SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Amikacin 250 mg/ml Solution for Injection/Infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml contains 250 mg of amikacin (as sulfate).
Each 2 ml vial contains 500 mg of amikacin (as sulfate).

Excipients with known effect:
Each 2 ml vial contains 13.20 mg of metabisulfite sodium (E223) (equivalent to 4.44 mg SO2).
Each 2 ml vial contains 14.92 mg of sodium.
For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for injection/infusion.
Colourless to pale yellow transparent solution, practically free from visible particles.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Amikacin is indicated in the treatment of following infections in adults and paediatric 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
- Endocarditis (only in combination with other antibiotics),
- 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

The dose must be adjusted individually, based on body weight and renal function, and the serum concentration must be monitored regularly.

Amikacin can be given intramuscularly or intravenously in the same dosage. For intravenous administration, the dose is added to the appropriate infusion solution (see section 6.6) and administered as an infusion over 30-60 minutes.

Adults and children over 12 years of age:

The recommended intramuscular or intravenous dose for adults and adolescents with normal renal function (creatinine clearance ≥50 mg/min) is 15 mg/kg/day given either as a single daily dose or as several equal doses (e.g. 7.5 mg/kg all 12 hours, or 2 mg/kg every 8 hours).

The total daily dose should not exceed 1.5 g. For endocarditis and febrile neutropenic patients, dosing should be done twice a day, as there is insufficient data for once-daily dosing.

Children from 4 weeks to 12 years of age:

The recommended intramuscular or intravenous (slow intravenous infusion) dosage for 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.

For endocarditis and febrile neutropenic patients, dosing should be done twice a day, as there is insufficient data for once-daily dosing.

Neonates:

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

Preterm infants:

The recommended dose for preterm 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).

Endocarditis:

In endocarditis caused by Enterococcus faecalis or alpha streptococcus, Amikacin should be combined with ampicillin and benzylpenicillin, respectively.

In case of endocarditis caused by staphylococci, Amikacin should be combined with an isoxazolyl penicillin.

Neutropenic patients:

When treating neutropenic patients, Amikacin should be combined with piperacillin and tazobactam.

In the case of serious infections of unknown etiology, Amikacin should be combined with a beta-lactam antibiotic while waiting for a culture and resistance report.

Systemic infections 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 1.5 g should not be exceeded.

In case of systemic infection caused by Pseudomonas aeruginosa, Amikacin can be combined with a beta-lactam antibiotic effective against Pseudomonas aeruginosa.

When treating infections caused by both aerobic and anaerobic bacteria, Amikacin should be combined with a preparation active against anaerobic bacteria.

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 alkalizing agent may be administered concurrently.

Impaired renal function

It is especially important in the case of impaired renal function that the serum concentration of amikacin is monitored regularly.

Since amikacin is mainly eliminated by the renal by glomerular filtration, the rate of elimination depends on the patient's renal

function and the recommended daily dose should therefore be adapted to renal function. If renal function is impaired and the dose is not reduced and/or the dosing intervals are not extended, abnormally high and possibly toxic concentrations can be achieved in blood and tissues due to accumulation. The degree of renal impairment should be controlled by determining serum creatinine or creatinine clearance.

As the effect of aminoglycosides is correlated to Cmax (see section 5.1), all patients are initially given a normal dose (15mg/kg body weight). In patients with mild to moderate renal impairment, the dosing interval is based on the trough value, see "Treatment control". There are no data for recommendations for repeated dosing in patients with severe renal impairment, i.e. where an adequate trough value is not reached within 48 hours.

Haemodialysis:

The documentation for dosing in patients undergoing haemodialysis is deficient. Commonly used dosage is 5 mg/kg body weight given after each dialysis session.

Peritoneal dialysis:

Patients who undergo peritoneal dialysis twice a week are given 5 mg/kg body weight after each dialysis session. Patients who undergo peritoneal dialysis every other day are given 5 mg/kg after the first dialysis session and 2.5 mg/kg after the following dialysis sessions.

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:

NOTE: In patients with impaired renal function (creatinine clearance <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 after 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 =

[observed CrCl in ml/min x calculated loading

dose in mg] [normal CrCl in ml/min]

(CrCl=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.

Serum amikacin concentrations should be monitored to ensure therapeutic, but not excessively high, levels. It is recommended that serum samples be taken on the second day of treatment and then regularly, 2-3 times a week, during treatment. Trough values (just before the next dosing session) should not exceed 10 micrograms/ml. A progressive increase in the trough value reveals

an ongoing accumulation, in which case the dosing interval should be extended.
Amikacin, like other aminoglycosides, is potentially nephrotoxic and ototoxic. Renal function, hearing and balance should, if possible, be checked regularly during amikacin treatment. It is extremely important to follow the dosage recommendations and to keep the patient well hydrated.

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 any of the excipients listed in section 6.1.
- Due to the known cross sensitivities previous hypersensitivity reactions or serious toxic reactions with any aminoglycosides may be a contraindication for the use of other aminoglycosides.
- Because of its sulfite content, Amikacin must not be used in asthmatics with sulfite hypersensitivity.

4.4 Special warnings and precautions for use

Allergic reactions

Amikacin contains sodium metabisulfite which may rarely cause severe hypersensitivity reactions in susceptible individuals, including anaphylactic symptoms and life-threatening bronchial spasms (bronchospasm). Sulfite sensitivity is generally uncommon and more frequent in asthmatics than in non-asthmatics.

Caution should be applied to patients with existing renal insufficiency, or with existing auditory or vestibular damage. Patients treated with parenteral aminoglycosides should be under close clinical observation due to potential ototoxicity and nephrotoxicity associated with treatment. The safety of treatment for longer than 14 days has not been established.

Neuro/Ototoxicity

Neurotoxicity manifesting as vestibular and/or bilateral auditory ototoxicity may occur in patients treated with aminoglycosides. The risk of aminoglycoside-induced ototoxicity is greater in patients with impaired renal function or in those where the duration of treatment is extended beyond 5-7 days, even in healthy patients. Often, deafness at high frequencies appears first and can only be detected by audiometric testing. Dizziness may occur and may be evidence of vestibular damage. Other signs of neurotoxicity may include numbness, skin tingling, muscle twitching, and convulsions. Patients who develop cochlear or vestibular damage do not need to have symptoms during treatment that alert them of eighth cranial nerve damage. Total or partially irreversible bilateral deafness or disabling vertigo may occur after discontinuation of the drug.

Aminoglycoside Induced ototoxicity is usually irreversible.

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. Alternative 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.

Neuromuscular toxicity

Neuromuscular blockade and respiratory paralysis have been reported following parenteral injection, topical installation as in orthopaedic flushing and abdominal lavage, or with local empyema treatment) and after oral administration of aminoglycosides. The risk of respiratory paralysis when administering aminoglycosides irrespective of the route of administration should be considered, especially in patients receiving anaesthetics or neuromuscular blockers (see section 4.5 “Interactions with other medications

and other forms of interaction"). If neuromuscular blockade occurs, calcium salts may relieve respiratory paralysis but mechanical ventilation may be necessary.

In animal studies, neuromuscular blockade and muscular paralysis have been reported after administration of high doses of amikacin.

Aminoglycosides should be used with caution in patients with muscular disorders such as myasthenia gravis or parkinsonism, as these drugs may aggravate muscle weakness due to their potential curare-like effect on the neuromuscular junction.

Renal toxicity

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 treatment.

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.

Elderly patients may have reduced renal function which may not be seen in the routine screening tests such as BUN (blood urea nitrogen) or serum creatinine. A creatinine clearance determination may be more helpful. Monitoring of renal function in elderly patients during treatment with aminoglycosides is particularly important.

Renal function and function of the eighth cranial nerve should be closely monitored, especially in patients with known or suspected renal impairment at the onset of treatment and also in those whose renal function is initially normal but who develop signs of renal impairment during treatment.

Serum concentrations of amikacin should be monitored (when possible) to ensure adequate levels and to avoid potential toxic levels. The urine should be examined for decreased density, increased excretion of proteins and the presence of cells or casts. BUN (blood urea nitrogen), serum creatinine, or creatinine clearance should be measured periodically. Repeat audiograms should be performed (if possible), especially in high-risk patients. Evidence of ototoxicity (dizziness, tinnitus, ringing in the ears and hearing loss) or nephrotoxicity require discontinuation of the drug or dose adjustment.

Concomitant 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.

Inactivation of aminoglycosides is clinically significant only in patients with severe renal impairment. Inactivation may persist in body fluid samples collected for analysis, resulting in incorrect aminoglycoside readings. Such samples should be handled properly (analyzed immediately, frozen, or treated with beta-lactamase).

Diarrhoea/pseudomembranous colitis caused by *Clostridium difficile* occurs. Patients with diarrhoea must therefore be monitored closely.

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.

Amikacin contains sodium

2 ml vial
This medicinal product contains 14.92 mg sodium per 2 ml vial, equivalent to 0.75 % of the WHO recommended maximum daily intake of 2 g sodium for an adult.

4.5 Interaction with other medicinal products and other forms of interaction

Concomitant or repeated use of other neurotoxic, ototoxic or nephrotoxic agents, particularly bacitracin, cisplatin, amphotericin B, cyclosporine, tacrolimus, cephaloridine, paromomycin, viomycin, polymyxin B, colistimethate/colistin, vancomycin, or other aminoglycosides should be avoided regardless of systemic or local administration due to the risk of additive effects. Increased nephrotoxicity has been reported following

concomitant parenteral administration of aminoglycoside antibiotics and cephalosporins. Concomitant treatment with a cephalosporin may result in falsely elevated 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.

A reduction in serum activity of aminoglycosides may occur with concomitant use of penicillin-type drugs.

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 co-administered with platinum compounds.

Concomitantly administered thiamine (vitamin B1) may be destroyed by the reactive sodium metabisulfite component of the amikacin sulfate formulation.

Indomethacin may increase the plasma concentration of amikacin in neonates.

In patients receiving anaesthetics or muscle-relaxing agents (such as 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.

Some antibiotics could, in rare cases, reduce the effectiveness of oral contraceptives by interfering with the bacterial hydrolysis of steroid conjugates in the gut and thus the reabsorption of unconjugated steroid. Thereby, the plasma levels of active steroid would decrease. This unusual interaction would occur in women with high biliary excretion of steroid conjugates. This interaction has not been reported for amikacin.

Breast-feeding

It is not known if amikacin passes into the breast milk. The decision should be made to either stop breastfeeding or stop the treatment.

Fertility

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

4.6 Fertility, pregnancy and lactation

Pregnancy

Amikacin should be used in pregnant women and newborns only if clearly indicated and under medical supervision (see section 4.4).

There is limited data on the use of aminoglycosides in pregnancy. Aminoglycosides can affect the development of the embryo/foetus in the womb. Aminoglycosides cross the placental barrier and there have been reports of total, irreversible, bilateral congenital deafness in children whose mothers were treated with streptomycin during pregnancy.

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

If amikacin is used during pregnancy or if the patient becomes pregnant during treatment with this drug, the patient should be informed of the possible risks to the foetus.

Breast-feeding

It is not known if amikacin passes into the breast milk. The decision should be made to either stop breastfeeding or stop the treatment.

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 ability to drive and the use of machines have been performed. However, the occurrence of some side effects (see section 4.8) may impair the ability to drive vehicles and operate machinery.

4.8 Undesirable effects

All aminoglycosides can induce ototoxicity, renal toxicity and neuromuscular blockade. The risk of these toxicities is greater in patients with already impaired renal function, in patients receiving more than the recommended dose, prolonged treatment and in patients treated with other ototoxic or nephrotoxic drugs (see section 4.4 "Special warnings and precautions for

use").

The frequency of the side effects listed below is defined using the following conventions:
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); not known (frequency cannot be estimated from the available data).

MedDRA system organ class	**Frequency**	**Adverse event**
Infections and infestations	Uncommon	Super infection or colonization with resistant bacteria or yeasts[a]
Blood and lymphatic system disorders	Rare	Anaemia, eosinophilia, granulocytopenia, leukopenia, thrombocytopenia
Immune system disorders	Not known	Anaphylactic response (anaphylactic reaction, anaphylactic shock and anaphylactoid reaction), hypersensitivity
Metabolism and nutrition disorders	Rare	Hypomagnesemia
Nervous system disorders	Common	Dizziness
	Rare	Tremor[a] , paraesthesia[a], headache, balance disorders
	Not known	Acute muscular paralysis[a]
Eye disorders	Rare	Blindness[b], retinal infarction[b]
Ear and labyrinth disorders	Common	Vestibular disorders with nausea
	Rare	Tinnitus[a], hearing loss[a]
	Not known	Deafness[a], neurosensory deafness[a]

Cardiovascular disorders	Rare	Hypotension, hypotonia, thrombophlebitis, tachycardia, myocarditis
Respiratory, thoracic and mediastinal disorders	Not known	Apnoea, bronchospasm
Gastrointestinal disorders	Uncommon	Vomiting, nausea
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	Proteinuria, urea increase
	Rare	Oliguria[a], serum creatinine increase[a],albuminuria[a], azotemia[a], presence of red and white blood cells in the urine[a]
	Not known	Acute renal failure, toxic nephropathy, cells in the urine[a]
General disorders and administration site conditions	Rare	Fever
	Not known	Pain in the injection site

a. See section 4.4 "Special warnings and precautions for use".

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

Description of selected adverse reactions

Cases of skin and mucosal reactions including Stevens-Johnson syndrome and toxic epidermal necrolysis have been reported, however with an unclear connection.

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 "Special warnings and precautions for use").

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 of suspected adverse reactions

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 Card Scheme, Website: www.mhra.gov.uk/yellowcard or search for ‘MHRA Yellow Card’ in the

Google Play or Apple App Store.

4.9 Overdose

In case of overdose, there is a significant risk of nephro, oto and neurotoxic (neuromuscular blockade) reactions. Respiratory neuromuscular blockade should be immediately treated, including the administration of calcium in ionised form (for example as gluconate or lactobionate in 10-20 % solution) (see section 4.4 “Special warnings and precautions for use”). In cases of overdose or toxic reactions, amikacin can be removed from the blood by peritoneal or haemodialysis. Continuous arteriovenous haemofiltration also leads to a reduction of amikacin. In neonates an exchange transfusion may be considered.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: antibiotics for systemic use, aminoglycoside antibiotics, ATC code: J01GB06.

Amikacin is a kanamycin-derived semisynthetic aminoglycoside antibiotic which works by stopping the bacteria's protein synthesis. The substance has a bactericidal effect.

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

The assay of amikacin is carried out using usual serial dilution. The following minimum inhibitory concentrations for sensitive and resistant pathogens have been established:

EUCAST Clinical MIC Breakpoints for amikacin (EUCAST Clinical Breakpoint table version 13.0, valid from 01-01-2023).

Pathogen	Species-related breakpoints, mg / L of amikacin (S ≤ / R >)
Enterobacterales (systemic infections)	8/8[1]
Enterobacterales (infections originating from the urinary tract)	8/8
Pseudomonas spp. (systemic infections)	16/16[1]
Pseudomonas spp. (infections originating from the urinary tract)	16/16
Acinetobacter spp. (systemic infections)	8/8[1]
Acinetobacter spp. (infections originating from the urinary tract)	8/8
Staphylococcus spp. (*S.aureus*)	16/16[1]
Staphylococcus spp. (coagulase-negative staphylococci	16/16
Enterococcus spp.	Note2/ Note2
Viridans group streptococci	Note2/ Note2
Haemophilus influenzae	IE/IE
Moraxella catarrhalis	IE/IE
PK-PD (Non-species related) breakpoints	1/1

[1] For systemic infections, aminoglycosides should be used in combination with other active therapy. In this circumstance, the value in brackets can be

used to distinguish between wild type organisms and organisms with acquired resistance mechanisms.

Note2 - Synergy with penicillins or glycopeptides can be expected if the isolate is susceptible to the penicillin or glycopeptide.

IE- Insufficient evidence

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.

Sensitive species

Aerobic gram positive micro-organisms

Staphylococcus aureus
Staphylococcus haemolyticus
Staphylococcus hominis

Aerobic gram negative micro-organisms

Coagulase negative staphylococci
Citrobacter freundii
Enterobacter aerogenes
Enterobacter cloacae
Escherichia coli
Haemophilus influenzae
Klebsiella oxytoca
Klebsiella pneumoniae
Morganella morganii
Proteus mirabilis
Proteus vulgaris
Providencia
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 micro-organisms

Staphylococcus epidermis

Aerobic gram-negative micro-organisms

Acinetobacter baumannii

Naturally resistant species

Aerobic gram-positive micro-organisms

Enterococcus spp.
Streptococcus spp.
Pneumococcus

Aerobic Gram-negative micro-organisms

Burkholderia cepacia
Stenotrophomonas maltophilia
Meningococcus

Anaerobic micro-

organisms

Other micro-organisms
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 %.

Resistance occurs (1-10%) in Pseudomonas aeruginosa and is common (>10%) in coagulase-negative staphylococci.

In combination with a beta-lactam antibiotic, a synergistic effect is often achieved against most bacteria including streptococci and enterococci.

5.2 Pharmacokinetic properties

Amikacin is rapidly absorbed after intramuscular administration. Doses of 250 mg and 500 mg intramuscularly give maximum serum concentrations of approximately 12 micrograms/ml and approximately 21 micrograms/ml after one hour, respectively. After 10 hours, the serum concentration is approximately 0.3 micrograms/ml and approximately 2.1 micrograms/ml, respectively.

In intravenous infusion of 500 mg (7.5 mg/kg) over 30 minutes, a maximum serum concentration of an average of 38 micrograms/ml is obtained immediately after the infusion and 30 minutes after the end of the infusion a concentration of 24 micrograms/ml. In the case of infusion of 15 mg/kg, the corresponding concentrations are 77 micrograms/ml and 47 micrograms/ml, respectively.

Plasma protein binding of amikacin is low and ranges from 0-11%. The volume of distribution is about 24 litres in an adult or about 28 % of body weight. Amikacin rapidly distributes itself to different tissues after parenteral administration. Amikacin passes into the cerebrospinal fluid in small amounts in intact meninges, while the blood- CSF barrier is penetrated more easily in meningitis. There is no accumulation with repeated dosing.

Amikacin is not metabolized and is excreted in active form almost exclusively by glomerular filtration. In normal renal function, the half-life is about 2 hours and 92% of a given dose is

excreted unchanged in the urine within 8 hours and 98% within 24 hours.

In case of impaired renal function, excretion is significantly delayed.

Data from trials with multiple daily doses show that levels in cerebrospinal fluid in normal children are about 10-20% of the serum concentration and may reach up to 50% in meningitis.

Intramuscular and intravenous administration:
Renal elimination of amikacin is reduced in newborns and especially in premature infants.

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 study of newborns (aged 1-6 days old) children were grouped by birth weight (<2000 g, 2000-3000 g and> 3000g). Amikacin was given intramuscularly and/or intravenously at a dose of 7.5 mg/kg. The neonatal clearance > 3000g 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.

Neuromuscular blockade has been seen in laboratory animals after high doses (see section 4.4)

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium metabisulfite (E 223)

Sodium citrate

Sulfuric acid

Water for injection

5.4 Incompatibilities

Aminoglycosides such as amikacin should not be combined with other medicines, but must be administered separately.
Aminoglycosides and penicillins can inactivate each other in vitro, with loss of antibacterial activity.

6.3 Shelf life

3 years

Intended for single use. To be administered immediately after dilution.
Residual quantities are to be discarded.
After dilution, chemical and physical in use stability has been demonstrated for 2 hours at room temperature (25°C).
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, unless dilution has taken place in controlled and validated aseptic conditions

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

2 ml clear Type-I glass vial with a bromobutyl rubber stopper and an aluminium cap with plastic flip-off.

2 ml (500 mg): 1, 5 and 10 vials

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements for disposal.

Like all parenterals, amikacin should be checked for particulate matter and discoloration before use. Only clear solutions which, at most, are slightly yellow in colour should be used. A pale yellow solution is not an indicator of reduced efficacy.

For intravenous infusion, Amikacin is given at the calculated dose in 100 ml or 200 ml of sterile infusion solution. The solution is administered to adults in a 30-60 minute infusion. For dosing in adults and children see section 4.2.

Suitable solvents for intravenous infusion are:
0.9 % NaCl solution for infusion
5 % glucose solution for infusion

7 MARKETING AUTHORISATION HOLDER

Neon Healthcare Ltd.
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Hertford, SG13 7NN.
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

PL 45043/0014

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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10 DATE OF REVISION OF THE TEXT

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