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 of solution for injection contains 250 mg amikacin (as sulfate).

Each ampoule with 2 ml contains 500 mg amikacin.

Excipient with known effect:
Each ml contains 3 mg sodium metabisulfite.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for injection/infusion (injection/infusion).
Clear, colourless to pale yellow solution, free from visible particles.
pH: 3.5-5.5

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Amikacin is indicated for the short-term treatment of the following serious infections due to susceptible strains of bacteria (see section 5.1) when less toxic antimicrobial agents are not effective:

- Severe infections of the respiratory tract
- Severe infections of bones and joints
- Severe infection of the central nervous system (including meninges)
- Severe skin and soft tissue infections including burn wounds
- Intra-abdominal infections, including peritonitis,
- Postoperative infections (including cardiovascular surgery)
- Severe complicated urinary tract infections
- Bacterial endocarditis

Treatment of patients with bacteraemia associated with, or suspected to be associated with, the above infections.

In some serious infections, such as neonatal sepsis, concomitant treatment with a penicillin-type drug may be appropriate, as these may be infections due to Gram-positive microorganisms such as streptococci and pneumococci.

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

4.2 Posology and method of administration

Amikacin is generally used in combination with other appropriate antibiotics. The dose of amikacin depends on the infection, the patient's status, and the renal function. Local guidance should be taken into consideration.

Posology
The patient's pre-treatment bodyweight 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. Reassessment of renal function should be made periodically during therapy. Blood urea measurement is much less reliable for this purpose.

Amikacin concentrations in serum should be measured whenever possible in order to assure adequate but not excessive levels. It is desirable to measure both peak and trough concentrations intermittently during treatment. Peak concentrations (30-90 minutes after injection) above 35 mcg/ml and trough concentrations (just prior to the next dose) above 10 mcg/ml should be avoided. The dosage should be adjusted as indicated. In patients with normal renal function, once daily dosing may be used. Peak concentrations in these cases may exceed 35 mcg/ml (see Single Daily Administration and Renal Impairment below).

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 every 12 hours. The total daily dose should not exceed 1.5 g. In endocarditis and in febrile neutropenic patients dosing should be twice daily, as there is not enough data to support once daily dosing.

Children aged 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 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 prematures is 7.5 mg/kg every 12 hours (see sections 4.4 and 5.2).

Data on single daily administration to patients with other systemic infections are limited (see also above for controlling peak and trough serum amikacin concentrations).

The duration of treatment is 7 to 10 days. In majority of cases, aminoglycosides are indicated only at the start of treatment when inoculum is potentially high and when there are uncertainties about the effectiveness of the treatment, and for a duration of treatment ≤ 5 days due to their benefit/safety ratio (bactericidal activity/toxicity correlated to the duration of treatment).The total daily dose with all modes of administration should not exceed 20 mg/kg/day. In difficult and complicated infections where treatment beyond 10 days is considered, the use of amikacin should be re-evaluated and, if continued, renal, auditory and vestibular function as well as serum amikacin levels should be monitored.
At the recommended dosage level, uncomplicated infections due to amikacin-sensitive microorganisms should respond within 24 to 48 hours. If no clear clinical response is observed after 3 to 5 days, treatment should be stopped and the susceptibility of the pathogen to the antibiotic should be re-tested. Failure to respond to infection may be due to resistance of the microorganism or the presence of septic foci requiring surgical drainage.

Impaired renal function

In patients with renal impairment reflected by creatinine clearance less than 50 mL/min, administration of the recommended total daily dose of amikacin in single daily doses is not desirable since these patients will have protracted exposure to high trough concentrations. See below for dosage adjustments in patients with impaired renal function.

For patients with impaired renal function receiving 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.

Both methods are based on the patient's creatinine clearance or serum creatinine values since these have been found to correlate with aminoglycoside half-lives in patients with diminished renal function. These dosage schedules must be used in conjunction with careful clinical and laboratory observations of the patient and should be modified as necessary, including modification when dialysis is being performed.

Normal dosing at extended intervals

If there is no data on creatinine clearance and the patient's condition is stable, a dosage interval in hours for the normal single dose (ie that would be given to patients with normal renal function on a twice daily schedule, 7.5 mg/kg per day) can be calculated by multiplying the patient's serum creatinine by nine. For example, if the serum creatinine concentration is 2 mg/100 ml, the recommended single dose (7.5 mg/kg) should be administered every 18 hours.

Reduced dosage at fixed time intervals between dosing

When amikacin should be administered at a fixed time interval in renal impairment, the dose must be reduced. In these patients, serum amikacin concentrations should be measured to assure accurate administration and to avoid excessive serum concentrations. If serum assay determinations are not available and the patient's condition is stable, serum creatinine or serum creatinine clearance values are the most readily available indicators of the degree of renal impairment that can be used as a dosing guide.

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.

To determine the size of maintenance doses to be 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 =

$$\frac{\text{observed CrCL in ml/min} \times \text{calculated loading dose in mg}}{\text{Normal CrCL in ml/min}}$$

(CrCl = creatinine clearance rate)

An alternative guide for determining reduced dosage at 12-hour intervals (for patients whose steady-state serum creatinine values are known) is to divide the normally recommended dose by the patient's serum creatinine.

The above dosage regimens are not intended to be rigid recommendations, but are provided as dosing guides when serum amikacin level measurement is not feasible.

Obese patients

Amikacin diffuses poorly into fatty tissue**.** The appropriate dose may be calculated using the patient's estimated ideal body weight, plus 40 % of the excess, as the weight on which to determine mg/kg. Dose adjustment should be made depending on plasma monitoring. The maximum dose of 1.5 g per day must not be exceeded. The duration of treatment should be limited to 7 to 10 days.

Patients with ascites

Higher doses must be administered in order to obtain adequate serum concentrations in view of the relatively greater distribution in the extracellular fluid compartment.

Method of administration

Amikacin can be given intramuscularly or intravenously. **Local guidance should be taken into consideration.**

Intravenous administration

In adults can be given either as is (2-3 minutes) or by slow infusion within 30 to 60 minutes.
A slow infusion over 30 minutes in addition to serum amikacin concentrations measured 30 minutes after the end of the infusion, can be considered as an appropriate management, taking into account the pharmacokinetic/pharmacodynamic objectives and drug concentrations monitored at adequate times with a standardized approach.

Special recommendation for intravenous administration in the paediatric population
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 mixed with other medicines, but can be given separately according to the recommended dose and route of administration.

For instructions on the dilution of the medicinal product before administration, see section 6.6

4.3 Contraindications

Amikacin sulfate injection is contraindicated in patients with hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Amikacin sulfate injection is contraindicated in patients with hypersensitivity toother aminoglycosides because of the known cross sensitivities of patients to drugs in this class.

Furthermore, amikacin sulfate injection is contraindicated:

- with concomitant use of ataluren (see section 4.5).

4.4 Special warnings and precautions for use

Caution is necessary in patients with pre-existing renal insufficiency or pre-existing auditory or vestibular damage. Patients undergoing parenteral aminoglycoside therapy should be closely monitored for possible ototoxicity and nephrotoxicity associated with their use. Safety for treatment periods longer than 14 days has not been established.

Neuro/Ototoxicity
Neurotoxicity, manifested as vestibular and/or bilateral auditory ototoxicity, can occur in patients treated with aminoglycosides. The risk of aminoglycoside-induced ototoxicity is greater in patients with impaired renal function or in those whose therapy is prolonged over 5-7 days of treatment, even in healthy patients. 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. Patients developing cochlear or vestibular damage may not have symptoms during therapy to warn them of developing eighth nerve toxicity, and total or partial irreversible bilateral deafness or disabling vertigo may occur after the medicinal product has been discontinued. 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 instillation (as in orthopaedic and abdominal irrigation or in local treatment of empyema) and following oral use of aminoglycosides. The possibility of respiratory paralysis should be considered if aminoglycosides are administered by any route, especially in patients receiving anesthetics, neuromuscular blocking agents (see section 4.5). If neuromuscular blockade occurs, calcium salts may

reverse respiratory paralysis, but mechanical respiratory assistance may be necessary.

Neuromuscular blockade and muscular paralysis have been demonstrated in laboratory animals given high doses of amikacin.

Administration of aminoglycosides to patients with neuromuscular disease such myasthenia gravis or parkinsonism requires extreme caution, since these drugs may aggravate muscle weakness because of their potential curare-like effect on the neuro-muscular junction.

Renal toxicity
Aminoglycosides are potentially nephrotoxic. Renal toxicity is independent of plasma obtained at the peak (C_{max}). The risk of nephrotoxicity is greater in patients with impaired renal function, and in those who receive high doses, or in those whose therapy is prolonged.

Patients must 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. Dose should be reduced in case of signs of renal dysfunction such as: cylindruria, the presence of leukocytes or red blood cells, albuminuria, reduction in creatinine clearance, hypodensity, hyperazotaemia, elevation of serum creatinine and oliguria. Treatment must be discontinued if azotemia increases or if urine volume decreases gradually.

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

Renal function and eighth-cranial nerve function should be closely monitored, especially in patients with known or suspected renal impairment at the onset of therapy, as well as in patients whose renal function is initially normal but who develop signs of renal dysfunction during therapy. Serum concentrations of amikacin should be monitored whenever possible to assure adequate levels and to avoid potentially toxic levels. Urine should be examined for decreased specific gravity, increased proteins' excretion, and the presence of cells or casts. Blood urea nitrogen, serum creatinine or creatinine clearance should be measured periodically. Serial audiograms should be obtained, where possible, in patients old enough to be tested, particularly high-risk patients. Indication of ototoxicity (dizziness, vertigo, tinnitus and hearing loss) or nephrotoxicity requires discontinuation of the antibiotic or adjustment of dosage.

Concurrent and / or sequential oral, or topical use of other neurotoxic or nephrotoxic products should be avoided. Other factors that can increase the risk of toxicity are advanced age dehydration and grades B and C cirrhosis according to the Child-Pugh classification.

Admixure of aminoglycosides with β-lactam antibiotics (penicillins or cephalosporins) *in vitro* may result in significant mutual inactivation. A reduction in serum activity may also occur when an aminoglycoside or penicillin-type antibiotic is administered *in vivo* by separate routes. Aminoglycoside inactivation is clinically significant only in patients with severe renal impairment. Inactivation may continue in specimens of body fluids collected for assays, resulting in inaccurate aminoglycoside readings. Such specimens should be properly handled (assayed promptly, frozen, or treated with beta-lactamase).

Allergic reactions
Amikacin contains sodium bisulfite, a sulfite that can cause allergic-type reactions in certain susceptible people, such as anaphylactic and life-threatening symptoms or less severe asthmatic episodes. Sulfite sensitivity in the general population is uncommon and the overall incidence is probably low. Sulfite sensitivity is more common in asthmatics than in non-asthmatics.

Paediatric population
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 active substances.

Others
Aminoglycosides are quickly and almost totally absorbed when they are applied topically, except to the urinary bladder, in combination 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. If this occurs, appropriate therapy should be instituted.

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

Excipients
Sodium: This medicine 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

The concurrent or serial use of other neurotoxic ototoxic (teicoplanin) or nephrotoxic drugs, particular bacitracin, cisplatin, amphotericin B, ciclosporin, tacrolimus, cephaloridine, paromomycin, viomycin, polymyxin B, colistin, vancomycin or other aminoglycosides should be avoided 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 concurrent use of amikacin sulfate injection with potent diuretics (ethacrynic acid or furosemide) should be avoided since diuretics by themselves may cause ototoxicity. In addition, when administered intravenously, diuretics may enhance aminoglycoside toxicity by altering antibiotic concentrations in serum and tissue.

A reduction in serum activity may also occur when an aminoglycoside or penicillin-type drug is administered *in vivo* by separate routes.

Biphosphonates
The risk of hypocalcaemia is increased when aminoglycosides are administered with bisphosphonates.

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

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

Indomethacin may increase the plasma concentrations of amikacin in neonates.

There is a risk of respiratory paralysis in patients receiving anesthetics, neuromuscular blocking agents such as succinylcholine, decamethonium, atracurium, rocuronium, vecuronium or in patients receiving large transfusions of citrate-anticoagulated blood.

Amikacin/muscle relaxants and other substances
On concurrent treatment with amikacin and a muscle-relaxant active substances (e.g. d-tubocurarin), curarising agents, botulinum toxin, polymyxin antibiotics, procainamide, large quantities of citrated blood or inhalation anaesthesia (e.g. halothane), it must be expected that the neuromuscular blockade exerted by those active substances will be increased. In the event of surgery the anaesthetist should be informed that this medicinal product is being administered. Injection of calcium salts may reverse the neuromuscular blockade due to aminoglycosides (see section 4.9).

Ataluren
Amikacin should not be co-administered with ataluren due to the risk of potentiation of the aminoglycoside nephrotoxicity (see section 4.3).

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 limited data on use of aminoglycosides in pregnancy. 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 effects on the foetus or newborns have not been reported in pregnant women treated with other aminoglycosides, the potential for harm exists. 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 foetus.

Breast-feeding
It is not known whether amikacin is excreted in human milk. A decision should be made whether to discontinue breast-feeding or to discontinue therapy.

Fertility
In reproduction toxicology studies in mice and rats with parenterally administered amikacin, no effect on fertility or foetal toxicity was reported (see section 5.3).

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. Due to the occurrence of some side effects (see section 4.8) the ability to drive and use machines may be affected.

4.8 Undesirable effects

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 (see section 4.4).

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

System Organ Class	Frequency	MedDRA term
Infections and Infestations	Uncommon	Superinfections or colonization with resistant bacteria or yeast [a]
Blood and lympahtic system disorders	Rare	Anemia, eosinophilia, leukopaenia, 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	Uncommon	Dizziness[1], vertigo[1]
	Not known	Paralysis [a]
	Rare	Tremor [a], paresthesia [a], headache, balance disorder [a], migraine
	Very rare	Neuromuscular blockage
Eye disorders	Uncommon	Nystagmus[1]
	Rare	Blindness [b], retinal infarction [b]
Ear and labyrinth disorders	Rare	Tinnitus [a], hypoacusis [a]
	Not known	Deafness [a], neurosensory deafness [a]
Vascular disorders	Rare	Hypotension
Respiratory, thoracic and mediastinal disorders	Not known	Apnea, bronchospasm
	Rare	Respiratory function depression[3]
	Very rare	Respiratory paralysis[3] (isolated cases)
Gastrointestinal disorders	Uncommon	Nausea, vomiting
Skin and subcutaneous tissue disorders	Rare	Prutitus, urticaria, exanthema, skin rash
Musculoskeletal, connective tissue and bone disorders	Rare	Arthralgia, muscle twitching [a]
Renal and urinary disorders	Uncommon	Damage to renal tubuli[2], renal impairment[2]
	Not known	Acute renal failure, toxic nephropathy, cells in urine [a]
	Rare	Oliguria [a], increase in serum creatinine [a], albuminuria [a], azotemia [a], erythrocytes in urine [a], leukocytes in urine [a]
General disorders and administration site conditions	Rare	Pyrexia

Investigations	Rare	Aspartate aminotransferase increased, alanine aminotransferase increased, alkaline phosphatase increased (slight and transient)

[a]See section 4.4
[b]Amikacin is not intended for intravitreal use. Retinal blindness and infarction have been reported after intravitreous injection (injection into the eye) of amikacin.
(1) These effects were seen in particular when the recommended dosage level was exceeded, in treatment lasting longer than 10 days, or when the dose was not adequately reduced for patients with renal dysfunction. Initial symptoms of vestibular disturbances are dizziness, nausea and vomiting. The clinical examination often reveals a nystagmus. Vestibular disturbances are reversible in almost any case. The first symptoms of cochlear dysfunction often include a loss of high-tone perception (≥4,000 Hertz) that precedes hearing loss and is detected only by audiometry.

(2) Another uncommon adverse effect is damage to the renal tubules with renal impairment. The mechanism of renal damage involves accumulation in the lysosomes, phospholipase inhibition and necrosis of tubular cells after repeated administration of amikacin. Once daily dosing may reduce the risk of nephrotoxicity. Renal damage is reversible to varying degrees but exacerbates the risk of a cumulation process which may cause or intensify ototoxic effects. An increase in the serum creatinine concentration, the presence of albumin, red and white blood cells or cylinders in urine, uraemia and oliguria are possible.

(3) In rare cases, if intravenous infusion of the medicinal product is too fast, respiratory functions may be seriously depressed. In isolated cases this can lead to respiratory paralysis; the risk also exists when amikacin is administered in combination with anaesthesia and muscle relaxants (see section 4.5).

Changes in renal function are usually reversible upon discontinuation of the drug.

Toxic effects in the eighth cranial nerve can lead to hearing loss, loss of balance or both. Amikacin mainly affects the auditory function. Cochlear impairment involves high-frequency deafness and usually occurs before hearing loss is clinically detected by an audiometric test (see section 4.4).

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 the HPRA Pharmacovigilance Website: www.hpra.ie.

4.9 Overdose

In case of overdosage there is a general risk for nephro-, oto- and neurotoxic (neuromuscular blockage) reactions. Neuromuscular blockage with respiratory arrest needs appropriate treatment including application of ionic calcium (e.g. as gluconate or lactobionat in 10-20% solution) (see section 4.4). In the event of overdosage or toxic reaction, peritoneal dialysis or haemodialysis will aid in the removal of amikacin from the blood.

Amikacin levels are also reduced during continuous arteriovenous hemofiltration.
In the newborn infant, exchange transfusion may also be considered.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

Mechanism of action
Amikacin acts via the inhibition of protein synthesis at the bacterial ribosome through interaction with the ribosomal RNS and subsequent inhibition of the translation in susceptible microbes. This results in a bactericidal action.

PK/PD

The most important PK/PD parameters to predict the bactericidal effect of amikacin is the ratio of the maximum concentration in serum (Cmax) and the minimal inhibitory concentration (MIC) of the respective pathogen. A Cmax/MIC ratio of 8:1 or 10:1 is considered to result in efficient bacterial
killing and prevention of bacterial re-growth. Amikacin shows a post-antibiotic effect in vitro and in vivo. The post-antibiotic effect permits the dosage interval to be extended without loss of efficacy against most Gram-negative bacilli.

Mechanism(s) of resistance
Resistance to amikacin may emerge from the following mechanisms:

– Enzymatic inactivation: An enzymatic modification of the aminoglycoside molecules is the most prevalent resistance mechanism. This is mediated by acetyltransferases, phosphotransferases, or nucleotidyltransferases, which are mainly encoded by plasmids. Amikacin has been shown to be effective against many aminoglycoside-resistant strains due to its ability to resist to degradation by aminoglycoside-inactivating enzymes.

– Reduced penetration and active efflux: These resistance mechanisms are observed in *Pseudomonas aeruginosa*. Recent data indicate the emergence of similar resistance mechanisms in *Acinetobacter* spp.

– Alteration of the target structure: Modifications within the ribosomes are only occasionally observed as the cause of resistance.

The emergence of resistance during therapy is unusual. A partial cross-resistance between amikacin and other aminoglycoside antibiotics exists.

Breakpoints
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

Spectrum of activity of amikacin:
The prevalence of acquired resistance may vary geographically and with time for selected species and local information on resistance is desirable, particularly when treating severe infections. As necessary, expert advice should be sought when the local prevalence of resistance is such that the utility of the agent in at least some types of infections is questionable.

Commonly susceptible species
Aerobic Gram-positive micro-organisms
Staphylococcus aureus
Staphylococcus haemolyticus
Staphylococcus hominis°
Aerobic Gram-negative micro-organisms
Acinetobacter pittii
Citrobacter freundii
Citrobacter koseri
Enterobacter aerogenes
Enterobacter cloacae
Escherichia coli
Klebsiella oxytoca
Klebsiella pneumoniae
Morganella morganii
Proteus mirabilis
Proteus vulgaris [0]
Pseudomonas aeruginosa [1]
Salmonella enterica [0]
Serratia liquefaciens[0]
Seratia marcescens
Shigella spp.
Species for which acquired resistance may be a problem
Aerobic Gram-positive micro-organisms

Staphylococcus epidermidis
Aerobic Gram-negative micro-organisms
Acinetobacter baumannii
Inherently resistant organisms
Aerobic Gram-positive micro-organisms
Enterococcus spp.
Streptococcus spp.
Aerobic Gram-negative micro-organisms
Burkholderia cepacia
Stenotrophomonas maltophila
Anaerobes
Bacteroides spp.
Prevotella spp.
Other microorganisms
Chlamydia spp.
Chlamydophila spp.
Mycoplasma spp.
Ureaplasma urealyticum

[1] The resistance rate of isolates from special patient groups e.g. patients with cystic fibrosis is ≥ 10 %.
[0] At the time of publication of these tables no up-to-date data were available. In primary literature, standard reference books and therapy recommendations susceptibility is assumed.

5.2 Pharmacokinetic properties

Generally:
In healthy adults, the mean serum half-life slightly exceeds 2 hours with an average total apparent distribution volume of 24 liters, approximately 28% of body weight. Serum plasma protein binding ranges from 0 to 11%. The average serum clearance rate is approximately 100 ml / min and the renal clearance rate is 94 ml / min in individuals with normal renal function.

Amikacin is eliminated by glomerular filtration as the predominant elimination pathway. Patients with impaired renal function or decreased glomerular filtration excrete the antibiotic much more slowly, extending the serum half-life. Therefore, renal function should be closely monitored and the dosage adjusted accordingly (see 4.2 Posology and method of administration, Renal impairment).

Following administration of the recommended dose, therapeutic levels of amikacin are found in bones, heart, gallbladder, and lung tissue along with significant concentrations in urine, bile, sputum, bronchial secretions, interstitial, pleural, and synovial fluid.

Data from multiple daily dose trials show that cerebrospinal fluid levels in normal infants are approximately 10 to 20% of serum concentrations and can reach 50% in meningeal inflammation.

Intramuscular administration:
Amikacin after intramuscular administration is rapidly absorbed and is well tolerated locally. In healthy adult volunteers, mean maximum serum concentrations of approximately 12, 16, and 21 mcg / ml are obtained one hour after single intramuscular doses of 250 mg (3.7 mg/kg), 375 mg (5 mg/kg), and 500 mg, (7.5 mg/kg), respectively. At 10 hours, plasma levels are approximately 0.3 mcg/ml, 1.2 mcg/ml and 2.1 mcg/ml, respectively. When the drug is administered at the recommended dose, there is no evidence of accumulation with repeated doses for 10 days.

In patients with normal renal function, 91.9% of an intramuscular dose is excreted unchanged in the urine within the first 8 hours and 98.2% within 24 hours. Mean urine concentrations for 6 hours are 563 mcg/ml after 250 mg, 697 mcg/ml after 375 mg and 832 mcg/ml after 500 mg.

Intravenous administration:
Single doses of 500 mg (7.5 mg/kg) that were administered to healthy adult volunteers with a 30-minute infusion gave mean maximal serum concentrations of 38 mcg/ml at the end of infusion and concentrations of 24 mcg/ml, 18 mcg/ml and 0,75 mcg/ml at 30 minutes, 1 hour and 10 hours after infusion, respectively. 84% of the administered dose was excreted in the urine in 9 hours and 94% in 24 hours. Repeated injections of 7.5 mg/kg every 12 hours in normal adults were well tolerated and did not result in drug accumulation.

Intravenous administration of single doses of 15 mg/kg over 30 minutes in adult volunteers with normal renal function resulted in mean peak serum concentrations of 77 mcg/ml and levels of 47 mcg/ml and 1 mcg/ml in 1 and 12 hours, respectively, after injection. Mean serum concentrations of 55 mcg/ml are observed after infusion of 15 mg/kg over 30 minutes in elderly patients (mean creatinine clearance 64 ml/min) with serum concentrations of 5.4 mcg/ml in 12 hours and 1.3 mcg/ml in 24 hours after infusion. In multiple dose studies, no accumulation effects have been shown in patients with normal renal function who have received single daily doses of 15 to 20 mg/kg.

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

In a single study of newborns (1-6 days of after birth) grouped by birth weight (<2000, 2000-3000 and >3000g) amikacin was administered intramuscularly and/or intravenously at a dose of 7.5 mg/kg. Clearance in neonates >3000 g was 0.84 ml/min/kg and terminal half-life was about 7 hours. In this group, the initial volume of distribution and volume of distribution at steady state was 0.3 ml/kg and 0.5 ml/kg, respectively. 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

Carcinogenicity
In a 2-year inhalation carcinogenicity study with inhaled liposomal amikacin in rats, squamous cell carcinoma was observed in the lungs of 2 of 120 rats. The relevance of the lung tumour findings with regards to humans receiving injected amikacin is unknown.

Genotoxicity
No evidence of mutagenicity or genotoxicity was observed in a battery of *in vitro* and *in vivo* genotoxicity studies with liposomal amikacin formulations.

Reproductive and development toxicity
In reproduction toxicology studies in mice and rats with parenterally administered amikacin, no effect of fertility or fetal toxicity was reported.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium citrate dihydrate
Sodium metabisulfite
Sulfuric acid (for pH adjustment)
Water for injections

6.2 Incompatibilities

This medicinal product must not be mixed with any other medicinal products (except those mentioned in section 6.6.).

Mixing aminoglycosides with β-lactam antibiotics (penicillins or cephalosporins) in an infusion solution can lead to significant mutual inactivation. Decreased serum activity may also be observed when an aminoglycoside or a penicillin-type antibiotic is administered *in vivo* by separate route. Aminoglycoside inactivation is of clinical importance only in patients with severe renal impairment. Inactivation may persist in body fluid samples taken for assays, resulting in inaccurate aminoglycoside measurements. Samples must be handled properly (direct examination, freezing or β-lactamase effect).

Chemical incompatibilities are known for amphotericin, chlorothiazides, erythromycin, heparin, nitrofurantoin, novobiocin, phenytoin, sulfadiazine, thiopentone, chlortetracycline, vitamin B and vitamin C. Amikacin must not be pre-mixed with these medicinal products.

6.3 Shelf life

Unopened: 2 years

After dilution:
Diluted solutions having final concentrations below 2.5 mg/ml should be used immediately.

Chemical and physical in-use stability has been demonstrated for 24 hours at 23-27 °C under artificial light and at 2-8°C with 0.9% Sodium Chloride Injection and Lactated Ringer's Injection, at a concentration of Amikacin of 2.5 mg/mL, 5.0 mg/mL, 7.5 mg/mL and 15.0 mg/mL.

Chemical and physical in-use stability has been demonstrated for 3 hours at 23-27 °C under artificial light and for 12 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, 5.0 mg/mL and 7.5 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 15.0 mg/mL**.**

From a microbiological point of view, unless the method of opening precludes the risk of microbial contamination, the product should be used immediately. If not used immediately, in-use storage times and conditions are the responsibility of the user.

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 in cartons of 1 and 10 ampoules.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

The medicinal product should be visually inspected for particulate matter and discoloration prior to administration. Only clear solutions free from particles should be used.

Single use only.

Unused solution should be discarded.

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

Intravenous administration: Preparation of solutions

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

In pediatric patients, the amount of fluid that will be used depends on the amount that will be tolerated by the patient. It should be sufficient in order to inject amikacin over a period of 30 to 60 minutes

7 MARKETING AUTHORISATION HOLDER

Noridem Enterprises Limited
Evagorou & Makariou
Mitsi Building 3, Office 115
1065 Nicosia
Cyprus

8 MARKETING AUTHORISATION NUMBER

PA1122/034/002

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 24th May 2024

10 DATE OF REVISION OF THE TEXT