APPROVED PACKAGE INSERT FOR AMIKACIN FRESENIUS

SCHEDULING STATUS

S4

PROPRIETARY NAMES AND DOSAGE FORM

Amikacin Fresenius 50 mg/2 ml

Amikacin Fresenius 100 mg/2 ml

Amikacin Fresenius 250 mg/2 ml

Amikacin Fresenius 500 mg/2 ml

Amikacin Fresenius 1 g/4 ml

Injection

COMPOSITION

Each single dose 2 ml vial contains:

50 mg, 100 mg, 250 mg or 500 mg amikacin (as amikacin sulphate)

Inactive ingredients:

Antioxidant: sodium metabisulphite - 0,1 % *m/v*, 0,13 % *m/v*, 0,33 % *m/v* and 0,66 % *m/v* respectively.

Water for injections.

Each single dose 4 ml solution (in a 5 ml vial) contains:

1 g amikacin (as amikacin sulphate)

Inactive ingredients:

Antioxidant: sodium metabisulphite - 0,66 % *m/v*

Water for injections.

PHARMACOLOGICAL CLASSIFICATION

A.20.1.1 Broad and medium spectrum antibiotics.

PHARMACOLOGICAL ACTION

Pharmacodynamic properties

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

Pharmacokinetic properties

It is a bactericidal and is minimally protein bound. It is largely excluded from most cells, from the central nervous system and eye. 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.

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

Elimination of amikacin is almost entirely by glomerular filtration. Amikacin has a half-life of 2 - 3 hours, most of the dose being excreted within 24 hours.

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.

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 “Dosage and directions for use”).

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

CONTRAINDICATIONS

Hypersensitivity to amikacin or other aminoglycoside antibiotics or to any other ingredient of **Amikacin Fresenius**.

Pregnancy and lactation.

Patients with myasthenia gravis.

Severe renal function impairment.

Hearing impairment.

WARNINGS AND SPECIAL PRECAUTIONS

Amikacin Fresenius may cause allergic-type reactions including anaphylactic reactions and life-threatening asthmatic episodes in certain susceptible people as it contains sodium metabisulphite.

Caution is advised in patients with partial hearing loss.

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 agent should be administered separately.

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

INTERACTIONS

Amikacin Fresenius toxicity may increase with the use of other nephrotoxic medicines (including other aminoglycosides, vancomycin, some cephalosporins, ciclosporin, cisplatin and fludarabine) or other potentially ototoxic medicines such as ethacrynic acid and furosemide.

Care is required if used with neuromuscular blocking medicines as this may provoke severe respiratory depression in patients given general anaesthetics or opioids.

Beta-lactam antibiotics must be given separately if both are required.

The renal excretion of zalcitabine has been reduced by **Amikacin Fresenius**.

There may be additive hypocalcaemiac effects if patients are treated with **Amikacin Fresenius** and bisphosphonates.

Agalsidase alfa or beta, as **Amikacin Fresenius** may inhibit alpha-galactosidase activity.

PREGNANCY AND LACTATION

Safety in pregnancy and lactation has not been established. Use of **Amikacin Fresenius** during pregnancy may damage the 8th cranial nerve of the fetus.

DOSAGE AND DIRECTIONS FOR USE

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 pretreatment 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.

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.

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:

$$\text{Maintenance doses*} = \frac{\text{observed CrCl in ml/ min}}{\text{normal CrCl in ml/ min}} \times \text{calculated loading dose in mg}$$

* 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 50 mg/2 ml, 100 mg/2 ml and 250 mg/2 ml is recommended.

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.

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.

SIDE EFFECTS

The following side effects have been reported but frequencies are unknown.

Blood and lymphatic system disorders:

Hypomagnesaemia, hypocalcaemia and hypokalaemia have occurred in association with antineoplastic agents.

Anaemia, purpura may occur.

Immune system disorders:

Hypersensitivity (skin itching, redness, rash or swelling) to **Amikacin Fresenius** and cross allergy among aminoglycosides has been demonstrated.

Increased serum aminotransferase values and increased serum bilirubin concentrations have been reported.

Nervous system disorders:

Neurotoxicity (numbness, skin tingling, muscle twitching and convulsions).

Convulsions may occur.

Eye disorder:

Visual disturbances

Ear and labyrinth disorders:

Irreversible ototoxicity (auditory with loss of hearing, ringing or buzzing, a feeling of fullness in the ears and vestibular with clumsiness, dizziness, nausea, vomiting, unsteadiness) as well as reversible nephrotoxicity may occur.

Gastrointestinal disorders:

Pseudomembranous colitis may occur.

Musculoskeletal, connective tissue and bone disorders:

Amikacin Fresenius possesses a neuromuscular blocking action and respiratory depression and muscular paralysis have been reported.

Renal and urinary disorders:

Acute renal failure may occur.

When patients are well hydrated and kidney function is normal, risk of nephrotoxic reactions with **Amikacin Fresenius** is low if the dosage recommendations (see Dosage and directions for use) are not exceeded.

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.

General disorders and administrative site conditions:

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.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT

See “Side effects”.

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.

IDENTIFICATION

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

PRESENTATION

Amikacin Fresenius 50 mg; 100 mg; 250 mg; 500 mg - 2 ml clear glass vials in packs of 10.

Amikacin Fresenius 1g - 4 ml solution in 5 ml clear glass vial in packs of 10.

STORAGE INSTRUCTIONS

Store at or below 25 ºC.

KEEP OUT OF REACH OF CHILDREN.

Discard any unused portion.

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

REGISTRATION NUMBER

Amikacin Fresenius 50 mg/2 ml: 30/20.1.1/0019

Amikacin Fresenius 100 mg/2 ml: Y/20.1.1/175

Amikacin Fresenius 250 mg/2 ml: Y/20.1.1/176

Amikacin Fresenius 500 mg/2 ml: Y/20.1.1/178

Amikacin Fresenius 1 g/4 ml: 29/20.1.1/0684

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION

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