For the use of a Registered Medical Practitioner or a Hospital or a Laboratory only.

℞ Amikacin Sulphate Injection IP 250 mg/2 ml

Amlek* 250

FOR I.M./I.V. USE ONLY

WARNINGS

Patients treated with parenteral aminoglycosides should be under close clinical observation because of the potential ototoxicity and nephrotoxicity associated with their use. Safety for treatment periods that are longer than 14 days has not been established.
Neurotoxicity, manifested as vestibular and permanent bilateral auditory ototoxicity, can occur in patients with pre-existing renal damage and in patients with normal renal function treated at higher doses and/or for periods longer than those recommended. The risk of aminoglycoside-induced ototoxicity is greater in patients with renal damage. High-frequency deafness usually occurs first and can be detected only by audiometric testing. Vertigo may occur and may be evidence of vestibular injury. Other manifestations of neurotoxicity may include numbness, skin tingling, muscle twitching, and convulsions. The risk of hearing loss due to aminoglycoside increases with the degree of exposure to either high peak or high trough serum concentrations. Patients developing cochlear damage may not have symptoms during therapy to warn them of developing eighth-nerve toxicity, and total or partial irreversible bilateral deafness may occur after the drug has been discontinued. Aminoglycoside-induced ototoxicity is usually irreversible.
Aminoglycoside are potentially nephrotoxic. The risk of nephrotoxiciy is greater in patients with impaired renal function and in those who receive high doses or prolonged therapy.
Neuromuscular blockade and respiratory paralysis have been reported following parenteral injection, topical instillation (as in orthopedic and abdominal irrigation or in local treatment of empyema), and following oral use of aminoglycosides. The possibility of these phenomena should be considered if aminoglycosides are administered by any route, especially in patients receiving anesthetics; neuromuscular-blocking agents such as tubocurarine, succinylcholine, or decamethonium; or in patients receiving massive transfusions of citrate-anticoagulated blood. If blockage occurs, calcium salts may reverse these phenomena, but mechanical respiratory assistance may be necessary.
Renal and eighth-nerve function should be closely monitored, especially in patients with known or suspected renal impairment at the onset of therapy and also in those whose renal function is initially normal but who develop signs of renal dysfunction during therapy. Serum concentrations of amikacin should be monitored when feasible to assure adequate levels and to avoid potentially toxic levels and prolonged peak concentrations above 35 micrograms per mL. Urine should be examined for decreased specific gravity, increased excretion of proteins, and the presence of cells or casts. Blood urea nitrogen (BUN), serum creatinine or creatinine clearance should be measured periodically. Serial audiograms should be obtained where feasible in patients old enough to be tested, particularly high-risk patients. Evidence of ototoxicity (dizziness, vertigo, tinnitus, roaring in the ears, and hearing loss) or nephrotoxicity requires discontinuation of the drug or dosage adjustment.
Concurrent and/or sequential systemic, oral or topical use of other neurotoxic or nephrotoxic products, particularly bacitracin, cisplatin, amphotericin B, cephaloridine, paromomycin, viomycin, polymyxin B, colistin, vancomycin or other aminoglycosides, should be avoided. Other factors that may increase risk of toxicity are advanced age and dehydration.
The concurrent use of amikacin with potent diuretics (ethacrynic acid or furosemide) should be avoided since diuretics by themselves may cause ototoxicity. In addition, when administered intravenously, diuretics may enhance aminoglycoside toxicity by altering the antibiotic concentrations in serum and tissue.

GENERIC NAME
Amikacin Sulphate Injection IP

COMPOSITION
Each 2ml contains:
Amikacin Sulphate IP
equivalent to Amikacin ..... 250 mg
Methyl Paraben IP 0.08%w/v
(As preservative)
Propyl Paraben IP 0.02%w/v
(As preservative)
Water for Injections IP ..... q.s.

DOSAGE FORM
Injection

INDICATIONS
Indicated in the treatment of serious infections due to amikacin sensitive organisms.

DOSAGE AND METHOD OF ADMINISTRATION
Amikacin Sulphate injection may be given intramuscularly or intravenously.

The patient's pre-treatment body weight should be obtained for calculation of correct dosage.

The status of renal function should beestimated by measurement of the serum creatinine concentration or calculation of the endogenous creatinine clearance rate. The BUN test is much less reliable for this purpose. Reassessment of renal function should be made periodically during therapy.

Whenever possible, amikacin concentrations in serum should be measured to assure adequate but not excessive levels. It is desirable to measure both peak and trough serum concentrations intermittently during therapy. Peak concentrations (30 to 90 minutes after injection) above 35 µg per mL and trough concentrations (just prior to the next dose) above 10 µg per mL should be avoided. Dosage should be adjusted as indicated.In patients with normal renal function, once-daily dosing may be used; peak concentrations in these cases may exceed 35 mcg/ml.

Intramuscular and intravenous administration
At the recommended dosage level, uncomplicated infections due to sensitive organisms should respond to therapy within 24 to 48 hours.

If clinical response does not occur within three to five days, consideration should be given to alternative therapy.

Intramuscular Administration for Patients with Normal Renal Function
The recommended dosage for adults, children and older infants with normal renal function is 15 mg/kg/day divided into two or three equal doses administered at equally divided intervals, i.e., 7.5 mg/kg q12h or 5 mg/kg q8h. Treatment of patients in the heavier weight classes should not exceed 1.5 g/day.

When amikacin is indicated in newborns, it is recommended that a loading dose of 10 mg/kg be administered initially to be followed with 7.5 mg/kg every 12 hours.

The usual duration of treatment is 7 to 10 days. It is desirable to limit the duration of treatment to the short term whenever feasible. The total daily dose by all routes of administration should not exceed 15 mg/kg/day. In difficult and complicated infections where treatment beyond 10 days is considered, the use of amikacin should be re-evaluated. If continued, amikacin serum levels and renal, auditory and vestibular functions should be monitored. At the recommended dosage level, uncomplicated infections due to amikacin-sensitive organisms should respond in 24 to 48 hours. If definite clinical response does not occur within 3 to 5 days, therapy should be stopped and the antibiotic susceptibility pattern of the invading organism should be rechecked.

Failure of the infection to respond may be due to resistance of the organism or to the presence of septic foci requiring surgical drainage. When amikacin is indicated in uncomplicated urinary tract infections, a dose of 250 mg twice daily may be used.

DOSAGE GUIDELINES				
ADULTS AND CHILDREN WITH NORMAL RENAL FUNCTION				
Patient Weight		Dosage		
lbs	kg	7.5 mg/kg		5 mg/kg
		q12h		q8h
99	45	337.5 mg		225 mg
110	50	375 mg		250 mg
121	55	412.5 mg		275 mg
132	60	450 mg		300 mg
143	65	487.5 mg	OR	325 mg
154	70	525 mg		350 mg
165	75	562.5 mg		375 mg
176	80	600 mg		400 mg
187	85	637.5 mg		425 mg
198	90	675 mg		450 mg
209	95	712.5 mg		475 mg
220	100	750 mg		500 mg

Intramuscular Administration for Patients with Impaired Renal Function
Whenever possible, serum amikacin concentrations should be monitored by appropriate assay procedures. Doses may be adjusted in patients with impaired renal function either by administering normal doses at prolonged intervals or by administering reduced doses at a fixed interval.

Both methods are based on the patient's creatinine clearance or serum creatinine values since these have been found to correlate with aminoglycoside half-lives in patients with diminished renal function. These dosage schedules must be used in conjunction with careful clinical and laboratory observations of the patient and should be modified as necessary. Neither method should be used when dialysis is being performed.

Normal Dosage at Prolonged Intervals

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

Reduced Dosage at Fixed Time Intervals

When renal function is impaired and it is desirable to administer amikacin at a fixed time interval, dosage must be reduced. In these patients, serum amikacin concentrations should be measured to assure accurate administration of amikacin and to avoid concentrations above 35 mcg/mL. 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 as a guide for dosage.

First, initiate therapy by administering a normal dose of 7.5 mg/kg, as a loading dose. This loading dose is the same as the normally recommended dose that would be calculated for a patient with normal renal function as described above.

To determine the size of maintenance doses administered every 12 hours, the loading dose should be reduced in proportion to the reduction in the patient's creatinine clearance rate:

$$\text{Maintenance dose every 12 hours} = \frac{\text{(observed CrCl in mL/min x calculated loading dose in mg.)}}{\text{Normal CrCl in mL/min}}$$

(CrCl = creatinine clearance rate)

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 not intended to be rigid recommendations, but are provided as guides to dosage when the measurement of amikacin serum levels is not feasible.

Intravenous Administration

The solution is administered to adults over a 30 to 60 minute period.The total daily dose should not exceed 15 mg/kg/day and may be divided into either two or three equally divided doses at equally-divided intervals.The solution for intravenous use is prepared by adding the contents of a 500 mg vial to 100 or 200 mL of sterile diluent such as 0.9% Sodium Chloride Injection or 5% Dextrose Injection, or any other compatible solution.

CONTRAINDICATIONS
Amikacin sulphate injection is contraindicated in patients with known allergy to amikacin or any component of the formulation.
A history of hypersensitivity or serious toxic reactions to aminoglycosides may contraindicate the use of any aminoglycoside because of the known cross sensitivities of patients to drugs in this class.
Aminoglycosides may impair neuromuscular transmission, and should not be given to patients with myasthenia gravis.

WARNINGS & PRECAUTIONS
Please refer the WARNINGS box given earlier.
Aminoglycosides can cause fetal harm when administered to a pregnant woman. Aminoglycosides cross the placenta and there have been several reports of total irreversible, bilateral congenital deafness in children whose mothers received streptomycin during pregnancy. Although serious side effects to the fetus or newborns have not been reported in the treatment of pregnant women with other aminoglycosides, the potential for harm exists. Reproduction studies of amikacin have been performed in rats and mice and revealed no evidence of impaired fertility or harm to the fetus due to amikacin. There are no well-controlled studies in pregnant women, but investigational experience does not include any positive evidence of adverse effects to the fetus. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus.

Clostridium difficile-associated diarrhea (CDAD) has been reported with the use of nearly all antibacterial agents, including amikacin, and may range in severity from mild diarrhea to fatal colitis. Treatment with antibacterial agents alters the normal flora of the colon, leading to the overgrowth of *C. difficile*.

C. difficile produces toxins A and B, which contribute to the development of CDAD. Hypertoxin-producing strains of *C. difficile* cause increased morbidity and mortality, as these infections can be refractory to antimicrobial therapy and may require a colectomy. CDAD must be considered in all patients who present with diarrhea following antibacterial use. Careful medical history is necessary since CDAD has been reported to occur over 2 months after the administration of antibacterial agents.

If CDAD is suspected or confirmed, ongoing antibiotic use not directed against *C. difficile* may need to be discontinued. Appropriate fluid and electrolyte management, protein supplementation, antibiotic treatment of *C. difficile*, and surgical evaluation should be instituted as clinically indicated.

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

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.

Amikacin sulphate injection is potentially nephrotoxic, ototoxic and neurotoxic. The concurrent or serial use of other ototoxic or nephrotoxic agents should be avoided either systemically or topically because of the potential for additive effects. Increased nephrotoxicity has been reported following concomitant parenteral administration of aminoglycosides, antibiotics and cephalosporins.

Concomitant cephalosporins may spuriously elevate creatinine determinations. Since amikacin is present in high concentrations in the renal excretory system, patients should be well-hydrated to minimize chemical irritation of the renal tubules. Kidney function should be assessed by the usual methods prior to starting therapy and daily during the course of treatment.

If signs of renal irritation appear (casts, white or red cells or albumin), hydration should be increased. A reduction in dosage may be desirable if other evidence of renal dysfunction occurs such as decreased ClCr; decreased urine specific gravity; increased BUN, creatinine, or oliguria. If azotemia increases or if a progressive decrease in urinary output occurs, treatment should be stopped.

Note: When patients are well hydrated and kidney function is normal, the risk of nephrotoxic reactions with amikacin is low if the dosage recommendations are not exceeded.

Elderly patients may have reduced renal function, which may not be evident in routine screening tests such as BUN or serum creatinine. A ClCr determination may be more useful. Monitoring of renal function during treatment with aminoglycosides is particularly important. Aminoglycosides should be used with caution in patients with muscular disorders such as myasthenia gravis or Parkinsonism since these drugs may aggravate muscle weakness because of their potential curare-like effect on the neuromuscular junction.

In vitro mixing of aminoglycosides with beta-lactam antibiotics (penicillin or cephalosporins) may result in a significant mutual inactivation. A reduction in serum half-life or serum level may occur when an aminoglycoside or penicillin-type drug is administered by separate routes. Inactivation of the aminoglycoside is clinically significant only in patients with severely impaired renal function.

Inactivation may continue in specimens of body fluids collected for assay, resulting in inaccurate aminoglycoside readings. Such specimens should be properly handled (assayed promptly, frozen or treated with beta-lactamase).

Cross-allergenicity among aminoglycosides has been demonstrated.
As with other antibiotics, the use of amikacin may result in overgrowth of non-susceptible organisms. If this occurs, appropriate therapy should be instituted.
Aminoglycosides should not be given concurrently with potent diuretics.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit.

Excipient with known effect
This product contains sodium metabisulfite, a sulfite that 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 non-asthmatic people.

DRUG INTERACTIONS
The concurrent or serial use of other neurotoxic, ototoxic or nephrotoxic agents, particularly bacitracin, cisplatin, amphotericin B, ciclosporin, tacrolimus, cephaloridine, paromomycin, viomycin, polymyxin B, colistin, vancomycin, or other aminoglycosides should be avoided either systemically or topically because of the potential for additive effects. Where this is not possible, monitor carefully.
Increased nephrotoxicity has been reported following concomitant parenteral administration of aminoglycoside antibiotics and cephalosporins. Concomitant cephalosporin use may spuriously elevate creatinine serum level determinations.
The concurrent use of amikacin sulphate injection with potent diuretics (ethacrynic acid or furosemide) should be avoided since diuretics by themselves may cause ototoxicity. In addition, when administered intravenously, diuretics may enhance aminoglycoside toxicity by altering antibiotic concentrations in serum and tissue.
In Vitro admixture of aminoglycosides with beta-lactam antibiotics (penicillin's or cephalosporins) may result in significant mutual inactivation. A reduction in serum activity may also occur when an aminoglycoside or penicillin-type drug is administered in vivo by separate routes. Inactivation of the aminoglycoside is clinically significant only in patients with severely impaired renal function. Inactivation may continue in specimens of body fluids collected for assay, resulting in inaccurate aminoglycoside readings. Such specimens should be properly handled (assayed promptly, frozen, or treated with beta-lactamase).
There is an increased risk of hypocalcaemia when aminoglycosides are administered with bisphosphonates.
There is an increased risk of nephrotoxicity and possibly of ototoxicity when aminoglycosides are administered with platinum compounds.
Concomitantly administered thiamine (vitamin B1) may be destroyed by the reactive sodium bisulfite component of the amikacin sulphate formulation.
The intraperitoneal use of amikacin is not recommended in patients under the influence of anaesthetics or muscle-relaxing drugs (including ether, halothane, d-tubocurarine, succinylcholine and decamethonium) as neuromuscular blockade and consequent respiratory depression may occur.
Indomethacin may increase the plasma concentration of amikacin in neonates.

USE IN SPECIAL POPULATIONS
Pregnancy and Lactation
Amikacin should be administered to pregnant women and neonatal infants only when clearly needed and under medical supervision.
It is not known whether amikacin is excreted in human milk. A decision should be made whether to discontinue breast-feeding or to discontinue therapy.

UNDESIRABLE EFFECTS
This list is presented by system organ class, MedDRA preferred term, and frequency using the following frequency categories: very common (≥1/10), common (≥1/100, < 1/10), uncommon (≥1/1000, < 1/100), rare (≥1/10000, < 1/1000), very rare (<1/10000) and not known (cannot be estimated from the available data).

System Organ Class	Frequency	MedDRA Term
Infections and Infestations	Uncommon	Superinfections or colonisation with resistant bacteria or yeast
Blood and lymphatic system disorders	Rare	Anaemia, eosinophilia
Immune system disorders	Not known	Anaphylactic response (anaphylactic reaction, anaphylactic shock and anaphylactoid reaction), hypersensitivity
Metabolism and nutrition disorders	Rare	Hypomagnesaemia
Nervous system disorders	Not known	Paralysis
	Rare	Tremor, paresthesia, headache, balance disorder
Eye disorders	Rare	Blindness, retinal infarction
Ear and labyrinth Disorders	Rare	Tinnitus, hypoacusis
	Not known	Deafness, deafness neurosensory
Vascular disorders	Rare	Hypotension
Respiratory, thoracic and mediastinal disorders	Not known	Apnoea, bronchopasm
Gastrointestinal disorders	Uncommon	Nausea, vomiting
Skin and subcutaneous tissue disorders	Uncommon	Rash
	Rare	Pruritus, urticaria
Musculoskeletal, connective tissue and bone disorders	Rare	Arthralgia, muscle twitching
Renal and urinary disorders	Not known	Renal failure acute, nephropathy toxic, cells in urine
	Rare	Oliguria, blood creatinine increased, albuminuria, azotemia, red blood cells urine, white blood cells urine
General disorders and administration site conditions	Rare	Pyrexia

All aminoglycosides have the potential to induce ototoxicity, renal toxicity, and neuromuscular blockade. These toxicities occur more frequently in patients with renal impairment, in patients treated with other ototoxic or nephrotoxic drugs, and in patients treated for longer periods and/or with higher doses than recommended.
Renal function changes are usually reversible when the drug is discontinued.
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 by audiometric testing.
Macular infarction sometimes leading to permanent loss of vision has been reported following intravitreous administration (injection into the eye) of amikacin.
When the recommended precautions and dosages are followed the incidence of toxic reactions, such as tinnitus, vertigo, and partial reversible deafness, skin rash, drug fever, headache, paraesthesia, nausea and vomiting is low. Urinary signs of renal irritation (albumin, casts, and red or white cells), azotaemia and oliguria have been reported although they are rare.
Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Kindly report any suspected adverse reactions to pharmavigil@jbpharma.com.

OVERDOSE
In case of overdosage there is a general risk for nephro-, oto- and neurotoxic (neuromuscular blockage) reactions. Neuromuscular blockage with respiratory arrest needs appropriate treatment including application of ionic calcium (e.g. as gluconat or lactobionat in 10-20% solution). In the event of overdosage or toxic reaction, peritoneal dialysis or haemodialysis will aid in the removal of amikacin from the blood. Amikacin levels are also reduced during continuous arteriovenous hemofiltration. In the newborn infant, exchange transfusion may also be considered.

PHARMACODYNAMIC AND PHARMACOKINETIC PROPERTIES
Pharmacodynamics
Amikacin is a semi-synthetic aminoglycoside antibiotic derived from Kanamycin A. It is active against a broad spectrum of Gram-negative organisms, including *pseudomonas*, *Escherichia coli* and some Gram-positive organisms, e.g. *Staphylococcus aureus.*
Aminoglycoside antibiotics are bactericidal in action. Although the exact mechanism of action has not been fully elucidated, the drugs appear to inhibit protein synthesis in susceptible bacteria by irreversibly binding to 30S ribosomal subunits.

Pharmacokinetic properties
Amikacin is rapidly absorbed after intramuscular injection. Peak plasma concentrations equivalent to about 20 mg/ml are achieved one hour after IM doses of 500 mg, reducing to about 2 µg/ml 10 hours after injections.
Twenty per cent or less is bound to serum protein and serum concentrations remain in the bactericidal range for sensitive organisms for 10 to 12 hours.
Single doses of 500 mg administered as an intravenous infusion over a period of 30 minutes produce a mean peak serum concentration of 38 µg/ml. Repeated infusions do not produce drug accumulation in adults with normal renal function. However, decreased renal function will lead to accumulation.
In adults with normal renal function the plasma elimination half-life of amikacin is usually 2-3 hours. 94 - 98% of a single IM or IV dose of amikacin is excreted unchanged by glomerular filtration within 24 hours. Urine concentrations of amikacin average 563 µg/ml in the first 6 hours following a single 250 mg IM dose and 163 µg/ml over 6-12 hours. Following a single 500 mg IM dose urine concentrations average 832 µg/ml in adults with normal renal function.
Amikacin diffuses readily through extracellular fluids and is excreted in the urine unchanged, primarily by glomerular filtration. It has been found in pleural fluid, amniotic fluid and in the peritoneal cavity following parenteral administration.

INCOMPATIBILITIES
Amikacin is incompatible with some penicillin's and cephalosporins, amphotericin chlorothiazide sodium, erythromycin gluceptate, heparin, nitrofurantoin sodium, phenytoin sodium, thiopentone sodium and warfarin sodium, and depending on the composition and strength of the vehicle, tetracyclines, vitamins of the B group with vitamin C, and potassium chloride.
At times, amikacin may be indicated as concurrent therapy with other antibacterial agents in mixed or superinfections. In such instances, amikacin should not be physically mixed with other antibacterial agents in syringes, infusion bottles or any other equipment. Each agent should be administered separately.

PACKAGING INFORMATION
Vial of 2ml

STORAGE AND HANDLING INSTRUCTIONS
Store in a cool place. Protect from light. Do not freeze.

Marketed by:
J. B. CHEMICALS & PHARMACEUTICALS LTD.
Neelam Centre, 'B' Wing, Hind Cycle Road, Worli, Mumbai - 400 030, India.
* Trade Mark under Registration

Note: This prescribing information is applicable for India Market only

DATE: January 2025.