Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Amikacin Caragen 250 mg/ml solution for injection/infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 1 ml of solution for injection/infusion contains 250 mg of amikacin (as sulfate).
Each vial of 2 ml of solution for injection/infusion contains 500 mg of amikacin (as sulfate).

Excipients with known effect
Sodium 7.5 mg/ml
Sodium metabisulfite 6.60 mg/ml
For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for injection/infusion
Clear, colourless to pale yellow solution
pH 3.5-5.5

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Amikacin is indicated in the short-term treatment of serious infections due to susceptible strains of Gram-negative bacteria, including *Pseudomonas* species, *Escherichia coli*, indole-positive and indole-negative *Proteus* species, *Providencia* sp, *Klebsiella* sp, *Enterobacter* sp, *Serratia* sp and *Acinetobacter* sp. Many strains of these Gram-negative organisms resistant to gentamicin and tobramycin show sensitivity to amikacin *in vitro*.

Amikacin may also be indicated for the treatment of known or suspected staphylococcal disease. The principal Gram-positive organism sensitive to amikacin is *Staphylococcus aureus*, including some methicillin-resistant strains. Amikacin has some activity against other Gram-positive organisms including certain strains of *Streptococcus pyogenes*, *Enterococci* and *Diplococcus pneumoniae*.

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

4.2 Posology and method of administration

Amikacin sulfate injection may be given intramuscularly or intravenously.

For most infections, the intramuscular route is preferred. However, in life-threatening infections or in patients for whom intramuscular administration is not possible, the medicine can be administered intravenously, either as is (2-3 minutes) or by slow infusion within 30 to 60 minutes. In infants, it should be administered as infusions lasting 1 to 2 hours.

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

The patient's pre-treatment 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. The blood urea nitrogen (BUN) is much less reliable for this purpose. Reassessment of renal function should be made periodically during therapy.

Amikacin concentrations in serum should be measured to assure adequate, but not excessive levels. It is desirable to measure both peak and trough serum concentrations intermittently during therapy. Peak concentrations (30-90 minutes after injection) above 35 mcg/ml and trough concentrations (just prior to the next dose) above 10 mcg/ml should be avoided. Dosage should

be adjusted as indicated. In patients with normal renal function, once-daily dosing may be used; peak concentrations in these cases may exceed 35 mcg/ml.

The usual duration of treatment is 7 to 10 days. In difficult and complicated infections where treatment beyond 10 days is considered, the use of amikacin sulfate injection should be re-evaluated and, if continued, renal, auditory, vestibular function should be monitored, as well as serum amikacin levels.

The total daily dose by all routes of administration should not exceed 15-20 mg/kg/day.

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

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

Adults and Children over 12 years
The recommended intramuscular or intravenous dosage for adults and adolescents with normal renal function (creatinine clearance ≥50 ml/min) is 15 mg/kg/day which may be administered as a single daily dose or divided into 2 equal doses i.e. 7.5 mg/kg q 12 h. 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 4 weeks to 12 years
The recommended intramuscular or intravenous (slow intravenous infusion) dose in children with normal renal function is 15-20 mg/kg/day which may be administered as 15-20 mg/kg, once a day; or as 7.5 mg/kg q 12 h. In endocarditis and in febrile neutropenic patients dosing should be twice daily, 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 q 12 h (see sections 4.4 and 5.2).

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

Intravenous administration
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.

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

Life-threatening infections and/or those caused by pseudomonas
The adult dose may be increased to 500 mg every eight hours but should never exceed 1.5 g/day nor be administered for a period longer than 10 days. A maximum total adult dose of 15 g (i.e. entire treatment course) should not be exceeded.

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

Impaired renal function
Patients suffering from pre-existing renal insufficiency should be assessed prior to therapy and periodically during therapy.

Regular monitoring of serum drug concentration and of renal function is particularly important in elderly patients, who may have reduced renal function that may not be evident in the results of routine screening tests i.e. blood urea and serum creatinine.

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.

In patients with renal impairment the interval between doses lengthened and/or the dose should be reduced in accordance with serum creatinine concentrations to avoid accumulation of abnormally high blood levels and to minimise the risk of ototoxicity. Both methods (described in detail below) 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 Dose at Prolonged Intervals Between Dosing: If the creatinine clearance rate is not available and the patient's condition is stable, a dosage interval in hours for the normal single dose (ie, that which would be given to patients with normal renal function on a twice daily schedule, 7.5 mg/kg) can be calculated by multiplying the patient's serum creatinine by nine; eg, if the serum creatinine concentration is 2mg/100mL, the recommended single dose (7.5 mg/kg) should be administered every 18 hours.

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

As renal function may alter appreciably during therapy, the serum creatinine should be checked frequently and the dosage regimen modified as necessary.
Reduced Dose at Fixed Time Intervals Between Dosing: When renal function is impaired and it is desirable to administer amikacin sulfate injection at a fixed time interval, dose must be reduced. In these patients, serum amikacin concentrations should be measured to assure accurate administration and to avoid excessive serum concentrations. If serum assay determinations are not available, and patient's condition is stable, serum creatinine and creatinine clearance values are the most readily available indicators of the degree of renal impairment to use as a guide for dosage.
First initiate therapy by administering a normal dose, 7.5 mg/kg, as a loading dose. This dose is the same as the normally recommended dose which would be calculated for a patient with a normal renal function as described above.
To determine the size of maintenance doses administered every 12 hours, the loading dose should be reduced in proportion to the reduction in the patient's creatinine clearance rate:

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

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

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

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). The intraperitoneal use of amikacin is not recommended in young children.

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

Method of administration

Amikacin sulfate injection may be given intramuscularly or intravenously, see earlier discussion in section 4.2. If required, suitable diluents for intravenous use are: Sodium chloride 0.9% (9 mg/ml) solution for injection or glucose 5 % (50 mg/ml) solution for injection
For instructions on dilution of the medicinal product before administration, see section 6.6.

4.3 Contraindications

Amikacin sulfate injection is contraindicated in patients with known allergy to amikacin or any of the excipients listed in section 6.1.

A history of hypersensitivity or serious toxic reactions to aminoglycosides may contraindicate the use of any aminoglycoside because of the known cross sensitivities of patients to drugs in this class.

Aminoglycosides may impair neuromuscular transmission, and should not be given to patients with myasthenia gravis.

4.4 Special warnings and precautions for use

General
Patients should be well hydrated during amikacin therapy.

Amikacin concentrations in serum should be measured to assure adequate, but not excessive levels. It is desirable to measure both peak and trough serum concentrations intermittently during therapy, see Section 4.2.

Patients treated with parenteral aminoglycosides should be under close clinical observation because of the potential ototoxicity and nephrotoxicity associated with their use, discussed in more detail below.

Evidence of ototoxicity (dizziness, vertigo, tinnitus, roaring in the ears, and hearing loss) or nephrotoxicity requires discontinuation of the drug or dosage adjustment.

Particular caution should be applied to patients with pre-existing renal insufficiency, pre-existing hearing or vestibular damage, and elderly patients.

Other factors that may increase risk of toxicity are advanced age and dehydration. Safety for treatment periods which are longer than 14 days has not been established.

Renal Toxicity
Aminoglycosides are potentially nephrotoxic. Renal toxicity is independent of plasma obtained at the peak (Cmax). The risk of nephrotoxicity is greater in patients with impaired renal function, and in those who receive higher doses, or in those whose therapy is prolonged. See section 4.2 for dose adjustment in patients with renal impairment.

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. Urine should be examined for decreased specific gravity, increased excretion of proteins, and the presence of cells or casts. 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 experience impairment of renal function that is not evident in routine tests such as blood urea nitrogen (BUN) or serum creatinine. Determining creatinine clearance may be more useful. It is especially important to monitor renal function in elderly patients during treatment with aminoglycosides.

Renal and 8th cerebral conjugation should be closely monitored, particularly in patients with impairment or suspected impairment of renal function at the beginning of treatment, as well as in patients in whom renal function is initially normal but who develop signs of renal impairment during treatment. Serum amikacin concentrations should, where practicable, be monitored to ensure adequate levels and to avoid levels that may cause toxicity. Urine should be examined for a decrease in specific gravity, an increase in albumin excretion and the presence of epithelium or cylinders. Blood urea nitrogen, serum creatinine or creatinine clearance should be measured periodically. Sequential audiograms should be performed, where possible, in patients who are of the age that can be examined, especially in high-risk patients. Evidence of ototoxicity (dizziness, vertigo, tinnitus and hearing loss) or nephrotoxicity requires discontinuation of the antibiotic or dosage adjustment.

Concomitant and/or sequential systemic, oral or topical use of other neurotoxic or nephrotoxic products should be avoided. Other factors that may increase the risk of toxicity are advanced age and dehydration.

A mixture of aminoglycosides with beta-lactam antibiotics (penicillins or cephalosporins) in vitro may lead to significant mutual inactivation. A decrease in serum activity may also be observed when an aminoglycoside or penicillin-like antibiotic is administered in vivo by a separate route. Inactivation of aminoglycosides is of clinical relevance only in patients with severe impairment of renal function. Inactivation may also continue in body fluid samples taken for determination, resulting in inaccurate measurements of aminoglycosides. Samples must be handled appropriately (direct examination, freezing or β-lactamase effect).

Serum concentrations of amikacin should be monitored when feasible to assure adequate levels and to avoid potentially toxic levels

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, and in those who receive high doses, or in those whose therapy is prolonged over 5-7 days of treatment, even in healthy patients. Deafness usually occurs first at high frequencies that can only be detected by an audiometric test. Vertigo can be observed and is a sign of vestibular damage. Other manifestations of neurotoxicity can be numbness, tingling, muscle twitching and spasms. Patients who develop cochlear or vestibular damage may not experience during treatment symptoms that warn them of the development of toxicity from the 8th conjugation, universal or partial irreversible bilateral deafness or intense vertigo may be observed after discontinuation of the antibiotic. Ototoxicity from aminoglycosides is usually irreversible.

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

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.

Serial audiograms should be obtained where feasible in patients old enough to be tested, particularly high risk patients.

Continued treatment with Amikacin should only occur following a risk/benefit assessment by a senior clinician (or similar).

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 anaesthetics, neuromuscular blocking agents such as tubocurarine, succinylcholine, decamethonium, atracurium, rocuronium, vecuronium or in patients receiving massive transfusions of citrate-anticoagulated blood. 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. Amikacin must not be used in patients with myasthenia gravis. 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.

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.

Other

The use of amikacin in patients with a history of allergy to aminoglycosides should be used only if, in the opinion of the physician, therapeutic advantages outweigh the potential risks.

Concurrent and/or sequential, oral, or topical use of other neurotoxic or nephrotoxic products, particularly bacitracin, cisplatin, amphotericin B, cephaloridine, paromomycin, viomycin, polymyxin B, colistin, vancomycin, or other aminoglycosides, should be avoided (see section 4.5)

The use of amikacin 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, 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.

Large doses of amikacin administered during surgery have been responsible for a transient myasthenic syndrome. Aminoglycosides are quickly and almost totally absorbed when they are applied topically, except to the urinary bladder, in association with surgical procedures. Irreversible deafness, renal failure and death due to neuromuscular blockade have been reported following irrigation of both small and large surgical fields with an aminoglycoside preparation.

As with other antibiotics, the use of amikacin may result in overgrowth of non-susceptible organisms. 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 medicinal product contains 15 mg sodium per vial, equivalent to 0.75% of the WHO recommended maximum daily intake of 2 g sodium for an adult.

Sodium metabisulfite: May rarely cause severe 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 or nephrotoxic agents, particularly bacitracin, cisplatin, amphotericin B, ciclosporin, tacrolimus, cephaloridine, paromomycin, viomycin, polymyxin B, colistin, vancomycin, or other aminoglycosides should be avoided either systemically or topically because of the potential for additive effects.

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.

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 bisulfite component of the amikacin sulfate formulation.

There is a risk of respiratory paralysis in patients takinganaesthetics, drugs that cause neuromuscular blockade such as succinylcholine,decamethonium, atracurium, rocuronium, vecuronium or in patients given largeblood transfusions with citrates as anticoagulants.

Indomethacin may increase the plasma concentration of amikacin in neonates.

4.6 Fertility, pregnancy and lactation

Pregnacy
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.
The safety of amikacin in pregnancy has not yet been established.

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 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. Due to the occurrence of some adverse reactions (see section 4.8) the ability to drive and use machines may be impaired.

4.8 Undesirable effects

This list is presented by system organ class, MedDRA preferred term, and frequency using the following frequency categories: very common (≥1/10), common (≥1/100, < 1/10), uncommon (≥1/1 000, < 1/100), rare (≥1/10 000, < 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	Anaemia, eosinophilia
Immune system disorders	Not known	Anaphylactic response (anaphylactic reaction, anaphylactic shock and anaphylactoid reaction), hypersensitivity
Metabolism and nutrition disorders	Rare	Hypomagnesaemia
Nervous system disorders	Not known	Paralysis[a]
	Rare	Tremor[a], paresthesia[a], headache, balance disorder[a]
Eye disorders	Rare	Blindness[b], retinal

		infarction[b]
Ear and labyrinth Disorders	Rare	Tinnitus[a], hypoacusis[a]
	Not known	Deafness[a], deafness neurosensory[a]
Vascular disorders	Rare	Hypotension
Respiratory, thoracic and mediastinal disorders	Not known	Apnoea, bronchopasm
Gastrointestinal disorders	Uncommon	Nausea, vomiting
Skin and subcutaneous tissue disorders	Uncommon	Rash
	Rare	Pruritus, urticaria
Musculoskeletal, connective tissue and bone disorders	Rare	Arthralgia, muscle twitching [a]
Renal and urinary disorders	Not known	Renal failure acute, nephropathy toxic, cells in urine[a]
	Rare	Oliguria[a], blood creatinine increased[a], albuminuria[a], azotemia[a], red blood cells urine[a], white blood cells urine[a]
General disorders and administration site conditions	Rare	Pyrexia

[a] See section 4.4.
[b]Amikacin is not formulated for intravitreal use. Blindness and retinal infarction have been reported following intravitreous admistrations (injection into the eye) of amikacin.

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)
Renal function changes are usually reversible when the drug is discontinued.

Toxic effects on the eighth cranial nerve can result in hearing loss, loss of balance, or both. Amikacin primarily affects auditory function. Cochlear damage includes high frequency deafness and usually occurs before clinical hearing loss can be detected by audiometric testing (see section 4.4).

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

When the recommended precautions and dosages are followed the incidence of toxic reactions, such as tinnitus, vertigo, and partial reversible deafness, skin rash, drug fever, headache, paraesthesia, nausea and vomiting is low. Urinary signs of renal irritation (albumin, casts, and red or white cells), azotaemia and oliguria have been reported although they are rare.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the 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:
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 gluconat 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

ATC code: J01G B06
Amikacin is a semi-synthetic aminoglycoside antibiotic derived from Kanamycin A. It is active against a broad spectrum of Gram-negative organisms, including *pseudomonas*, *Escherichia coli* and some Gram-positive organisms, e.g. *Staphylococcus aureus*.

Aminoglycoside antibiotics are bactericidal in action. Although the exact mechanism of action has not been fully elucidated, the drugs appear to inhibit protein synthesis in susceptible bacteria by irreversibly binding to 30S ribosomal subunits.

Strains of the above microorganisms resistant to other aminoglycosides such as gentamicin, tobramycin and kanamycin may be susceptible *in vitro* to amikacin. Amikacin is resistant to degradation by most enzymes that inactivate aminoglycosides and are known to affect gentamicin, tobramycin and kanamycin.

In vitro studies have shown that amikacin in combination with a beta-lactam antibiotic acts synergistically against many clinically important Gram-negative microorganisms. Persistent suppression of bacterial growth of many Gram-negative microorganisms occurs after *in vitro* exposure to amikacin.

Gram-positive bacteria: penicillinase-producing and non-penicillinase-producing *Staphylococcus sp,* including methicillin-resistant strains. Methicillin-resistant *Staphylococcus aureus* (MRSA)may not be fully susceptible to amikacin. Aminoglycosides have generally been shown to have little activity against other Gram-positivemicroorganisms e.g. *Streptococcus pyogenes,* enterococci and *Streptococcuspneumoniae*.

Disc susceptibility tests
Quantitative methods that require measurement of zone diameters provide accurate estimates of antibiotic susceptibility. Such a disk procedure is recommended for testing susceptibility to amikacin. Interpretation involves correlating the diameters obtained in the disk test with the MIC values of amikacin. When the causative organism is tested by the Kirby-Bauer disk susceptibility method, a 30 mcg amikacin disk must give a zone of 17 mm or greater to indicate susceptibility. Zone sizes of 14 mm or less indicate resistance. Zone sizes of 15 to 16 mm indicate moderate susceptibility. With this procedure, a report of "susceptible" by the laboratory indicates that the pathogen is likely to respond to therapy. A report of "resistant" indicates that the pathogen is unlikely to respond to therapy. The report "intermediately susceptible" indicates that the microorganism would be susceptible if the infection were limited to tissues and fluids (e.g. urine) in which high concentrations of the antibiotic are achieved.

5.2 Pharmacokinetic properties

Amikacin is rapidly absorbed after intramuscular injection. Peak plasma concentrations equivalent to about 20 mg/ml are achieved one hour after IM doses of 500 mg, reducing to about 2 µg/ml 10 hours after injections.

Twenty per cent or less is bound to serum protein and serum concentrations remain in the bactericidal range for sensitive organisms for 10 to 12 hours.

Single doses of 500 mg administered as an intravenous infusion over a period of 30 minutes produce a mean peak serum concentration of 38 µg/ml. Repeated infusions do not produce drug accumulation in adults with normal renal function. However, decreased renal function will lead to accumulation.

In adults with normal renal function the plasma elimination half-life of amikacin is usually 2-3 hours with a mean total apparent volume of distribution of 24 liters, approximately 28% of body. weight. Serum protein binding ranges from 0 to 11%. The mean rate of Serum clearance is approximately 100 ml/min and the renal clearance rate is 94 ml/min in subjects with normal renal function. 94 - 98% of a single IM or IV dose of amikacin is excreted unchanged by glomerular filtration within 24 hours. Urine concentrations of amikacin average 563 µg/ml in the first 6 hours following a single 250 mg IM dose and 163 µg/ml over 6-12 hours. Following a single 500 mg IM dose urine concentrations average 832 µg/ml in adults with normal renal function.

Amikacin is excreted mainly by glomerular filtration. Patients with impaired renal function or reduced glomerular filtration excrete the antibiotic much more slowly, prolonging the serum half-life. Therefore, renal function should be carefully monitored and dosing adjusted accordingly (see 4.2 Posology and method of administration, Impaired renal function).

After administration at recommended doses, therapeutic levels are found in bones, heart, gallbladder and lung tissue together with significant concentrations in urine, bile, sputum, bronchial secretions, median, pleural and synovial fluid.

Data from multiple daily dose trials show that spinal fluid levels in normal infants are approximately 10 to 20% of the serum concentrations and may reach 50% in meningitis.

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

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

Intravenous administration:
Single doses of 500 mg (7.5 mg/kg) administered to normal adult volunteers by infusion over 30 minutes gave mean maximum serum concentrations of 38 mcg/ml at the end of the 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 dose administered was excreted in urine in 9 hours and 94% in 24 hours. Repeated infusions of 7.5 mg/kg every 12 hours in normal adults were well tolerated and did not cause drug aggregation.

Intravenous administration of single doses of 15 mg/kg over 30 minutes to adult volunteers with normal renal function resulted In mean maximum serum concentrations of 77 mcg/ml and levels of 47 mcg/ml and 1 mcg/ml in 1 and 12 hours, respectively, after infusion. Mean maximum 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 studies with multiple doses, no summation was observed in patients with normal renal function receiving doses of 15 to 20 mg/kg once daily.

Intramuscular and intravenous administration
In neonates and particularly in premature babies, the renal elimination of amikacin is reduced.
In a single study in newborns (1-6 days of postnatal age) grouped according to birth weights (<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 mg/kg, respectively. In the groups with lower birth weight clearance/kg was lower and half-life longer. Repeated dosing every 12 hours in all the above groups did not demonstrate accumulation after 5 days.

5.3 Preclinical safety data

Carcinogenesis, mutagenicity, impairment of fertility
No long-term studies in laboratory animals have been performed to assess the potential for carcinogenicity, and mutagenicity has not been studied. Amikacin, after administration to rats at doses up to 10 times the human daily dose, did not impair male or female fertility.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium citrate
Sodium metabisulfite

Sulfuric acid (for pH adjustment)
Water for Injections

6.2 Incompatibilities

Amikacin is incompatible with some penicillins and cephalosporins, amphotericin, chlorothiazide sodium, erythromycin gluceptate, heparin, nitrofurantoin sodium, phenytoin sodium, sodium thiopental, warfarin sodium, and depending on the composition and strength of the vehicle, tetracyclines, vitamins of the B group with vitamin C, and potassium chloride.

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

6.3 Shelf life

Unopened: 2 years.

Following dilution in sodium chloride 0.9 % (9 mg/ml) solution for injection or glucose 5 % (50 mg/ml) solution for injection, chemical and physical in-use stability has been demonstrated for 24 hours at 2-8 °C and at 25 °C, in non-PVC bags.

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 2-8 °C, 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.
For storage conditions after dilution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

Glass vial with a bromobutyl rubber stopper, aluminium cap and plastic flip-off top.
Pack size: 1 vial

6.6 Special precautions for disposal and other handling

The medicinal product should be inspected visually for particulate matter and discolouration prior to administration.
Before intravenous infusion, the desired dose of Amikacin is added to 100 or 200 ml of sodium chloride 9 mg/ml (0.9%) solution for injection or glucose 50 mg/ml (5%) solution for injection.
Single use only.
Discard any unused contents.

7 MARKETING AUTHORISATION HOLDER

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8 MARKETING AUTHORISATION NUMBER

PA22939/001/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 25th June 2021

Date of last renewal: 1st May 2026

10 DATE OF REVISION OF THE TEXT

May 2026