**Composition**

Netromycine Injection contains netilmicin sulfate, a semi-synthetic, water soluble antibiotic of the aminoglycoside group. Each ml of Netromycine Injection contains netilmicin sulfate equivalent to 200, 100, 50, 25 or 10 mg of netilmicin base.

Inactive ingredients:

*Pediatric:* Sodium metabisulfite, edetate disodium, sodium sulfate, methylparaben, propylparaben, and water for injection.

*Adult:* Benzyl alcohol, sodium sulfite anhydrous, sodium hydroxide, and water for injection.

**Properties**

Microbiology: Netilmicin is a rapidly acting bactericidal antibiotic which probably acts by inhibiting normal protein synthesis in susceptible organisms. It is active at low concentrations against a wide variety of pathogenic bacteria including Escherichia coli, bacteria of the Klebsiella-Enterobacter-Serratia group, Citrobacter sp., Proteus sp. (indole-positive and indole-negative) including Proteus mirabilis, P. morganii, P. rettgeri, P. vulgaris, Pseudomonas aeruginosa and Neisseria gonorrhoeae. Netilmicin is also active *in vitro* against isolates of Haemophilus influenzae, Salmonella sp., Shigella sp., and against penicillinase and non-penicillinase-producing Staphylococcus including methicillin-resistant strains. Some strains of Providencia sp., Acinetobacter sp., and Aeromonas sp. are also sensitive to netilmicin.

Many strains of the above organisms which are found to be resistant to other aminoglycosides, such as kanamycin, gentamicin, tobramycin and sisomicin are susceptible to netilmicin *in vitro*.

Occasionally, strains have been identified which are resistant to amikacin but susceptible to netilmicin. The combination of netilmicin and penicillin G has a synergistic bactericidal effect against most strains of Streptococcus faecalis (enterococcus). The combined effect of netilmicin and carbenicillin or ticarcillin is synergistic for many strains of Pseudomonas aeruginosa. In addition, many isolates of Serratia, which are resistant to multiple antibiotics, are inhibited by synergistic combinations of netilmicin with carbenicillin, azlocillin, mezlocillin, cefamandole, cefotaxime or moxalactam. Tests for antibiotic synergy are necessary.

Susceptibility Testing - A disc method of susceptibility testing may be that described by Bauer et al (Am J Clin Path 45:943, 1966, Federal Register 37:20525/20529, 1972). A disc containing 30 µg of netilmicin should give a zone of inhibition of ≥17 mm to indicate susceptibility for isolates other than Pseudomonas aeruginosa. For Pseudomonas aeruginosa, a zone size of ≥12 mm indicates susceptibility. A zone of <12 mm for Pseudomonas aeruginosa and <17 mm for other organisms indicates that the infecting organism is likely to be resistant.

Since pseudomonas responds differently to the netilmicin diffusion gradient in agar plate sensitivity testing than the enterobacteriaceae and staphylococci, a different zone size is used to differentiate sensitive from resistant organisms. This difference does not imply lower activity clinically. Should the zone of inhibition on sensitivity culturing lie between 12 and 17 mm, a positive oxidase test as well as other identification procedures will indicate the probable presence of a sensitive pseudomonas.

In certain circumstances, particularly with strains of Pseudomonas aeruginosa, it may be desirable to do additional susceptibility testing by the tube or agar dilution method; netilmicin standard solution is available for this purpose.

**Indications**

Netromycine Injection is indicated in the treatment of infections caused by susceptible strains of the following microorganisms:
Escherichia coli, Klebsiella-Enterobacter Serratia sp., Citrobacter sp., Proteus sp. (indole-positive and indole-negative), Pseudomonas aeruginosa, and Staphylococcus sp. (coagulase-positive and coagulase-negative, including penicillin- and methicillin-resistant strains) and Neisseria gonorrhoeae. Clinical studies have shown netilmicin to be effective in: bacteremia, septicemia (including neonatal sepsis); serious infections of respiratory tract; kidney and genitourinary tract infections; skin, soft tissue infections; bone, joint infections; burns, wounds, peri-operative infections; intra-abdominal infections (including peritonitis); infections of gastrointestinal tract. Netromycine Injection is recommended as initial therapy in suspected or confirmed Gram-negative infections. In suspected Gram-negative infections, decision to continue therapy with Netromycine Injection should be based on results of the sensitivity tests and the patient’s clinical response and tolerance to the drug. In serious infections when causative organisms are unknown, Netromycin Injection may be administered as initial therapy in conjunction with a penicillin- or cephalosporin- type drug before obtaining results of susceptibility testing. If anaerobic microorganisms are suspected, suitable antimicrobial therapy in conjunction with Netromycin Injection should be given. Following identification of the organism and its susceptibility, Netromycin Injection or other appropriate antibiotic therapy should then be continued.

Netromycin Injection has been used effectively in combination with carbenicillin or ticarcillin for the treatment of life threatening infections caused by Pseudomonas aeruginosa and in conjunction with a penicillin-type drug for the treatment of endocarditis caused by Streptococcus species. In the neonate with suspected sepsis or staphylococcal pneumonia, a penicillin-type drug usually is indicated as concomitant therapy with netilmicin.

Since Netromycin Injection also has demonstrated effectiveness in the treatment of serious staphylococcal infections; it may be considered for the treatment of serious staphylococcal infections when penicillins or other less potentially toxic drugs are contraindicated and bacterial susceptibility tests and clinical judgement indicate its use. It may also be considered in mixed infections caused by susceptible strains of staphylococci and Gram-negative organisms.

In the pre-operative period, Netromycin Injection may be started pro-operatively and continued post-operatively for treatment of suspected or proven infection due to susceptible microorganisms.

Netromycin Injection is indicated in the treatment of acute, uncomplicated gonococcal infection in male (urethra, rectum) and female (urethra, cervix, rectum) with normal renal function.

Clinical studies have shown netilmicin to be effective in: bacteremia, septicemia (including neonatal sepsis); serious infections of respiratory tract; kidney and genitourinary tract infections; skin, soft tissue infections; bone, joint infections; burns, wounds, peri-operative infections; intra-abdominal infections (including peritonitis); infections of gastrointestinal tract. Netromycine Injection is recommended as initial therapy in suspected or confirmed Gram-negative infections. In suspected Gram-negative infections, decision to continue therapy with Netromycine Injection should be based on results of the sensitivity tests and the patient’s clinical response and tolerance to the drug. In serious infections when causative organisms are unknown, Netromycin Injection may be administered as initial therapy in conjunction with a penicillin- or cephalosporin- type drug before obtaining results of susceptibility testing. If anaerobic microorganisms are suspected, suitable antimicrobial therapy in conjunction with Netromycin Injection should be given. Following identification of the organism and its susceptibility, Netromycin Injection or other appropriate antibiotic therapy should then be continued.

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Since Netromycin Injection also has demonstrated effectiveness in the treatment of serious staphylococcal infections; it may be considered for the treatment of serious staphylococcal infections when penicil-
The risk of toxic reactions is low in patients with normal renal function who receive Netromycine Injection either at higher doses or for longer periods of time than recommended.

Some patients who have had previous neurotoxic reactions to other aminoglycosides have been treated safely with Netromycine Injection. Other rarely reported reactions possibly related to netilmicin include: headache, malaise, visual disturbances, disorientation, tachycardia, hypotension, palpitations, thrombocytosis, paresthesia, fluid retention, rash, chills, fever, vomiting and diarrhea. Very rarely, anaphylaxis has been reported.

Laboratory abnormalities possibly netilmicin related: increased blood sugar; increased alkaline phosphatase; increased SGOT or SGPT; bilirubin; other abnormal liver function tests; increased potassium; decreased hemoglobin, WBC, and platelets; eosinophilia, anemia and increase in prothrombin time.

While local tolerance of Netromycine Injection is generally excellent; occasional report of pain at the injection site or local reaction.

In a randomized comparative clinical trial of netilmicin and amikacin, pain associated with intramuscular injections was significantly milder with netilmicin than with amikacin.

### Table 1:

<table>
<thead>
<tr>
<th>Serum Percent of Creatinine (mg/100 ml)</th>
<th>Clearance Rate (ml/min/1.73 m²)</th>
<th>Approximate Creatinine Usual Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;10</td>
<td>&gt;100</td>
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</tr>
<tr>
<td>1.1</td>
<td>70-100</td>
<td>80</td>
</tr>
<tr>
<td>1.4-1.6</td>
<td>55-70</td>
<td>65</td>
</tr>
<tr>
<td>1.7-1.9</td>
<td>45-55</td>
<td>55</td>
</tr>
<tr>
<td>2.0-2.2</td>
<td>40-45</td>
<td>50</td>
</tr>
<tr>
<td>2.3-2.5</td>
<td>35-40</td>
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</tr>
<tr>
<td>2.6-3.0</td>
<td>30-35</td>
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<tr>
<td>3.1-3.5</td>
<td>25-30</td>
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</tr>
<tr>
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<td>20-25</td>
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<td>15-20</td>
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</tr>
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<td>5.2-6.6</td>
<td>10-15</td>
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</tr>
<tr>
<td>6.7-8.0</td>
<td>&lt;10</td>
<td>10</td>
</tr>
</tbody>
</table>

### Precautions

Patients treated with aminoglycosides should be under close clinical observation because of the potential toxicity associated with their use. Nephrotoxicity with netilmicin has been mild. However, as with other aminoglycosides, renal function should be closely monitored during therapy. The risk of nephrotoxicity is greater in patients with impaired renal function, in those who receive high dosage or prolonged therapy and in the elderly. Although ototoxicity with netilmicin has been infrequent and appears to be milder than with other aminoglycosides, hearing loss and vestibular dysfunction can occur, primarily in patients with pre-existing renal damage and in patients with normal renal function treated with higher doses and/or for longer periods than recommended. Monitoring of renal and eighth cranial nerve functions is recommended during therapy, particularly for patients with known or suspected reduced renal function either at onset of therapy or during therapy. Urine should be examined for decreased specific gravity, increased protein excretion and presence of cells or casts. Blood urea nitrogen, serum creatinine or creatinine clearance should be determined periodically. When feasible, serial audiograms are recommended, particularly in high-risk patients. Evidence of ototoxicity or nephrotoxicity requires dosage adjustment or drug discontinuance. As with other aminoglycosides, on rare occasions changes in renal and eighth cranial nerve function may not become manifest until after completion of therapy.

Aminoglycoside serum concentrations should be monitored when feasible to assure adequate levels and to avoid potentially toxic levels. When monitoring netilmicin peak concentrations, adjust dosage to avoid prolonged levels above 16 µg/ml with multiple dosing. When trough concentrations are monitored (just prior to the next dose), they should be in the range of 0.5 to 2 µg/ml at the recommended dosage. Trough concentrations above 4 µg/ml are to be avoided.

Excessive peak and/or trough aminoglycoside serum concentrations may increase risk of renal and eighth cranial nerve toxicities.

In patients with extensive body surface burns, altered pharmacokinetics may result in reduced aminoglycosides serum concentrations.
Measurement of netilmicin serum concentrations is particularly important in these patients for dosage adjustment. Concurrent and/or sequential systemic or topical use of other potentially neurotoxic and/or nephrotoxic drugs, such as cisplatin, bacitracin, polymyxin B, colistin, cephaloridine, amphotericin B, kanamycin, acyclovir, gentamicin, amikacin, sisomycin, tobramycin, neomycin, streptomycin, paromomycin, viomycin and vancomycin should be avoided. Advanced age and dehydration may increase risk of toxicity. Avoid concurrent use of netilmicin with potent diuretics, such as ethacrynic acid or furosemide, since these diuretics by themselves may cause ototoxicity. In addition, when administered intravenously, diuretics may enhance aminoglycoside toxicity by altering antibiotic concentration in serum and tissue.

Neurotoxic or nephrotoxic antibiotics may be absorbed in significant quantities from body surfaces after local irrigation or application. Potential toxic effect of antibiotics administered in this fashion should be considered. Increased nephrotoxicity has been reported following concomitant administration of aminoglycosides with some cephalosporins. Although neuromuscular blockade and respiratory paralysis have not been a problem in clinical trials, they have been reported in animals receiving netilmicin at doses considerably above those clinically recommended. The possibility of these phenomena occurring in man should be considered, particularly if aminoglycosides are administered to patients receiving neuromuscular blocking agents, such as succinylcholine, tubocurarine or decamethonium; anesthetics or massive transfusions of citrate-anticoagulated blood. If neuromuscular blockage occurs, calcium salts may reverse it. Aminoglycosides should be used with caution in patients with neuromuscular disorders, such as myasthenia gravis, parkinsonism or infant botulism since these drugs theoretically may aggravate muscle weakness because of their potential curare-like effects on the neuromuscular junction.

Elderly patients may have reduced renal function which 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 is particularly important in these patients. A Fanconi-like syndrome, with aminoaciduria and metabolic acidosis, has been reported in some adults and infants treated with netilmicin sulfate. Crossallergenicity among aminoglycosides has been demonstrated.

Patients should be well hydrated during treatment. In vitro mixing of aminoglycoside with beta-lactam-type antibiotics (penicillins or cephalosporins) may result in a significant mutual inactivation. When aminoglycoside and penicillin-type drug are administered separately by different routes, reduction in aminoglycoside serum half-life or serum levels has been reported in patients with impaired renal function and with normal renal function. Usually such aminoglycoside inactivation is clinically significant only in patients with severely impaired renal function. Treatment with netilmicin sulfate may result in overgrowth of nonsusceptible organisms; if this occurs, appropriate therapy is indicated.

Netromycine Injection contains sodium metabisulfite and sodium sulfite; these may cause allergictype reactions including anaphylactic symptoms and life-threatening or less severe asthmatic episodes in certain susceptible people. Sulfite sensitivity is observed more frequently in asthmatic than in non-asthmatic people.

Pregnancy and Lactation
Safety for use during pregnancy has not been established. Small amounts of netilmicin sulfate are excreted in breast milk; decision should be made either to discontinue nursing or to discontinue the drug.

Overdosage
In the event of overdose or toxic reaction, hemodialysis or peritoneal dialysis will aid in the removal of netilmicin sulfate from the blood. However, the rate of removal is considerably less by peritoneal dialysis. These procedures are of particular importance for patients with impaired renal function.
doses every eight hours, two equal doses every twelve hours or once daily.

In general, within this dose range, lower dosage will be used for urinary tract infections and the higher dosage for systemic infections. For both uses, adjust dosage depending on severity of infection and patient condition.

For adults weighing 50-90 kg, a dose of 150 mg may be given every twelve hours or 100 mg every eight hours. For adults smaller or larger than the above range, dosage should be calculated in mg/kg of lean bodyweight.

For patients with life-threatening infections, dosages up to 7.5 mg/kg/day may be administered in three equal doses every eight hours, this dosage should be reduced to 6 mg/kg/day or less as soon as clinically indicated, usually within 48 hours.

Pediatric Patients
Premature or full-term neonate one week of age or less: 6 mg/kg/day (3.0 mg/kg administered every twelve hours). Neonates over one week of age and infants: 7.5-9.0 mg/kg/day (2.5-3.0 mg/kg administered every eight hours). Children 6.0-7.5 mg/kg/day (2.0-2.5 mg/kg administered every eight hours).

Patients with Impaired Renal Function
Dosage must be adjusted in patients with impaired renal function. Whenever possible, monitor netilmicin serum concentrations. Dose schedules are not intended as rigid recommendations, but provided as dosing guides when netilmicin serum levels measurement is not feasible. If serum assay determinations are not available and renal function is stable, serum creatinine and creatinine clearance values are the most reliable, readily available indicators of degree of renal impairment as a guide for dosage adjustment.

Variable Frequency Regimen: One method of adjustment is to increase interval between usual dose administered. Since serum creatinine concentration has a high correlation with netilmicin serum half-life, this laboratory test may provide guidance for adjustment of the interval between doses. The interval
between doses (in hours) may be approximated by multiplying serum creatinine level by 8. For example, a patient weighing 60 kg with a serum creatinine level of 3.0 mg/100 ml could be given 120 mg (2 mg/kg) every 24 hours (3.0 x 8).

Variable Dosage Regimen: In patients with serious systemic infections and renal impairment, it may be desirable to administer the antibiotic more frequently but in reduced dose. In such patients, measure netilmicin serum concentration should be measured.

Suggested methods are: After usual initial or loading dose, a rough guide for determining reduced dosage at eight-hour intervals is to divide normally recommended dose by serum creatinine level (Table 1). For example after an initial dose of 120 mg (2 mg/kg), a patient weighing 60 kg with a serum creatinine level of 3.0 mg/100 ml could be given 40 mg every eight hours (120-3).

If the rate of creatinine clearance is known, the maintenance dose to be administered every 8 hours may be calculated using the following formula:

\[
\text{Maintenance Dose (every 8 hours)} = \frac{\text{Observed CCr}^* \times \text{Usual maintenance dose}}{\text{Normal CCr}}
\]

\* CCr = Creatinine Clearance Rate in ml/min./1.73 m².

The initial or loading dose is the same as that recommended for patients with normal renal function.

The above dosage schedules are provided as dosage guides when the measurement of netilmicin serum levels is not feasible.

Deteriorating renal function may require a greater reduction in dosage than that specified in the guidelines for patients with stable renal impairment.

I.V Administration: The intravenous administration of netilmicin may be particularly useful for treating patients with septicemia or those in shock. It may be preferred route for some patients with congestive heart failure, hematologic disorders, severe burns or those with reduced muscle mass.

For IV administration in adults, a single dose of Netromycine Injection may be diluted in 50 to 200 ml of sterile normal saline or in a sterile solution of dextrose 5% in water; in infants and children the volume of diluent should dependent on the patient’s fluid requirements. The solution may be infused over a period of one-half to two hours. In certain circumstances, a dose may be injected directly into a vein or IV. tubing slowly over a period of 3 to 5 minutes.

Netromycin Injection is physically compatible with parenteral solutions and exhibits no loss of potency at 3 mg/ml (as the base) concentration when refrigerated or stored at room temperature for up to seven days:

**Sterile Water for Injection**
Normal Saline, 3% and 5% Sodium Chloride Injection, 5% Dextrose in Water
5% Dextrose with Electrolyte No. 48, 5% Dextrose with Electrolyte No. 75, 5%
Dextrose and 0.9% Sodium Chloride Injection, 50% Dextrose Injection, 5% Sodium Bicarbonate Injection, 6% Dextran 75 in 50% Dextrose, 10% Dextran 40, 10% Dextrose in Water, Ringer’s Injection, Lactated Ringer’s Injection Lactated Ringer’s Injection with 5% Dextrose, ISOLYTE P+ with 5% Dextrose, ISOLYTE M+ with 5% Dextrose, ISOLYTE E+ with 5% Dextrose, 10% and 20%
OSMITROL Injection+, Plasma-Lyte M Injection 5%
Dextrose, Plasma-Lyte 148 Injection, Plasma-Lyte 56 with 5% Dextrose, Plasma-Lyte 148 with 5% Dextrose, Ionsol B in D5-W Ionsol T in 5%
Dextrose, 10% TRAVERT++ with Electrolyte No. 2, 10% TRAVERT++ with Electrolyte No. 3, 10%
GENTRAN++ 40 and 5% Dextrose, 5% Dextrose in POLYSAL++, 5% Amigen Injection alone or with 5% Dextrose Normosol-R, Polysal (Plain), Aminosol
5% Injection, Fre-Amine II Injection, 10% Fructose Injection, Rheomacrodex 10% in 5% Dextrose.

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+++ Trademarks of Cutter Laboratories, Inc.

**Special Dosage Regimens**

**Gonorrhea in Males and Females**
A single IM. injection of 300 mg Netromycine Injection is recommended. The injection (100 mg/ml) should be made deep in the upper outer quadrant of the gluteal muscle, with one-half dose in each but-
tock. Dose adjustments using lean bodyweight recommended for small or large patients.

*Urinary Tract Infections (UTI)*
Patients with uncomplicated UTI, particularly if chronic and recurrent and without evidence of renal insufficiency, may be treated with a single daily dose of 3 mg/kg, for example 150-200 mg of netilmicin administered intramuscularly for 7 to 10 days.

*Hemodialysis*
In adults with renal failure undergoing hemodialysis, the amount of netilmicin removed from the blood may vary depending upon several factors, including the dialysis method used.

An eight-hour hemodialysis may reduce serum concentrations of netilmicin by approximately 63%. A shorter dialysis session will remove less drug. The recommended dose at the end of each dialysis period is 2 mg/kg. In children, a dose of 2 to 2.5 mg/kg may be administered, depending upon the severity of infections.

*Concomitant Therapy*
Dosages recommended above for patients with normal or impaired renal function should not be reduced when netilmicin is administered concomitantly with other antibiotics.