APPROVED PROFESSIONAL INFORMATION

SCHEDULING STATUS

S4

1 NAME OF THE MEDICINE

AMIKACIN 100 mg/2 ml FRESENIUS, solution for injection

AMIKACIN 250 mg/2 ml FRESENIUS, solution for injection

AMIKACIN 500 mg/2 ml FRESENIUS, solution for injection

AMIKACIN 1 g/4 ml FRESENIUS, solution for injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each single dose 2 ml vial contains: 100 mg, 250 mg or 500 mg amikacin (as amikacin sulphate)

Each single dose 4 ml solution (in a 5 ml vial) contains: 1 g amikacin (as amikacin sulphate)

Excipients with known effect

AMIKACIN 100 mg/2 ml; 250 mg/2 ml; 500 mg/2 ml FRESENIUS contains 2,97 mg; 7,44 mg; 15,52 mg of sodium respectively.

AMIKACIN 1 g/4 ml FRESENIUS contains 29,84 mg of sodium.

Sugar free.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for injection.

A clear colourless to slightly yellowish solution in 2 ml and 5 ml clear glass vials.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

AMIKACIN FRESENIUS is indicated for the treatment of serious nosocomial gram-negative bacillary infections.

AMIKACIN FRESENIUS is not indicated in the treatment of uncomplicated urinary tract infection unless the causative organisms are not susceptible to antibiotics having less potential toxicity. In these cases, reduced dosage may be prescribed (see section 4.2).

Concomitant therapy with a ß-lactam antibiotic may be indicated in certain severe infections.

4.2 Posology and method of administration

Posology

Normal dosage at prolonged intervals:

If the creatinine clearance rate is not available and the patient's condition is stable, Dosage interval (in hours) = serum creatinine concentration in mmol/l (mg/ml) x 9 e.g., if the serum creatinine concentration is 0,176 mmol/l (2 mg/100 ml), the recommended single dose (7,5 mg/kg) should be administered every 18 hours.

Reduced dosage at fixed time intervals:

When renal function is impaired and it is desirable to administer **AMIKACIN FRESENIUS** at a fixed time interval, dosage must be reduced. In these patients, serum amikacin concentrations should be measured to assure accurate administration and to avoid concentration above local laboratory practices value. If serum assay determinations are not available and the patient's condition is stable, 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 dose, calculated for a patient with a normal renal function, 7,5 mg/kg, as a loading dose, then calculate:

Maintenance doses* =

$$\frac{\text{observed CrCl in ml/ min}}{\text{normal Crack in ml/ min}} \times \text{calculated loading dose in mg}$$

* Administered every 12 hours

CrCl = creatinine clearance rate

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.

Adults and children (with normal renal function):

15 mg per kg lean body mass daily in divided doses every 8 to 12 hours to a maximum of 1,5 g daily in adults.

Cystic fibrosis and burn patients may require larger doses, but because they eliminate the **AMIKACIN FRESENIUS** faster than average, the dosing interval may need to be decreased too.

To ensure the accurate measurement of the appropriate dose in children and infants, use of the 100 mg/2 ml and 250 mg/2 ml is recommended.

Paediatric population

Neonates:

A loading dose of 10 mg per kg lean body mass followed by 15 mg per kg daily in two divided doses.

Preterm neonates:

9 mg per kg intravenously every 18 hours in infants under 30 weeks post conceptional age and every 12 hours in those over 30 weeks.

If a dose of **AMIKACIN FRESENIUS** is missed, give it as soon as possible. However, if it is almost time for the next dose, skip the missed dose and go back to the regular dosing schedule. Do not double doses.

Discard any unused portion.

Method of Administration

It is recommended that a needle not larger than 21 gauge is used to reduce fragmentation of the rubber stopper.

AMIKACIN FRESENIUS may be given intramuscularly or intravenously.

Intravenous injections should be slow over 2 to 3 minutes or by infusion over 30 to 60 minutes in adults or 1 to 2 hours in infants. Suitable diluents are 100 to 200 ml sodium chloride 0,9 % or dextrose 5 % injection (proportionally less fluid should be given to children).

Should clinical response not occur in 3 to 5 days, alternate therapy should be considered. Treatment should preferably not continue for longer than 7 to 10 days and the total dosage in adults should not exceed 15 g.

Because the risk of side effects is increased at high plasma concentrations it is desirable to determine dosage requirements by individual monitoring by means of serum concentrations and creatinine clearance. This is especially important in patients receiving high doses or prolonged courses, in infants and the elderly and in patients with impaired renal function in whom it is crucial to reduce maintenance dosage.

The patient’s pre-treatment body weight should be obtained for calculation of correct dosage.

Serum concentrations should be monitored, in patients without renal function impairment, and especially in patients with impaired renal function to ensure adequate concentrations and to avoid potentially toxic concentrations. Therapeutic concentration for amikacin should be in line with local laboratory practices.

Prolonged peak (post-distributional) concentrations (measured 15 to 30 minutes after injection) and trough concentrations (measured immediately prior to the next dose) greater than 30 µg/ml and 10 µg/ml respectively should be avoided.

Dosage adjustments should be individualised and based on peak and trough serum concentrations.

Special populations

Renal impairment:

The status of renal function should be estimated by measurement of the serum creatinine concentration or calculation of endogenous creatinine clearance rate. Reassessment of renal function should be made periodically during therapy. The patients should be well hydrated.

Adults and children (with impaired renal function):

Doses may be adjusted in patients with impaired renal function either by administering normal doses at prolonged intervals or by administering reduced doses at a fixed interval. 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 including **AMIKACIN FRESENIUS** in patients with diminished renal function. Neither method should be used when dialysis is being performed.

4.3 Contraindications

- Hypersensitivity to amikacin or other aminoglycoside antibiotics or to any other ingredients of **AMIKACIN FRESENIUS** listed in section 6.1.

- Pregnancy and lactation.
- Patients with myasthenia gravis.
- Severe renal function impairment.
- Hearing impairment.

4.4 Special warnings and precautions for use

Since **AMIKACIN FRESENIUS** forms complexes with a number of medicines, leading to incompatibilities and loss of activity, extemporaneous admixtures with **AMIKACIN FRESENIUS** are not recommended. Each medicine should be administered separately. Patients should be well hydrated during **AMIKACIN FRESENIUS** therapy.

Caution is advised in patients with pre-existing renal insufficiency, pre-existing hearing or vestibular damage and diminished glomerular filtration. Patients treated with parenteral aminoglycosides should be under close clinical observation because of the potential ototoxicity and nephrotoxicity associated with their use. Safety for treatment periods which are longer than 14 days has not been established.

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.

Renal toxicity

Aminoglycosides, such as **AMIKACIN FRESENIUS**, 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 higher doses, or in those whose therapy is prolonged.

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 with

AMIKACIN FRESENIUS. 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 blood urea nitrogen (BUN), serum creatinine, or oliguria. If azotaemia increases, or if a progressive decrease in urinary output occurs, treatment should be stopped.

Elderly patients may have reduced renal function which may not be evident in routine screening tests such as 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 and eighth-cranial nerve function should be closely monitored especially in patients with known or suspected renal impairment 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, as in **AMIKACIN FRESENIUS**, 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 **AMIKACIN FRESENIUS** or dosage adjustment.

Concurrent and/or sequential, oral, or topical use of other neurotoxic or nephrotoxic medicines, particularly bacitracin, cisplatin, amphotericin B, cephaloridine, paromomycin, viomycin, polymyxin B, colistin, vancomycin, or other aminoglycosides, should be avoided. Other factors that may increase risk of toxicity are advanced age and dehydration.

Patients suffering from pre-existing renal insufficiency should be assessed by the usual methods prior to therapy and periodically during therapy with **AMIKACIN FRESENIUS**. 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.

Neurotoxicity/ototoxicity

Neurotoxicity, manifested as vestibular and/or bilateral ototoxicity, can occur in patients treated with aminoglycosides, such as **AMIKACIN FRESENIUS**. 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. 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. The risk of ototoxicity due to aminoglycosides, such as increases with the degree of exposure to either persistently high peak or high trough serum concentrations. 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 treatment with **AMIKACIN FRESENIUS** 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 **AMIKACIN FRESENIUS** is administered by any route, especially in patients receiving anaesthetics, neuromuscular blocking medicines 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, as in **AMIKACIN FRESENIUS**.

AMIKACIN FRESENIUS must not be used in patients with myasthenia gravis. **AMIKACIN FRESENIUS** should be used with caution in patients with muscular disorders such as Parkinsonism since it may aggravate muscle weakness because of the potential curare-like effect it may have on the neuromuscular junction.

Allergic reactions

The use of **AMIKACIN FRESENIUS** 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 medicines 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 FRESENIUS** should be used only if, in the opinion of the medical practitioner, therapeutic advantages outweigh the potential risks.

Large doses of **AMIKACIN FRESENIUS** administered during surgery may be responsible for a transient myasthenic syndrome.

AMIKACIN FRESENIUS contains sodium metabisulphite. In certain susceptible people it may cause allergic-type reactions including anaphylactic reactions and life-threatening asthmatic episodes.

Other

Aminoglycosides, such as **AMIKACIN FRESENIUS** 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 FRESENIUS** 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.

Paediatric population

AMIKACIN FRESENIUS 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 **AMIKACIN FRESENIUS**.

Excipient information

AMIKACIN 100 mg/2 ml; 250 mg/2 ml; 500 mg/2 ml and **1 g/4 ml FRESENIUS** contains 2,97 mg; 7,44 mg; 15,52 mg and 29,84 mg sodium respectively equivalent to 0,1 %; 0,3 % 0,8 % and 1,5 % of the WHO recommended maximum daily intake of 2 g sodium for an adult.

4.5 Interaction with other medicines and other forms of interaction

The renal excretion of zalcitabine has been reduced by **AMIKACIN FRESENIUS**.

Agalsidase alfa or beta, as **AMIKACIN FRESENIUS** may inhibit alpha-galactosidase activity.

The concurrent or serial use of other neurotoxic, ototoxic or nephrotoxic medicines, 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. 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.

The concurrent use of **AMIKACIN FRESENIUS** 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 medicine 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 if patients are treated with **AMIKACIN FRESENIUS** and 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 **AMIKACIN FRESENIUS**.

The intraperitoneal use of amikacin is not recommended in patients under the influence of anaesthetics or muscle relaxing medicines (including ether, halothane, d-tubocurarine, succinylcholine and decamethonium) as neuromuscular blockade and consequent respiratory depression may occur.

Indomethacin may increase the plasma concentration of **AMIKACIN FRESENIUS** in neonates.

4.6 Fertility, pregnancy and lactation

Pregnancy

The safety of **AMIKACIN FRESENIUS** in pregnancy has not been established.

Use of **AMIKACIN FRESENIUS** during pregnancy may damage the 8th cranial nerve of the foetus.

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

Breastfeeding

The safety of **AMIKACIN FRESENIUS** in breastfeeding has not been established.

It is not known whether **AMIKACIN FRESENIUS** is excreted in breast milk. A decision should be made whether to discontinue breastfeeding or to discontinue therapy.

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

Tabulated summary of adverse reactions

MedDRA system organ class	**Frequency**	**Adverse reactions**
Infections and infections	Less frequent	Superinfections or colonisation with resistant bacteria or yeast[a]
Blood and lymphatic system disorders	Less frequent	Anaemia, eosinophilia
	Frequency unknown	Purpura.
Immune system disorders	Frequency unknown:	Anaphylactic response (anaphylactic reaction, anaphylactic shock and anaphylactoid reaction), hypersensitivity
Metabolism and nutrition disorders	Less frequent	Hypomagnesaemia, hypocalcaemia and hypokalaemia have occurred in association with antineoplastic medicines
Nervous system disorders	Less frequent	Tremor[a], paraesthesia[a], headache, balance disorder[a]
	Frequency unknown	Paralysis[a], neurotoxicity, convulsions
Eye disorders	Less frequent	Blindness[b], retinal infarction[b]
	Frequency unknown	Visual disturbances
Ear and labyrinth	Less frequent	Tinnitus[a], hypoacusis[a]

MedDRA system organ class	**Frequency**	**Adverse reactions**
disorders	Frequency unknown	Deafness[a], deafness neurosensory[a], irreversible ototoxicity, reversible nephrotoxicity
Vascular disorders	Frequency unknown	Hypotension
Respiratory, thoracic and mediastinal disorders	Less frequent	Apnoea, bronchospasm
Gastrointestinal disorders	Frequency unknown	Nausea, vomiting, pseudomembranous colitis.
Hepato-biliary disorders	Frequency unknown	Increased serum aminotransferase, increased serum bilirubin
Skin and subcutaneous tissue disorders	Less frequent	Rash, pruritus, urticaria
Musculoskeletal, connective tissue and bone disorders	Less frequent	Arthralgia, muscle twitching[a]
	Frequency unknown	Muscular paralysis, neuromuscular blocking action, respiratory depression
Renal and urinary disorder	Less frequent	Oliguria[a], increased blood creatinine[a], albuminuria[a], azotaemia[a], red blood cells

MedDRA system organ class	Frequency	Adverse reactions
		in urine[a], white blood cells in urine[a]
	Frequency unknown	Acute renal failure, nephropathy toxic, cells in urine[a]
General disorders and administration site conditions	Less frequent	Pyrexia

[a] See section 4.4.

[b] **AMIKACIN FRESENIUS** is not formulated for intravitreal use. Blindness and retinal infarction have been reported following intravitreous administrations (injection into the eye) of amikacin.

Description of selected adverse reactions:

All aminoglycosides, such as **AMIKACIN FRESENIUS**, 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 medicines, and in patients treated for longer periods and/or with higher doses than recommended (see section 4.4).

Volume depletion or hypotension, liver disease or females have been reported as additional risk factors for nephrotoxicity.

Because of the high concentrations of amikacin in the urine and kidney, patients should be well hydrated to prevent or minimize chemical irritation of the renal tubules.

AMIKACIN FRESENIUS 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 medicines.

Renal function changes are usually reversible when treatment with **AMIKACIN FRESENIUS** is discontinued.

Toxic effects on the eighth cranial nerve can result in hearing loss, loss of balance, or both. **AMIKACIN FRESENIUS** 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 dosage recommendations are followed when patients are well hydrated and kidney function is normal, 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.

Concurrent use of nephrotoxic medicines, including other aminoglycosides, vancomycin and some of the cephalosporins, or potentially ototoxic medicines such as ethacrynic acid and furosemide, may increase the risk of toxicity; care is also required if other medicines with a neuromuscular blocking action are given concomitantly. Non-Steroidal Anti-inflammatory Drugs (NSAIDs) have been reported to increase the plasma concentrations of aminoglycosides including **AMIKACIN FRESENIUS** when given concomitantly.

In addition to potential ototoxicity caused by diuretics such as ethacrynic acid or furosemide, diuretics may (when administered intravenously) enhance amikacin toxicity by increasing the antibiotic concentration in serum and tissue.

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. Health care providers are requested to report any suspected adverse drug reactions to SAHPRA via

the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website.

Health care providers are asked to report any suspected adverse reactions to the Holder of the Certificate of Registration at the following email address: safety.fksa@fresenius-kabi.com, and to the relevant medicine's regulatory authority in the country where the medicine is marketed.

4.9 Overdose

See section 4.8

Since there is no specific antidote, treatment of **AMIKACIN FRESENIUS** overdose or toxic reactions should be symptomatic and supportive.

Haemodialysis or peritoneal dialysis to remove aminoglycosides from the patients with impaired renal function.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Category and class: A.20.1.1 Broad and medium spectrum antibiotics

Pharmacotherapeutic group: ATC code: J01G B06.

Amikacin is a semisynthetic aminoglycoside, with a broad antimicrobial activity and exhibits resistance to aminoglycoside-inactivating enzymes.

5.2 Pharmacokinetic properties

Amikacin is effective *in vitro* against many species of gram-negative bacteria including species of: *Citrobacter, Escherichia, Enterobacter, Klebsiella, Proteus, Providencia, Pseudomonas* and *Serratia*. It is effective against most strains of *Staphylococcus aureus*.

Listeria monocytogenes and some *Staphylococcus epidermidis* may also be sensitive. *In-vitro* activity does not necessarily imply *in-vivo* efficacy.

Inadequate concentrations for the treatment of meningitis are achieved in the cerebrospinal fluid in adults.

Absorption

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.

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 accumulation in adults with normal renal function. However, decreased renal function will lead to accumulation.

Distribution

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

Penetration into respiratory secretions is poor. Diffusion into pleural and synovial fluid is relatively slow, but concentrations that approximate those in the plasma may be achieved after repeated administration. High concentrations are found in the renal cortex and in the endolymph and perilymph of the inner ear. Inflammation increases its penetration into peritoneal and pericardial cavities.

Elimination

In adults with normal renal function the plasma elimination half-life of amikacin is usually 2 – 3 hours. 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 diffuses readily through extracellular fluids and is excreted in the urine unchanged, primarily by glomerular filtration. It has been found in pleural fluid, amniotic fluid and in the peritoneal cavity following parenteral administration.

Special patient populations

Paediatric population

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 and intravenous administration

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

In a study in newborns (1 - 6 days of post-natal age) grouped according to birth weights (< 2 000, 2 000 – 3 000 and > 3 000 g). Amikacin was administered intramuscularly and/or intravenously at a dose of 7,5 mg/kg. Clearance in neonates > 3 000 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

Not applicable.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

AMIKACIN 100 mg/2 ml FRESENIUS:

Sodium metabisulphite

Sodium citrate dihydrate

Sulphuric acid (for pH-adjustment)

Water for injection

AMIKACIN 250 mg/2 ml FRESENIUS; AMIKACIN 500 mg/2 ml FRESENIUS; AMIKACIN 1 g/4 ml FRESENIUS:

Sodium metabisulphite

Sodium citrate dihydrate

Water for injection

6.2 Incompatibilities

AMIKACIN FRESENIUS is incompatible (*in vitro*) with beta-lactam antibacterials (penicillin and cephalosporins), aminophylline, amphotericin, hydrochlorothiazide, dexamethasone sodium phosphate, erythromycin, heparin, phenytoin sodium, potassium chloride, tetracyclines, sodium thiopentone, vitamin B and C complex and warfarin sodium.

6.3 Shelf life

AMIKACIN 100 mg/2 ml; 250 mg/2 ml; 500 mg/2 ml FRESENIUS: 5 years

AMIKACIN 1g/4 ml FRESENIUS: 3 years

6.4 Special precautions for storage

Store at or below 30 °C.

Protect from light.

Note: The solution may darken from colourless to a pale yellow. This does not indicate a loss of potency.

6.5 Nature and contents of container

AMIKACIN 100 mg/2 ml; 250 mg/2 ml; 500 mg/2 ml FRESENIUS are packed in 2 ml clear glass vials (Type I) sealed with bromobutyl rubber stoppers in packs of 10.

AMIKACIN 1g/4 ml FRESENIUS is packed in 5 ml clear glass vials (Type I) sealed with bromobutyl rubber stoppers in packs of 10.

6.6 Special precautions for disposal and other handling

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

7 HOLDER OF CERTIFICATE OF REGISTRATION

Fresenius Kabi Manufacturing SA (Pty) Ltd

6 Gibaud Road

Korsten, 6020

Gqeberha

South Africa

8 REGISTRATION NUMBERS

AMIKACIN 100 mg/2 ml FRESENIUS: Y/20.1.1/175

AMIKACIN 250 mg/2 ml FRESENIUS: Y/20.1.1/176

AMIKACIN 500 mg/2 ml FRESENIUS: Y/20.1.1/178

AMIKACIN 1 g/4 ml FRESENIUS: 29/20.1.1/0684

9 DATE OF FIRST AUTHORISATION

AMIKACIN 100 mg/2 ml; 250 mg/2 ml FRESENIUS; 500 mg/2 ml: 26 June 1991

AMIKACIN 1 g/4 ml FRESENIUS: 12 February 1997

10 DATE OF REVISION OF THE TEXT

04 December 2023.