SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Amikacin Kabi 5 mg/ml solution for infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml solution for infusion contains 5 mg amikacin (as sulfate).

Each bottle with 50 ml contains 250 mg amikacin.
Each bottle with 100 ml contains 500 mg amikacin.
Each bottle with 200 ml contains 1000 mg amikacin.

Excipient(s) with known effect

Each ml also contains 3.54 mg sodium (equivalent to 0.154 mmol sodium).

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for infusion
A clear colourless aqueous solution
pH: 3.5 – 5.5
Osmolality: 270 – 330 mOsmol/kg.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Amikacin Kabi is indicated for the treatment of the following severe infections in adults and paediatric patients (including neonates) when other antimicrobial agents are not appropriate (see section 5.1).

- Nosocomial lower respiratory tract infections including hospital-acquired pneumonia (HAP) and ventilator-associated pneumonia (VAP),
- Complicated and recurrent urinary tract infections including pyelonephritis,
- Complicate intra-abdominal infections including peritonitis,
- Acute bacterial skin and skin structure infections including burn-wound infections,
- Bacterial endocarditis (only in combination with other antibiotics).

Treatment of patients with bacteraemia that occurs in association with, or is suspected to be associated with, any of the infections listed above.

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

4.2 Posology and method of administration

Posology
Amikacin Kabi is commonly used in combination with other appropriate antibiotics to cover the bacterial spectrum encountered in the respective infection.

The dosage as well as the use of amikacin would notably depend on the type of infection and the patient status. Local therapeutic guidance should be taken into consideration.

Patients with normal renal function
Adults and adolescents ≥ 12 years (over 33 kg body weight):
The recommended intravenous dosage for adults and adolescents with normal renal function (creatinine clearance ≥50 ml/min) is 15 mg/kg body weight per day which may be administered as a single daily dose or divided into 2 equal doses i.e. 7.5 mg/kg body weight every 12 hours.

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

Infants, toddlers and children (4 weeks to 11 years):
The recommended intravenous (slow intravenous infusion) dose in children with normal renal function is 15-20 mg/kg body weight/day which may be administered as 15-20 mg/kg body weight, once a day; or as 7.5 mg/kg body weight every 12 hours. In endocarditis and in febrile neutropenic patients dosing should be twice daily, as there is not enough data to support once daily dosing.

Neonates (0 to 27 days):
An initial loading dose of 10 mg/kg body weight followed by 7.5 mg/kg body weight every 12 h (see sections 4.4 and 5.2).

Preterm newborn infants:
The recommended dose in prematures is 7.5 mg/kg body weight every 12 hours (see sections 4.4 and 5.2).

Infusion volumes in patients with normal renal function:

Amikacin 5 mg/ml													
	Body weight												
	2.5 kg	5 kg	10 kg	12.5 kg	20 kg	30 kg	40 kg	50 kg	60 kg	70 kg	80 kg	90 kg	100 kg
Amikacin in mg/kg BW													
7.5	3.75 ml	7.50 ml	15.00 ml	18.75 ml	30.00 ml	45.00 ml	60.00 ml	75.00 ml	90.00 ml	105.00 ml	120.00 ml	135.00 ml	150.00 ml
10	5.00 ml	10.00	20.00	25.00	40.00	60.00 ml	80.00 ml	100.00	120.00	140.00	160.00	180.00	200.00

		ml	ml	ml	ml			ml	ml	ml	ml	ml	ml
15	7.50 ml	15.00 ml	30.00 ml	37.50 ml	60.00 ml	90.00 ml	120.00 ml	150.00 ml	180.00 ml	210.00 ml	240.00 ml	270.00 ml	300.00 ml
20	10.00 ml	20.00 ml	40.00 ml	50.00 ml	80.00 ml	120.00 ml	160.00 ml	200.00 ml	240.00 ml	280.00 ml	320.00 ml	360.00 ml	400.00 ml

Accuracy of dosing is improved if Amikacin 5 mg/ml solution for infusion is administered with an Accuracy of dosing is improved if Amikacin 5 mg/ml solution for infusion is administered with an infusion pump.

Maximum daily dose:
The daily dose of amikacin is based on body weight, consequently the maximum dose should equally be based on body weight unless otherwise justified.
In life-threatening infections and/or infections caused by *Pseudomonas, Acinetobacter* or *Enterobacteriales* the dose may be increased to 1.5 g per day but should not be administered for a period longer than 10 days and only under constant monitoring. A maximum total adult dose of 15 g should not be exceeded; other aminoglycoside treatment given previously must be included in this calculation**.**

Due to the requirement for dose adjustments once daily dosing of amikacin is not recommended for patients with febrile neutropenia, renal failure.

Duration of treatment
The total duration of therapy should be limited to 7 to 10 days, depending on severity of infection. In severe and complicated infections, where treatment with amikacin exceeds 10 days, the suitability of treatment with amikacin should be re-evaluated, as eventual treatment continuation requires the monitoring of serum amikacin levels and of renal, auditory and vestibular functions.

Patients with infections caused by susceptible microorganisms should respond to therapy within 24 to 48 hours with the recommended dosage regime. When no clinical response is seen within three to five days an alternative therapy should be considered.

Monitoring advice
Assessment of renal function should be performed at the start of therapy and should be re-evaluated at regular intervals during treatment.
Monitoring of amikacin plasma concentrations is strongly recommended in all patients, and especially in the elderly, newborns, obese patients and those with renal impairment or cystic fibrosis.
The amikacin serum concentrations should be monitored on the second or third day after initiation of treatment and then twice weekly and after a dose change (see section 4.4). Blood samples are taken at the end of a dosage interval (trough level) and 30- 90 minutes after the end of the infusion (peak level). In case of multiple daily doses, peak levels should not exceed 30 - 35 micrograms/ml. The trough level should be less than 10 micrograms/ml. For once daily dose regimens, local guidelines on serum concentration monitoring should be considered.

Patients with impaired renal function
Renal function should be monitored in all patients receiving amikacin and is mandatory in those with renal impairment.
Note: Once daily administration of amikacin is not recommended in patients with renal function disorders (creatinine clearance <50 ml/min).

In renal impairment with a glomerular filtration rate of less than 70 ml/minute, dose reduction or longer dose intervals are advised, because an accumulation of amikacin can be expected.

For patients with renal impairment, the loading dose is amikacin 7.5 mg/kg body weight. The dose interval for individual patients is calculated as 9 times the serum creatinine level. If for example the creatinine concentration is 2 mg/100 ml, then the recommended individual dose (7.5 mg/kg body weight) must be administered every 2 x 9 = 18 hours.
For patients with chronic renal failure and known creatinine clearance, the maintenance dose given at intervals of 12 hours is calculated with the formula:
(patient creatinine clearance in ml/minute ÷ normal creatinine clearance in ml/minute) x amikacin 7.5 mg/kg body weight.
The values presented in the following table may be taken as guidance.

Creatinine clearance [ml/min]	Daily dose of amikacin [mg/kg body weight per day]	Dose of amikacin per 12 hours for a patient of 70 kg body weight [mg]
70 – 80	7.6 – 8	266 – 280
60 – 69	6.4 – 7.6	224 – 266
50 – 59	5.4 – 6.4	186 – 224
40 – 49	4.2 – 5.4	147 – 186
30 – 39	3.2 – 4.2	112 – 147
20 – 29	2.1 – 3.1	77 – 112
15 – 19	1.6 – 2.0	56 – 77

Patients undergoing haemodialysis or peritoneal dialysis receive half of the normal dose at the end of the dialysis procedure.

Elderly patients
In elderly patients renal function may be impaired.
As amikacin is excreted by the renal route, renal function should be assessed whenever possible and dose adjusted where appropriate.

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

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

Method of administration
For intravenous use only.
Amikacin Kabi should only be administered by intravenous infusion. The preferred time period is 30 minutes but may be up to 60 minutes.

Specific recommendation for intravenous use in paediatric patients
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 minutes period. Infants should receive a 1 to 2 hour infusion.

In case a dilution is advisable in paediatric patients the solution for infusion is prepared by adding the desired dose to an identical amount (1 + 1 dilution) of one of the diluents

mentioned in section 6.6 to obtain a 0.25 % solution (2.5 mg/ml) of amikacin (see section 6.6).

Infusion volumes of the diluted amikacin 2.5 mg/ml solution:

Diluted to Amikacin 2.5 mg/ml													
	Body weight												
	2.5 kg	5 kg	10 kg	12.5 kg	20 kg	30 kg	40 kg	50 kg	60 kg	70 kg	80 kg	90 kg	100 kg
Amikacin in mg/kg BW													
7.5	7.50 ml	15.00 ml	30.00 ml	37.50 ml	60.00 ml	90.00 ml	120.00 ml	150.00 ml	180.00 ml	210.00 ml	240.00 ml	270.00 ml	300.00 ml
10	10.00 ml	20.00 ml	40.00 ml	50.00 ml	80.00 ml	120.00 ml	160.00 ml	200.00 ml	240.00 ml	280.00 ml	320.00 ml	360.00 ml	400.00 ml
15	15.00 ml	30.00 ml	60.00 ml	75.00 ml	120.00 ml	180.00 ml	240.00 ml	300.00 ml	360.00 ml	420.00 ml	480.00 ml	540.00 ml	600.00 ml
20	20.00 ml	40.00 ml	80.00 ml	100.00 ml	160.00 ml	240.00 ml	320.00 ml	400.00 ml	480.00 ml	560.00 ml	640.00 ml	720.00 ml	800.00 ml

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- Hypersensitivity to other aminoglycosides.

4.4 Special warnings and precautions for use

Caution is necessary on administration to patients with renal impairment, to patients with auditory or vestibular damage, to patients with neuromuscular disorders, and if patients were treated with another aminoglycoside active substance immediately prior to amikacin.

Neuro/Ototoxicity

Neurotoxicity, manifested as vestibular and/or bilateral auditory ototoxicity, can occur in patients treated with aminoglycosides. The risk of aminoglycoside-induced ototoxicity is greater in patients with impaired renal function, or in those whose therapy is prolonged over 5-7 days of treatment, even in healthy patients. High frequency deafness usually occurs first and can be detected only by audiometric testing. Vertigo and loss of balance may occur and may be evidence of vestibular injury.

Other manifestations of neurotoxicity may include numbness, skin tingling, muscle twitching and convulsions. Patients developing cochlear or vestibular damage may not have symptoms during therapy to warn them of developing eighth nerve toxicity, and total or partial irreversible bilateral deafness or disabling vertigo may occur after the medicinal product has been discontinued. Aminoglycoside-induced ototoxicity is usually irreversible.

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 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.

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.

Renal toxicity

Aminoglycosides are potentially nephrotoxic. Renal toxicity is independent of plasma obtained at the peak (C_{max}).

The toxic effects of aminoglycosides, including amikacin, are more frequent in patients with renal impairment, if doses in excess of those recommended are administered, and if the recommended duration of treatment is exceeded. The safety of treatment over periods longer than 14 days has not been established. Other factors that increase the risk of aminoglycoside toxicity include advanced age and dehydration. Daily doses should be reduced and/or the interval between doses extended in the case of signs of renal dysfunction such as: cylindruria, the presence of leukocytes or red blood cells, albuminuria, reduction in creatinine clearance, decreased urine specific gravity, azotaemia, elevation of serum creatinine and oliguria. Treatment must be discontinued if azotaemia increases or if urine volume decreases gradually.

Elderly patients may have reduced renal function which may not be evident in routine screening tests such as BUN (blood urea nitrogen) 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.

During treatment the patient must be well-hydrated and renal function should be determined at the onset of treatment, particularly in patients with renal impairment. Renal function should also be monitored closely during treatment.

It is recommended to perform repeat audiometric examinations, especially in the case of patients at high risk. Whenever possible it is recommended to monitor amikacin serum concentrations twice weekly in order to avoid high concentrations that are potentially toxic (see section 4.2).

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

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).

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 or neuromuscular blocking agents (see section 4.5). If neuromuscular blockade occurs, calcium salts may reverse respiratory paralysis, but mechanical respiratory assistance may be necessary. Neuromuscular blockade and muscular paralysis have been demonstrated in laboratory animals given high doses of amikacin.
Administration of aminoglycosides to patients with neuromuscular disease such as myasthenia gravis or parkinsonism requires extreme caution, as aminoglycosides act on the neuro-muscular junction similarly to curare and they may thus worsen muscle weakness.

Other
Aminoglycosides applied locally as part of a surgical procedure are quickly and nearly completely absorbed (with the exception of the urinary bladder). In association with irrigation of the surgical field using aminoglycoside preparations (regardless of the extent) development of irreversible deafness, renal failure and death due to neuromuscular blockade have been reported.

Paediatric population
Aminoglycosides should be used with caution in premature and neonatal infants because of the renal immaturity of these patients and the resulting prolongation of serum half-life of these active substances.

This medicinal product contains 177 /354 /708 mg sodium per 50 /100 /200 ml, equivalent to 8.85 /17.7 /35.4 % of the WHO recommended maximum daily intake of 2 g sodium for an adult.

4.5 Interaction with other medicinal products and other forms of interaction

A synergistic antibacterial effect results from the combination with beta-lactam antibiotics.

Concomitant or subsequent administration and systemic or topical administration of other neurotoxic, ototoxic or nephrotoxic substances should be avoided in view of the possibility of additive effects. Amikacin toxicity may be increased by the following neuro-, oto- and/or nephrotoxic substances:
- Other aminoglycosides
- Other anti-infective chemotherapeutics e.g. bacitracin, amphotericin B, cephalosporins, vancomycin, kanamycin, paromomycin, polymyxin B, colistin
- There is an increased risk of nephrotoxicity and possibly of ototoxicity when aminoglycosides are administered with platinum based cytostatic drugs: carboplatin (at high doses), cisplatin, oxaliplatin (particularly in cases of pre-existing renal insufficiency)
- Immunosuppressants: ciclosporin, tacrolimus
- Rapid acting diuretics e.g. furosemide or ethacrynic acid (functional renal insufficiency due to dehydration, potential ototoxic action by themselves). Irreversible deafness may result.

When amikacin is combined with a potentially nephro- or ototoxic agent**,** hearing capacity and renal function must be monitored very closely. In the case of concurrent use with a rapid acting diuretic the patient’s hydration status should be monitored.

Amikacin/methoxyflurane anaesthesia
Aminoglycosides may increase the kidney damaging effect of methoxyflurane. When used concurrently, extremely severe neuropathies are possible.

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

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

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.

Indomethacin may increase the plasma concentration of amikacin in neonates.

4.6 Fertility, pregnancy and lactation

Pregnancy
There are limited amount of data from the use of aminoglycosides in pregnant women. 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 medicinal product, the patient should be apprised of the potential hazard to the foetus.
Amikacin Kabi should not be used during pregnancy unless the clinical condition of the woman requires treatment with amikacin. If treatment is deemed necessary this should only happen under medical supervision (see section 4.4).

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

Breast-feeding
It is unknown whether amikacin/metabolites are excreted in human milk. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from Amikacin Kabi therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

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.

In the case of administration to outpatients, caution is advised when driving and using machines in view of the possible undesired effects such as balance disturbances.

4.8 Undesirable effects

Under certain conditions amikacin shows ototoxic and/or nephrotoxic effects. Renal impairment is uncommonly observed in patients treated with amikacin and is usually reversible upon withdrawal of the medicinal product.

Important note on therapy:
Renal impairment and hearing impairment due to neurological effects can be for the most part avoided with the observance of precautionary measures. Control renal status as well as the senses of hearing and equilibrium before, during and after therapy. Maintain adequate hydration and ensure adequate urine production. Monitor the active substance concentration in serum for patients at particular risk and adjust dosage accordingly (see section 4.2).
The adverse reactions considered at least possibly related to treatment are listed below by body system organ class and absolute frequency. The following terminologies have been used in order to classify the occurrence of undesirable effects:

- Very common (≥ 1/10)
- Common (≥1/100 to < 1/10)
- Uncommon (≥ 1/1,000 to < 1/100)
- Rare (≥ 1/10,000 to < 1/1,000)
- Very rare (< 1/10,000)
- Not known (cannot be estimated from the available data)

Infections and infestations:	
Uncommon:	Superinfection or colonisation (with resistant microbes or yeast-like fungi)
Blood and lymphatic system disorders:	
Rare:	anaemia, leukopaenia, granulocytopenia, thrombocytopenia, eosinophilia
Immune system disorders:	
Rare:	Hypersensitivity reactions[3]
Very rare:	Anaphylactic shock
Not known	Cross-allergy between aminoglycosides
Metabolism and nutrition disorders:	
Rare:	Hypomagnesaemia
Nervous system disorders:	
Uncommon:	Dizziness[1], vertigo[1]
Rare:	Headache, migraine, paraesthesia, tremor
Eye disorders:	

Uncommon:	Nystagmus[1]
Rare:	Blindness[5], retinal infarction[5]
Ear and labyrinth disorders:	
Uncommon:	Tinnitus[1], pressure in the ears[1], hearing impairment[1]
Very rare:	Deafness[1]
Vascular disorders:	
Rare:	Hypotension
Respiratory, thoracic and mediastinal disorders:	
Rare:	Respiratory function depression[4]
Very rare:	Respiratory paralysis[4]
Not known:	Apnoea, bronchospasm
Gastrointestinal disorders:	
Uncommon:	Nausea[1]
Rare:	Vomiting
Skin and subcutaneous tissue disorders:	
Rare:	Skin rash, exanthema, pruritus, urticaria (hypersensitivity reactions)[3]
Musculoskeletal and connective tissue disorders:	
Rare:	Arthralgia
Very rare:	Neuromuscular blockage
Renal or urinary disorders:	
Uncommon:	Damage to renal tubuli[2], renal impairment[2]
Very rare:	Toxic nephropathy, acute renal failure
General disorders and administration site conditions:	
Rare:	Drug-related fever[3]
Investigations:	
Rare:	Aspartate aminotransferase increased, Alanine aminotransferase increased, alkaline phosphatase increased (slight and transient)

Further information on particular undesirable effects

(1) These effects were seen in particular when the recommended dosage level was exceeded, in treatment lasting longer than 10 days, or when the dose was not adequately reduced for patients with renal dysfunction. Initial symptoms of vestibular disturbances are dizziness, nausea and vomiting. The clinical examination often reveals a nystagmus. Vestibular disturbances are reversible in almost any case. The first symptoms of cochlear dysfunction often include a loss of high-tone perception (≥4,000 Hertz) that precedes hearing loss and is detected only by audiometry.

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

(3) Rare adverse effects are hypersensitivity reactions such as exanthema, itching, hives, and drug fever.

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

(5) Amikacin is not formulated for intavitreal use. Blindness and retinal infarction have been reported following intravitreous administration (injection into the eye) of amikacin.

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 the Yellow Card Scheme Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

Overdosing may cause nephrotoxicity, ototoxicity or a curarising effect (neuromuscular blockage).

Treatment

In the case of overdose or toxic reactions infusion of amikacin has to be stopped and forced diuresis may be applied to accelerate the removal of amikacin from blood if necessary. Peritoneal dialysis or haemodialysis may help to eliminate amikacin, which accumulates in the blood. Haemodialysis is more effective than peritoneal dialysis in removing amikacin from blood.

An exchange transfusion may be considered in neonates, however, expert advice must be sought before such a measure is implemented.

Calcium salts are indicated to neutralise the curarising effect. Mechanical ventilation may be necessary in respiratory paralysis.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

Amikacin is a semisynthetic aminoglycoside antibiotic derived from kanamycin. It was obtained by acylation with an amino-hydroxybutyric acid at the C-1 aminogroup of the 2-deoxystreptamine moiety.

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

PK/PD
The most important PK/PD parameters to predict the bactericidal effect of amikacin is the ratio of the maximum concentration in serum (C_{max}) and the minimal inhibitory concentration (MIC) of the respective pathogen. A C_{max}/MIC ratio of 8:1 or 10:1 is considered to result in efficient bacterial killing and prevention of bacterial re-growth.

Amikacin shows a post-antibiotic effect in vitro and in vivo. The post-antibiotic effect permits the dosage interval to be extended without loss of efficacy against most Gram-negative bacilli.

Mechanism(s) of resistance

Resistance to amikacin may emerge from the following mechanisms:

- Enzymatic inactivation: An enzymatic modification of the aminoglycoside molecules is the most prevalent resistance mechanism. This is mediated by acetyltransferases, phosphotransferases, or nucleotidyltransferases, which are mainly encoded by plasmids. Amikacin has been shown to be effective against many aminoglycoside-resistant strains due to its ability to resist to degradation by aminoglycoside-inactivating enzymes.
- Reduced penetration and active efflux: These resistance mechanisms are observed in *Pseudomonas aeruginosa*. Recent data indicate the emergence of similar resistance mechanisms in *Acinetobacter* spp.
- Alteration of the target structure: Modifications within the ribosomes are only occasionally observed as the cause of resistance.

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

Susceptibility testing breakpoints

MIC (minimum inhibitory concentration) interpretive criteria for susceptibility testing have been established by the European Committee on Antimicrobial Susceptibility Testing (EUCAST) for Amikacin and are listed here: https://www.ema.europa.eu/documents/other/minimum-inhibitory-concentration-mic-breakpoints_en.xlsx

Spectrum of activity of amikacin:

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

Commonly susceptible species
Aerobic Gram-positive micro-organisms
Staphylococcus aureus
Staphylococcus haemolyticus
Staphylococcus hominis°
Aerobic Gram-negative micro-organisms
Acinetobacter pittii
Citrobacter freundii
Citrobacter koseri
Enterobacter aerogenes
Enterobacter cloacae
Escherichia coli
Klebsiella oxytoca
Klebsiella pneumoniae

Morganella morganii
Proteus mirabilis
Proteus vulgaris°
Pseudomonas aeruginosa[1]
Salmonella enterica (*Enteritis-Salmonellen*)°
Serratia liquefaciens°
Serratia marcescens
Shigella spp.
Species for which acquired resistance may be a problem
Aerobic Gram-positive micro-organisms
Staphylococcus epidermidis
Aerobic Gram-negative micro-organisms
Acinetobacter baumannii
Inherently resistant organisms
Aerobic Gram-positive micro-organisms
Enterococcus spp.
Streptococcus spp.
Aerobic Gram-negative micro-organisms
Burkholderia cepacia
Stenotrophomonas maltophila
Anaerobes
Bacteroides spp.
Prevotella spp.
Other microorganisms
Chlamydia spp.
Chlamydophila spp.
Mycoplasma spp.
Ureaplasma urealyticum

° No current data were available when the table was published. Sensitivity is assumed in the primary literature, standard works and therapy recommendations.
[1] The resistance rate of isolates from special patient groups e.g. patients with cystic fibrosis is ≥10%.

Other notes:
Aminoglycosides are suitable combination partners for other antibiotics against Gram-positive cocci.

5.2 Pharmacokinetic properties

Absorption
On oral administration, practically no amikacin is absorbed; it can only be applied in parenteral administration. Peak serum concentration levels are attained 1 - 2 hours after

infusion. The serum half-life is 2.2 - 2.4 hours. A longer half-life can be expected for patients with renal failure and in premature or newborn infants.
Administration of a dose of 7.5 mg/kg by continuous 30 minute i.v. infusion results in a serum concentration of 38 µg/ml at the end of the infusion. In healthy volunteers, administration of a dose of 15 mg/kg by a continuous 30 minute i.v. infusion results in a serum concentration of approximately 77 µg/ml at the end of infusion and 47 µg/ml and 1 µg/ml, 1 and 12 hours after the end of the infusion, respectively.
In the elderly with a mean creatinine clearance of 64 ml/min, administration of a dose of 15 mg/kg by a 30 minute i.v. infusion results in a serum concentration of 55 µg/ml at the end of the infusion and 5.4 µg/ml and 1.3 µg/ml, 12 and 24 hours after the end of the infusion, respectively.
In multiple dose studies, no accumulation effects have been shown in people with normal renal function, who have received single daily doses of 15 to 20 mg/kg.

Distribution
The apparent distribution volume of amikacin is approximately 24 l (28 % of body weight). The plasma protein binding rate has been determined at 4% - 10 %.
After administration of the recommended dose, therapeutic levels of amikacin are found in bone, the heart, the gallbladder, lung tissue, urine, bile, bronchial secretions, sputum, interstitial fluid, pleural fluid and synovial fluid.
It diffuses sufficiently into the inflamed meninges. Approximately 10 % to 20 % of the serum concentration passes through healthy meninges, which may rise to 50 % when the meninges are inflamed.
Amikacin accumulates in the renal cortex and inner ear fluid, and it is only slowly eliminated from these deep compartments.
Amikacin passes the placental barrier and is excreted in human milk. Concentrations reaching 20 % of those in the mother have been found in foetal blood and in amniotic fluid.

Biotransformation
Amikacin is not metabolised in the human body.

Elimination
In patients with normal renal function mean amikacin serum clearance is 100 ml/min and renal clearance is 94 ml/min. Amikacin is eliminated by glomerular filtration as the predominant elimination pathway. Most of the volume (60 % - 82 %) is excreted unchanged in the urine within the first 6 hours. Only very small amounts are excreted in bile. In patients with normal renal function 91 % and 95 % of the dose of amikacin (i.m.) is excreted unchanged in urine within 8 and 24 hours, respectively.
Amikacin can be eliminated via haemodialysis and at a lower rate by peritoneal dialysis. Depending on the dialysis method 50 % (range 29 % - 81 %) or 40 % - 80 % of the administered dose is removed within four or 8 hours, respectively.

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

Intravenous use
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 birthweights (< 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 ml/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

In repeat-dose toxicity studies, the main effects were nephrotoxicity and ototoxicity.
No studies of the mutagenic or carcinogenic potential of amikacin have been conducted.
In studies on reproductive toxicity, amikacin caused dose-related nephrotoxicity in pregnant rats and their foetuses, and reproductive toxicity studies in offspring of mice, rats and rabbits revealed increased foetal death rates. There is a potential risk of inner ear and renal damage to the foetus as was observed for the class of aminoglycoside antibiotics.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium chloride

Hydrochloric acid (for pH adjustment)

Sodium hydroxide (for pH adjustment)

Water for injections

6.2 Incompatibilities

Amikacin Kabi is a ready-to-use formulation and must not be mixed with any other medicinal products (except those mentioned in 6.6) but must be administered separately, in accordance with the recommended dose and method for administration.
On no account may aminoglycosides be mixed in an infusion solution with beta-lactam antibiotics (e.g. penicillins, cephalosporins), as this may cause chemical-physical inactivation of the combination partner.

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

Inactivation when aminoglycosides and beta-lactam antibiotics are mixed may also persist when samples are taken to measure the serum levels of antibiotics and may result in considerable underestimation with dosage errors and risks of toxicity as a consequence. Samples must be handled rapidly and placed on ice or beta-lactamase should be added.

6.3 Shelf life

3 years

<u>In-use shelf-life (after first opening/dilution):</u>

Chemical and physical in-use stability has been demonstrated for 24 hours at 25ºC and 2 to 8ºC.

From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior the use are responsibility of the user and would normally not be longer than 24 h at 2 to 8 ºC, unless the method of opening / 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 first opening and dilution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

The solution for infusion is presented in bottles of low-density polyethylene closed with a cap containing a rubber disc to allow insertion of the needle.

Pack sizes: 10 x 50 ml, 10 x 100 ml and 10 x 200 ml solution for infusion.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

The solution is to be inspected visually for particulate matter and discoloration prior to administration.
Only clear solutions free from particles should be used.
The solution should be administered with sterile equipment using an aseptic technique. The equipment should be primed with the solution in order to prevent air entering the system.
Unused solution should be discarded.
Any unused medicinal product or waste material should be disposed of in accordance with local requirements, immediately after use.

Amikacin Kabi is compatible with the following infusion solutions:
- Ringer's solution
- Lactated Ringer solution
- Sodium chloride 9 mg/ml (0.9 %) solution for injection
- Glucose 50 mg/ml (5 %) solution for injection
- Glucose 100 mg/ml (10 %) solution for injection

Instructions for dilution
To obtain an Amikacin concentration of 2.5 mg/ml the respective amount (in ml) of Amikacin 5 mg/ml for the desired dose has to be compounded with the identical amount of one of the above mentioned infusion solutions.

7 MARKETING AUTHORISATION HOLDER

Fresenius Kabi Ltd.
Cestrian Court, Eastgate way
Manor Park, Runcorn
Cheshire WA7 1NT
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

PL 08828/0283

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

26/07/2024

10 DATE OF REVISION OF THE TEXT

29/08/2025