN should be discontinued and appropriate therapy should be initiated. Patients should be advised to consult a physician if improvement fails to occur, or if signs of superinfection occur. Patients should also be advised to avoid contamination of the dropper tip by the eye, or other objects.

APO-TOBRAMYCIN contains the preservative benzalkonium chloride. Benzalkonium chloride has been reported to cause punctate keratopathy and/or toxic ulcerative keratopathy. Contact lens wear is not recommended during treatment of an ocular inflammation or infection. Benzalkonium chloride may cause eye irritation and is known to discolour soft contact lenses. Avoid contact with soft contact lenses. In case patients are allowed to wear contact lenses, they must be instructed to remove contact lenses prior to application of APO-TOBRAMYCIN and wait at least 15 minutes before re-insertion.

Temporary blurred vision or other visual disturbances may affect the ability to drive or use machines. If blurred vision occurs at application, the patient must wait until the vision clears before driving or using machinery.

Studies have not been performed to evaluate the effect of topical ocular administration of tobramycin ophthalmic solution on human fertility.

Pregnant Women: 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, APO-TOBRAMYCIN should be used during pregnancy only if clearly needed**.**

Nursing Women: It is unknown whether tobramycin is excreted in human milk following topical ocular administration. Tobramycin is excreted in human milk after systemic administration. 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.

ADVERSE REACTIONS

Clinical Trial Adverse Drug Reactions

The most frequent adverse reactions to tobramycin ophthalmic solution are localized ocular toxicity and hypersensitivity, including lid itching and swelling and conjunctival erythema. These reactions occur in approximately 3% of patients treated with tobramycin ophthalmic solution.

Post-Market Adverse Drug Reactions

Adverse reactions identified in subsequent clinical trials with tobramycin that have not been previously reported include the following:

Eye disorders: conjunctival edema, corneal abrasion, dry eye, erythema of eyelid, eye discharge, eyelid edema, eye pain, eye pruritus, keratitis, lacrimation increased, ocular discomfort, ocular hyperemia, vision blurred, visual impairment;

Immune system disorders: hypersensitivity;

Nervous system disorders: headache;

Skin and subcutaneous tissue disorders: dermatitis, dry skin, madarosis, leukoderma, pruritus, urticaria.

Additional adverse reactions identified via spontaneous reporting include:
Eye disorders: eye allergy, eye irritation (including localized ocular toxicity), eyelid pruritus;
Immune system disorders: anaphylactic reaction;
Skin and subcutaneous tissue disorders: Stevens-Johnson syndrome, erythema multiforme, rash.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

Clinically apparent signs and symptoms of an overdose of tobramycin ophthalmic solution (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 mcg/mL should be avoided. Hemodialysis will help remove tobramycin from the blood. Such reactions and the necessity for counter measures are not expected from the use of tobramycin ophthalmic solution.

For management of a suspected drug overdose, contact your regional Poison Control Centre immediately.

DOSAGE AND ADMINISTRATION

APO-TOBRAMYCIN (Adults and Children - above the age of 1 year)
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.

In case of concomitant therapy with other topical ocular medicinal products, an interval of 5 minutes should be allowed between successive applications. Eye Ointments should be administered last.

Missed dose:
In the case of a missed dose, a patient should take the missed dose as soon as possible. If it is almost time for the next dose, the patient should be instructed to skip the missed dose and return to their regular schedule as planned. Patients should not use a double dose to make up for the missed dose.

Special Instructions:
Patients should be advised to avoid contamination of the dispensing tip, by avoiding contact with the eye, skin or other surfaces. Keep tightly closed.

PHARMACEUTICAL INFORMATION

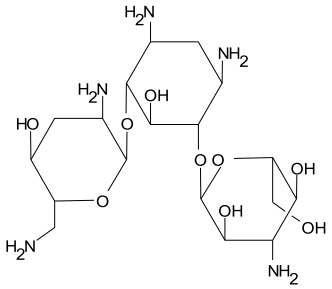
Drug Substance

Proper Name: Tobramycin

Chemical Name: 1) D-Streptamine, *O*-3-amino-3-deoxy-α-D-glucopyranosyl-(166)-*O*-[2,6-diamino-2,3,6-trideoxy-α-D-*ribo*-hexopyranosyl-(164)]-2-deoxy-;

2) *O*-3-Amino-3-deoxy-α-D-glucopyranosyl-(164)-*O*-[2,6-diamino-2,3,6-trideoxy-α-D-*ribo*-hexopyranosyl-(166)]-2-deoxy-L-streptamine.

Structural Formula:



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

Molecular Weight: 467.52 g/mol

Description: Tobramycin is a white to off-white powder. It is soluble in 1.5 parts of water; very slightly soluble in 95% ethanol; practically insoluble in chloroform and ether. A 10% (w/v) solution of tobramycin in water has a pH of 9 to 11. In one publication, three pKa values (6.7, 8.3 and 9.9) and in another four pKa values (6.2, 7.4, 7.6 and 8.6) have been reported. Melting point of approximately 217EC has been reported.

COMPOSITION

Each mL of APO-TOBRAMYCIN Ophthalmic Solution contains tobramycin 0.3% w/v (3 mg), as active ingredient, and benzalkonium chloride 0.01% as preservative. Inactive ingredients are boric acid, sodium chloride, sodium hydroxide and/or sulfuric acid (to adjust pH), sodium sulfate anhydrous, tyloxapol and water for injection.

STABILITY AND STORAGE RECOMMENDATIONS

Store at room temperature 15ºC to 30ºC. Use within 28 days after opening container.

AVAILABILITY OF DOSAGE FORMS

APO-TOBRAMYCIN (Tobramycin Ophthalmic Solution, USP) 0.3% w/v, is supplied as a sterile ophthalmic solution in white opaque LDPE bottles of 5 mL.

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

PHARMACOLOGY

Animal Pharmacokinetics:
Ocular tissue concentrations were determined in pigmented rabbits following a single bilateral dose of 50 mcL administration of tobramycin ophthalmic solution (0.3% w/v). Results of tobramycin concentrations reached in the rabbit tear from the single administration of the tobramycin ophthalmic solution (0.3% w/v) are shown in the table below.

Concentration of Tobramycin in rabbit tear after single administration

Treatment	Time (min)	Mean (mcg/mL) ± SD	n
Tobramycin Ophthalmic Solution, 0.3% w/v	0	1841 ± 485	6
	5	202 ± 388	12
	10	212 ± 371	12
	30	39 ± 39	24
	60	14 ± 15	36
	120	18 ± 26	24

Ocular tissue concentrations were also determined in pigmented rabbits following repeated bilateral dosing of 50 mcL administration of tobramycin ophthalmic solution (0.3% w/v). Three doses were administered at 2 hour intervals and the quantity of tobramycin was determined. The results are shown in the table below.

Concentration of Tobramycin in rabbit tear after repeated administration

Treatment	Time (min)	Mean (mcg/mL) ± SD	n
Tobramycin Ophthalmic Solution, 0.3% w/v	60	65 ± 99	12
	120	34 ± 44	18

Human Pharmacokinetics:
Tear film concentrations were studied in sixteen (16) healthy male and female subjects who were administered one drop of tobramycin ophthalmic solution (0.3% w/v) in each eye daily for nine (9) consecutive days. To allow enough time for tear sampling, dosing of the two eyes was separated by 20 minutes. Under direct visualisation (slit-lamp biomicroscopy), glass capillary tubes were used to collect tear samples at a predetermined time following dosing (i.e. 1, 2, 3, 5, 10, 20, 40, 120 and 240 minutes postdose). LC-MS analyses of tobramycin in tear film were carried out.

The area under the tobramycin tear fluid concentration versus time curve (AUC_I) of tobramycin ophthalmic solution (0.3% w/v) was 3494.27 min·gxmL^{-1}The area within the tobramycin tear fluid concentration versus time curve, exceeding the minimal inhibitory concentration$_{90}$ (AUC over MIC_{90}) was obtained as 2282.47 min·gxmL^{-1} following single administration of tobramycin ophthalmic solution (0.3% w/v). The duration of time over which the tobramycin tear fluid concentrations remained above MIC_{90} was 25.1 minutes after single administration of tobramycin ophthalmic solution (0.3% w/v).

Human Pharmacodynamics:
In a randomized, masked, multicentre controlled study 204 per protocol patients were treated with one drop of tobramycin ophthalmic solution (0.3% w/v) four times a day for 7±1 days. In patients who were culture positive for bacteria on Day 1, 99% treated with tobramycin ophthalmic solution (0.3% w/v) were categorized as having sustained cure/presumed eradication.

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 species
Citrobacter species
Providencia species
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. *Streptococcus 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 mcg 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 tables.

In Vitro Susceptibility of Clinical Isolates to Tobramycin (1976-1987)
Cumulative Percent of Strains Inhibited in Broth or Agar Dilution Studies Tobramycin (mcg/mL)

		Tobramycin (mcg/ml) Cumulative Percent									
Bacteria	# 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

Tobramycin (mcg/ml) Cumulative Percent											
Bacteria	# 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
Klebsiella sp. *Klebsiella -*	1244	3	5	20	47	50	86	94	97	99	99
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.

Susceptibility of Pre-therapy Ocular Isolates to Tobramycin (Clinical Study C-99-98)

	Tobramycin (mcg/ml)							
	Cumulative Percent							
Bacteria	Number of Strains[1]	0.016 - 0.06	0.13 - 0.25	0.50 - 1.0	2.0 - 4.0	8.0 - 16	32 - 64	128 or greater
Acinetobacter calcoaceticus	3	0.0	0.0	100.0				
Acinetobacter genospecies 9	2	0.0	50.0	100.0				
Acinetobacter ursingii	3	0.0	0.0	100.0				
Chryseobacterium indologenes	2	0.0	0.0	0.0	0.0	0.0	0.0	100.0
Corynebacterium accolens	2	100.0						
Corynebacterium macginleyi	3	66.6	66.6	66.6	66.6	66.6	100.0	
Corynebacterium pseudodiphtheriticum	3	33.0	100.0					
Escherichia coli	5	0.0	0.0	20.0	100.0			
Haemophilus influenzae	28	0.0	0.0	0.0	17.9	100.0		
Klebsiella oxytoca	2	0.0	0.0	50.0	100.0			
Morganella morganii	2	0.0	0.0	0.0	100.0			
Proteus mirabilis	4	0.0	0.0	50.0	100.0			
Pseudomonas aeruginosa	5	0.0	0.0	100.0				
Serratia liquefaciens	2	0.0	0.0	50.0	100.0			
Serratia marcescens	4	0.0	0.0	25.0	100.0			
Staphylococcus aureus	52	1.9	15.4	88.5	90.4	90.4	96.2	100.0
Staphylococcus caprae	2	100.0						
Staphylococcus epidermidis	197	28.4	69.0	70.5	78.6	94.3	98.9	100.0
Staphylococcus haemolyticus	4	0.0	0.0	0.0	0.0	100.0		
Staphylococcus hominis	5	40.0	40.0	80.0	100.0			
Staphylococcus lugdunensis	5	40.0	100.0					
Staphylococcus warneri	9	55.6	66.7	66.7	100.0			
Stenotrophomonas maltophilia	2	0.0	0.0	0.0	0.0	0.0	50.0	100.0
Streptococcus mitis	8	0.0	0.0	0.0	0.0	50.0	100.0	
Streptococcus pneumoniae	36	0.0	0.0	0.0	0.0	61.1	100.0	
Streptococcus sanguis	2	0.0	0.0	0.0	0.0	100.0		

[1] Excludes cases of only 1 isolate

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 LD_{50} values ranged from 53 to 107 mg/kg for mice and 131 to 134 mg/kg for rats, while the subcutaneous LD_{50} 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 to 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.

Rabbits**:** A four week topical ocular irritation study of an ophthalmic vehicle with xanthan gum at concentrations of 0.6% and 1.0% and four times daily (QID) ocular dosing, showed no relevant clinically signs of toxicity. Biomicroscopic observations were limited to minimal conjunctival congestion (hyperemia) similar in frequency with the ophthalmic vehicle with 0.6% xanthan gum, Lacryvisc (with viscosizing agent Carbomer 934P) and untreated control animals.

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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19) Product Monograph. TOBREX® (Tobramycin Ophthalmic Solution, USP) 0.3% w/v, TOBREX® (Tobramycin Ophthalmic Ointment, USP) 0.3% w/v, Novartis Pharmaceuticals Canada Inc., February 12, 2020; Submission Control number: 233358

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE
PATIENT MEDICATION INFORMATION

[Pr] APO-TOBRAMYCIN
Tobramycin Ophthalmic Solution USP, 0.3% w/v

Read this carefully before you start taking APO-TOBRAMYCIN and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about APO-TOBRAMYCIN.

What is APO-TOBRAMYCIN used for?
APO-TOBRAMYCIN is used in adults and children above the age of 1 year to treat bacterial infections of the external part of the eye, such as conjunctivitis.

Antibacterial drugs like APO-TOBRAMYCIN treat only bacterial infections. They do not treat viral infections. Although you may feel better early in treatment, APO-TOBRAMYCIN should be used exactly as directed. Misuse or overuse of APO-TOBRAMYCIN could lead to the growth of bacteria that will not be killed by APO-TOBRAMYCIN (resistance). This means that APO-TOBRAMYCIN may not work for you in the future. Do not share your medicine.

How does APO-TOBRAMYCIN work?
APO-TOBRAMYCIN contains a medicine called tobramycin. Tobramycin belongs to the aminoglycoside class of antibiotic. Tobramycin works by killing bacteria that cause infections.

The signs of your eye infections [eye redness, increased tearing, discharge (pus or mucus) etc.] may start to improve within 3 days after starting APO-TOBRAMYCIN.

What are the ingredients in APO-TOBRAMYCIN?
Medicinal ingredients: tobramycin 0.3% w/v (3 mg/mL)
Non-medicinal ingredients:
Preservative: benzalkonium chloride 0.01% w/v
Other ingredients: boric acid, sodium chloride, sodium hydroxide and/or sulfuric acid (to adjust pH) , sodium sulfate anhydrous, tyloxapol and water for injection.

APO-TOBRAMYCIN comes in the following dosage forms:
APO-TOBRAMYCIN (Tobramycin Ophthalmic Solution USP) 0.3% w/v, is supplied as a sterile ophthalmic solution in white opaque LDPE bottles of 5 mL.

Do not use APO-TOBRAMYCIN if you are allergic to:
- tobramycin,

- any of the other ingredients in APO-TOBRAMYCIN (see **What are the ingredients in APO-TOBRAMYCIN?**),
- other aminoglycoside antibiotics such as amikacin, gentamycin, kanamycin, paromomycin, streptomycin.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take APO-TOBRAMYCIN. Talk about any health conditions or problems you may have, including if you:

- are pregnant, you think you may be pregnant or are planning to have a baby. You will need to talk to your healthcare professional about the benefits and risks of using APO-TOBRAMYCIN while you are pregnant.
- are breast-feeding. APO-TOBRAMYCIN is not recommended during breastfeeding. It is unknown whether APO-TOBRAMYCIN will get into your milk.
- have or if you have ever had conditions such as myasthenia gravis or Parkinson's disease. Antibiotics of this kind may worsen muscle weakness.

Other warnings you should know about:

While you are using APO-TOBRAMYCIN

- **Driving and using machines**: your vision may be blurred for a time just after you apply APO-TOBRAMYCIN. Do not drive or use machines until this has worn off.
- **If you wear contact lenses**:
    - APO-TOBRAMYCIN Eye Drops contains the preservative benzalkonium chloride. This can cause eye inflammation, including inflammation and damage to the cornea. Benzalkonium chloride discolours soft contact lenses. It is best not to wear contact lenses while you are using APO-TOBRAMYCIN.
    - You should not wear contact lenses if you have an eye infection. If you are allowed to wear contact lenses, remove them before using APO-TOBRAMYCIN. Wait at least 15 minutes after using APO-TOBRAMYCIN to put your lenses back into your eyes.
- If the signs of your eye infection do not improve within 3 days or if they become worse, tell your healthcare professional.

Tell your healthcare professional about all the medicines you are using, have recently used or might use, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The use of APO-TOBRAMYCIN with other medicines has not been studied.

Tell your healthcare professional if you are using:

- Other antibiotics of the same family (aminoglycosides) such as amikacin, gentamycin, kanamycin, paromomycin, streptomycin

Always keep a list of your medicines and show it to your healthcare professional when you get a new medicine. It is important that your healthcare professional reviews all medications and supplements you are taking before prescribing APO-TOBRAMYCIN.

How to take APO-TOBRAMYCIN

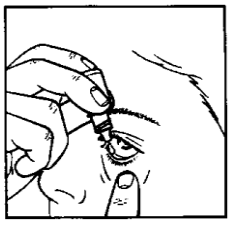
Usual dose (adults and children 1 year and older):

The usual dose will depend on the type and severity of your infection

- In **mild to moderate eyes infections** your healthcare professional may recommend one drop or two drops into the affected eye(s), every four hours.
- In **severe eyes infections** this may be increased to two drops every hour.

Your healthcare professional will tell you how much you need to use each day. Ask your healthcare professional if you have any questions about the drug.

How to use:



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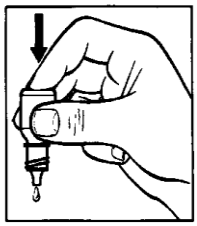

2

1. Wash your hands.
2. Get the APO-TOBRAMYCIN bottle and a mirror.
3. **Shake well before use.**
4. After removing the cap: if the security snap collar is loose, remove it before using APO-TOBRAMYCIN.
5. Hold the bottle, pointing down, between your thumb and fingers.
6. Tilt your head back.
7. Pull down your lower eyelid with a clean finger until there is a “v” pocket between your eyelid and your eye. The drop will go in here (picture 1).
8. Bring the bottle tip close to the eye. Do this in front of a mirror if it helps.
9. **Do not touch your eye, eyelid**, surrounding areas or other surfaces with the dropper, to avoid contaminating the suspension.
10. Gently press on the base of the bottle to release one drop at a time. Do not squeeze the bottle. It is designed so that a gentle press on the bottom is all that it needs (picture 2).

11. If you miss, wipe up and try again.
12. Close the bottle immediately after use.

If your doctor has prescribed other eye drop or ointment medicines to be used along with APO-TOBRAMYCIN, apply each medicine at least 5 minutes apart. Eye ointments should be administered last.

Overdose:

If you think you have taken too much or accidentally swallowed APO-TOBRAMYCIN, contact your healthcare professional, hospital emergency department or regional poison control centre immediately, even if there are no symptoms.

Missed Dose:
If you forget to use APO-TOBRAMYCIN, continue with the next dose as planned. However, if it is almost time for your next dose, skip the missed dose and go back to your regular dosing schedule. **Do not** use a double dose to make up for forgotten individual doses.

What are possible side effects from using APO-TOBRAMYCIN?
These are not all the possible side effects you may feel when taking APO-TOBRAMYCIN. If you experience any side effects not listed here, contact your healthcare professional. Please also see Warnings and Precautions.

The following side effects are common and about 3 in 100 people experienced them:
- itchy and swollen eyelid
- eye redness
- watery eye(s).

Other side effects include:
- eye problems such as:
    - eye discharge
    - dry, itchy or swollen eyes
    - increased tearing
    - corneal damage (the corneal is the clear surface of your eye)
    - blurred vision
    - eye allergy
    - loss of eyelashes
- headache
- skin problems such as swollen skin, hives, itchy or dry skin, white patches on the skin.

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
UNKNOWN • Signs of an allergic reaction: • rash • hives • itching • red, swollen, blistered, or peeling skin with or without fever • wheezing • tightness in the chest or throat • trouble breathing or talking • unusual hoarseness • swelling of the mouth, face, lips, tongue, or throat			✓
UNKNOWN Keratitis (an inflammation of the cornea — the clear front portion of your eye): • change in eyesight, • eye pain • sensitivity to light (photophobia) • difficulty opening your eyelid because of pain or irritation			✓

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, talk to your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

Store at room temperature 15ºC to 30ºC. Use within 28 days after opening container.
Keep out of the reach and sight of children.

If you want more information about APO-TOBRAMYCIN:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this patient medication information by visiting the Health Canada website (https://health-products.canada.ca/dpd-bdpp/index-eng.jsp). Find the Patient Medication Information on the manufacturer's website http://www.apotex.ca/products, or by calling 1-800-667-4708.

This leaflet was prepared by Apotex Inc., Toronto, Ontario, M9L 1T9.

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