NEW ZEALAND DATA SHEET

1. PRODUCT NAME

Amikacin Medsurge 500 mg/2 mL solution for Injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Amikacin is a semisynthetic aminoglycoside antibiotic derived from kanamycin. The injection consists of the sulfate salt.

Each 2 mL vial contains amikacin sulfate equivalent to amikacin activity 500 mg (500,000 I.U.).

Excipient(s) with known effect

- Sodium metabisulfite

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Amikacin Medsurge Injection is a sterile clear, colourless to pale yellow solution pH 3.5 - 5.5, free from specks, lint, or other visible evidence of contamination.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Amikacin Injection is indicated in the short-term treatment of serious infections caused by susceptible strains of Gram-negative bacteria (see section 5.1).

Staphylococcus aureus, including methicillin-resistant strains is the principal Gram-positive organism sensitive to amikacin.

The use of amikacin in the treatment of staphylococcal infections should be restricted to second-line therapy, and should be confined to patients suffering from severe infections caused by susceptible strains of staphylococcus who have failed to respond or are allergic to other available antibiotics.

Amikacin Injection is indicated in the treatment of neonatal sepsis when sensitivity testing indicates that other aminoglycosides cannot be used.

In certain severe infections such as neonatal sepsis, concomitant therapy with a penicillin type drug may be indicated because of the possibility of infections due to Gram-positive organisms such as streptococci or pneumococci. If concomitant treatment with a penicillin type drug is indicated, then the drugs should be administered separately and at different sites because *in-vitro* mixing of the two drugs causes inactivation of amikacin.

Clinical studies have shown amikacin to be effective in treating bacteraemia, septicaemia including neonatal sepsis and serious infections of the respiratory tract, bones and joints, central nervous system, skin and skin structures (including those resulting from burns), intra-abdominal organs, post-operative infections and complicated and recurrent urinary tract infections, when caused by susceptible organisms.

4.2 Dose and method of administration

Uncomplicated infections due to sensitive organisms should respond to treatment within 24 to 48 hours at the recommended dosage. If no improvement occurs within three to five days, the use of amikacin sulfate should be re-evaluated and consideration be given to alternative therapy. Failure of the infection to respond may be due to resistance of the organism or to the presence of septic foci requiring surgical drainage.

Whenever possible, and especially in patients with impaired renal function, peak and trough amikacin serum concentrations should be determined and dosage adjusted where necessary to maintain desired serum concentrations. In general, desired peak concentrations are between 15 to 30 micrograms/mL, and trough concentrations should not exceed 5 to 10 micrograms/mL. An increased risk of toxicity may be associated with prolonged peak amikacin serum concentrations greater than 30 to 35 micrograms/mL.

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.

The patient's pre-treatment bodyweight should be obtained for calculation of correct dosage.

Intramuscular or Intravenous Administration

The intramuscular route is preferred for most infections, but in life-threatening infections or when an intramuscular injection is not feasible, an intravenous infusion (0.25% over 30 to 60 minutes) may be used.

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

Dosage

Dosage of amikacin sulfate is expressed in terms of amikacin and calculated on a body weight basis. Dosage is identical for both routes of administration.

Adults and Children

The usual recommended dose of amikacin is 15 mg/kg daily given in two or three equally divided doses.

Neonates and Premature Infants

Dosage given for patients with normal renal function. Initiate treatment with a loading dose of 10 mg/kg followed by 7.5 mg/kg every 12 hours. The maximum total daily dose should not exceed 15 mg/kg. Solution infusions via the I.V. route should be given over a 1 to 2 hour period.

Insufficient clinical use has not enabled firm dosage guidelines to be established for the use of amikacin in premature infants.

Elderly

Amikacin is excreted by the renal route. Since renal function could be failing in the elderly, it should be assessed whenever possible and the dosage adjusted accordingly, if necessary. Refer to "Impaired renal function" of dosage description.

Urinary Tract Infections (other than pseudomonal infections)

500 mg/day in two equally divided doses is recommended.

Impaired Renal Function

In patients with impaired renal function, either the dose or the dosage interval needs to be adjusted to avoid accumulation. The dosage interval may be calculated using the following formula:

Serum creatinine concentration (mg / 100 mL) x 9 = dosage interval (hours)

This formula should not be used to calculate the dosage interval for elderly patients. Instead, it is advisable to base dosage on creatinine clearance.

Serum Creatinine Concentration (mg / 100 mL)		**Interval between doses of 7.5 mg/kg (hours)**
1.5		13.5
2.0		18
2.5		22.5
3.0		27
3.5		31.5
4.0	x 9 =	36
4.5		40.5
5.0		45
5.5		45.9
6.0		54

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

If it is desired to administer amikacin at a fixed time interval, the dosage must be reduced. It is recommended that the drug be given every 12 hours. Serum concentrations of the drug should be measured in these patients to ensure accurate administration and to avoid toxic serum levels.

If serum assay determinations are not available and the 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 in determining the dosage.

First, begin therapy by administering 7.5 mg/kg, which is half the normal daily dose.

To determine the size of maintenance doses administered every 12 hours, the initial dose should be reduced in proportion to the reduction in the patient's creatinine clearance rate (cc):

Maintenance dose every 12 hours	=	Observed cc in mL/min normal cc in mL/min	x	Calculated initial dose in mg

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 provided as guides to dosage when the measurement of amikacin serum levels is not feasible and are not intended to be rigid recommendations.

4.3 Contraindications

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

Amikacin Injection is contraindicated in patients with a known history of hypersensitivity to amikacin, any constituents of the injection (see section 6.1) or in patients who may have subclinical renal or eighth nerve damage induced by prior administration of nephrotoxic and/or ototoxic agents, as the toxicity may possibly be additive.

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.

4.4 Special warnings and precautions for use

Patients should be well hydrated during amikacin therapy.

Caution should be applied to patients with pre-existing renal insufficiency, pre-existing hearing or vestibular damage and diminished glomerular filtration. Treatment with amikacin for more than 14 days has not been established as being safe. Patients undergoing treatment with parenteral aminoglycosides should be under close clinical observation and evaluation because of the potential ototoxicity and nephrotoxicity associated with their use.

Allergic reactions

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

Sulfite-sensitivity

Amikacin Medsurge injection contains sodium metabisulfite, which may cause allergic-type reactions including anaphylactic symptoms and life-threatening or less severe asthmatic episodes in susceptible people. The overall prevalence of sulfite sensitivity in the general

population is uncommon and probably low. Sulfite sensitivity is seen more frequently in asthmatic than in non-asthmatic subjects.

Neurotoxicity

Neurotoxicity, manifested as vestibular and/or bilateral ototoxicity, can occur in patients treated with aminoglycosides. Other manifestations of neurotoxicity may include numbness, skin tingling, muscle twitching and convulsions.

Ototoxicity

In patients treated at higher doses or those whose therapy is prolonged over 5-7 days of treatment, even in healthy patients, ototoxicity, both auditory and vestibular can occur. Patients with impaired renal function have the highest risk of developing amikacin induced ototoxicity. The risk of ototoxicity due to aminoglycosides increases with the degree of exposure to either persistently high peak or high trough serum concentrations. As with other aminoglycosides, on rare occasions changes in renal and eighth cranial nerve function may not become manifest until soon after completion of therapy. Aminoglycoside induced ototoxicity is usually irreversible.

A pre-treatment audiogram should be obtained and repeated during therapy in patients with renal impairment undergoing treatment for 7 days or more as well as in other patients being treated for 10 days. High frequency deafness usually occurs first and can be detected only by audiometric testing. If tinnitus, dizziness, vertigo, roaring in the ears or subjective hearing loss develops; or if follow-up audiograms show significant loss of high frequency response, the use of amikacin sulfate therapy should be discontinued immediately. Lost function may not be fully restored.

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 and neuromuscular blockade 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 (e.g. in cats with high doses of amikacin [188 mg/kg].

Patients with muscular disorders

Amikacin must not be used in patients with myasthenia gravis. Aminoglycosides, including amikacin, 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 neuromuscular junction.

Visual disturbances

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

Monitoring of serum levels

Whenever possible, and especially in patients with renal impairment, peak and trough serum concentrations of amikacin should be determined periodically, and dosage should be adjusted, to maintain desired serum concentrations. In general, desirable peak concentrations of amikacin are 15-30 micrograms/mL, and trough concentrations of the drug should not exceed 5-10 micrograms/mL. An increased risk of toxicity may be associated with prolonged peak amikacin serum concentrations greater than 30-35 micrograms/mL.

Concurrent use with other antibiotics or potent diuretics

Since the risk of ototoxicity, irreversible deafness and nephrotoxicity is increased when amikacin is used in conjunction with the systemic or topical use of other potentially neurotoxic and/or nephrotoxic drugs (see section 4.5), such therapy should be avoided. This includes concurrent use with potent diuretics and other aminoglycosides. Other factors which may increase the risk of toxicity are dehydration and advancing age.

Superinfection

If overgrowth of nonsusceptible organisms occurs, appropriate therapy should be initiated.

Topical use

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.

Use in renal impairment

As with other aminoglycosides, amikacin sulfate is potentially nephrotoxic and neurotoxic; therefore, precautions on dosage and adequate hydration should be observed. 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.

Amikacin is present in high concentrations in the renal excretory system; therefore, patients should be well hydrated to minimise chemical irritation/damage of the renal tubules. Prior to initiating therapy, kidney function should be assessed by the usual methods and monitored periodically during the course of treatment.

A reduction in dosage (see section 4.2) is required if evidence of renal dysfunction occurs such

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

Renal and eighth-cranial nerve function should be closely monitored especially in patients with known or suspected renal impairment (e.g. diminished glomerular filtration) at the onset of therapy, and also in those whose renal function is initially normal but who develop signs of renal dysfunction during therapy. Serum concentrations of amikacin should be monitored when feasible to assure adequate levels and to avoid potentially toxic levels. Urine should be examined for decreased specific gravity, increased excretion of proteins, 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 feasible in patients old enough to be tested, particularly high risk patients. Evidence of ototoxicity (dizziness, vertigo, tinnitus, roaring in the ears, and hearing loss) or nephrotoxicity requires discontinuation of the drug or dosage adjustment.

Concurrent and/or sequential, oral, or topical use of other neurotoxic or nephrotoxic products, particularly bacitracin, cisplatin, amphotericin B, cefaloridine, 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.

Patients suffering from pre-existing renal insufficiency should be assessed by the usual methods prior to therapy and periodically during therapy. Daily doses should be reduced and/or the interval between doses lengthened in accordance with serum creatinine concentrations to avoid accumulation of abnormally high blood levels and to minimise the risk of ototoxicity. 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.

Use in the elderly

Because of its toxicity, amikacin should be used with caution in elderly patients only after less toxic alternatives have been considered and/or found ineffective. Elderly patients are more likely to have an age-related decrease in renal function. This may not be evident in the results of routine screening tests such as BUN or serum creatinine. A creatinine clearance determination may be more useful. Recommended doses should not be exceeded, and monitoring of renal function in elderly patients during treatment with aminoglycosides is particularly important. Elderly patients may require smaller daily doses of amikacin in accordance with their increased age, decreased renal function, and possibly, decreased weight. In addition, loss of hearing may result even in patients with normal renal function.

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 drugs.

4.5 Interaction with other medicines and other forms of interaction

Potent diuretics

If possible, do not give amikacin in conjunction with etacrynic acid, furosemide or other potent diuretics which may themselves cause ototoxicity or enhance aminoglycoside toxicity by altering antibiotic concentrations in serum and tissue.

Other neurotoxic and/or nephrotoxic agents

The concurrent or sequential use of other ototoxic, neurotoxic and/or nephrotoxic agents, particularly bacitracin, cisplatin, amphotericin B, ciclosporin, tacrolimus, cefaloridine, paromomycin, viomycin, polymyxin B, colistin, vancomycin, clindamycin, and cephalosporins, or other aminoglycosides, should be avoided either systemically or topically because of the potential for additive effects. Where this is not possible, monitor carefully.

Increased nephrotoxicity has been reported following concomitant parenteral administration of aminoglycoside antibiotics and cephalosporins. Concomitant cephalosporin use may spuriously elevate creatinine serum level determinations.

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

Anaesthetics/neuromuscular blocking agents or medications with neuromuscular blocking activity

Concurrent use of amikacin with agents with neuromuscular blocking activity e.g. succinylcholine, tubocurarine, decamethonium, halogenated hydrocarbon inhalation anaesthetics (including halothane, ether), opioid analgesics and massive transfusions with citrated anticoagulated blood, should be carefully monitored; neuromuscular blockade may be enhanced, resulting in skeletal muscle weakness and respiratory depression or paralysis (apnoea); caution is recommended when these medications and amikacin are used concurrently during surgery or in the postoperative period, especially if there is a possibility of incomplete reversal of neuromuscular blockade postoperatively; treatment with anticholinesterase agents or calcium salts may help to reverse the blockade.

Beta-lactam antibiotics

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. Therefore, when amikacin and penicillins are used together in patients with renal failure, the time of administration of each drug should be staggered so that several hours separate each infusion. 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).

Other

There is an increased risk of hypocalcaemia when aminoglycosides are administered with bisphosphonates.

Concomitantly administered thiamine (vitamin B1) may be destroyed by the reactive sodium

bisulfite component of the amikacin sulfate formulation.

Indometacin may increase the plasma concentration of amikacin in neonates.

4.6 Fertility, pregnancy and lactation

Fertility

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

Pregnancy

Category D

There are limited data on use of aminoglycosides in pregnancy. Aminoglycosides can cause fetal harm. Gentamicin and other aminoglycosides cross the placenta and there have been reports of total, irreversible, bilateral congenital deafness in children whose mothers received streptomycin during pregnancy. Adverse effects on the fetus or newborns have been reported in pregnant women treated with other aminoglycosides, therefore, the potential for harm exists. There is evidence of selective uptake of gentamicin by the fetal kidney resulting in damage (probably reversible) to immature nephrons. Eighth cranial nerve damage has also been reported following in-utero exposure to some of the aminoglycosides. Because of the chemical similarity, all aminoglycosides must be considered potentially nephrotoxic and ototoxic to the fetus. It should also be noted that therapeutic blood levels in the mother do not equate with safety for the fetus. In reproduction toxicity studies in mice and rats no effects on fertility or fetal toxicity were reported. If amikacin is used during pregnancy or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus.

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

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

Lactation

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

4.7 Effects on ability to drive and use machinery

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

Amikacin induced hepatotoxicity is not a common side effect, however it may occur. Increased

serum transaminases (ALT, AST) increased serum bilirubin, hepatomegaly, and hepatic necrosis have been reported.

The percentages below refer to incidence in clinical trials.

More common reactions

Auditory and Vestibular	Hearing loss (4%) (permanent in some cases) Hearing loss is usually manifested initially by diminution of high-tone acuity.
Biochemical abnormalities	Increased serum urea, decreased creatinine clearance, elevated serum creatinine[a], azotaemia[a].
Genitourinary	Reduced renal function, oliguria[a]
Injection site reactions	Pain at site of intramuscular injection (6%).

Less common reactions

Auditory and Vestibular	Tinnitus, vertigo, dizziness, nystagmus, changes in caloric testing or electronystagmograms.
Biochemical abnormalities	Casts, cells[a] or protein in the urine, eosinophilia, increase in AST.
Dermatological	Pruritus, rash
Gastrointestinal	Nausea, vomiting
General	Drug fever
Genitourinary	Renal failure
Haematological	Anaemia
Musculoskeletal	Arthralgia
Nervous system	Paraesthesia[a], tremor[a]

[a] See section 4.4.

This following 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 (≥1/1000, <1/100), rare (≥1/10000, <1/1000), very rare (<1/10000) and not known (cannot be estimated from the available data).

Uncommon

Infections and Infestations	Superinfections or colonisation with resistant bacteria or yeast[a]

Rare

Metabolism and nutrition disorders	Hypomagnesaemia

Nervous system disorders	Headache, balance disorder[a]
Eye disorders	Blindness[b], retinal infarction[b]
Ear and labyrinth disorders	Hypoacusis[a]
Vascular disorders	Hypotension
Skin and subcutaneous tissue disorders	Urticaria
Musculoskeletal, connective tissue and bone disorder	Muscle twitching[a]
Renal and urinary disorders	Albuminuria[a], red blood cells urine[a], white blood cells urine[a]
General disorders and administration site conditions	Pyrexia

Not Known

Immune system disorders	Anaphylactic response (anaphylactic reaction, anaphylactic shock and anaphylactoid reaction), hypersensitivity
Nervous system disorders	Paralysis[a]
Ear and labyrinth disorders	Deafness[a], deafness neurosensory[a]
Respiratory, thoracic and mediastinal disorders	Apnoea, bronchospasm
Renal and urinary disorders	Renal failure acute, nephropathy toxic, cells in urine

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

Serious or life-threatening reactions

All aminoglycosides have the potential to induce ototoxicity, renal toxicity, and neuromuscular blockade. Serious adverse effects on both vestibular and auditory branches of the eighth cranial nerve have been reported, primarily in patients with renal impairment (especially if dialysis is required), and in patients on high doses and/or prolonged therapy. Other factors which may increase the risk of toxicity include excessive dosage, dehydration and previous exposure to ototoxic or nephrotoxic drugs. 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.

Other reactions

Other adverse reactions reported with the use of aminoglycosides include: respiratory

depression, lethargy, confusion, depression, visual disturbances, decreased appetite, weight loss, anorexia, hypertension, generalised burning, laryngeal edema, increased salivation, stomatitis, purpura, pseudotumor cerebri, acute organic brain syndrome, pulmonary fibrosis, alopecia, joint pain, transient hepatomegaly, splenomegaly, convulsions and a myasthenia gravis-like syndrome.

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.

Laboratory tests

Laboratory abnormalities possibly related to aminoglycosides include: increased levels of serum transaminase (ALT, AST) serum LDH and bilirubin; decreased serum calcium, magnesium, sodium and potassium; anaemia, leukopenia, granulocytopenia, transient agranulocytosis, eosinophilia, increased and decreased reticulocyte counts, and thrombocytopenia. While clinical laboratory test abnormalities may be isolated findings, they may also be associated with clinically related signs and symptoms. For example, tetany and muscle weakness may be associated with hypomagnesemia, hypocalcemia and hypokalemia.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions https://pophealth.my.site.com/carmreportnz/s/

4.9 Overdose

Management

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 lactobionate in 10-20% solution) (see section 4.4). In the event of overdosage or toxic reactions peritoneal dialysis or haemodialysis should be considered. Amikacin levels are also reduced during continuous arteriovenous hemofiltration. These procedures are of particular importance in patients with impaired renal function. In the newborn infant, exchange transfusion may also be considered.

Clinical features

Likely signs and symptoms include tinnitus, vertigo, reversible or irreversible deafness, skin rash, drug fever, headache, paraesthesia, reduced renal function or renal failure.

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Mechanism of action

Microbiology

Amikacin is active, *in vitro*, against the following organisms:

Gram-negative	**MIC microgram/mL**
Pseudomonas species	1.6 - 12.5
Proteus species (indole-positive and indole negative)	1.6 - 3.1
Klebsiella pneumoniae	1.6 - 3.1
Enterobacter cloacae	1.6 - 3.1
Serratia species	0.8 - 3.1
Acinetobacter	No information available
Providencia stuartii	3.1
Citrobacter freundii	1 - 8
Escherichia coli	1.6 - 3.1
Gram-positive	
Staphylococcus species (penicillinase and nonpenicillinase producing, including methicillin resistant strains)	0.4 - 5.0

Amikacin's structure has been altered to reduce the possible route of enzymatic deactivation, thus reducing bacterial resistance. Many strains of Gram-negative organisms resistant to gentamicin and tobramycin have shown to be sensitive to amikacin *in vitro.*

Susceptibility Testing

The Kirby-Bauer test can determine the sensitivity of an organism to amikacin. This test operates on the principle that antibiotics will diffuse from a paper disc into an agar medium containing test organisms. Inhibition is observed as a failure of the organism to grow in the region of the antibiotic.

When the Kirby-Bauer method of disc susceptibility is used, a 30 microgram amikacin disc should give a zone of 17 mm or greater when tested against an amikacin susceptible bacterial strain. Such a result indicates that the infecting organism is likely to respond to therapy. A zone size of 14 mm or less indicates resistance, or that the infecting organism is unlikely to respond

to therapy. Zone sizes of 15 to 16 mm indicate intermediate susceptibility, in other words the organism will probably be susceptible if the infection is confined to tissues and fluids (e.g. urine) in which high antibiotic levels are obtained.

5.2 Pharmacokinetic properties

Absorption

Following IM administration of a single dose of amikacin of 7.5 mg/kg in adults with normal renal function, peak plasma amikacin concentrations of 17 to 25 micrograms/mL are attained within 45 minutes to 2 hours.

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.

Following IV infusion of the same dose given over 1 hour, peak plasma concentrations of the drug average 38 micrograms/mL immediately following the infusion, 5.5 micrograms/mL at 4 hours, and 1.3 micrograms/mL at 8 hours. Repeated infusions do not produce drug accumulation in adults with normal renal function. However, decreased renal function will lead to accumulation. 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.

Distribution

Amikacin diffuses readily through extracellular fluids and is excreted in the urine unchanged, primarily by glomerular filtration. Following administration of usual dosages of amikacin, amikacin has been found in bone, heart, gallbladder, and lung tissue. Amikacin is also distributed into bile, sputum, bronchial secretions, and interstitial, pleural, and synovial fluids. It has been found in pleural fluid, amniotic fluid and in the peritoneal cavity following parenteral administration.

Elimination

The plasma elimination half-life of amikacin is usually 2 to 3 hours in adults with normal renal function and is reported to range from 30 to 86 hours in adults with severe renal impairment.

In adults with normal renal function, 94 to 98% of a single IM or IV dose of amikacin is excreted unchanged by glomerular filtration within 24 hours. The drug may be completely recovered within approximately 10 to 20 days in patients with normal renal function. Terminal elimination half-lives of greater than 100 hours have been reported in adults with normal renal function following repeated IM or IV administration of the drug.

In patients with impaired renal function, the clearance of amikacin is decreased; the more severe the impairment, the slower the clearance. Therefore, the interval between doses should be adjusted according to the degree of renal impairment. Endogenous creatinine clearance rate and serum creatinine which have high correlation with serum half-life of amikacin, may be used as a guide for this purpose (see section 4.2).

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 post-natal age) grouped according to birth weights (<2000, 2000-3000 and >3000 g), 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

Genotoxicity

No data available.

Carcinogenicity

No data available.

Reproductive and developmental toxicity

See section 4.6.

6. PHARMACEUTICAL PARTICUALRS

6.1 List of excipients

- Sodium citrate dihydrate
- Sodium Metabisulfite
- Sodium hydroxide
- Sulfuric acid
- Water for injection

No antimicrobial preservative is added to the formulation.

6.2 Incompatibilities

Amikacin Medsurge Injection may be prescribed as concurrent therapy with other antibacterial agents in mixed or superinfections. In such situations, Amikacin Medsurge Injection should never be physically mixed with other antibacterial agents in infusion bags, syringes or any other container equipment. Each agent should be administered separately and at different sites following the manufacturer's recommended route.

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

6.3 Shelf life

24 months.

6.4 Special precautions for storage

Store below 25°C.

In use: Following dilution in 0.9% sodium chloride and 5% glucose solutions chemical and physical in-use stability has been demonstrated for 24 hours at temperature not above 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 and would normally not be longer than 24 hours at 2 to 8°C, unless dilution has taken place in controlled and validated aseptic conditions.

6.5 Nature and contents of container

Strength	Pack Size
500 mg (500,000 I.U.)/2 mL	5 x 2 mL vials

6.6 Special precautions for disposal and other handling

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

Compatibilities

Amikacin sulfate is stable for 24 hours at room temperature in the presence of light at 5 mg/mL and 2.5 mg/mL in 0.9% Sodium Chloride Intravenous Infusion B.P. and 5% Glucose Intravenous Infusion B.P. solutions.

The compatible diluents for intravenous use if required are as follows: 5% Glucose Intravenous Infusion B.P. in Water for Injections B.P. and Sodium Chloride Intravenous Infusion B.P. (0.9%). Use solutions for I.V. administration within 12 hours after preparation.

7. MEDICINE SCHEDULE

Prescription Only Medicine

8. SPONSOR

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9. DATE OF FIRST APPROVAL

06 June 2024

10. DATE OF REVISION OF THE TEXT

Not applicable

Summary table of changes

New Data sheet