AMIKACIN

AMIKACIDE®

50 mg/mL Solution for Injection (100 mg in 2 mL ampule)
125 mg/mL Solution for Injection (250 mg in 2 mL ampule)
250 mg/mL Solution for Injection (500 mg in 2 mL ampule)

INTRAVENOUS / INTRAMUSCULAR

ANTIBACTERIAL

FORMULATIONS

Each ampule contains: Amikacin (as sulfate), BP.....100 mg, 250 mg or 500 mg

PRODUCT DESCRIPTION

Amikacin (Amikacide®) is a clear, colorless to pale yellow, sterile, nonpyrogenic solution in 2 mL clear ampule. It contains the following ingredients: amikacin sulfate, trisodium citrate dihydrate, sodium metabisulfite, sulfuric acid, and water for injection to make a volume of 2 mL. The solution has a pH of 4-5.

PHARMACODYNAMICS

Amikacin is a semisynthetic aminoglycoside antibiotic derived from kanamycin. The addition of the side chain renders it resistant to degradation by most aminoglycoside-modifying enzymes. It binds irreversibly to the 30S subunit of the bacterial ribosome, blocking protein synthesis by inhibiting the movement of peptidyl-tRNA associated with translocation as well as increasing the frequency of misreading of the genetic code owing to incorrect codon-anticodon interaction. This leads to cell death.

PHARMACOKINETICS

Peak plasma concentrations of 17-25 mcg/mL are attained within 45 minutes to 2 hours after a single 500 mg intramuscular (IM) dose in adults with normal renal function. Average plasma concentration after 10 hours is 2.1 mcg/mL. When the same dose is administered by intravenous (IV) infusion over 1 hour, average peak plasma concentration of the drug is 38 mcg/mL immediately after the infusion, 5.5 mcg/mL at 4 hours, and 1.3 mcg/mL at 8 hours.

After usual dosages of amikacin, therapeutic concentrations of the drug are achieved in bone, heart, gallbladder, and lung tissue. Amikacin is also well distributed into bile, sputum, bronchial secretions, and interstitial, pleural, and synovial fluids. It crosses the placenta and can be detected in the fetus. Due to its low lipid solubility it is expected that the amount of amikacin in breast milk is insignificant.

The plasma elimination half-life of amikacin is usually 2-3 hours in adults with normal renal function and is reported to range from 30-86 hours in adults with severe renal impairment. In full terms infants 7 days or older and low-birth weight infants 1-3 days old, the plasma elimination half-life is 4-5 hours and 7-8 hours, respectively. In adults with normal renal function, 94-98% of a single IM or IV dose of amikacin is excreted unchanged by glomerular filtration within 24 hours.

ANTIMICROBIAL SPECTRUM OF ACTIVITY

Amikacin is active against the following organisms, both *in vitro* and in clinical infections:

Aerobic Gram-Positive Microorganisms	*Staphylococcus aureus* *Staphylococcus epidermidis*
Gram-Negative Microorganisms	*Pseudomonas aeruginosa* *Escherichia coli* *Klebsiella pneumoniae* *Morganella morganii* *Proteus mirabilis* *Proteus vulgaris* *Providentia stuartii* *Salmonella spp.* *Serratia spp.* *Citrobacter spp.* *Enterobacter spp.*

Amikacin is active *in vitro* against the following organisms:

Aerobic Gram-Positive Microorganisms	Penicillinase and non-penicillinase-producing *Staphylococcus aureus* (including methicillin resistant-strains)
Gram-Negative Microorganisms	*Pseudomonas species* *Escherichia coli* *Proteus species (indole positive and indole negative)* *Providencia species* *Klebsiella-Enterobacter-Serratia species* *Acinetobacter species* *Citrobacter freundii* Many strains of the above organisms that are resistant to other aminoglycosides (e.g., gentamicin, tobramycin and kanamycin) are susceptible to amikacin *in vitro*.

Aminoglycosides in general, have low activity against other gram-positive organisms such as *Streptococcus pyogenes, Enterococci, and Streptococcus pneumoniae*.

Amikacin combined with a beta-lactam antibiotic or penicillin-type drug acts synergistically against many clinically significant gram-negative organisms.

INDICATIONS

For the treatment of the following infections caused by susceptible microorganisms:

- Bacterial septicemia including neonatal sepsis
- Respiratory tract infections
- Infections of the bones and joints
- Intra-abdominal infections (including peritonitis)
- Burns and postoperative infections
- Serious and complicated urinary tract infections
- Initial therapy in suspected gram-negative infections

DOSAGE AND ADMINISTRATION

Obtain the patient's pretreatment body weight for calculation of correct dosage. Amikacin may be given intravenously (IV) or intramuscularly (IM). Because of the potential toxicity of aminoglycosides, fixed-dosage recommendations that are not based on body weight are not advised.

Determine the status of renal function by measuring the exogenous creatinine clearance. Periodic monitoring of serum concentrations is required. Avoid peak serum concentrations above 35 mcg/mL (30-90 minutes after injection) and trough levels above 10 mcg/mL (just prior to the next dose).

Intramuscular/Intravenous Administration in Patients with Normal Renal Function

Adults, children and older infants: Recommended dose is 15 mg/kg body weight/day given as a single dose or divided into 2 to 3 equal doses administered at equally divided intervals, i.e., 7.5 mg/kg every 12 hours or 5 mg/kg every 8 hours. Treatment of patients in the heavier weight classes should not exceed 1.5 g/day. A single dose of 500 mg daily or 250 mg twice daily may be given for uncomplicated urinary tract infection.

Newborns: Amikacin should be used with caution in premature and full term neonates because of possible prolongation of serum half-life due to renal immaturity. Loading dose of 10 mg/kg body weight is recommended followed by 7.5 mg/kg every 12 hours. In newborns 0 to 7 days old whose body weight is less than 2 kilograms, a dose of 7.5 mg/kg every 18-24 hours is recommended.

The usual duration of treatment is 7-10 days. In difficult and complicated infections where treatment beyond 10 days is considered, the use of amikacin should be re-evaluated.

If definite clinical response does not occur within 3 to 5 days, stop the therapy and recheck the antibiotic susceptibility pattern.

Intramuscular/Intravenous Administration in Patients with Impaired Renal Function

Adjust doses either by administering normal doses at prolonged intervals or by administering reduced doses at a fixed interval. Do not use either method when dialysis is being performed.

Dose in Dialysis Patients

Approximately half the normal mg/kg dose can be given after hemodialysis; in peritoneal dialysis, give a parenteral dose of 7.5 mg/kg and then instill amikacin in peritoneal dialysate at a concentration desired in serum.

Normal Dosage at Prolonged Intervals

If the creatinine clearance rate is not available and the patient's condition is stable, calculate the dosage interval in hours for the normal dose by multiplying the serum creatinine by 9. Administer the recommended single dose (7.5 mg/kg) every 18 hours if the serum creatinine concentration is 2 mg/100 mL.

Reduced Dosage by Fixed Intervals

Reduce the dosage if renal function is impaired and administer amikacin at a fixed time interval. In patients with renal impairment, measure serum amikacin concentration to assure accurate administration of the amikacin to avoid concentrations above 35 mcg/mL. If serum assay determinations are not available and the patient's condition is stable, serum creatinine and clearance values are the most readily available indicators of the degree of renal impairment to use as a guide for dosage.

First, initiate therapy by administering a normal dose, 7.5 mg/kg as a loading dose. To determine the size of maintenance doses administered every 12 hours, reduce the loading dose in proportion to the reduction in the patient's creatinine clearance (CrCl).

$$\text{Maintenance dose every 12 hours} = \frac{\text{observed CrCl (mL/min)}}{\text{normal CrCl (mL/min)}} \times \text{calculated loading dose (mg)}$$

An alternate rough guide for determining reduced dosage at 12 hour intervals (for patients whose steady-state serum creatinine values are known) is to divide the normal recommended dose by the patient's serum creatinine.

Note: The above dosage schedule is not a rigid recommendation. It is only a guide to dosage when the measurement of amikacin serum levels is not feasible.

Below is a dosage guide of amikacin in patients with renal impairment based on exogenous creatinine clearance derived from the recommended dose for patients with normal renal function (15 mg/kg daily or 7.5 mg/kg every 12 hours):

Traditional Multiple Daily Doses For Patients with Renal Impairment

Exogenous Creatinine Clearance (mL/min)	Multiple Daily Doses (% of dose for Patients with Normal Renal Function)
>50-90	60-90% every 12 hours
10-50	30-70% every 12-18 hours
<10	20-30% every 24-48 hours

Once Daily Dosing For Patients with Renal Impairment

Exogenous Creatinine Clearance (mL/min)	Dose (mg/kg body weight)
>80	15 every 24 hours
60-80	12 every 24 hours
40-60	7.5 every 24 hours
30-40	4 every 24 hours
20-30	7.5 every 48 hours
10-20	4 every 48 hours
<10	3 every 72 hours

When only serum creatinine is available, the following formula (Cockcroft and Gault equation) may be used to estimate creatinine clearance in adults. Serum creatinine should represent a steady state of renal function:

Males: Creatinine clearance (mL/min) = $\frac{\text{Weight (kg) x (140 - age in years)}}{\text{72 x serum creatinine (mg/dL)}}$

Females: 0.85 x value calculated using the above formula

Supplement Doses for Patients with Renal Impairment Undergoing Hemodialysis or CAPD (IV Infusion or IM)

Continuous Ambulatory Peritoneal Dialysis (CAPD)	15-20 mg per liter dialysate per day (e.g., 2 liters of dialysis fluid placed every 6 hours or 8 liters per day ⟶ 8 L x 20 mg = 160 mg of amikacin per day)
Hemodialysis	Extra ½ of normal renal function dose after dialysis.

Intravenous Administration:

The individual dose, total daily dose and total cumulative dose of amikacin are identical to the dose recommended for IM administration.

Preparation of solution for IV infusion:

Add the contents of a 100, 250 or 500 mg ampule to 100 or 200 mL of sterile diluent such as Normal Saline or any of the compatible solutions listed below.

Adults: The solution is administered over a 30 to 60 minute period. The total daily dose should not exceed 15 mg/kg/day and may be given as a single dose or in 2 or 3 equally divided doses at equally divided intervals.

Children: The amount of fluid used will depend on the amount ordered for the patient. It should be a sufficient amount to infuse amikacin over a 30 to 60 minute period. Infants should receive a 1 to 2 hour infusion.

Inspect visually for particulate matter and discoloration prior to administration.

Do not premix amikacin with other drugs. It should be administered separately according to the recommended dose and route.

Discard unused portion after opening the ampule.

COMPATIBILITY, STORAGE AND STABILITY

Amikacin is stable in 24 hours at room temperature at concentrations of 0.25 and 5 mg/mL in the following solutions:

5% Dextrose Injection
5% Dextrose and 0.2 % Sodium Chloride Injection
5% Dextrose and 0.45% Sodium Chloride Injection
0.9% Sodium Chloride Injection
Lactated Ringer's Injection
Normosol M in 5% Dextrose Injection
Normosol R in 5% Dextrose Injection

Cutting Instruction: Without using any file,

- Hold the ampule body in an upright position with one hand.
- Place the right or left index finger on the one-color dot.
- Apply thumb pressure on the bulb opposite the one-color dot.
- Snap-break away from the body.

DISCARD UNUSED PORTION AFTER OPENING THE AMPULE

CONTRAINDICATIONS

- Known hypersensitivity to amikacin and other components of this product.
- History of hypersensitivity or toxic reactions to aminoglycosides.

WARNINGS AND PRECAUTIONS

This product contains metabisulfite which may cause allergic-type reactions including anaphylactic symptoms and life-threatening or less severe asthmatic episodes in certain susceptible people. The overall prevalence of sulfite sensitivity in the general population is unknown and probably low. Sulfite sensitivity is seen more frequently in asthmatic than in non-asthmatic people.

Safety for treatment periods longer than 14 days has not been established.

Patients treated with parenteral aminoglycosides should be under close clinical observation. Amikacin sulfate injection is potentially nephrotoxic, ototoxic and neurotoxic. Avoid concurrent use of other ototoxic or nephrotoxic agents because of the potential additive effects.

Patients with preexisting tinnitus, vertigo, subclinical high-frequency hearing loss, or renal impairment and patients who are receiving high doses and/or prolonged therapy with aminoglycosides or who have received prior ototoxic drugs are especially susceptible to ototoxicity and should be carefully observed for signs of eighth cranial nerve damage during aminoglycoside therapy.

Assess kidney function by the usual methods prior to starting therapy and daily during the course of treatment. If signs of renal irritation appear, increase hydration. A reduction in dosage may be recommended if other evidence or renal dysfunction occurs such as decreased creatinine clearance, decreased urine specific gravity, and increased BUN, creatinine or oliguria. Stop the treatment if azotemia increases or if a progressive decrease in urinary output occurs.

Amikacin should be used with caution in patients with neuromuscular disorders such as myasthenia gravis or parkinsonism since these drugs may aggravate muscle weakness because of their potential curare-like effect on the neuromuscular function.

Use of amikacin may result in overgrowth of nonsusceptible organisms. If this occurs, appropriate therapy should be instituted.

GENERAL

Prescribing amikacin in the absence of a proven or strongly suspected bacterial infection or a prophylactic indication is unlikely to provide benefit to the patients and increases the risk of the development of drug-resistant bacteria.

DRUG INTERACTIONS

- **Neurotoxic, Ototoxic or Nephrotoxic Drugs**

  Avoid concurrent and/or sequential use with other drugs with similar toxic potential (e.g., other aminoglycosides, acyclovir, amphotericin B, bacitracin, capreomycin, cephalosporins, colistin, cisplatin, methoxyflurane, polymyxin B, vancomycin), if possible. In addition, do not give amikacin concurrently with ethacrynic acid, furosemide, urea, or mannitol because of the possibility of an increased risk of ototoxicity due to additive effects of altered serum and tissue concentrations of the antibiotics. Keep in mind the possibility that dimenhydrinate and other anti-emetics may mask symptoms of vestibular ototoxicity.

- **General Anesthetics and Neuromuscular Blocking Agents**

  Concurrent use of an aminoglycoside with general anesthetics of neuromuscular blocking agents (e.g., succinylcholine, tubocurarine) may potentiate neuromuscular blockade and cause respiratory paralysis. Use with caution in patients receiving such agents and observe signs of respiratory depression.

- **Neomycin**

  Oral neomycin may potentiate the effects of oral anticoagulants. Monitor prothrombin times in patients receiving concomitant oral aminoglycoside and oral anticoagulant therapy and adjust the dose of the anticoagulant as required.

- **Anti-infective Agents**

  In vitro studies indicate that the antibacterial activity of aminoglycosides and beta-lactam antibiotics or vancomycin may be additive or synergistic against some organisms including enterococci and *P. aeruginosa*. *In vitro* studies also indicate that aminoglycosides and extended-spectrum penicillins also exert a synergistic bactericidal effect against *Enterobacteriaceae*.

STATEMENT ON USAGE FOR HIGH RISK GROUPS

Pregnancy: (Pregnancy Category D) Aminoglycosides can cause fetal harm when administered to pregnant women, but potential benefits from use of the drugs may be acceptable in certain conditions despite possible risks to the fetus. Aminoglycosides should be used during pregnancy only in life-threatening situations or severe infections for which safer drugs cannot be used or are ineffective.

Lactation: It is not known whether amikacin is excreted in human milk. Since many drugs are excreted in human milk and because of potential serious adverse reactions from amikacin in breastfeeding infants, a decision should be made whether to discontinue breastfeeding or to discontinue the drug, taking into account the importance of the drug to the mother.

Use in children: Use amikacin with caution and in reduced dose in premature and full-term neonates because of the renal immaturity of these patients and resulting prolongation of serum half-life of the drug.

Use in elderly: Special care is required when using amikacin in the elderly in whom renal function may be impaired, as old age appears to be an independent risk factor for ototoxicity and nephrotoxicity. Measure blood levels frequently and give the drug for no longer than is essential.

UNDESIRABLE EFFECTS

All aminoglycosides have the potential to induce auditory, vestibular, and renal toxicity and neuromuscular blockade. They occur more frequently in patients with present or past history of renal impairment, of treatment with other ototoxic or nephrotoxic drugs, and in patients treated for longer periods and/or with higher doses than recommended.

Neurotoxicity-ototoxicity: Toxic effects on the eighth cranial nerve can result in hearing loss, loss of balance or both. Amikacin primarily affects auditory function. Cochlear damage includes high frequency deafness and usually occurs before clinical hearing loss can be detected.

Neurotoxicity-Neuromuscular Blockage: Acute muscular paralysis and apnea can occur after treatment with aminoglycosides.

Nephrotoxicity: Elevated serum creatinine, albuminuria, presence of casts, red and white blood cells in the urine, azotemia, and oliguria have been reported. Renal function changes are usually reversible when the drug is discontinued.

Others: Rarely, skin rash, drug fever, headache, paresthesia, tremor, nausea and vomiting, eosinophilia, arthralgia, anemia, hypotension, and hypomagnesemia.

OVERDOSE AND MANAGEMENT

Peritoneal dialysis or hemodialysis will help in the removal of amikacin in blood. In the newborn infant, exchange transfusion may also be considered.

STORAGE CONDITION

Store at temperatures not exceeding 30°C.

AVAILABILITY

Amikacide 50 mg / mL Solution for Injection (100 mg in 2 mL Ampule) - Box of 5 ampules
FDA Registration Number: DR-XY17730; Date of First Authorization: 05 / 1997
Amikacide 125 mg / mL Solution for Injection (250 mg in 2 mL Ampule) - Box of 5 ampules
FDA Registration Number: DR-XY17729; Date of First Authorization: 06 / 1998
Amikacide 250 mg / mL Solution for Injection (500 mg in 2 mL Ampule) - Box of 5 ampules
FDA Registration Number: DR-XY17731; Date of First Authorization: 05 / 1997

For suspected adverse drug reaction, seek medical attention immediately and report to the FDA at www.fda.gov.ph. **AND** Unilab at (+632) 858-1000 or productsafety@unilab.com.ph. By reporting undesirable effects, you can help provide more information on the safety of this medicine.

CAUTION: Foods, Drugs, Devices, and Cosmetics Act prohibits dispensing without prescription.

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