PRODUCT MONOGRAPH

Pr  **TOBREX**
Tobramycin Ophthalmic Solution, USP
0.3% w/v

Pr  **TOBREX**
Tobramycin Ophthalmic Ointment, USP
0.3% w/w

Pr  **TOBREXAN**
Tobramycin Viscous Ophthalmic Solution
0.3% w/v

Antibacterial (ophthalmic)

ALCON CANADA INC.
2665 Meadowpine Blvd.
Mississauga, Ontario
L5N 8C7
www.alcon.ca

Date of Preparation
December 20, 1983

Date of Revision:
May 17, 2016

Submission Control No.: 193426

* a trademark of Novartis
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 TOBREX® and TOBREXAN®.

The gram positive bacteria against which TOBREX® 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 TOBREX® solution has been shown to have clinical effectiveness include most strains of Pseudomonas aeruginosa, Escherichia coli, Klebsiella pneumonia, Enterobacter aerogenes, Proteus mirabilis (indole negative) and indole-positive Proteus species, as well as Haemophilus spp., Moraxella spp., and Acinetobacter calcoacetiis (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.

Pharmacokinetics
Tear film concentrations were studied in sixteen (16) healthy male and female subjects who were administered one drop of TOBREXAN® or TOBREX® solution in each eye daily for nine (9) consecutive days. TOBREXAN® showed a significantly greater area under the tobramycin tear fluid concentration versus time curve (AUC), a significantly greater area within the tobramycin tear fluid concentration versus time curve exceeding the minimal inhibitory concentration90 (AUC over MIC90), and a greater duration of time over which the tobramycin tear fluid concentrations remained above MIC90 (see PHARMACOLOGY Human Pharmacokinetics).
INDICATIONS AND CLINICAL USE

TOBREX® (Tobramycin Ophthalmic Solution, USP), TOBREX® (Tobramycin Ophthalmic Ointment, USP) and TOBREXAN® (Tobramycin Viscous Solution) 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® and TOBREXAN®.

CONTRAINDICATIONS

TOBREX® and TOBREXAN® are contraindicated in:
Patients who are hypersensitive to tobramycin or any ingredient in the formulation (see PHARMACEUTICAL INFORMATION).

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 tobramycin therapy. Caution is advised when used concomitantly. If TOBREX® is administered concomitantly with systemic aminoglycoside antibiotics, care should be taken to monitor the total serum concentration.

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

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 TOBREX® 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.

Contact lens wear is not recommended during treatment of an ocular infection. TOBREX® solution contains the preservative benzalkonium chloride while TOBREXAN® contains the preservative benzododecinium bromide. Both preservatives may cause eye irritation and are
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 TOBREX® solution or TOBREXAN® 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 TOBREX® solution or ointment 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, TOBREX® 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 TOBREX® 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®.

The most frequent adverse reactions to TOBREXAN® are localized ocular toxicity and hypersensitivity, including lid itching and swelling and tearing. These reactions occur in approximately 1.5% of patients treated with TOBREXAN®.

**Post-Market Adverse Drug Reactions**
Adverse reactions identified in subsequent clinical trials 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 TOBREX® and TOBREXAN® (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 μg/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 TOBREX® or TOBREXAN®.

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

**DOSAGE AND ADMINISTRATION**

**TOBREX® Solution** (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.

**TOBREX® Ophthalmic Ointment** (Adults and Children - above the age of 1 year)
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.

**TOBREXAN® Viscous Ophthalmic Solution** (Adults only)
In mild to moderate disease, instill one drop into the affected eye(s) twice per day (morning and evening) for 7 days. In severe infections, for the first day, instill one drop into the eye(s) four times per day while awake and then twice per day while awake until completion of the total treatment period.

**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: Tobramycin

Structural Formula:

Molecular Formula: C_{18}H_{37}N_{5}O_{9}
Molecular Weight: 467.54
Chemical Name: 0-3-amino-3-deoxy-\(\alpha\)-D-glucopyranosyl-(1\(\rightarrow\)4)-0-[2,6-diamino-2,3,6-trideoxy-\(\alpha\)-D-ribohexopyranosyl-(1\(\rightarrow\)6)]-2-deoxy-L-streptamine.

Composition:
TOBREX\textsuperscript{*} solution is a sterile ophthalmic solution of tobramycin. Each mL contains:
Medicinal ingredient: tobramycin 0.3% w/v (3 mg/mL)
Preservative: benzalkonium chloride 0.01% w/v
Non-medicinal ingredients: boric acid, sodium sulfate, sodium chloride, tyloxapol, sulfuric acid and/or sodium hydroxide (to adjust pH) and purified water.

TOBREX\textsuperscript{*} ointment is a sterile ophthalmic ointment containing:
Medicinal ingredient: itobramycin 0.3% w/w (3.0 mg/g)
Preservative: chlorobutanol 0.5% w/w
Non-medicinal ingredients: mineral oil, petrolatum base.

TOBREXAN\textsuperscript{*} is a sterile ophthalmic solution of tobramycin. Each mL contains:
Medicinal ingredient: tobramycin 0.3% w/v (3 mg/mL)
Preservative: benzododecinium bromide 0.012% w/v
Non-medicinal ingredients: mannitol, trometamol, xanthum gum, boric acid, polysorbate 80, sulfuric acid and/or sodium hydroxide (to adjust pH) and purified water.

DOSAGE FORM

TOBREX® solution and TOBREXAN® Viscous Ophthalmic Solution are available in 5mL opaque plastic DROPTAINER® dispensers.

TOBREX® ointment is available in 3.5g metal ophthalmic ointment tubes.
**INFORMATION FOR THE CONSUMER** (TOBREXAN® Viscous Ophthalmic Solution)

**TOBREXAN® eye drops**

Tobramycin

Medicine to treat Bacterial Infections of the eye.

**Information for the Patient:** TOBREXAN® (tobramycin) viscous ophthalmic solution.

Read all of this leaflet carefully before you start using this medicine.

**Keep this leaflet.** You may need to read it again. If you still have questions after reading it, please ask your doctor or your pharmacist.

**The active substance** is tobramycin 3 mg/ml.

**Other ingredients:** Xanthan gum, benzododecinium bromide (BDAB) as a preservative, mannitol, trometamol, boric acid, polysorbate 80, and purified water. Tiny amounts of sulphuric acid and/or sodium hydroxide are sometimes added to maintain proper pH balance.

**1. WHAT TOBREXAN® DOES**

TOBREXAN® is used for the treatment of bacterial infections on the surface of the eye, such as conjunctivitis.

**Bacterial infections on the surface of the eye.** Some microbes (bacteria) may cause inflammatory reactions resulting in redness, discharge, and other irritation symptoms on the surface of your eye.

TOBREXAN® is a medicine for the treatment of bacterial infections on the surface of the eye. It is an antibiotic which acts against the microbes which cause the infection.

TOBREXAN® is a clear liquid (a solution) supplied in a 5 ml plastic (DROPTAINER®) bottle with a screw cap.

**2. BEFORE YOU USE TOBREXAN®**

Do not use TOBREXAN®...

- If you are allergic to tobramycin or any of the other ingredients.

Ask your doctor for advice.

Take special care using TOBREXAN®...

- If you are breastfeeding or planning to breast-feed. TOBREXAN® may get into your milk in very small amounts; the possibility of it passing to your child is very low. Talk to your doctor before you use TOBREXAN®.
• If you wear contact lenses. Contact lens wear is not recommended when you have an eye infection. If you must wear contact lenses, do not use the drops while your contact lenses are in your eyes. Remove your contact lenses and wait 10-15 minutes after using TOBREXAN® before putting your lenses back into your eyes. A preservative in TOBREXAN® (benzododecinium bromide) can irritate the eyes and affect soft lenses.

• Pregnant women. If you are pregnant, or might get pregnant, talk to your doctor before you use TOBREXAN®.

• If you are taking another form of tobramycin or another aminoglycoside antibiotic.

Stop using TOBREXAN® and talk to your doctor or pharmacist...
• If you develop signs of an allergic reaction, such as itchy skin or a rash, while using TOBREXAN®.
• If you develop another eye infection.

Driving or using machines
You may find that your vision is blurred for a time just after you use TOBREXAN®. Do not drive or use machines until your vision is clear.

TOBREXAN® and other medicines
Tell your doctor or pharmacist if you are taking (or have recently taken) any other medicines. Don’t forget to mention any other medicines that you have bought yourself without prescription.

3. HOW TO USE TOBREXAN®

The usual dose
One drop in the eye or eyes, twice a day – morning and evening. Use this much unless your doctor tells you to do differently. Only use TOBREXAN® in both eyes if your doctor told you to. Use it for as long as your doctor told you to.

Only use TOBREXAN® as an eye drop.
How much to use

- Get the TOBREXAN® bottle and a mirror (if needed).
- Wash your hands.
- Take the bottle and twist off the cap.
- Hold the bottle, pointing down, between your thumb and middle finger.
- Tilt your head back. Pull down your eyelid with a clean finger, until there is a ‘pocket’ between the eyelid and your eye. The drop will go in here (picture 1).
- Bring the bottle tip close to the eye. Use the mirror if it helps.
- Don’t touch your eye or eyelid, surrounding areas or other surfaces with the dropper. It could infect the drops left in the bottle.
- Gently press on the base of the bottle to release one drop of TOBREXAN® at a time.
- Don’t squeeze the bottle: It is designed so that just a gentle press on the bottom is needed (picture 2).
- If you use drops in both eyes, repeat the steps for your other eye.
- Put the bottle cap back on firmly immediately after use.

If a drop misses your eye, try again.

If you get too much in your eyes, rinse it all out with warm water. Don’t put in any more drops until it’s time for your next regular dose.

If you forget to use TOBREXAN®, use a single drop as soon as you remember, and then go back to your regular routine. Do not use a double dose to make up for the one missed.

If you are using other eye drops, wait at least five to ten minutes between putting in TOBREXAN® and the other drops.

4. POSSIBLE SIDE EFFECTS

A small number of people who use TOBREXAN® may get side effects. These can be unpleasant, but most of them disappear quickly.
In clinical studies up to 3 in 100 people experienced side effects.

The most common side effects were itching, swelling and watering of the eye. Less than 2 in 100 people experienced these.

Other side effects include: dry eye, damage to the eye, eyelid redness or swelling, eye discharge, eye pain, increased tearing, eye discomfort or irritation, blurred or impaired vision, eye allergy headache, dry skin, skin inflammation, loss of eyelashes, white skin patches.

Severe allergic (hypersensitivity) reactions have occurred with topical aminoglycosides similar to TOBREXAN®. Stop using TOBREXAN® and talk to your doctor or pharmacist if you:

- Develop signs of an allergic reaction, including swelling of the skin, mouth, tongue, throat and/or extremities; difficulty breathing; skin redness; itching; and rash.
- Develop flu-like symptoms followed by a painful skin rash that spreads and blisters.

You can usually continue using the drops, unless the effects are serious. If you're worried, talk to a doctor or pharmacist.

If you notice any other side effects, apart from these, tell your doctor or pharmacist.

5. STORING TOBREXAN®

Keep out of the reach and sight of children.

Store at room temperature (15 – 30°C). Keep tightly closed. Discard 28 days after initial opening.

This medicine has been prescribed for you personally. You should not pass it on to other people. It may harm them even if they have the same symptoms as you.

Do not use the drops after the expiry date (marked ‘Exp’) on the bottle and the box.

If you have any other questions about your medicines you should ask your doctor or pharmacist.
Animal Pharmacokinetics:
Ocular tissue concentrations were determined in pigmented rabbits following a single bilateral
dose of 50 µL administration of either 0.3% TOBREXAN* or TOBREX* solution. Results from
the single administration of 0.3% TOBREXAN* show significantly higher tobramycin
concentrations reached in the rabbit tear than those reached with the marketed TOBREX*
solution (see table below). The bioavailability of tobramycin in the tear determined by
calculating the AUC “concentration of tobramycin vs time” throughout the study (between 0 and
120 min) was significantly higher (P<0.05) in the 0.3% TOBREXAN* treated group than in the
TOBREX* treated group.

Concentration of Tobramycin in rabbit tear after single administration

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Time (min)</th>
<th>Mean (µg/mL) ± SD</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>TOBREXAN*</td>
<td>0</td>
<td>2503 ± 351</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>1196 ± 475</td>
<td>12</td>
</tr>
<tr>
<td></td>
<td>10</td>
<td>1230 ± 587</td>
<td>12</td>
</tr>
<tr>
<td></td>
<td>30</td>
<td>485 ± 331</td>
<td>24</td>
</tr>
<tr>
<td></td>
<td>60</td>
<td>117 ± 195</td>
<td>36</td>
</tr>
<tr>
<td></td>
<td>120</td>
<td>36 ± 56</td>
<td>24</td>
</tr>
<tr>
<td>TOBREX*</td>
<td>0</td>
<td>1841 ± 485</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>202 ± 388</td>
<td>12</td>
</tr>
<tr>
<td></td>
<td>10</td>
<td>212 ± 371</td>
<td>12</td>
</tr>
<tr>
<td></td>
<td>30</td>
<td>39 ± 39</td>
<td>24</td>
</tr>
<tr>
<td></td>
<td>60</td>
<td>14 ± 15</td>
<td>36</td>
</tr>
<tr>
<td></td>
<td>120</td>
<td>18 ± 26</td>
<td>24</td>
</tr>
</tbody>
</table>

Ocular tissue concentrations were also determined in pigmented rabbits following repeated
bilateral dosing of 50 µL administration of either 0.3% TOBREXAN* or TOBREX* solution.
Three doses were administered at 2 hour intervals and the quantity of tobramycin determined.
The results indicate that the concentration of tobramycin is significantly higher (P<0.05) in the
0.3% TOBREXAN* treated group at both 1 and 2 hours following the last administration (see
table below).

Concentration of Tobramycin in rabbit tear after repeated administration

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Time (min)</th>
<th>Mean (µg/mL) ± SD</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>TOBREXAN*</td>
<td>60</td>
<td>451 ± 464</td>
<td>12</td>
</tr>
<tr>
<td></td>
<td>120</td>
<td>191 ± 273</td>
<td>18</td>
</tr>
<tr>
<td>TOBREX*</td>
<td>60</td>
<td>65 ± 99</td>
<td>12</td>
</tr>
<tr>
<td></td>
<td>120</td>
<td>34 ± 44</td>
<td>18</td>
</tr>
</tbody>
</table>

Another study was to determine if the concentration of tobramycin in the rabbit tear, 10 minutes
after the single bilateral administration of a 0.3% Tobramycin Ophthalmic Solution formulation,
varied significantly when the xanthan gum concentration was increased in the formulation.
Treatments were administered with a micropipette, sampling by Schirmer tear strips and analysis of tobramycin by HPLC. The results show there is a relationship between xanthan gum concentration, and consequently the viscosity of the formulation, and the concentration of Tobramycin in the tear 10 minutes following the administration (see table below).

<table>
<thead>
<tr>
<th>Xanthan Gum in the formula</th>
<th>0.07%</th>
<th>0.135%</th>
<th>0.27%</th>
<th>0.54%</th>
<th>0.6%</th>
<th>0.81%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Viscosity (cps)</td>
<td>13</td>
<td>18</td>
<td>30</td>
<td>88</td>
<td>112</td>
<td>249</td>
</tr>
<tr>
<td>Tobramycin in the tear (µg/ml, mean ± s.d.)</td>
<td>259.97 ± 258.34</td>
<td>580.77 ± 299.95</td>
<td>587.05 ± 186.00</td>
<td>869.37 ± 152.81</td>
<td>1243.35 ± 394.03</td>
<td>1357.31 ± 444.39</td>
</tr>
</tbody>
</table>

Gradually higher concentrations of tobramycin in the rabbit tear were obtained on increasing the xanthan gum concentration in the TOBREXAN® formulation. Maximum mean tobramycin concentration was found after dosing with a formulation of 249 cps of viscosity (0.81% xanthan gum). However, no statistically significant differences were found in tobramycin concentration after dosing with formulations of 112 cps or 249 cps (0.6% and 0.81% xanthan gum formulations, respectively).

**Human Pharmacokinetics:**
Tear film concentrations were studied in sixteen (16) healthy male and female subjects who were administered one drop of TOBREXAN® or TOBREX® solution 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 (ie. 1, 2, 3, 5, 10, 20, 40, 120 and 240 minutes postdose). LC-MS analyses of tobramycin in tear film were carried out.

A significantly higher area under the tobramycin tear fluid concentration versus time curve (AUC) was obtained following single administration of TOBREXAN® (9406.29 minx:gxmL⁻¹) compared with that obtained following single administration of TOBREX® solution (3494.27 minx:gxmL⁻¹), p=0.0001. A significantly higher area within the tobramycin tear fluid concentration versus time curve, exceeding the minimal inhibitory concentration₉₀ (AUC over MIC₉₀) was obtained following single administration of TOBREXAN® (9019.33 minx:gxmL⁻¹) when compared to TOBREX® solution (2282.47 minx:gxmL⁻¹), p=0.0001. The duration of time over which the tobramycin tear fluid concentrations remained above MIC₉₀ was also significantly longer following single administration of TOBREXAN® (44.4 minutes) when compared with that obtained after single administration of TOBREX® solution (25.1 minutes), p=0.046.

**Human Pharmacodynamics:**
In a randomized, masked, multicentre controlled study 204 per protocol patients were treated with one drop of TOBREXAN® two times a day for 7±1 days or one drop of TOBREX® solution four times a day for 7±1 days. In patients who were culture positive for bacteria on Day 1, 98% treated with TOBREXAN® and 99% treated with TOBREX® were categorized as having sustained cure/presumed eradication. There were no statistically significant differences between the two treatments for the final clinical judgement at the test of cure visit (p=0.6037). There was no statistically significant differences between TOBREXAN® and TOBREX® for Microbiological
Eradication rate at the test of cure visit (p=0.6051). For clinical signs and symptoms, no statistically significant differences were found between treatments at any visit in resolving bulbar conjunctiva, resolving conjunctival discharge/exudate, resolving the palpebral conjunctival reaction, resolving erythema/swelling, for the presence of epithelial disease, or in reducing the severity of tearing.

**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. retgeri* 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 synergy 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 μg 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

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

* (Providencia, Bethesda-Ballerup, Arizona sp)

Data from published sources: 10³ - 10⁵ cells/mL inoculum in broth or agar dilution assays
### Susceptibility of Pre-therapy Ocular Isolates to Tobramycin (Clinical Study C-99-98)

<table>
<thead>
<tr>
<th>Bacteria</th>
<th>Number of Strains&lt;sup&gt;1&lt;/sup&gt;</th>
<th>Tobramycin (µg/ml)</th>
<th>Cumulative Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>0.016 - 0.06</td>
<td>0.13 - 0.25</td>
</tr>
<tr>
<td>Acinetobacter calcoaceticus</td>
<td>3</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>Acinetobacter genospecies 9</td>
<td>2</td>
<td>0.0</td>
<td>50.0</td>
</tr>
<tr>
<td>Acinetobacter ursingii</td>
<td>3</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>Chryseobacterium indologenes</td>
<td>2</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>Corynebacterium accolens</td>
<td>2</td>
<td>100.0</td>
<td></td>
</tr>
<tr>
<td>Corynebacterium macginleyi</td>
<td>3</td>
<td>66.6</td>
<td>66.6</td>
</tr>
<tr>
<td>Corynebacterium pseudodiphtheriticum</td>
<td>3</td>
<td>33.0</td>
<td>100.0</td>
</tr>
<tr>
<td>Escherichia coli</td>
<td>5</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>Haemophilus influenzae</td>
<td>28</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>Klebsiella oxytoca</td>
<td>2</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>Morganella morganii</td>
<td>2</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>Proteus mirabilis</td>
<td>4</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>Pseudomonas aeruginosa</td>
<td>5</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>Serratia liquefaciens</td>
<td>2</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>Serratia marcescens</td>
<td>4</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>Staphylococcus aureus</td>
<td>52</td>
<td>1.9</td>
<td>15.4</td>
</tr>
<tr>
<td>Staphylococcus caprae</td>
<td>2</td>
<td>100.0</td>
<td></td>
</tr>
<tr>
<td>Staphylococcus epidermidis</td>
<td>197</td>
<td>28.4</td>
<td>69.0</td>
</tr>
<tr>
<td>Staphylococcus haemolyticus</td>
<td>4</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>Staphylococcus hominis</td>
<td>5</td>
<td>40.0</td>
<td>40.0</td>
</tr>
<tr>
<td>Staphylococcus lugdunensis</td>
<td>5</td>
<td>40.0</td>
<td>100.0</td>
</tr>
<tr>
<td>Staphylococcus warneri</td>
<td>9</td>
<td>55.6</td>
<td>66.7</td>
</tr>
<tr>
<td>Stenotrophomonas maltophilia</td>
<td>2</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>Streptococcus mitis</td>
<td>8</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>Streptococcus pneumoniae</td>
<td>36</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>Streptococcus sanguis</td>
<td>2</td>
<td>0.0</td>
<td>0.0</td>
</tr>
</tbody>
</table>

<sup>1</sup> 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<sub>50</sub> values ranged from 53 to 107 mg/kg for mice and 131 to 134 mg/kg for rats, while the subcutaneous LD<sub>50</sub> 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.

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.

In a three-generation reproduction study performed in rat with xanthan gum administered up to 0.5 g/kg in feed, test and control litters were comparable in number of litters per group, numbers of live births, physical condition, mean weights at birth and weaning, percent young alive at weaning, and gross autopsy observations. No effect of xanthan gum on fetal reabsorption was observed. Gross necropsy observations for the test and control litters were comparable. Organ weights of the F3b litters were comparable. Dietary feeding of xanthan gum during a 3 generation reproduction study had no adverse effect on reproduction.
BIBLIOGRAPHY


