**NETSPAN Injection (Netilmicin sulfate)**

### Composition

**NETSPAN 10**
Each ml contains:
- Netilmicin sulfate USP equivalent to netilmicin .............................. 10 mg
- Benzyl alcohol BP ............. 1% v/v (as preservative)
- Water for Injection BP ........... q.s

**NETSPAN 25**
Each 1 ml contains:
- Netilmicin sulfate USP equivalent to netilmicin .............................. 25 mg
- Benzyl alcohol BP ............. 1% v/v (as preservative)
- Water for Injection BP ........... q.s

**NETSPAN 50**
Each 1 ml contains:
- Netilmicin sulfate USP equivalent to netilmicin .............................. 50 mg
- Benzyl alcohol BP ............. 1% v/v (as preservative)
- Water for Injection BP ........... q.s

**NETSPAN 200**
Each 2 ml contains:
- Netilmicin sulfate USP equivalent to netilmicin .............................. 200 mg
- Benzyl alcohol BP ............. 1% v/v (as preservative)
- Water for Injection BP ........... q.s

**NETSPAN 300**
Each 3 ml contains:
- Netilmicin sulfate USP equivalent to netilmicin .............................. 300 mg
- Benzyl alcohol BP ............. 1% v/v (as preservative)
- Water for Injection BP ........... q.s
**Dosage Form**

Solution for intravenous (I.V.)/intramuscular and (I.M.) administration.

**Pharmacology**

**Pharmacodynamics**

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 that 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 the *Serratia* group, 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.

**Pharmacokinetics**

Like other aminoglycosides, netilmicin is poorly absorbed after oral administration. Therefore, it is given parenterally. Following I.M. administration, peak serum concentrations are achieved in 30-40 minutes. After an I.V. “slow bolus”, serum concentrations follow a biphasic curve. The mean plasma half-life is 2.5 hours after both I.V. and I.M. administration. T1/2 increases as the dose increases. It is less in severely burnt, anemic and febrile patients. The volume of distribution is 270 ml/kg (i.e., 20% of body weight). Netilmicin exhibits a low plasma protein binding.

Following parenteral administration, netilmicin is rapidly distributed into tissues and can be detected in serum, tissue, sputum and pericardial, pleural, synovial and peritoneal fluids. Netilmicin is excreted via the kidney tubules by glomerular filtration and tubular reabsorption. About 80% of the dose appears unchanged in urine within 24 hours. The elimination of netilmicin is reduced in renal disease and in the elderly as renal function declines. This needs dose adjustment (please refer **DOSAGE AND ADMINISTRATION**). There is no evidence of enterohepatic circulation.
**Indications**

**NETSPAN Injection** is indicated in the treatment of patients with serious or life-threatening bacterial infections caused by susceptible strains of the following organisms: *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:

- Complicated urinary tract infections
- Bacteremia, septicemia (including neonatal sepsis concomitantly with penicillin-type drug)
- Acute, uncomplicated gonococcal infection in male (urethra, rectum) and female (urethra, cervix, rectum) with normal renal function
- Skin and soft tissue infections
- Intra-abdominal infections (including peritonitis and intra-abdominal abscess)
- Serious infections of the respiratory tract (*nosocomial pneumonia, lung abscess, cystic fibrosis, severe community-acquired pneumonia; in neonate with suspected staphylococcal pneumonia, concomitantly with a penicillin-type drug*)
- Kidney and genitourinary tract infections
- Bone and joint infections
- Burns, wounds, peri-operative infections
- Gastrointestinal tract infections
- Endocarditis (**NETSPAN** to be used in conjunction with a penicillin-type drug caused by species of streptococcus)
- Central nervous system (CNS) infections (*Gram-negative meningitis and ventriculitis*)
- Infections in immunocompromised patients
- Surgical prophylaxis (**NETSPAN** may be started pre-operatively and continued post-operatively)

**NETSPAN Injection** is recommended as initial therapy in suspected or confirmed Gram-negative infections.

In serious infections when the causative organisms are unknown, **NETSPAN 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 **NETSPAN Injection** should be given. Following identification of the organism and its susceptibility, **NETSPAN Injection** or other appropriate antibiotic therapy should then be continued.

**NETSPAN Injection** has been used effectively in combination with carbenicillin or ticarcillin for the treatment of life-threatening infections caused by *Pseudomonas aeruginosa*.

Since **NETSPAN 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.
Clinical studies have shown that NETSPAN Injection has been effective in the treatment of infections caused by microorganisms resistant to other aminoglycosides, such as kanamycin, gentamicin, tobramycin, sisomicin and amikacin.

**Dosage And Administration**

**Dosage**

The recommended dosage of NETSPAN Injection for I.M. and I.V. administration is identical. The patient's pre-treatment body weight should be obtained for calculation of the correct dosage. Aminoglycoside dosage in obese patients should be based on an estimate of lean body mass.

It is desirable to measure peak and trough netilmicin serum concentrations to assure adequate but not excessive levels. With the administration of NETSPAN Injection in two or three daily doses, the peak concentration, measured 30 minutes to 1 hour after administration, is expected to be in the range of 4 to 12 mcg/ml; dosage should be adjusted to avoid prolonged peak serum concentrations above 16 mcg/ml. Trough concentrations above 4 mcg/ml, measured just before the next dose is given, should be avoided. With once daily administration of NETSPAN Injection, peak concentrations between 20 - 30 mcg/ml can be anticipated.

**Adults**

The recommended dosage of NETSPAN Injection for patients with urinary tract or non-life-threatening systemic infections with normal renal function is 4.0 - 6.0 mg/kg/day given in three equal doses every eight hours, two equal doses every twelve hours or once daily.

In general, within this dose range, the lower dosage will be used for urinary tract infections and the higher dosage for systemic infections.

For adults weighing 40 - 60 kg, a dose of 100 mg may be given every twelve hours. For adults smaller or larger than the above range, dosage should be calculated in mg/kg of lean body weight. (4-6 mg/kg/day)

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 body weight. (4-6 mg/kg/day)

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 6mg/kg/day or less as soon as clinically indicated, usually within 48 hours.

**Gonorrhea in Males and Females**

A single IM injection of 300mg netilmicin 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 buttock. Dosage adjustments using lean body weight are 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 7-10 days.
Pediatric

**Premature or full-term neonates, 1 week of age or less:** 6 mg/kg daily in two divided doses.

**Neonates over 1 week of age and infants:** 7.5-9.0 mg/kg daily in three divided doses.

**Children:** 6.0-7.5 mg/kg daily in three divided doses.

The duration of treatment is usually 7-14 days. In complicated infections, a longer course of therapy may be necessary. Patients treated beyond the usual period should be carefully monitored for changes in renal, auditory and vestibular function.

**Renal Impairment**

Dosage must be adjusted in patients with impaired renal function. Whenever possible, netilmicin serum concentrations should be monitored.

**Variable Frequency Regimen:** One method of adjustment is to increase the interval between the usual doses administered. The interval between doses (in hours) may be approximated by multiplying the serum creatinine level (mg/100 ml) 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 dosages. In such patients, netilmicin serum concentrations should be measured.

After the usual initial or loading dose, a rough guide for determining the reduced dosage at 8-hour intervals is to divide the normally recommended dose by the serum creatinine level (Table 1).

**Table 1: Dosage Adjustment Guide for Patients with Renal Impairment (Dosage at 8-Hour intervals after the Usual Initial Dose)**

<table>
<thead>
<tr>
<th>Serum Creatinine (mg/100 ml)</th>
<th>Approximate Creatinine Clearance Rate (mL/min/1.73m²)</th>
<th>Percentage of Usual Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;1.0</td>
<td>&gt;100</td>
<td>100</td>
</tr>
<tr>
<td>1.1-1.3</td>
<td>70-00</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>
<td>40</td>
</tr>
<tr>
<td>2.6-3.0</td>
<td>30-35</td>
<td>35</td>
</tr>
<tr>
<td>3.1-3.5</td>
<td>25-30</td>
<td>30</td>
</tr>
<tr>
<td>3.6-4.0</td>
<td>20-25</td>
<td>25</td>
</tr>
<tr>
<td>4.1-5.1</td>
<td>15-20</td>
<td>20</td>
</tr>
<tr>
<td>5.2-6.6</td>
<td>10-15</td>
<td>15</td>
</tr>
<tr>
<td>6.7-8.0</td>
<td>&lt;10</td>
<td>10</td>
</tr>
</tbody>
</table>

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.

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

\[
\text{Maintenance Dose} = \frac{\text{Observed CCr} \times \text{Usual Maintenance Dose}}{\text{Normal CCr}}
\]

Every 8 Hours

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

**Hemodialysis**

An 8-hour hemodialysis may reduce serum concentrations of netilmicin by approximately 63%. The recommended dose at the end of each dialysis period is 2 mg/kg. In children, a dose of 2-2.5 mg/kg may be administered, depending upon the severity of infection.

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

**Method of Preparation**

For I.V. administration in adults, a single dose of **NETSPAN Injection** may be diluted in 50-200 ml of sterile normal saline or in a sterile solution of dextrose 5% in water; in infants and children the volume of diluents should be dependent on the patient’s fluid requirements.

**Method of Administration**

The solution may be infused over a period of about 30 minutes to 2 hours. In certain circumstances, a dose may be injected directly into the vein or I.V. tubing slowly over a period of 3 to 5 minutes.

**Stability and Compatibility**

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

Sterile Water for Injection; Normal saline; 5% Glucose in Water; 10% Glucose in Water; Ringer's Injection; Lactated Ringer's Injection; 5% Sodium Bicarbonate Injection.

**NETSPAN Injection** should not be physically pre-mixed with other drugs, but should be administered separately in accordance with the recommended route of administration and dosage schedule.

**Note:** **Netspan Injection** range in colour from water white to pale yellow. Dark yellow solutions should not be used.

**Contraindications**

Hypersensitivity or serious toxic reactions to netilmicin or other aminoglycosides contraindicates its use.
Warnings And Precautions

General

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 the therapy. The risk of nephrotoxicity is more in patients with impaired renal function and in those who receive high dosages or prolonged therapy, and in the elderly.

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 the 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 discontinuance of the drug. 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 peak concentrations of netilmicin, adjust dosage so that prolonged levels above 16 mcg/ml are avoided. When trough concentrations are monitored (just prior to the next dose), they should be in the range of 0.5 to 2 mcg/ml at the recommended dosage. Trough concentrations above 4 mcg/ml are to be avoided. Excessive peak and/or trough aminoglycoside serum concentrations may increase the risk of renal and eighth cranial nerve toxicities.

In patients with extensive body surface burns, altered pharmacokinetics may result in reduced serum concentrations of aminoglycosides. Measurement of netilmicin serum concentrations is particularly important in these patients as a basis for dosage adjustment.

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.

A Fanconi-like syndrome, with aminoaciduria and metabolic acidosis, has been reported in some adults and infants treated with netilmicin.

Patients should be well hydrated during treatment.

Treatment with netilmicin sulfate may result in overgrowth of non-susceptible organisms. If this occurs, appropriate therapy is indicated.
Drug interactions

- Concurrent and/or sequential systemic or topical use of other potentially neurotoxic and/or nephrotoxic drugs, such as cisplatin, bacitracin, polymyxin B, colistin, cephalaridine, amphotericin B, kanamycin, acyclovir, gentamicin, amikacin, sisomicin, tobramycin, neomycin, streptomycin, paramomycin, cephalothin, viomycin and vancomycin, should be avoided. Advanced age and dehydration may also increase the risk of toxicity.
- The concurrent use of netilmicin with potent diuretics, such as ethacrynic acid or frusemide, should be avoided since these diuretics by themselves may cause ototoxicity. In addition, when administered intravenously, diuretics may enhance aminoglycoside toxicity by altering the antibiotic concentration on serum and tissue.
- Neurotoxic or nephrotoxic antibiotics may be absorbed in significant quantities from body surfaces after local irrigation or application. The 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.
- The possibility of neuromuscular blockade and respiratory paralysis should be borne in mind when administering neuromuscular blocking drugs such as succinylcholine, tubocurarine or decamethonium; anesthetics or massive transfusions of citrate-anti-coagulated blood in patients receiving netilmicin. If neuromuscular blockade occurs, calcium salts may reverse it.
- Cross-allergenicity among aminoglycosides has been demonstrated.

*In vitro* mixing of an aminoglycoside with beta-lactam-type antibiotics (penicillins or cephalosporins) may result in a significant mutual inactivation. Even when an aminoglycoside and a penicillin-type drug are administered separately by different routes, a reduction in aminoglycoside serum half-life or serum levels has been reported in patients with impaired renal function and in some patients with normal renal function. Usually such inactivation of the aminoglycoside is clinically significant only in patients with severely impaired renal function.

**NETSPAN Injection** contains sodium metabisulfite and sodium sulfite; these may cause allergic-type 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.

Renal impairment

Please refer **DOSAGE AND ADMINISTRATION**.

Pregnancy

Aminoglycoside antibiotics cross the placenta and may cause fetal harm when administered to pregnant women. There have been reports of total irreversible bilateral congenital deafness in children whose mothers received aminoglycosides, including netilmicin, during pregnancy. If netilmicin is used during pregnancy or if the patient becomes pregnant while taking netilmicin, she should be apprised of the potential hazard to the fetus.

Lactation
Studies in nursing mothers indicate that small amounts of netilmicin sulfate are excreted in breast milk. Because of the potential for serious adverse reactions, a decision should be made whether to discontinue breastfeeding or to discontinue the drug.

Pediatric use

The risk of nephrotoxicity is greater in children, neonates and infants due to immature kidneys. Patients treated for longer than 14 days should be carefully monitored for changes in renal, auditory and vestibular function.

Geriatric Use

The risk of nephrotoxicity is greater in elderly patients. One should reduce the dose if renal function is impaired.

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 netilmicin treatment, as with other aminoglycosides, is particularly important in these patients.

Undesirable Effects

Nephrotoxicity: Adverse renal effects, generally mild in nature, have been reported infrequently after netilmicin administration. They occur more frequently in the elderly, in patients with a history of renal impairment, in patients treated for longer periods or with larger than the recommended dosage, and are most often reversible.

Neurotoxicity: Unlike other aminoglycosides, incidence of vestibular and cochlear toxicity with netilmicin is very low. Impairment of vestibular function may be transient due to compensatory mechanisms. The rarely reported cochlear impairment is usually irreversible. These adverse effects occur primarily in patients with renal impairment and in patients treated with high doses and/or prolonged periods. Other factors may increase the risk of aminoglycoside-induced ototoxicity. Symptoms of aminoglycoside-induced ototoxicity are often transient and may include dizziness, vertigo, tinnitus, roaring in the ears and hearing loss. The latter is usually manifested by diminution of high-tone acuity.

The risk of toxic reactions is low in patients with normal renal function who do not receive netilmicin 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 netilmicin injection.

Other rarely reported adverse reactions possibly related to netilmicin include: headache, malaise, visual disturbances, disorientation, tachycardia, hypotension, palpitations, thrombocytosis, paresthesia, rash, chills, fever, fluid retention, vomiting and diarrhea.

Very rarely, anaphylaxis has been reported.

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

While local tolerance of netilmicin is generally excellent, there has been an 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.

**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.

**Incompatibility**

**NETSPAN** injection should not be physically pre-mixed with other drugs, but should be administered separately in accordance with the recommended route of administration and dosage schedule.

**Storage And Handling Instructions**

Do not freeze. Store between 2°C and 30°C

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

Sterile Water for Injection; Normal saline; 5% Glucose in Water; 10% Glucose in Water; Ringer's Injection; Lactated Ringer's Injection; 5% Sodium Bicarbonate Injection.

**Packaging Information**

**NETSPAN 10**: Ampoule of 1 mL  
**NETSPAN 25**: Ampoule of 1 ml  
**NETSPAN 50**: Ampoule of 1 mL  
**NETSPAN 200**: Ampoule of 2 mL  
**NETSPAN 300**: Ampoule of 3 mL

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NETSPAN Injection

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