SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Amikacin 125 mg/ml Solution for injection/infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml of solution for injection/infusion contains 125 mg amikacin (as sulphate).

Each ampoule with 2 ml contains 250 mg amikacin.

Excipient with known effect:

Each ml contains 1.5 mg sodium metabisulfite.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for injection/infusion.

Clear, colourless to pale yellow solution.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Amikacin is indicated in the treatment of following infections in adults and pediatric patients including neonates (see section 5.1)

- Hospital-acquired pneumonia (HAP) including ventilator-associated pneumonia (VAP) - Complicated Urogenital tract infections including pyelonephritis
- Complicated Intraabdominal infections

- o Endocarditis (only in combination with other antibiotics)
- o Infected burns

Treatment of patients with bacteraemia that occurs in association with, or is suspected to be associated with, any of the infections listed above.

Amikacin may be used in the management of neutropenic patients with fever that is suspected to be due to a bacterial infection.

Consideration should be given to official guidance on the appropriate use of antibacterial agents.

4.2 Posology and method of administration

Posology

Adults and children over 12 years

The recommended intramuscular or intravenous dosage for adults and adolescents with normal renal function (creatinine clearance ≥50 mg/min) is 15 mg/kg/day which may be administered as a single daily dose or several equal doses (e.g. 7.5 mg/kg every 12 hours, or 5 mg/kg every 8 hours).

The total daily dose should not exceed 1.5 g. For 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, given either as a single daily dose of 15-20 mg/kg, or divided into two doses of 7.5 mg/kg every 12 hours.

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

Neonates

An initial loading dose of 10 mg/kg followed by 7.5 mg/kg every 12 hours (see sections 4.4 and 5.2).

Premature infants

The recommended dose in premature infants is 7.5 mg/kg every 12 hours (see sections 4.4 and 5.2).

Dosage in elderly patients (≥65 years):

Renal function should be taken into account in elderly patients (see section 5.2).

Life-threatening infections and/or those caused by Pseudomonas

The adult dose may be increased to 500 mg every eight hours but should neither exceed 1.5 g/day nor be administered for a period longer than 10 days. A maximum total adult dose of 15 g should not be exceeded.

Urinary tract infections (other than pseudomonal infections):

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

Other routes of administration

Amikacin in concentrations of 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.

Intraperitoneal use

Following exploration for established peritonitis, or after peritoneal contamination due to faecal spill during surgery, amikacin may be used as an irrigant after recovery from anaesthesia in concentrations of 0.25% (2.5 mg/mL). If instillation is desired in adults, a single dose of 500 mg is diluted in 20 mL of sterile distilled water and may be instilled through a polyethylene catheter sutured into the wound at closure. If possible, instillation should be postponed until the patient has fully recovered from the effects of anaesthesia and muscle-relaxing drugs.

Monitoring

The renal function status should be evaluated by measuring the serum creatinine concentration or preferably by estimation of creatinine clearance. Blood urea nitrogen (BUN) is far less reliable for this purpose. Assessment of renal function should be performed at the start of therapy and should be re-evaluated at regular intervals during treatment.

Amikacin concentrations in serum should be measured in all patients receiving parenteral amikacin and must be measured in obesity, if high doses are being given, the elderly and in cystic fibrosis. Both peak and trough serum concentrations should be measured intermittently during therapy to ensure adequate but not excessive serum levels. In patients receiving multiple daily dosing peak concentrations (30-90 minutes after injection) of above 35 μg/ml and trough concentrations (just before the next dose) of above 10 μg/ml should be avoided.

In patients receiving once daily (or extended interval) dosing pre-dose (‘trough’) concentration should be less than 5 mcg/ml. Peak concentrations (approximately 60 minutes after administration) may exceed 35 mcg/ml.

If the pre-dose (‘trough’) concentration is high, the interval between doses must be increased. If the post-dose (‘peak’) concentration is high, the dose must be decreased.

Auditory and vestibular function should also be monitored during treatment, in particular if longer treatment duration (>7-10 days) is considered.

Dosage in renal impairment

In patients with impaired renal function (creatinine clearance less than 50 mL/min) the recommended dose has to be decreased and adjusted to the renal function. This can be achieved by increasing the dose interval and/or reducing the dose.

In all patients with renal impairment, serum amikacin peak and trough concentration and renal function must be monitored regularly and the dose regimen altered as necessary (see below).

Once daily/extended interval dosing

Patients with renal impairment in whom once daily dosing would be considered appropriate if their renal function were normal may receive extended interval dosing. The initial dose may be the same as in normal renal function. The dose interval should be at least 24 hours and extended according to the degree of renal impairment and the results of serum amikacin level measurements (see Monitoring Advice).

In severe renal impairment, the initial dose may have to be reduced in addition.

Once daily or extended interval dosing should be avoided in patients with a creatinine clearance less than 20 ml/minute.

A once daily/extended interval dose regimen should be avoided in children over 1 month of age with a creatinine clearance less than 20 ml/minute/1.73 m^2.

Reduced Dose at Fixed Intervals:

If patients with renal impairment are given amikacin at fixed time intervals, the dose must be reduced. In these patients, the serum amikacin concentration should be measured to ensure accurate administration and to avoid excessive serum concentrations. If a determination of serum concentration is not possible and the patient's condition is stable, serum creatinine and creatinine clearance rates are the most readily available indicators of the extent of renal dysfunction and the consequent reduction in dose.

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

Multiple daily dosing

In patients with renal impairment in whom multiple daily dosing at fixed intervals would be considered appropriate if their renal function were normal, the dose must be reduced while the dose interval is maintained. Serum amikacin concentrations should be measured and creatinine clearance should be estimated regularly (see Monitoring Advice).

Treatment should be initiated 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.

To initially 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:

Maintenance dose every 12 hours =

$$\frac{\text{(observed CrCL in mL/min x calculated loading dose in mg)}}{\text{Normal CrCL in mL/min}}$$

(CrCI = creatinine clearance rate)

Subsequent doses should be determined based on amikacin serum concentrations (see Monitoring Advice).

Treatment duration

At recommended dosages, infections caused by susceptible pathogens should respond to therapy within 24-48 hours. If clinical response does not occur within 3-5 days, therapy should be discontinued and the antibiotic susceptibility pattern of the invading organism should be rechecked. If necessary, alternative therapy should be considered. Failure of therapy may be due to the resistance of the organism or to septic locus requiring surgical drainage.

The average duration of treatment is 7-10 days. For all routes of administration, the maximum daily dose should not exceed 15-20 mg/kg/day. If prolonged treatment is required, it should be carried out after reviewing the necessity of using amikacin, determination of serum amikacin concentrations and additionally monitoring of renal, auditory and vestibular functions as closely as possible daily.

Method of administration

IM use or IV use after dilution.

The solution for intravenous use is prepared by adding the desired dose to 100 mL or 200 mL of sterile diluent such as normal saline or 5% dextrose in water or any other compatible solution. The solution is administered to adults over a 30 to 60-minute period.

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

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

For the dilution of Amikacin see section 6.6.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Due to the known cross sensitivities in this class of drugs, a history of hypersensitivity or serious toxic reactions to aminoglycosides may be a contraindication to all aminoglycosides.

Because of its sulphite content, Amikacin must not be used in asthmatics with sulphite hypersensitivity.

4.4 Special warnings and precautions for use

Allergic reactions

Amikacin contains sodium metabisulfite.

Sodium metabisulfite may rarely cause severe hypersensitivity reactions in susceptible individuals, including anaphylactic symptoms and life- threatening bronchial spasms (bronchospasm).

Sulphite hypersensitivity is generally uncommon and more common in asthmatics than non-asthmatics.

Neuromuscular toxicity

Neuromuscular blockade and respiratory paresis have been reported following parenteral injection, topical lavage (such as orthopedic and abdominal irrigation, or with local empyema treatment) or after oral administration of aminoglycosides. The risk of respiratory paresis when administering aminoglycosides irrespective of the route of administration should be considered, especially in patients receiving anesthetics or neuromuscular blockers(see section 4.5).

Antidote in neuromuscular blockade: supply of calcium in ionized form (to relieve respiratory paralysis) and neostigmine. Mechanical ventilation may be necessary. In animal studies, neuromuscular blocks and myoparesis were found after administration of high doses of amikacin.

Aminoglycosides should be used with extreme caution in patients with myasthenia gravis as the curare-like effect on the neuromuscular junction may increase myasthenia with the potential for respiratory failure.

Aminoglycosides 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 the neuromuscular junction.

Ototoxicity/Neurotoxicity and nephrotoxicity

Amikacin is potentially nephrotoxic and ototoxic; therefore, patients must be carefully monitored clinically. Particular caution should be applied to patients with pre-existing renal insufficiency, or pre-existing hearing or vestibular damage. Safety for treatment periods which are longer than 14 days has not been established.

Precautions regarding the dose should be observed and adequate hydration maintained.

Neurotoxicity occurring in patients treated with aminoglycosides is manifested as vestibular and / or bilateral ototoxicity.

Ototoxicity:

The risk of aminoglycoside-induced ototoxicity is greater in patients with impaired renal function, and in those who receive high doses, or in those whose therapy is prolonged over 5-7 days. High frequency deafness usually occurs first and can be detected only by audiometric testing. Vertigo or dizziness may occur and may be evidence of vestibular injury.

Other manifestations of neurotoxicity include numbness, tingling of the skin, muscle twitching and muscle spasms. At the first sign of hearing and / or balance disorders, therapy with amikacin should be discontinued.

The risk of ototoxicity due to aminoglycosides increases with the level of exposure either through consistently high peak serum concentrations or high serum trough concentrations. Patients who develop auditory or vestibular damage may not have any symptoms during therapy that may alert them to 8th nerve damage, and total or partial irreversible bilateral deafness or disabling vertigo may occur after the drug has been discontinued. Aminoglycoside-induced ototoxicity is usually irreversible.

Evidence of ototoxicity (dizziness, vertigo, tinnitus, roaring in the ears and hearing loss)

or nephrotoxicity requires discontinuation of the drug or dosage adjustment.

The use of amikacin in patients with a history of allergy to aminoglycosides or in patients who may have subclinical renal or eighth nerve damage induced by prior administration of nephrotoxic and/or ototoxic agents such as streptomycin, dihydrostreptomycin, gentamicin, tobramycin, kanamycin, bekanamycin, neomycin, polymyxin B, colistin, cephaloridine, or viomycin should be considered with caution, as toxicity may be additive.

In these patients amikacin should be used only if, in the opinion of the physician, therapeutic advantages outweigh the potential risks.

There is an increased risk of ototoxicity in patients with mitochondrial DNA mutations (particularly the nucleotide 1555 A to G substitution in the 12S rRNA gene), even if aminoglycoside serum levels are within the recommended range during treatment. Alternatively treatment options should be considered in such patients.

In patients with a family history of relevant mutations or aminoglycoside induced deafness, alternative treatments or genetic testing prior to administration, should be considered.

Nephrotoxicity:

Aminoglycosides are potentially nephrotoxic. Renal toxicity appears independent of plasma obtained at the peak (C_{max}). The risk of nephrotoxicity is increased in patients with impaired renal function and in patients receiving high doses or prolonged drug therapy.

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, such as presence of urinary casts, white or red cells, albuminuria, decreased creatinine clearance, decreased urine specific gravity, increased BUN, serum creatinine, or oliguria. If azotemia increases, or if a progressive decrease in urinary output occurs, treatment should be stopped..

Aminoglycosides may be inactivated by betalactams. Inactivation may continue in samples (serum, cerebrospinal fluid, etc.) taken for laboratory testing and then

interfere with aminoglycoside level assays. The samples should therefore be adequately treated after collection (immediate determination, storage in the freezer or addition of betalactamase).

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.

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.

- Prolonged antibiotic use may occasionally lead to overgrowth of resistant pathogens.

The patient should be constantly monitored in this regard. Should a superinfection occur during therapy, appropriate measures must be taken.

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

Paediatric use

Aminoglycosides should be used with caution in premature and neonatal infants because of the renal immaturity of these patients and the resulting prolongation of serum half-life of these drugs.

This medicinal product contains less than 1 mmol sodium (23 mg) per ampoule, that is to say essentially ‘sodium free’.

Sodium metabisulfite: May rarely cause sever hypersensitivity reactions and bronchospasm.

4.5 Interaction with other medicinal products and other forms of interaction

Concurrent or serial use with other neurotoxic ototoxic or nephrotoxic agents, particularly bacitracin, cisplatin, amphotericin B, cyclosporine, 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. 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 risk of ototoxicity is increased when amikacin is used in conjunction with rapidly acting diuretic drugs, particularly when the diuretic is administered intravenously. Diuretics may enhance aminoglycoside toxicity by altering antibiotic concentrations in serum and tissue. Such agents include furosemide and ethacrynic acid which is itself an ototoxic agent. Irreversible deafness may result.

There is an increased risk of nephrotoxicity and possible ototoxicity when aminoglycosides are co-administered with platinum compounds.

The use of amikacin is not recommended in patients under the influence of anaesthetics or muscle-relaxing drugs (including ether, halothane, d-tubocurarine, succinylcholine decamethonium, atracurium, rocuronium, vecuronium or in patients receiving massive transfusions of citrate-anticoagulated blood) as neuromuscular blockade and consequent respiratory depression may occur. If blockade occurs, calcium salts may reverse this phenomenon.

Indomethacin may increase the plasma concentration of amikacin in neonates.

In patients with severely impaired renal function, a reduction in activity of aminoglycosides may occur with concomitant use of penicillin-type drugs.

In vitro admixture of aminoglycosides with beta-lactam antibiotics (penicillins 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 metabisulfite component of the amikacin sulfate formulation.

Sulfite is a very reactive compound. Therefore, mixtures with other medicinal products (other than those indicated in section 6.6) should be avoided.

4.6 Fertility, pregnancy and lactation

Pregnancy

Amikacin should be administered to pregnant women and neonatal infants only when clearly needed and under medical supervision (see section 4.4).

There are no or limited amount of data from the use of aminoglycosides in pregnant women. Aminoglycosides can cause foetal harm. Aminoglycosides cross the placenta and there have been reports of total, irreversible, bilateral congenital deafness in children whose mothers received streptomycin during pregnancy.

Although adverse reactions on the unborn or neonate in pregnant women who have been treated with other aminoglycosides have not been reported, there is potential for harm.

If a pregnant patient is to be treated or becomes pregnant during treatment, medical advice should be provided on the risk of the potential hazard to the fetus.

Breastfeeding

It is unknown whether amikacin is excreted in human milk. A decision must be made whether to discontinue breastfeeding or to discontinue therapy taking into account the benefit of breast feeding for the child and the benefit of therapy for the woman.

Fertility

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

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. However, the occurrence of some side effects (see section 4.8) may affect the ability to drive and use machines.

4.8 Undesirable effects

All aminoglycosides have oto-, nephro- and neurotoxic potential. The risk of these side effects is greater in patients with already impaired renal function, in patients receiving more than the recommended doses, prolonged therapy and in patients treated with other ototoxic or nephrotoxic drugs (see section 4.4).

Frequency is defined using the following convention:

Very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000), very rare (<1/10,000) 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[a]
Blood and lymphatic system disorders	Rare	Anemia, eosinophilia, granulocytopenia, thrombocytopenia
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 [a]
	Rare	Tremor [a], paraesthesia [a], headache, balance disoder [a]
Eye disorders	Rare	Blindness [b], retinal occlusion [b]
Ear and labyrinth disorders	Common	Tinnitus [a], hypoacusis[a]
	Not known	Chochlear damage Deafness [a], deafness neurosensory [a]
Vascular disorders	Rare	Hypotonia, thrombophlebitis
Cardiac disorders	Rare	Tachycardia and myocarditis
Respiratory, thoracic and mediastinal disorders	Not known	Apnoea, bronchospasm
Gastrointestinal disorders	Uncommon	Nausea, vomiting
Hepatobiliary disorders	Rare	Elevation of liver enzymes in plasma (SGOT, SGPT, LDH, alkaline phosphatase and bilirubin)
Skin and subcutaneous tissue disorders	Uncommon	Rash
	Rare	Pruritus, urticaria
Musculoskeletal and connective tissue disorders	Rare	Arthralgia, myokymia[a]
Renal and urinary disorders	Common	Nephrotoxicity, oliguria[a]
	Not known	Increase in serum creatinine [a], albuminuria [a], azotemia [a], red blood cells urine [a], white blood cells urine [a], cells in the urine Acute renal failure
General disorders and administration site conditions	Rare	Fever
	Not known	Pain in the injection site **

[a] See section 4.4

[b] Amikacin is not formulated for intavitreal use. Blindness and retinal infarction have been reported following intravitreous administration (injection into the eye) of amikacin.

*Changes in renal function are usually reversible at the end of therapy.

**Amikacin is not intended for administration to the vitreous body. When amikacin was injected directly into the eye, maculopathies were observed, occasionally leading to complete loss of vision.

Description of selected adverse reactions

Kidney and urinary tract disorders

Nephrotoxicity is manifested as increased excretion of tubule epithelia, cylindruria, increase in β2-microglobulin excretion, enzyme excretion via urine (e.g. alanine aminopeptidase, glutamine transferase, β-galactosidase, N-acetyl-glucosaminidase), azotemia, decrease in urine osmolarity, increase in blood urea nitrogen and serum creatinine, decrease in creatinine clearance. In case of minor irritations (albumin, erythrocytes, leukocytes or cylinders in urine) the fluid intake should be increased. After discontinuation of the drug, renal impairment is usually reversible.

As with all aminoglycosides, there have been reports of nephrotoxicity and acute renal failure following approval of amikacin.

Disorders of the ear and the labyrinth

Ototoxic reactions involving the 8th cranial nerve occur in approximately 0.5 - 5% of the treated patients. This may involve vestibular or cochlear function (see section 4.4).

When treating with amikacin, special attention should be paid to cochlear damage. These are manifested as tinnitus, pressure in the ears and initially merely as audiometrically detectable decrease of acoustic perceptions in the high frequency range (> 4000 Hertz) above the speech range. However, hearing loss can develop to complete, irreversible deafness despite discontinuation of the aminoglycoside. Vestibular disorders manifest in initial symptoms such as dizziness, nausea, and vomiting. In the clinical examination usually a nystagmus is detected. At the first sign of hearing or balance disorders, amikacin therapy should be discontinued.

Disorder of the nervous system

Neuromuscular blockades:

Specific risks are very rare when taking aminoglycosides. The occurrence of neuromuscular blockade, which can lead to respiratory arrest, can occur especially with intrapleural or intraperitoneal administration. The neuromuscular blocking properties of the aminoglycosides are enhanced by inhalation narcotics or muscle relaxants or curare-like drugs. Particularly at risk are patients with myasthenia gravis. Respiratory paresis requires artificial respiration. In addition, the application of potassium salts may be considered as a countermeasure.

Immune system disorders

Due to the content of sulfite it can lead to hypersensitivity reactions that may manifest as vomiting, diarrhoea, wheezing, acute asthma attack, disturbance of consciousness or shock in individual cases, especially in bronchial asthma. These reactions can vary widely individually and can lead to life-threatening conditions.

Reporting possible side effects

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via Yellow Cad Scheme, Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow card in the Google Play or Apple App Store.

4.9 Overdose

Significant risk of overdose is a potential nephro, oto and neurotoxic (neuromuscular blockade) effect. Respiratory neuromuscular blockade should be appropriately treated, including the administration of calcium in ionised form (for example as gluconate or lactobionate in 10-20% solution) (see section 4.4). In case of overdose or toxic reactions, amikacin can be removed by peritoneal or hemodialysis. Continuous arteriovenous hemofiltration also leads to a reduction of amikacin. In neonates an exchange transfusion may be considered.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antibacterials for systemic use, aminoglycoside antibacterials, other aminoglycosides, ATC code: J01GB06

Mechanism of action

The mechanism of action of amikacin is due to a disruption of protein biosynthesis on the bacterial ribosome by interaction with the rRNA and subsequent inhibition of translation. This results in a bactericidal effect.

Relationship between pharmacokinetics and pharmacodynamics

The efficacy depends essentially on the quotient of maximum serum concentration (C_{max}) and minimal inhibitory concentration (MIC) of the pathogen.

Resistance mechanisms

Resistance to amikacin may be due to the following mechanisms:

- Enzymatic Inactivation: Enzymatic modification of aminoglycoside molecules is the most common mechanism of resistance. Acetyltransferases, phosphotransferases or nucleotidyltransferases are responsible for this, most of which are plasmid-encoded. Amikacin is highly stable to aminoglycoside-inactivating enzymes. It can therefore inhibit bacteria that are resistant to gentamicin and other aminoglycosides.
- Reduced penetration and active efflux: These resistance mechanisms are mainly found in Pseudomonas aeruginosa.

Alteration of the target structure: Modifications within the ribosomes are the cause of resistance. There is partial cross-resistance of amikacin with other aminoglycoside antibiotics.

Threshold values

Susceptibility testing breakpoints MIC (minimum inhibitory concentration) interpretive criteria for susceptibility testing have been established by the European Committee on Antimicrobial Susceptibility Testing (EUCAST) for Amikacin and are listed here: https://www.ema.europa.eu/documents/other/minimum-inhibitory-concentration-mic-breakpoints_en.xlsx

The prevalence of acquired resistance of individual species may vary over place and over time. Therefore, local information about the resistance situation is required, especially for the adequate treatment of severe infections. If the efficacy of amikacin is questionable due to the local resistance situation, expert therapy counselling should be sought. Particularly in the case of severe infections or treatment failures, a microbiological diagnosis with detection of the pathogen and its sensitivity to amikacin should be sought.

Usually sensitive species

Aerobic Gram positive microorganisms

Staphylococcus aureus

Staphylococcus haemolyticus

Staphylococcus hominis

Aerobic Gram negative microorganisms

Citrobacter freundii

Enterobacter aerogenes

Enterobacter cloacae

Escherichia coli

Klebsiella oxytoca

Klebsiella pneumoniae

Morganella morganii

Proteus mirabilis

Proteus vulgaris

Pseudomonas aeruginosa 1)

Salmonella enterica (enteritis salmonella)

Serratia liquefaciens °

Serratia marcescens

Shigella spp.

Species in which acquired resistance can be a problem

Aerobic Gram positive microorganisms

Staphylococcus epidermis

Aerobic gram-negative microorganisms

Acinetobacter baumannii

Naturally resistant species

Aerobic Gram-positive microorganisms

Enterococcus spp.

Streptococcus spp.

Aerobic Gram-negative microorganisms

Burkholderia cepacia

Stenotrophomonas maltophilia

Anaerobic microorganisms

Bacteroides spp.

Prevotella spp.

Other microorganisms

Chlamydia spp.

Chlamydophila spp.

Mycoplasma spp.

Ureaplasma urealyticum

[o] There were no latest data when the tables were published. The primary literature, standard works and therapy recommendations presume sensitivity.

1) For isolates of particular patient groups, e.g. Patients with cystic fibrosis, the resistance rate ≥10%.

5.2 Pharmacokinetic properties

After IM injection, amikacin is well tolerated locally and rapidly absorbed. After administration of 250 mg amikacin IM average serum peak concentrations of 11 μg / ml are achieved within one hour when amikacin 21 μg / ml is administered. I.V. short infusion of 500 mg amikacin results in an average serum concentration of 38 μg / ml (end of infusion). After 1 hour, 18 μg / ml were still detectable. In elderly patients (with mean creatinine clearance of 64 ml / min) the blood levels are 55 μg / ml after a 30- minute infusion of 15 mg / kg, 5.4 μg / ml after 12 hours and 1.3 μg/ ml after 24 hours.

Serum half-life in patients with normal renal function is 2.4 hours, with an average volume of distribution of 24 litres and about 28% of body weight. Plasma protein binding ranges from 0-11%. The average serum clearance rate is 100 ml / min; The renal clearance rate in normal renal function is 94 ml / min. Amikacin is not metabolized and excreted almost exclusively by glomerular filtration. In normal renal function, approximately 91% of the IM administered dose is excreted within the first 8 hours via urine in active form and 98% within 24 hours.

Amikacin is removable by both peritoneal dialysis and hemodialysis. By peritoneal dialysis (patients without infection) about 20% of the administered amikacin dose could be removed within 8-12 hours. Hemodialysis is much more effective. Depending on the dialysis method, either 50% (range 29-81%) of the administered dose was removed within 4 hours or 40-80% was removed within 8 hours.

Experiences in children

Data from dosing studies on a daily basis show that levels in CSF in normal children are around 10 to 20% of serum concentrations and may reach 50% in meningitis. The elimination of amikacin was reduced in newborns and especially in preterm infants.

In a single study of newborns (1-6 days after birth) grouped by birth weight (3000g), amikacin was given intramuscularly and/or intravenously at a dose of 7.5 mg/kg. The neonatal clearance > 3000 g was 0.84 ml/min/kg and the terminal half-life was about 7 hours. In this group, the initial volume of distribution was 0.3 ml/kg and the volume of distribution at steady state was 0.5 ml/kg. In the lower birth weight groups, the clearance/kg was lower and the half-life longer. Repeated dosing every 12 hours in all the specified groups showed no accumulation after 5 days.

5.3 Preclinical safety data

No long-term studies have been performed to evaluate the carcinogenic or mutagenic potential. Studies in rats have shown that daily doses up to 10 times recommended dose for humans, did not cause any adverse effects on male and female fertility.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium citrate dihydrate

Sodium metabisulfite

Sulfuric acid (2N)

Water for injections

6.2 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.

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.

6.3 Shelf life

Unopened: 3 years

After dilution:

Chemical and physical in-use stability has been demonstrated for 24 hours at 23-27°C under artificial light and 2-8°C with 0.9% Sodium Chloride Injection and Lactated Ringer's Injection, at a concentration of Amikacin of 2.5 mg/ml and 5.0 mg/ml.

Chemical and physical in-use stability has been demonstrated for 6 hours at 23-27°C under artificial light and for 24 hours at 2-8°C with 5% Dextrose Injection, 5%

Dextrose and 0.2% Sodium Chloride Injection, 5% Dextrose and 0.45% Sodium Chloride Injection and Lactated Ringer's Injection with 5% Dextrose, at a concentration of Amikacin of 2.5 mg/ml.

Chemical and physical in-use stability has been demonstrated for 12 hours at 23-27°C under artificial light and for 24 hours at 2-8°C with 5% Dextrose Injection, 5% Dextrose and 0.2% Sodium Chloride Injection, 5% Dextrose and 0.45% Sodium Chloride Injection and Lactated Ringer's Injection with 5% Dextrose, at a concentration of Amikacin of 5 mg/ml.

From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2 to 8ºC or than the times stated above for the chemical and physical in-use stability, whichever is the shorter unless opening/dilution has taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage

Store below 25°C.

For storage conditions after dilution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

Type I, clear glass ampoules containing 2 ml of solution, in cartons of 1 and 10 ampoules.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

For single use only, discard any unused solution.

The solution for intravenous use is prepared by adding the desired dose to 100 ml or 200 ml of sterile solvent such as sodium chloride solution or 5% dextrose in water or any other compatible solution.

Amikacin 125 mg/ml and Amikacin 250 mg/ml are diluted under aseptic conditions with:

- 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
- Lactated Ringer's Injection with 5% Dextrose

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

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

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England

8 MARKETING AUTHORISATION NUMBER(S)

125 mg/ml: PL 55035/0016

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

18/11/2024

10 DATE OF REVISION OF THE TEXT

18/11/2024