



For Healthcare Professionals Only

Amkay[®] IM / IV Injection

(Amikacin Sulfate)

ایمکے انجکشن
(امیکاسین سلفیٹ)

BOXED 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 which are longer than 14 days has not been established.

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.

Aminoglycosides are potentially nephrotoxic. The risk of nephrotoxicity is greater in patients with impaired renal function and in those who receive high doses or prolonged therapy.

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. 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. Aminoglycoside-induced ototoxicity is usually irreversible.

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). Evidence of ototoxicity or nephrotoxicity requires discontinuation of the drug or dosage adjustment.

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.

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 antibiotic concentrations in serum and tissue.

QUALITATIVE AND QUANTITATIVE COMPOSITION

Amkay 25mg/mL Injection

Each ampoule contains:
Amikacin Sulfate USP eq. to Amikacin 25mg
(Product Specs: USP)

Amkay 50mg/mL Injection

Each ampoule contains:
Amikacin Sulfate USP eq. to Amikacin 50mg
(Product Specs: USP)

Amkay 100mg/2mL Injection

Each ampoule contains:
Amikacin Sulfate USP eq. to Amikacin 100mg
(Product Specs: USP)

Amkay 250mg/2mL Injection

Each ampoule contains:
Amikacin Sulfate USP eq. to Amikacin 250mg
(Product Specs: USP)

Amkay 500mg/2mL Injection

Each ampoule contains:
Amikacin Sulfate USP eq. to Amikacin 500mg
(Product Specs: USP)

PHARMACEUTICAL FORM

Solution for Injection.

CLINICAL PARTICULARS

Therapeutic indications

Amkay Injection is a semi-synthetic, aminoglycoside antibiotic which is active against a broad spectrum of Gram-negative organisms, including pseudomonas and some Gram-positive organisms.

Sensitive Gram-negative organisms include; *Pseudomonas aeruginosa*, *Escherichia coli*, indole-positive and indole-negative *Proteus spp.*, *Klebsiella*, *Enterobacter* and *Serratia spp.*, *Minea-Herrae*, *Citrobacter freundii*, *Salmonella*, *Shigella*, *Acinetobacter* and *Providencia spp.*

Many strains of these Gram-negative organisms resistant to gentamicin and tobramycin show sensitivity to amikacin in vitro. The principal Gram-positive organism sensitive to amikacin is *Staphylococcus aureus*, including some methicillin-resistant strains.

Amkay has some activity against other Gram-positive organisms including certain strains of *Streptococcus pyogenes*, *Enterococci* and *Diplococcus pneumoniae*.

Amikacin is indicated in the short-term treatment of serious infections due to susceptible strains of Gram-negative bacteria, including *Pseudomonas species*. Although amkay is not the drug of choice for infections due to staphylococci, at times it may be indicated for the treatment of known or suspected staphylococcal disease. These situations include: the initiation of therapy for severe infections when the organisms suspected are either Gram-negative or staphylococci, patients allergic to other antibiotics, and mixed staphylococcal/Gram-negative infections.

Therapy with amikacin may be instituted prior to obtaining the results of sensitivity testing. Surgical procedures should be performed where indicated.

Posology and method of administration

Amkay Injection may be given intramuscularly or intravenously.

Amkay should not be physically premixed with other drugs, but should be administered separately according to the recommended dose and route.

The patient's pre-treatment body weight should be obtained for calculation of correct dosage. The status of renal function should be estimated by measurement of the serum creatinine concentration or calculation of the endogenous creatinine clearance rate.

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 (30-90 minutes after injection) above 35mcg/mL and trough concentrations (just prior to the next dose) above 10mcg/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 35mcg/mL.

For most infections the intramuscular route is preferred, but in life-threatening infections, or in patients in whom intramuscular injection is not feasible, the intravenous route, either slow bolus (2 to 3 minutes) or infusion (0.25% over 30 minutes) may be used.

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.

If required, suitable diluents for intravenous use are: Normal saline, 5% dextrose in water.

Once the product has been diluted the solution must be used as soon as possible and not stored.

Adults and Children over 12 years

The recommended intramuscular or intravenous dosage for adults and adolescents with normal renal function (creatinine clearance ≥ 50 mL/min) is 15 mg/kg/day which may be administered as a single daily dose or divided into 2 equal doses i.e., 7.5 mg/kg q 12h. The total daily dose should not exceed 1.5g.

In endocarditis and in febrile neutropenic patients, dosing should be twice daily, as there is not enough data to support once daily dosing.

Children 4 weeks to 12 years

The recommended intramuscular or intravenous (slow intravenous infusion) dose in children with normal renal function is 15-20 mg/kg/day which may be administered as 15-20 mg/kg, once a day; or as 7.5 mg/kg q 12 h.

In endocarditis and in febrile neutropenic patients dosing should be twice daily.

Neonates: An initial loading dose of 10 mg/kg followed by 7.5 mg/kg q 12h.

Premature Infants: The recommended dose in pre-matures is 7.5 mg/kg in every 12 hours. The usual duration of treatment is 7 to 10 days. The total daily dose by all routes of administration should not exceed 15-20 mg/kg/day. In difficult and complicated infections where treatment beyond 10 days is considered, the use of amikacin injection should be re-evaluated and, if continued, renal, auditory, vestibular function should be monitored, as well as serum amikacin levels.

Specific recommendation for intravenous administration:

In pediatric patients the number of diluents used will depend on the amount of amikacin tolerated by the patient. The solution should normally be infused in adults over a 30-to-60-minute period. Infants should receive a 1-to-2-hour infusion.

Elderly:

Amikacin is excreted by the renal route; renal function should be assessed whenever possible and dosage adjusted as described under impaired renal function.

Life-threatening infections and/or those caused by pseudomonas:

The adult dose may be increased to 500 mg every eight hours but should never exceed 1.5g/day nor be administered for a period longer than 10 days. A maximum total adult dose of 15g should not be exceeded.

Urinary tract infections: (other than pseudomonas infections)

7.5 mg/kg/day in two equally divided doses (equivalent to 250 mg b.i.d. in adults). As the activity of amikacin is enhanced by increasing the pH, a urinary alkalinizing agent may be administered concurrently.

Impaired renal function:

In patients with renal impairment reflected by creatinine clearance less than 50 mL/min, a total daily dose of amikacin is not desirable. For patients with impaired renal function receiving the usual twice or three times daily dosing, whenever possible, serum amikacin concentrations should be monitored by appropriate assay procedures.

Doses should be adjusted in patients with impaired renal function either by administering normal doses at prolonged intervals or by administering reduced doses at fixed intervals.

Normal Dose at Prolonged Intervals Between Dosing:

If the creatinine clearance rate is not available and the patient's condition is stable, a dosage interval in hours for the normal single dose (i.e., that which would be given to patients with normal renal function on a twice daily schedule, 7.5 mg/kg) can be calculated by multiplying the patient's serum creatinine by nine; 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.

Serum Creatinine Concentration (mg/100mL)		Interval between Amikacin doses of 7.5 mg/kg IM (hours)
1.5		13.5
2.0		18.0
2.5		22.5
3.0		27.0
3.5	X9=	31.5
4.0		36.0
4.5		40.5
5.0		45.0
5.5		49.5
6.0		54.0

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

Reduced Dose at Fixed Time Intervals Between Dosing:

When renal function is impaired and it is desirable to administer amikacin sulfate injection at a fixed time interval, dose must be reduced. In these patients, serum amikacin concentrations should be measured to assure accurate administration, if serum assay determinations are not available, and 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, 7.5 mg/kg, as a loading dose. This dose is the same as the normally recommended dose which would be calculated for a patient with a normal renal function as described above.

Intraperitoneal use:

Following exploration for established peritonitis, or after peritoneal contamination due to fecal spill during surgery, amikacin may be used as an irrigant after recovery from anesthesia in concentrations of 0.25% (2.5 mg/mL). The intraperitoneal use of amikacin is not recommended in young children.

Other routes of administration

Amikacin in concentrations 0.25% (2.5 mg/mL) may be used satisfactorily as an irrigating solution in abscess cavities, the pleural space, the peritoneum and the cerebral ventricles.

Contraindications

- Hypersensitivity to the active substance
- Amikacin sulfate injection is contraindicated in patients with known allergy to amikacin or any component of the formulation
- Aminoglycosides may impair neuromuscular transmission, and should not be given to patients with myasthenia gravis

Special warnings and precautions for use

Patients should be well hydrated during amikacin therapy. Caution should be applied to patients with pre-existing renal insufficiency, pre-existing hearing or vestibular damage and diminished glomerular filtration.

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 which are longer than 14 days has not been established.

If therapy is expected to last seven days or more in patients with renal impairment, or 10 days in other patients, a pre-treatment audiogram should be obtained and repeated during therapy

Renal Toxicity:

Aminoglycosides are potentially nephrotoxic. Patients should be well hydrated during treatment and renal function should be assessed by the usual methods prior to starting therapy and daily during the course of treatment. A reduction of dosage is required if evidence of renal dysfunction occurs.. Concurrent and/or sequential, 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.

Neurotoxicity:

Neurotoxicity, manifested as vestibular and/or bilateral ototoxicity, can occur in patients treated with aminoglycosides. 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.

Ototoxicity:

The risk of ototoxicity due to aminoglycosides increases with the degree of exposure to either persistently high peak or high trough serum concentrations. Aminoglycoside-induced ototoxicity is usually irreversible.

Cases of ototoxicity with aminoglycosides have been observed in patients with certain variants in the mitochondrially encoded 12S rRNA gene (MT-RNR1), particularly the m.1555A>G variant. Ototoxicity occurred in some patients even when their aminoglycoside serum levels were within the recommended range.

Neuromuscular Toxicity:

Neuromuscular blockade and respiratory paralysis have been reported following parenteral injection. Amikacin must not be used in patients with myasthenia gravis.

The possibility of respiratory paralysis should be considered if aminoglycosides are administered by any route, especially in patients receiving anaesthetics, neuromuscular blocking agents such as tubocurarine, succinylcholine, decamethonium, atracurium, rocuronium, vecuronium or in patients receiving massive transfusions of citrate-anticoagulated blood.

Aminoglycosides Should be used with caution in patients with muscular disorders such as Parkinsonism since these drugs may aggravate muscle weakness.

Allergic reactions:

The use of amikacin in patients with a history of allergy to aminoglycosides.

Large doses of amikacin administered during surgery have been responsible for a transient Myasthenic syndrome. Amikacin sulfate injection in vials contains sodium bisulfite, a sulfite that may cause allergic-type reactions including anaphylactic symptoms and life-threatening or less severe asthmatic episodes in certain susceptible people.

Pediatric use:

It should be used with caution in premature and neonatal infants.

Other:

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.

As with other antibiotics, the use of amikacin may result in overgrowth of non-susceptible organisms.

Macular infarction sometimes leading to permanent loss of vision has been reported following intravitreal administration (injection into the eye) of amikacin.

Clostridium difficile associated diarrhea (CDAD) has been reported with use of nearly all antibacterial agents, including amikacin sulfate injection, and may range in severity from mild diarrhea to fatal colitis. Treatment with antibacterial agents alters the normal flora of the colon leading to 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 colectomy. CDAD must be considered in all patients who present with diarrhea following antibiotic use. 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.

Interaction with other medicinal products and other forms of interaction

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.

The concurrent use of amikacin sulfate injection with potent diuretics (ethacrynic acid or furosemide) should be avoided since diuretics by themselves may cause ototoxicity.

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.

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.

Fertility, Pregnancy and Lactation

Pregnancy

Amikacin should be administered to pregnant women and neonatal infants only when clearly needed and under medical supervision. If amikacin 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. Aminoglycosides can cause fetal harm.

Lactation

Amikacin is excreted in human milk. A decision should be made whether to discontinue breast-feeding or to discontinue therapy.

Fertility

No effects on fertility or fetal toxicity were reported.

Effects on ability to drive and use machines

Due to the occurrence of some adverse reactions the ability to drive and use machines may be impaired.

Undesirable effects

This list is presented by system organ class, MedDRA preferred term, and frequency using the following frequency categories: very common ($\geq 1/10$), common ($\geq 1/100$, $< 1/10$), uncommon ($\geq 1/1000$, $< 1/100$), rare ($\geq 1/10000$, $< 1/1000$), very rare ($< 1/10000$) and not known.

System Organ Class	Frequency	MedDRA Term
Infections and Infestations	Uncommon	Super infections or colonization with resistant bacteria or yeast
Blood and lymphatic system disorders	Rare	Anemia, 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
Vascular disorders	Not known	Deafness, deafness neurosensory
	Rare	Hypotension
Respiratory, thoracic and mediastinal disorders	Not known	Apnea, bronchospasm
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
	Not known	Renal failure acute, nephropathy toxic, cells in urine
Renal and urinary disorders	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.

Overdose

In case of overdosage, there is a general risk for nephro, oto and neurotoxic reactions. Neuromuscular blockade with respiratory arrest needs appropriate treatment including application of ionic calcium. 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 arterio-venous hemofiltration. In the newborn infant, exchange transfusion may also be considered.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamic properties

Therapeutic Classification: Aminoglycoside Antibacterials

ATC code: J01GB06

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 20mg/mL are achieved one hour after IM doses of 500mg, reducing to about 2µg/mL 10 hours after injections. .

Twenty percent (20%) 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 500mg administered as an intravenous infusion over a period of 30 minutes produce a mean peak serum concentration of 38µg/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 563µg/mL in the first 6 hours following a single 250mg IM dose and 163µg/mL over 6-12 hours. Following a single 500mg IM dose urine concentrations average 832µg/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.

Intramuscular and intravenous administration

In neonates and particularly in premature babies, the renal elimination of amikacin is reduced.

PHARMACEUTICAL PROPERTIES

Incompatibilities

Amikacin is incompatible with some penicillins 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.

Shelf life: 03 years

Nature and contents of container/ Presentation

Amkay 25mg/mL Injection: Pack of 5 ampoules.

Amkay 50mg/mL Injection: Pack of 5 ampoules.

Amkay 100mg/2mL Injection: Pack of 1 & 5 ampoules.

Amkay 250mg/2mL Injection: Pack of 1 ampoule.

Amkay 500mg/2mL Injection: Pack of 1 ampoule.

Special precautions for storage and Instruction

Protect from heat & sunlight, store at room temperature 15°C-30°C.

The expiration date refers to the product correctly stored at the required condition.

Keep out of the reach of children.

With the passage of time injection may become pale yellow, this does not indicate decrease in potency.

Precautions: Do not use if injection is leaking, solution is cloudy or contains un-dissolved particles.

To be sold on the prescription of a registered medical practitioner only.

REGISTRATION HOLDER / MARKETING AUTHORIZATION HOLDER

Head office:

Bosch Pharmaceuticals (Pvt.) Ltd.,

8, Modern Society, Tipu Sultan Road, Karachi-Pakistan

Manufacturer:

Bosch Pharmaceuticals (Pvt.) Ltd.,

221-223, Sector 23, Korangi Industrial area, Karachi-Pakistan

REGISTRATION/MARKETING AUTHORIZATION NUMBER

Amkay 25mg/mL Injection: 027163

Amkay 50mg/mL Injection: 027164

Amkay 100mg/2mL Injection: 025419

Amkay 250mg/2mL Injection: 025420

Amkay 500mg/2mL Injection: 025421

DATE FROM WHICH MARKETING IS AUTHORIZED/ RENEWAL OF THE AUTHORIZATION

Amkay 25mg/mL Injection: 24-07-2001/23-07-2021

Amkay 50mg/mL Injection: 24-07-2001/23-07-2021

Amkay 100mg/2mL Injection: 17-11-1999/16-11-2019

Amkay 250mg/2mL Injection: 17-11-1999/16-11-2019

Amkay 500mg/2mL Injection: 17-11-1999/16-11-2019

DATE OF REVISION OF THE TEXT

23-04-2024

پٹنوں / ورید کی استعمال کے لئے۔

ہدایات :-

دوبارہ اور گرمی سے محفوظ کر کے کے دہرہ جرات ۱۵-۳ ڈگری سینٹی گریڈ پر رکھیں۔

پٹنوں کی تیج سے ڈور رکھیں۔

وقت گزرنے کے ساتھ انکیشن گہرا ہوتا ہے لیکن اس سے دوا کی افادیت میں کمی نہیں آتی۔

احتیاط : انکیشن ایک ہونے ، دھندلا ہونے یا اس میں کوئی غیر مرسل پڑنے سے نظر آنے کی صورت میں

ہرگز استعمال نہ کریں۔ صرف مستعد ڈاکٹر کے نسخے پر فروخت کریں۔