



## OSTEOSET™ T BONE GRAFT PRODUCTS

150826-2

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*Attention Operating Surgeon*  
**IMPORTANT MEDICAL INFORMATION**

**WRIGHT MEDICAL**  
**OSTEOSET™ T BONE GRAFT PRODUCTS**  
**(150826-2)**

**OUTLINE:**

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**I. GENERAL PRODUCT INFORMATION**

OSTEOSET™ T Bone Graft Substitute is made of medical grade calcium sulfate incorporating approximately 4% Tobramycin Sulfate and stearic acid as a tableting aid.<sup>1</sup> This product is

<sup>1</sup> Based on nominal loading, -10%/+20%

supplied sterile for single patient use. The biodegradable, radiopaque pellets are used to fill bone voids and are resorbed in approximately 30-60 days when used according to labeling. The action of the tobramycin sulfate (i.e. to reduce the possibility of infection during surgery) is ancillary to the bone void filler properties of the pellet.

**WARNING: Prior to using this product, carefully read the included *TOBRAMYCIN SULFATE, USP*, section of this package insert for important information related to *WARNINGS, PRECAUTIONS, CONTRAINDICATIONS*, and *ADVERSE REACTIONS* for Tobramycin Sulfate.**

The OSTEASET™ Pellet Injector is a biocompatible, polypropylene disposable device provided pre-loaded and pre-sterilized for single patient use. The injector delivers controlled, precise, and efficient placement of the OSTEASET™ T Bone Graft Substitute Pellets. The disposable injector provides the ideal mechanism for the careful placement of each pellet.

#### **A. INDICATIONS**

OSTEASET™ T Bone Graft Substitute is intended to be gently packed into non-load bearing voids in long bones. These bone voids may be surgically created osseous defects, osseous defects created from traumatic injury to the bone or osteomyelitis. The pellets provide a bone void filler that resorbs and is replaced with bone during the healing process.

OSTEASET™ Pellet Injector is indicated for use with OSTEASET™ T Bone Graft Substitute. The pellet injector is supplied pre-loaded and dispenses a controlled dose of OSTEASET™ T Bone Graft Substitute Pellets directly to specific regions to fill bony voids or gaps. The pellet injector is designed to be minimally invasive where it can dispense bone graft material through small bone void openings.

#### **B. CONTRAINDICATIONS**

OSTEASET™ T Bone Graft Substitute is contraindicated:

- When the device is intended as structural support in load-bearing bone

- Uncooperative patients who will not or cannot follow postoperative instructions, including individuals who abuse drugs and/or alcohol
- Hypercalcemia
- When intra-operative soft tissue coverage is not planned or possible

In addition, OSTEASET™ T Bone Graft Substitute is relatively contraindicated for the following conditions due to the addition of Tobramycin Sulfate. The conditions include:

- Hypersensitivity to any aminoglycoside
- Severe peripheral vascular or neurological disease
- Renal impairment
- Uncontrolled diabetes
- Pregnancy
- Premature or full-term neonates one week of age or less
- Nursing mothers
- Myasthenia Gravis
- OSTEASET™ T Bone Graft Substitute should not be administered concurrently with certain drugs, including potentially ototoxic, neurotoxic or nephrotoxic drugs
- Pre-existing deafness of the inner ear
- For patients with severe degenerative bone disease

See the included **TOBRAMYCIN SULFATE, USP** section of this package insert for more detailed information.

### C. POTENTIAL COMPLICATIONS

Proper surgical procedures and techniques are the responsibility of the medical professional. Each surgeon must evaluate the appropriateness of the procedure used based on personal medical training and experience. Although Wright Medical cannot recommend a particular surgical technique suitable for all patients, a detailed surgical technique is available for surgeon reference.

### D. PRECAUTIONS

As with any surgical procedure, care should be exercised in treating individuals with preexisting conditions that may affect the success of the surgical procedure. This includes individuals with bleeding disorders of any etiology, long-term steroidal therapy, or immunosuppressive therapy. Calcium, magnesium and sodium levels should be monitored in the post operative period.

This device has not been evaluated for safety and compatibility in the MR environment. This device has not been tested for heating or migration in the MR environment.

Use this device as supplied and according to the **HANDLING AND USE** information provided.

### E. ADVERSE EFFECTS

Possible adverse effects include but are not limited to:

- Wound complications including hematoma, site drainage, bone fracture, infection, and other complications that are possible with any surgery
- Fracture or extrusion of the OSTEOSET™ T Bone Graft Substitute with or without generation of particulate debris
- Deformity of the bone at the site
- Incomplete, or lack of, osseous ingrowth into the bone void

- In vitro testing suggests that sustained, high local concentrations of tobramycin may effect the rate of osteoblast formation and bone regeneration.
- Transient hypercalcemia

In the event of a severe adverse reaction to the Tobramycin, a second surgery may be required to remove any remaining pellets.

**For possible adverse reactions related to Tobramycin Sulfate, refer to the *ADVERSE REACTIONS* in the included *TOBRAMYCIN SULFATE, USP* section of this package insert.**

### **MAXIMUM USAGE**

The maximum recommended usage of OSTEASET™ T Bone Graft Substitute for an adult with normal renal function is 4 pellets/kg when using the 4.8 mm pellets. Usage in excess of this amount may cause serum levels of Tobramycin to be elevated above recommended maximums. (See the Tobramycin Sulfate section of this package insert.) Concurrent systemic treatment with tobramycin sulfate or any other neurotoxic and/or nephrotoxic antibiotics, particularly other aminoglycosides should be avoided.

**Table 1: Maximum Usage Guidelines for Adults with Normal Renal Function**

For patients weighing:		Maximum Number of 4.8 mm Pellets
in kilograms	in pounds	
40	88	160
50	110	200
60	132	240

70	154	280
80	176	320
90	198	360
100	220	400

If the maximum usage of OSTEASET™ T Bone Graft Substitute is insufficient in volume to fill the bone void, standard OSTEASET™ Bone Graft Substitute may be mixed with the OSTEASET™ T Bone Graft Substitute to create the necessary volume of material to fill the void.

#### **F. HANDLING AND STERILIZATION**

Use this device as supplied and according to the **HANDLING AND USE** information provided.

#### **HANDLING AND USE**

OSTEASET™ T Bone Graft Substitute and the OSTEASET™ Pellet Injector with OSTEASET™ T Bone Graft Substitute Pellets are provided sterile and should be considered sterile unless the inner packaging has been opened or damaged. This product should not be resterilized. This product is for single patient use and should never be reused. Devices labeled for single-use only should never be reused. Reuse of these devices may potentially result in serious patient harm. Examples of hazards related to the reuse of these devices include, but are not limited to: significant degradation in device performance, cross-infection, and contamination. Use OSTEASET™ T Bone Graft Substitute aseptically according to the following surgical technique:

*Gently pack the OSTEASET™ T Bone Graft Substitute into the treatment site. Avoid overfilling the bone void or compressing the treatment site. Close the site using standard closure*

*techniques. Discard any unused OSTEASET™ T Bone Graft Substitute.*

Use the OSTEASET™ Pellet Injector with OSTEASET™ T Bone Graft Substitute aseptically according to the following surgical technique:

Place the OSTEASET™ Pellet Injector in the void where you wish the OSTEASET™ T Bone Graft Substitute to be placed. Begin with the half-length plunger to begin dispensing the first 25 pellets in to the bony void. Dispense the remaining pellets with the full-length plunger. Gently push the plungers using hand pressure to dispense OSTEASET™ T Bone Graft Substitute into the treatment site. If required the syringe tip can flex 10° to 15° degrees to facilitate delivery into a bony void. Gently pack the OSTEASET™ T Bone Graft Substitute Pellets into the treatment site. Remove excess material from the treatment site. Close the site using standard closure techniques. Discard any unused OSTEASET™ T Bone Graft Substitute and discard the disposable OSTEASET™ Pellet Injector.

**Warning:** Do not force the injector into any void or try to over-flex the injector. Do not use excessive force on the rod or use as a trocar.

**Warning:** Carefully read the enclosed *TOBRAMYCIN SULFATE* section of this package insert prior to using this product.

**Warning:** Do not use this device if the glass vial is cracked or broken.

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## STERILE TOBRAMYCIN SULFATE, USP

### Warnings

Patients treated with Tobramycin Sulfate Injection, USP, and other amino glycosides should be under close clinical observation, because these drugs have an inherent potential for causing ototoxicity and nephrotoxicity.



Neurotoxicity, manifested as both auditory and vestibular ototoxicity, can occur. The auditory changes are irreversible, are usually bilateral, and may be partial or total. Eighth-nerve impairment and nephrotoxicity may develop, primarily in patients having preexisting renal damage and in those with normal renal function to whom aminoglycosides are administered for longer periods or in higher doses than those recommended. Other manifestations of neurotoxicity may include numbness, skin tingling, muscle twitching, and convulsions. The risk of aminoglycoside-induced hearing loss increases with the degree of exposure to either high peak or high trough serum concentrations. Patients who develop cochlear damage may not have symptoms during therapy to warn them of eighth-nerve toxicity, and partial or total irreversible bilateral deafness may continue to develop after the drug has been discontinued.

Rarely, nephrotoxicity may not become apparent until the first few days after cessation of therapy. Aminoglycoside-induced nephrotoxicity usually is reversible.

Renal and eighth-nerve function should be closely monitored in patients with known or suspected renal impairment and also in those whose renal function is initially normal but who develop signs of renal dysfunction during therapy. Peak and trough serum concentrations of aminoglycosides should be monitored periodically during therapy to assure adequate levels and to avoid potentially toxic levels. Prolonged serum concentrations above 12 µg/mL should be avoided. Rising trough levels (above 2 µg/mL) may indicate tissue accumulation. Such accumulation, excessive peak concentrations, advanced age, and cumulative dose may contribute to ototoxicity and nephrotoxicity (see **Precautions**). Urine should be examined for decreased specific gravity and increased excretion of protein, cells, and casts. Blood urea nitrogen, serum creatinine, and creatinine clearance should be measured periodically. When feasible, it is recommended that serial audiograms be obtained in patients old enough to be tested, particularly high-risk patients. Evidence of impairment of renal, vestibular, or auditory function requires discontinuation of the drug or dosage adjustment.

Tobramycin Sulfate, USP, should be used with caution in premature and neonatal infants because of their renal immaturity and the resulting prolongation of serum half-life of the drug.

Concurrent and sequential use of other neurotoxic and/or nephrotoxic antibiotics, particularly other aminoglycosides (e.g., amikacin, streptomycin, neomycin, kanamycin, gentamycin, and paromomycin), cephaloridine, viomycin, polymyxin B, colistin, cisplatin, and vancomycin, should be avoided. Other factors that may increase patient risk are advanced age and dehydration.

Aminoglycosides should not be given concurrently with potent diuretics, such as ethacrynic acid and furosemide. Some diuretics themselves cause ototoxicity, and intravenously administered diuretics enhance aminoglycoside toxicity by altering antibiotic concentrations in serum and tissue.

Aminoglycosides can cause fetal harm when administered to a pregnant woman (see **Precautions**).

### **Description**

Tobramycin Sulfate, USP, a water-soluble antibiotic of the aminoglycoside group, is derived from the actinomycete *Streptomyces tenebrarius*. Sulfuric acid and/or sodium hydroxide may have been added during manufacture to adjust the pH. The product contains no preservative or sodium bisulfate.

Tobramycin Sulfate, USP, is *O*-3-amino-3-deoxy- $\alpha$ -D-glucopyranosyl-(164)-*O*-[2,6-diamino-2,3,6-trideoxy- $\alpha$ -D-*ribo*-hexopyranosyl-(166)]-2-deoxy-L-streptamine, sulfate (2:5)(salt) and has the chemical formula  $(C_{18}H_{37}N_5O_9)_2 \cdot 5H_2SO_4$ . The molecular weight is 1425.45.

### **Clinical Pharmacology**

Therapeutic serum levels of Tobramycin Sulfate, USP, are generally considered to range from 4 to 6  $\mu$ g/mL.

However, in patients with reduced renal function and in neonates, the serum concentration of the antibiotic is usually higher and can be measured for longer periods of time than in normal adults. Dosage for such patients must, therefore, be adjusted accordingly. Following parenteral administration, little, if any, metabolic transformation occurs, and tobramycin is eliminated almost exclusively by glomerular filtration. Renal clearance is similar to that of

endogenous creatinine. Ultrafiltration studies demonstrate that practically no serum protein binding occurs. In patients with normal renal function, up to 84% of the dose is recoverable from the urine in 8 hours and up to 93% in 24 hours.

Peak urine concentrations ranging from 75 to 100 µg/mL have been observed following the intramuscular injection of a single dose of 1 mg/kg. After several days of treatment, the amount of tobramycin excreted in the urine approaches the daily dose administered. When renal function is impaired, excretion of Tobramycin is slowed, and accumulation of the drug may cause toxic blood levels.

The serum half-life in normal individuals is 2 hours. An inverse relationship exists between serum half-life and creatinine clearance, and the dosage schedule should be adjusted according to the degree of renal impairment. In patients undergoing dialysis, 25% to 70% of the administered dose may be removed, depending of the duration and type of dialysis.

Tobramycin can be detected in tissues and body fluids after parenteral administration. Concentrations in bile and stools ordinarily have been low, which suggests minimum biliary excretion. Tobramycin has appeared in low concentration in the cerebrospinal fluid following parenteral administration, and concentrations are dependent on dose, rate of penetration, and degree of meningeal inflammation. It has also been found in sputum, peritoneal fluid, synovial fluid, and abscess fluids, and it crosses the placental membranes. Concentrations in the renal cortex are several times higher than the usual serum levels.

Probenecid does not affect the renal tubular transport of tobramycin.

*Microbiology.* Tobramycin acts by inhibiting synthesis of protein in bacterial cells. *In vitro* tests demonstrate that tobramycin is bactericidal.

Tobramycin has been shown to be active against most strains of the following organisms both *in vitro* and in clinical infections as described in the **Indications** section:

### **Aerobic Gram-positive microorganisms**

*Staphylococcus aureus*

### **Aerobic Gram-negative microorganisms**

*Citrobacter* species

*Enterobacter* species

*Escherichia coli*

*Klebsiella* species

*Morganella morganii*

*Pseudomonas aeruginosa*

*Proteus mirabilis*

*Proteus vulgaris*

*Providencia* species

*Serratia* species

Aminoglycosides have a low order of activity against most gram-positive organisms, including *Streptococcus pyogenes*, *Streptococcus pneumoniae*, and enterococci.

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

Cross resistance between aminoglycosides may occur.

### *Susceptibility Tests*

**Diffusion techniques:** Quantitative methods that require measurement of zone diameters give the most precise estimates of susceptibility of bacteria to antimicrobial agents. One such procedure is the National Committee for Clinical Laboratory Standards (NCCLS)-approved procedure.<sup>2</sup> This method has been recommended for use with disks to test susceptibility to Tobramycin. Interpretation involves correlation of the diameters obtained in the disk test with minimum inhibitory concentrations (MIC) for tobramycin.

Reports from the laboratory giving results of the standard single-disk susceptibility test with a 10- $\mu$ g tobramycin disk should be interpreted according to the following criteria:

<u>Zone Diameter (mm)</u>	<u>Interpretation</u>
$\geq 15$	(S) Susceptible
13-14	(I) Intermediate
12	(R) Resistant

A report of "Susceptible" indicates that the pathogen is likely to be inhibited by generally achievable blood levels. A report of "Intermediate" suggests that the organism would be susceptible if high dosage is used or if the infection is confined to tissues and fluids in which high antimicrobial levels are obtained. A report of "Resistance" indicates that achievable concentrations are unlikely to be inhibitory and other therapy should be selected.

Standardized procedures require the use of laboratory control organisms. The 10- $\mu$ g tobramycin disk should give the following zone diameters:

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<sup>2</sup> National Committee for Clinical Laboratory Standards, Performance standards for antimicrobial disk susceptibility test -5th ed. Approved Standard NCCLS Document M2-A5, Vol 13, No 24, NCCLS, Villanova, PA, 1993.

<u>Organism</u>	<u>Zone Diameter (mm)</u>
<i>E. coli</i> ATCC 25922	18-26
<i>P. aeruginosa</i> ATCC 27853	19-26
<i>S. aureus</i> ATCC 25923	19-29

**Dilution techniques:** Broth and agar dilution methods, such as those recommended by the NCCLS,<sup>3</sup> may be used to determine the minimum inhibitory concentrations (MICs) of tobramycin. MIC test results should be interpreted according to the following criteria:

<u>MIC (µg/mL)</u>	<u>Interpretation</u>
≤4	(S) Susceptible
8	(I) Intermediate
≥16	(R) Resistant

As with standard diffusion methods, dilution procedures require the use of laboratory control organisms. Tobramycin laboratory reagent should give the following MIC values:

<u>Organism</u>	<u>MIC Range (µg/mL)</u>
<i>E. faecalis</i> ATCC 29212	8.0-32.0
<i>E. coli</i> ATCC 25922	0.25-1
<i>P. aeruginosa</i> ATCC 27853	0.12-1
<i>S. aureus</i> ATCC 29213	0.12-1

### **Indications and Usage**

Tobramycin Sulfate, USP, is indicated for the treatment of serious bacterial infections caused

<sup>3</sup> National Committee for Clinical Laboratory Standards, Methods for dilution antimicrobial susceptibility tests for bacteria that grow aerobically -3rd ed. Approved Standard NCCLS Document M7-A3, Vol 13, no 25, NCCLS, Villanova, PA, 1993.

by susceptible strains of the designated microorganisms in the diseases below:

Bone infections caused by *P. aeruginosa*, *Proteus* spp (indole-positive and indole-negative), *E. coli*, *Klebsiella* spp, *Enterobacter* spp, and *S. aureus*

Tobramycin may be considered in serious staphylococcal infections when penicillin or other potentially less toxic drugs are contraindicated and when bacterial susceptibility testing and clinical judgement indicate its use.

Bacterial cultures should be obtained prior to and during treatment to isolate and identify etiologic organisms and to test their susceptibility to tobramycin. If susceptibility tests show that the causative organisms are resistant to tobramycin, other appropriate therapy should be instituted. In patients in whom a serious life-threatening gram-negative infection is suspected, including those in whom concurrent therapy with a penicillin or cephalosporin and an aminoglycoside may be indicated, treatment with Tobramycin Sulfate, USP, may be initiated before the results of susceptibility studies are obtained. The decision to continue therapy with tobramycin should be based on the results of susceptibility studies, the severity of the infection, and the important additional concepts discussed in the Warnings above.

### **Contraindications**

A hypersensitivity to any aminoglycoside is a contraindication to the use of tobramycin. A history of hypersensitivity or serious toxic reactions to aminoglycosides may also contraindicate the use of any other aminoglycosides because of the known cross-sensitivity of patients to drugs in this class.

### **Warnings**

See Warnings above.

## **Precautions**

Serum and urine specimens for examination should be collected during therapy, as recommended in the Warnings section. Serum calcium, magnesium, and sodium should be monitored.

Peak and trough serum levels should be measured periodically during therapy. Prolonged concentrations above 12 µg/mL should be avoided.

Rising trough levels (above 2 µg/mL) may indicate tissue accumulation. Such accumulation, advanced age, and cumulative dosage may contribute to ototoxicity and nephrotoxicity. It is particularly important to monitor the serum levels closely in patients with known renal impairment.

It is important that there be consistency of serum level monitoring within the individual patient program unless computerized pharmacokinetic dosing programs are available in the institution. These serum-level assays may be especially useful for monitoring the treatment of severely ill patients with changing renal function or of those infected with less susceptible organisms or those receiving maximum dosage.

Neuromuscular blockade and respiratory paralysis have been reported in cats receiving very high doses of Tobramycin (40 mg/kg). The possibility of prolonged or secondary apnea should be considered if Tobramycin is administered to anesthetized patients who are also receiving neuromuscular blocking agents, such as succinylcholine, tubocurarine, or decamethonium, or to patients receiving massive transfusions of citrated blood. If neuromuscular blockade occurs, it may be reversed by the administration of calcium salts.

Cross-allergenicity among aminoglycosides has been demonstrated.

In patients with extensive burns, altered pharmacokinetics may result in reduced serum concentrations of aminoglycosides. In such patients treated with Tobramycin Sulfate, USP, measurement of serum concentration is especially important as a basis for determination of



appropriate dosage.

Elderly patients may have reduced renal function that may not be evident in the results of routine screening tests, such as BUN or serum creatinine. A creatinine clearance determination may be more useful. Monitoring of renal function during treatment with aminoglycosides is particularly important in such patients.

An increased incidence of nephrotoxicity has been reported following concomitant administration of aminoglycoside antibiotics and cephalosporins.

Aminoglycosides should be used with caution in patients with muscular disorders, such as myasthenia gravis or Parkinsonism, since these drugs may aggravate muscle weakness because of their potential curare-like effects on neuromuscular function.

Aminoglycosides may be absorbed in significant quantities from body surfaces after local irrigation or application and may cause neurotoxicity and nephrotoxicity.

Physicians are advised that macular necrosis has been reported following administration of aminoglycosides, including Tobramycin, by these routes.

See **Warnings** regarding concurrent use of potent diuretics and concurrent and sequential use of other neurotoxic or nephrotoxic drugs.

The inactivation of Tobramycin and other aminoglycosides by  $\beta$ -lactam-type antibiotics (penicillins or cephalosporins) has been demonstrated in vitro and in patients with severe renal impairment. Such inactivation has not been found in patients with normal renal function who have been given the drugs by separate routes of administration.

Therapy with Tobramycin may result in overgrowth of nonsusceptible organisms. If overgrowth of nonsusceptible organisms occurs, appropriate therapy should be initiated.

**Pregnancy Category D:** Aminoglycosides can cause fetal harm when administered to a pregnant woman. Aminoglycoside antibiotics cross the placenta, and there have been several

reports of total irreversible bilateral congenital deafness in children whose mothers received streptomycin during pregnancy. Serious side effects to mother, fetus, or newborn have not been reported in the treatment of pregnant women with other aminoglycosides. If Tobramycin is used during pregnancy or if the patient becomes pregnant while taking Tobramycin, she should be apprised of the potential hazard to the fetus.

### **Adverse Reactions**

**Neurotoxicity:** Adverse effects on both the vestibular and auditory branches of the eighth nerve have been noted, especially in patients receiving high doses or prolonged therapy, in those given previous courses of therapy with an ototoxin, and in cases of dehydration. Symptoms include dizziness, vertigo, tinnitus, roaring in the ears, and hearing loss. Hearing loss is usually irreversible and is manifested initially by diminution of high-tone acuity. Tobramycin and gentamicin sulfates closely parallel each other in regard to ototoxic potential.

**Nephrotoxicity:** Renal function changes, as shown by rising BUN, NPN, and serum creatinine and by oliguria, cylindruria, and increased proteinuria, have been reported, especially in patients with a history of renal impairment who are treated for longer periods or with higher doses than those recommended. Adverse renal effects can occur in patients with initially normal renal function.

Clinical studies and studies in experimental animals have been conducted to compare the nephrotoxic potential of Tobramycin and gentamicin. In some of the clinical studies and in the animal studies, Tobramycin caused nephrotoxicity significantly less frequently than gentamicin. In some other clinical studies, no significant difference in the incidence of nephrotoxicity between Tobramycin and gentamicin was found.

Other reported adverse reactions possibly related to Tobramycin Sulfate, USP, include anemia, granulocytopenia, and thrombocytopenia; and fever, rash, itching, urticaria, nausea, vomiting, diarrhea, headache, lethargy, mental confusion, and disorientation. Laboratory

abnormalities possibly related to Tobramycin Sulfate, USP, include increased serum transaminases (AST, ALT); increased serum LDH and bilirubin; decreased serum calcium, magnesium, sodium, and potassium; and leukopenia, leukocytosis, and eosinophilia.

### **Overdosage**

**Signs and Symptoms:** The severity of the signs and symptoms following a Tobramycin overdose are dependent on the dose administered, the patient's renal function, state of hydration, and age and whether or not other medications with similar toxicities are being administered concurrently. Toxicity may occur in patients treated more than 10 days, in adults given more than 5 mg/kg/day, in children given more than 7.5 mg/kg/day, or in patients with reduced renal function whose dose has not been appropriately adjusted.

Nephrotoxicity following the parenteral administration of an aminoglycoside is most closely related to the area under the curve of the serum concentration versus time graph. Nephrotoxicity is more likely if trough blood concentrations fail to fall below 2 µg/mL and is also proportional to the average blood concentration. Patients who are elderly, have abnormal renal function, are receiving other nephrotoxic drugs, or are volume depleted are at greater risk for developing acute tubular necrosis. Auditory and vestibular toxicities have been associated with aminoglycoside overdose. These toxicities occur in patients treated longer than 10 days, in patients with abnormal renal function, in dehydrated patients, or in patients receiving medications with additive auditory toxicities. These patients may not have signs or symptoms, or may experience dizziness, tinnitus, vertigo, and a loss of high-tone acuity as ototoxicity progresses. Ototoxicity signs and symptoms may not begin to occur until long after the drug has been discontinued.

Neuromuscular blockade or respiratory paralysis may occur following administration of aminoglycosides. Neuromuscular blockade, respiratory failure, and prolonged respiratory paralysis may occur more commonly in patients with myasthenia gravis or Parkinson's disease. Prolonged respiratory paralysis may also occur in patients receiving decamethonium,

tubocurarine, or succinylcholine. If neuromuscular blockade occurs, it may be reversed by the administration of calcium salts, but mechanical assistance may be necessary.

If Tobramycin were ingested, toxicity would be less likely because aminoglycosides are poorly absorbed from an intact gastrointestinal tract.

**Treatment:** In all cases of suspected overdose, call your Regional Poison Control Center to obtain the most up-to-date information about the treatment of overdose. This recommendation is made because, in general, information regarding the treatment of overdose may change more rapidly than the package insert. In managing overdose, consider the possibility of multiple drug overdoses, interaction among drugs, and unusual drug kinetics in your patient.

The initial intervention in a Tobramycin overdose is to establish an airway and ensure oxygenation and ventilation. Resuscitative measures should be initiated promptly if respiratory paralysis occurs. Patients who have received an overdose of Tobramycin and who have normal renal function should be adequately hydrated to maintain a urine output of 3 to 5 mL/kg/hr. Fluid balance, creatinine clearance, and Tobramycin plasma levels should be carefully monitored until the serum Tobramycin level falls below 2 µg/mL.

Patients in whom the elimination half-life is greater than 2 hours or whose renal function is abnormal may require more aggressive therapy. In such patients, hemodialysis may be beneficial.

## G. STORAGE CONDITIONS

**OSTEOSET™ T Bone Graft Substitute** products must be stored in a clean, dry environment and be protected from sunlight and extremes in temperature. The **OSTEOSET™ T Bone Graft Substitute** should be stored at 15 °C/25 °C – 59 °F/77 °F.