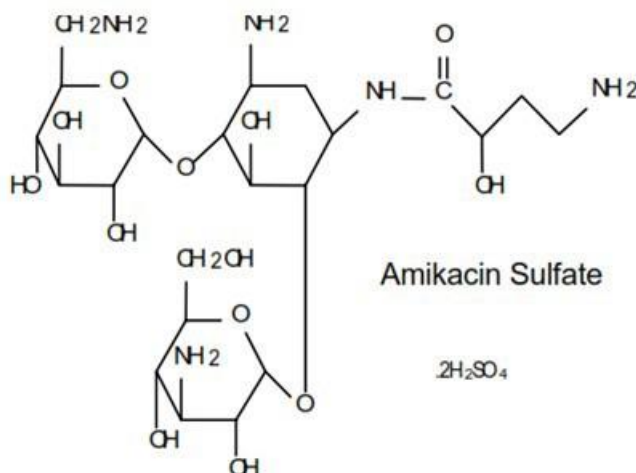


AMIKACIN WOCKHARDT™ SOLUTION FOR INJECTION OR INFUSION

NAME OF THE MEDICINE

Amikacin sulfate

The structural formula is shown below.



Molecular formula: C₂₂H₄₃N₅O₁₃·2H₂SO₄

Molecular weight: 781.8

CAS Registry No: 39831-55-5

DESCRIPTION

Amikacin is a semisynthetic aminoglycoside antibiotic derived from kanamycin. It is described chemically as 6-O-(3-Amino-3-deoxy-α-D-glucopyranosyl)-4-O-(6-amino-6-deoxy-α-D-glucopyranosyl)-1-N-[(2S)-4-amino-2-hydroxybutanoyl]-2-deoxy-D-streptamine sulfate

Amikacin sulfate is a white crystalline powder. It is freely soluble in water and practically insoluble in alcohol and acetone. 1.3 g of amikacin sulfate is approximately equivalent to 1 g of amikacin.

Amikacin Injection is a sterile clear, colourless solution of amikacin sulfate, sodium citrate and sodium metabisulfite in water for injections. Sulfuric acid is added to adjust pH to 4.5. Each mL contains amikacin sulfate equivalent to amikacin activity 250 mg (250,000 IU). Amikacin Injection is available in 500 mg/2 mL strength.

No antimicrobial preservative is added to the formulation. This product is for single use in one patient only. Discard any residue.

PHARMACOLOGY**Microbiology**

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

Gram-negative	MIC microgram/mL
<i>Pseudomonas species</i>	1.6 - 12.5
<i>Proteus species (indole-positive and indole negative)</i>	1.6 - 3.1
<i>Klebsiella pneumoniae</i>	1.6 - 3.1
<i>Enterobacter cloacae</i>	1.6 - 3.1
<i>Serratia species</i>	0.8 - 3.1
<i>Acinetobacter</i>	no information available
<i>Providencia stuartii</i>	3.1
<i>Citrobacter freundii</i>	1 - 8
<i>Escherichia coli</i>	1.6 - 3.1
Gram-positive	
<i>Staphylococcus species</i> (penicillinase and nonpenicillinase producing, including methicillin resistant strains)	0.4 - 5.0

Amikacin's structure has been altered to reduce the possible route of enzymatic deactivation, thus reducing bacterial resistance. Many strains of Gram-negative organisms resistant to gentamicin and tobramycin have shown to be sensitive to amikacin *in vitro*.

Susceptibility testing

The Kirby-Bauer test can determine the sensitivity of an organism to amikacin. This test operates on the principle that antibiotics will diffuse from a paper disc into an agar medium containing test organisms. Inhibition is observed as a failure of the organism to grow in the region of the antibiotic.

When the Kirby-Bauer method of disc susceptibility is used, a 30 microgram amikacin disc should give a zone of 17 mm or greater when tested against an amikacin susceptible bacterial strain. Such a result indicates that the infecting organism is likely to respond to therapy. A zone size of 14 mm or less indicates resistance, or that the infecting organism is unlikely to respond to therapy. Zone sizes of 15 to 16 mm indicate intermediate susceptibility, in other words the organism will probably be susceptible if the infection is confined to tissues and fluids (eg urine) in which high antibiotic levels are obtained.

Pharmacokinetics

Absorption

Following IM administration of a single dose of amikacin of 7.5 mg/kg in adults with normal renal function, peak plasma amikacin concentrations of 17 to 25 micrograms/mL are attained within 45 minutes to 2 hours.

Following IV infusion of the same dose given over 1 hour peak plasma concentrations of the drug average 38 micrograms/mL immediately following the infusion, 5.5 micrograms/mL at 4 hours, and 1.3 micrograms/mL at 8 hours.

Distribution

Following administration of usual dosages of amikacin, amikacin has been found in bone, heart, gallbladder, and lung tissue. Amikacin is also distributed into bile, sputum, bronchial secretions, and interstitial, pleural, and synovial fluids.

Excretion

The plasma elimination half-life of amikacin is usually 2 to 3 hours in adults with normal renal function and is reported to range from 30 to 86 hours in adults with severe renal impairment.

In adults with normal renal function, 94 to 98% of a single IM or IV dose of amikacin is excreted unchanged by glomerular filtration within 24 hours. The drug may be completely recovered within approximately 10 to 20 days in patients with normal renal function. Terminal elimination half-lives of greater than 100 hours have been reported in adults with normal renal function following repeated IM or IV administration of the drug.

In patients with impaired renal function, the clearance of amikacin is decreased; the more severe the impairment, the slower the clearance. Therefore, the interval between doses should be adjusted according to the degree of renal impairment. Endogenous creatinine clearance rate and serum creatinine which have high correlation with serum half-life of amikacin, may be used as a guide for this purpose (see **DOSAGE AND ADMINISTRATION - Impaired renal function**).

INDICATIONS

AMIKACIN WOCKHARDT is indicated in the short-term treatment of serious infections caused by susceptible strains of Gram-negative bacteria, (see **Microbiology**).

Staphylococcus aureus, including methicillin-resistant strains is the principal Gram-positive organism sensitive to amikacin.

The use of amikacin in the treatment of staphylococcal infections should be restricted to second-line therapy, and should be confined to patients suffering from severe infections caused by susceptible strains of staphylococcus who have failed to respond or are allergic to other available antibiotics.

AMIKACIN WOCKHARDT is indicated in the treatment of neonatal sepsis when sensitivity testing indicates that other aminoglycosides cannot be used.

In certain severe infections such as neonatal sepsis, concomitant therapy with a penicillin type drug may be indicated because of the possibility of infections due to Gram-positive organisms such as streptococci or pneumococci. If concomitant treatment with a penicillin type drug is indicated, then the drugs should be administered separately because *in-vitro* mixing of the two drugs causes inactivation of amikacin.

Clinical studies have shown amikacin to be effective in treating bacteraemia, septicaemia including neonatal sepsis and serious infections of the respiratory tract, bones and joints, central nervous system, skin and skin structures (including those resulting from burns), intra-abdominal organs, post-operative infections and complicated and recurrent urinary tract infections, when caused by susceptible organisms.

CONTRAINDICATIONS

Myasthenia gravis

Amikacin Injection is contraindicated in patients with a known history of hypersensitivity to amikacin, any constituents of the injection (see **DESCRIPTION**) or in patients who may have subclinical renal or eighth nerve damage induced by prior administration of nephrotoxic and/or ototoxic agents, as the toxicity may possibly be additive.

Pregnancy (see **Use in pregnancy**); Lactation (see **Use in lactation**).

PRECAUTIONS

Treatment with amikacin for more than 14 days has not been established as being safe. Patients undergoing treatment with parenteral aminoglycosides should be under close clinical observation and evaluation because of the potential ototoxicity and nephrotoxicity associated with their use.

1. **Cross allergenicity:**

Cross allergenicity among aminoglycosides has been demonstrated. Therefore, caution should be exercised in patients who have shown hypersensitivity to this class of drugs.

2. **Nephrotoxicity:**

As with other aminoglycosides, amikacin sulfate is potentially nephrotoxic and neurotoxic; therefore, precautions on dosage and adequate hydration should be observed. Renal function should be closely monitored in patients with known or suspected renal impairment (eg diminished glomerular filtration), and also in those whose renal function is initially normal but who develop signs of renal dysfunction during therapy.

Amikacin is present in high concentrations in the renal excretory system; therefore, patients should be well hydrated to minimize chemical irritation/damage of the renal tubules. Prior to initiating therapy, kidney function should be assessed by the usual methods and monitored periodically during the course of treatment.

Hydration should be increased upon signs of renal irritation (casts, white or red cells, or albumin). A reduction in dosage (see **DOSAGE in Impaired renal function**) may be desirable if other evidence of renal dysfunction occurs such as decreased creatinine clearance, decreased urine specific gravity, increased serum urea, increased serum creatinine or oliguria. If azotaemia or a progressive decrease in urinary output occurs, treatment should be stopped.

3. **Ototoxicity:**

In patients treated at higher doses or for periods longer than those recommended, ototoxicity, both auditory and vestibular can occur. Patients with renal damage have the highest risk of developing amikacin induced ototoxicity. The risk of hearing loss due to aminoglycosides increases with the degree of exposure to either high peak or high trough serum concentrations. As with other aminoglycosides, on rare occasions changes in renal and eighth cranial nerve function may not become manifest until soon after completion of therapy. Aminoglycoside induced ototoxicity is usually irreversible.

A pre-treatment audiogram should be obtained and repeated during therapy in patients with renal impairment undergoing treatment for seven days or more as well as in other patients being treated for 10 days. If tinnitus or subjective hearing loss develops; or if follow-up audiograms show significant loss of high frequency response, the use of amikacin sulfate therapy should be discontinued immediately. Lost function may not be fully restored.

4. Neurotoxicity:

Muscular paralysis and neuromuscular blockade have been demonstrated in the cat with high doses of amikacin (188 mg/kg). The possibility of respiratory paralysis and neuromuscular blockade should be considered when amikacin is administered concomitantly with neuromuscular blocking drugs or anaesthetics. If blockade occurs, calcium salts may reverse this phenomenon. Other manifestations of neurotoxicity may include numbness, skin tingling, muscle twitching and convulsions.

5. Monitoring of serum levels:

Whenever possible, and especially in patients with renal impairment, peak and trough serum concentrations of amikacin should be determined periodically, and dosage should be adjusted, to maintain desired serum concentrations. In general, desirable peak concentrations of amikacin are 15 to 30 micrograms/mL, and trough concentrations of the drug should not exceed 5 to 10 micrograms/mL. An increased risk of toxicity may be associated with prolonged peak amikacin serum concentrations greater than 30 to 35 micrograms/mL.

6. Concurrent use with other antibiotics or potent diuretics:

Since the risk of ototoxicity, irreversible deafness and nephrotoxicity is increased when amikacin is used in conjunction with the systemic or topical use of other potentially neurotoxic and/or nephrotoxic drugs, (see **Interactions with other medicines**), such therapy should be avoided. This includes concurrent use with potent diuretics and other aminoglycosides. Other factors which may increase the risk of toxicity are dehydration and advancing age.

7. Geriatric:

Because of its toxicity, amikacin should be used with caution in elderly patients only after less toxic alternatives have been considered and/or found ineffective. Elderly patients are more likely to have an age-related decrease in renal function. This may not be evident in the results of routine screening tests such as serum urea or serum creatinine. A creatinine clearance determination may be more useful. Recommended doses should not be exceeded, and the patient's renal function should be carefully monitored during therapy. Geriatric patients may require smaller daily doses of amikacin in accordance with their increased age, decreased renal function, and possibly, decreased weight. In addition, loss of hearing may result even in patients with normal renal function.

8. Paediatric:

The nephrotoxic and ototoxic potential of amikacin in newborn infants is not known. Until more safety reports are available, amikacin should be used in infants only in those specific circumstances where susceptibility testing indicated that other aminoglycosides cannot be used or are otherwise contraindicated, and when the infant can be observed for evidence of toxicity.

9. Patients with muscular disorders:

Amikacin must not be used in patients with myasthenia gravis. Aminoglycosides, including amikacin, should be used with caution in patients with muscular disorders such as parkinsonism, since these drugs may aggravate muscle weakness because of their potential curare-like effect on neuromuscular junction.

10. Superinfection:

If overgrowth of nonsusceptible organisms occurs, appropriate therapy should be initiated.

11. Sulfite-sensitivity:

Amikacin Injection contains sodium metabisulfite, which may cause allergic-type reactions, including anaphylactic symptoms and life threatening or less severe asthmatic episodes in susceptible people.

12. Topical use:

Aminoglycosides are quickly and almost totally absorbed when they are applied topically, except to the urinary bladder, in association with surgical procedures. Irreversible deafness, renal failure and death due to neuromuscular blockade have been reported following irrigation of both small and large surgical fields with an aminoglycoside preparation.

Use in pregnancy (Category D[†])

Gentamicin and other aminoglycosides cross the placenta. There is evidence of selective uptake of gentamicin by the foetal kidney resulting in damage (probably reversible) to immature nephrons. Eighth cranial nerve damage has also been reported following in-utero exposure to some of the aminoglycosides. Because of the chemical similarity, all aminoglycosides must be considered potentially nephrotoxic and ototoxic to the foetus. It should also be noted that therapeutic blood levels in the mother do not equate with safety for the foetus.

In reproduction toxicity studies in mice and rats, no effects on fertility or fetal toxicity were reported

Use in lactation

It is not known whether amikacin is excreted in breast milk. Since the possible harmful effect on the infant is not known, it is recommended that if nursing mothers must be given amikacin, the infants should not be breast fed during therapy.

Laboratory tests:

Laboratory abnormalities possibly related to aminoglycosides include: increased levels of serum transaminase (ALT, AST) serum LDH and bilirubin; decreased serum calcium, magnesium, sodium and potassium; anemia, leukopenia, granulocytopenia, transient agranulocytosis, eosinophilia, increased and decreased reticulocyte counts, and thrombocytopenia. While clinical laboratory test abnormalities may be isolated findings, they may also be associated with clinically related signs and symptoms. For example, tetany and muscle weakness may be associated with hypomagnesemia, hypocalcemia and hypokalemia.

INTERACTIONS WITH OTHER MEDICINES**Potent diuretics:**

If possible, do not give amikacin in conjunction with ethacrynic acid, frusemide or other potent diuretics which may themselves cause ototoxicity or enhance aminoglycoside toxicity by altering antibiotic concentrations in serum and tissue.

Other neurotoxic and/or nephrotoxic agents:

If possible, avoid concurrent or sequential use of other neurotoxic and/or nephrotoxic antibiotics, including other aminoglycosides, polymyxin B, colistin, cisplatin, vancomycin, amphotericin B, clindamycin and cephalosporins.

Anaesthetics/neuromuscular blocking agents or medications with neuromuscular blocking activity:

Concurrent use of amikacin with agents with neuromuscular blocking activity eg succinylcholine, tubocurarine, decamethonium, halogenated hydrocarbon inhalation anaesthetics, opioid analgesics and massive transfusions with citrated anticoagulated blood, should be carefully monitored; neuromuscular blockade may be enhanced, resulting in skeletal muscle weakness and respiratory depression or paralysis (apnea); caution is recommended when these medications and amikacin are used concurrently during surgery or in the postoperative period, especially if there is a possibility of incomplete reversal of neuromuscular blockade postoperatively; treatment with anticholinesterase agents or calcium salts may help to reverse the blockade.

Penicillins:

Aminoglycosides are inactivated by solutions containing penicillins. This inactivation is brought about by the opening of the beta-lactam ring and combination of the penicillin with an amino group of the aminoglycoside to form a biologically inactive amide. For this reason, amikacin and penicillins should

[†] Category D: Drugs which have caused, are suspected to have caused or may be caused or maybe expected to cause, an increased incidence of human foetal malformations or irreversible damage. These drugs may also have pharmacological effects.

not be combined in intravenous injections/infusions. The inactivation of some aminoglycosides by penicillins has been reported *in vivo*, especially in patients with renal failure who maintain a higher level of the penicillin for a longer period of time compared to patients with normal renal function. Therefore, when amikacin and penicillins are used together in patients with renal failure, the time of administration of each drug should be staggered so that several hours separate each infusion.

Compatibilities

Amikacin sulfate is stable for 24 hours at room temperature in the presence of light at 5 mg/mL and 0.25 mg/mL in 0.9% Sodium Chloride Intravenous Infusion BP and 5% Glucose Intravenous Infusion BP solutions.

Incompatibilities

Amikacin Injection may be prescribed as concurrent therapy with other antibacterial agents in mixed or superinfections. In such situations, Amikacin Injection should never be physically mixed with other antibacterial agents in infusion bags, syringes or any other container equipment. Each agent should be administered separately following the manufacturer’s recommended route.

ADVERSE EFFECTS

Amikacin induced hepatotoxicity is not a common side effect, however it may occur. Increased serum transaminases (ALT, AST) increased serum bilirubin, hepatomegaly, and hepatic necrosis have been reported.

The percentages below refer to incidence in clinical trials.

More common reactions:

Auditory and Vestibular:	Hearing loss (4%) (permanent in some cases) Hearing loss is usually manifested initially by diminution of high-tone acuity.
Biochemical abnormalities:	Increased serum urea, decreased creatinine clearance, elevated serum creatinine, azotaemia.
Genitourinary:	Reduced renal function, oliguria
Injection site reactions:	Pain at site of intramuscular injection(6%).

Less common reactions:

Auditory and Vestibular:	Tinnitus, vertigo, dizziness, nystagmus, changes in caloric testing or electronystagmograms.
Biochemical abnormalities:	Casts, cells or protein in the urine, eosinophilia, increase in AST.
Dermatological:	Pruritus, rash
Gastrointestinal:	Nausea, vomiting
General:	Drug fever
Genitourinary:	Renal failure
Haematological:	Anaemia
Musculoskeletal:	Arthralgia
Nervous system:	Paraesthesia, tremor

Serious or life-threatening reactions:

Serious adverse effects on both vestibular and auditory branches of the eighth cranial nerve have been reported, primarily in patients with renal impairment (especially if dialysis is required), and in patients on high doses and/or prolonged therapy. Other factors which may increase the risk of toxicity include excessive dosage, dehydration and previous exposure to ototoxic drugs.

Other reactions:

Other adverse effects reported with the use of aminoglycosides include: respiratory depression, lethargy, confusion, depression, visual disturbances, decreased appetite, weight loss, anorexia, hypotension and hypertension, urticaria, generalised burning, laryngeal edema, anaphylactoid reactions, headache, increased salivation, stomatitis, purpura, pseudotumor cerebri, acute organic brain syndrome, pulmonary fibrosis, alopecia, joint pain, transient hepatomegaly, splenomegaly, convulsions and a myasthenia gravis-like syndrome.

DOSAGE AND ADMINISTRATION

Amikacin Injection is for use in one patient on one occasion only. Discard any residue.

Uncomplicated infections due to sensitive organisms should respond to treatment within 24 to 48 hours at the recommended dosage. If no improvement occurs within three to five days, the use of amikacin sulfate should be re-evaluated and consideration be given to alternative therapy. Failure of the infection to respond may be due to resistance of the organism or to the presence of septic foci requiring surgical drainage.

Whenever possible, and especially in patients with impaired renal function, peak and trough amikacin serum concentrations should be determined and dosage adjusted where necessary to maintain desired serum concentrations. In general, desired peak concentrations are between 15 to 30 micrograms/mL, and trough concentrations should not exceed 5 to 10 micrograms/mL. An increased risk of toxicity may be associated with prolonged peak amikacin serum concentrations greater than 30 to 35 micrograms/mL.

Intramuscular or intravenous administration

The intramuscular route is preferred for most infections, but in life-threatening infections or when an intramuscular injection is not feasible, an intravenous infusion (0.25% over 30 to 60 minutes) may be used.

The compatible diluents for intravenous use if required are as follows: 5% Glucose Intravenous Infusion BP in Water for Injections BP and Sodium Chloride Intravenous Infusion BP (0.9%). To reduce microbiological hazard, use as soon as practicable after dilution. Refer to **PRESENTATION AND STORAGE CONDITIONS** for storage instructions

Dosage

Dosage of amikacin sulfate is expressed in terms of amikacin and calculated on a body weight basis. Dosage is identical for both routes of administration.

Adults and children:

The usual recommended dose of amikacin is 15mg/kg daily given in two or three equally divided doses.

Neonates and premature infants:

Dosage given for patients with normal renal function. Initiate treatment with a loading dose of 10 mg/kg followed by 7.5 mg/kg every 12 hours. The maximum total daily dose should not exceed 15 mg/kg. Solution infusions via the IV route should be given over a 1 to 2 hour period.

Insufficient clinical use has not enabled firm dosage guidelines to be established for the use of amikacin in premature infants.

Elderly:

Amikacin is excreted by the renal route. Since renal function could be failing in the elderly, it should be assessed whenever possible and the dosage adjusted accordingly, if necessary. Refer to "**Impaired renal function**" of dosage description.

Urinary tract infections (other than pseudomonal infections):

500 mg/day in two equally divided doses is recommended.

Impaired renal function:

In patients with impaired renal function, either the dose or the dosage interval needs to be adjusted to avoid accumulation. The dosage interval may be calculated using the following formula:

Serum creatinine concentration (mmol / L) x 101.8 = dosage interval (hours)

This formula should not be used to calculate the dosage interval for elderly patients. Instead, it is advisable to base dosage on creatinine clearance.

Serum Creatinine Concentration (mmol / L)		Interval between doses of 7.5 mg/kg (hours)
0.12		12
0.15		15
0.20		20
0.25		25.5
0.30	x 101.8 =	30.5
0.35		35.5
0.40		40.5
0.45		46
0.50		51
0.55		56
0.60		61

As renal function may alter appreciably during therapy, the serum creatinine should be checked frequently and the dosage regimen modified accordingly.

If it is desired to administer amikacin at a fixed time interval, the dosage must be reduced. It is recommended that the drug be given every 12 hours. Serum concentrations of the drug should be measured in these patients to ensure accurate administration and to avoid toxic serum levels.

If serum assay determinations are not available and the patient's condition is stable, serum creatinine and creatinine clearance values are the most readily available indicators of the degree of renal impairment to use in determining the dosage.

First, begin therapy by administering 7.5 mg/kg, which is half the normal daily dose. To determine the size of maintenance doses administered every 12 hours, the initial dose should be reduced in proportion to the reduction in the patient's creatinine clearance rate (cc):

Maintenance dose every 12 hours	$\frac{\text{Observed cc in ml/min}}{\text{normal cc in mL/min}}$	Calculated initial dose in 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 normally recommended dose by the patient's serum creatinine.

The above dosage schedules are provided as guides to dosage when the measurement of amikacin serum levels is not feasible and are not intended to be rigid recommendations.

OVERDOSAGE

Management

In the event of overdosage or toxic reactions peritoneal dialysis or haemodialysis should be considered. These procedures are of particular importance in patients with impaired renal function. In the newborn infant, exchange transfusion may also be considered.

Clinical features

Likely signs and symptoms include tinnitus, vertigo, reversible or irreversible deafness, skin rash, drug fever, headache, paraesthesia, reduced renal function or renal failure.

In the case of overdose, immediately contact the Poisons Information Centre for advice (In Australia, call 13 11 26).

PRESENTATION AND STORAGE CONDITIONS

Strength	Pack Size
500 mg (500,000 IU)/2 mL	1 x 2 mL clear, type I, glass vials with rubber stopper and aluminium seal in carton with product information leaflet.

AUST R 288798

Unopened vial: Store below 25°C.

Opened/Diluted vial: To reduce microbiological hazard, use as soon as practicable after dilution. If storage is necessary, hold at 25°C for not more than 6 hours.

NAME AND ADDRESS OF THE SPONSOR

Wockhardt Bio Pty Ltd,
Suite 103,
39 East Esplanade
Manly NSW 2095
Australia

POISON SCHEDULE OF THE MEDICINE

Schedule 4 (Prescription Only Medicine)

DATE OF FIRST INCLUSION IN THE AUSTRALIAN REGISTER IF THERAPEUTIC GOODS (THE ARTG)

14 February 2018