Package leaflet: Information for the patient

Amikacin 125 mg/ml solution for injection/infusion
Amikacin 250 mg/ml solution for injection/infusion
amikacin

Read all of this leaflet carefully before you are given this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Amikacin is and what it is used for

Amikacin is part of a group of antibiotics called 'aminoglycosides'.
It is indicated for the short-term treatment of serious infections due to susceptible strains of bacteria.

You may receive Amikacin to treat the following infections:
- Infections of the lungs and lower airways including pneumonia
- Infections of bones and joints
- Infection of the central nervous system (including meningitis)
- Skin and soft tissue infections including burn wounds
- Infections within the abdomen, including inflammation of the peritoneum (membrane which lines the abdominal cavity and covers the abdominal organs)
- Infections after surgical operations
- Infections of kidneys, urinary ducts and bladder
- Bacterial inflammation of the inner lining of the heart

This medicine can also be used in the treatment of patients with an inflammation of the entire body that occurs in association with, or is suspected to be associated with, any of the infections listed above.

2. What you need to know before you are given Amikacin

Amikacin must not be given:
- if you are allergic to amikacin or any of the other ingredients of this medicine (listed in section 6)
- if you are allergic to other similar substances (other aminoglycosides)
- if you are being treated with ataluren (medicine used in Duchenne muscular dystrophy, a rare genetic neuromuscular disease)

Warnings and precautions
Talk to your doctor before you are given this medicine if:
- you have kidney problems
- you had any kidney or hearing problems after taking other antibiotics
- you have hearing difficulties or dizziness (tinnitus)
- you develop muscle disorders, such severe myasthenia gravis (a disease that causes muscle

weakness) or parkinsonism
- you are elderly
- in the event of a fairly advanced stage of cirrhosis of the liver (severe chronic liver disease),
- if you or your family members have a mitochondrial mutation disease (a genetic condition) or loss of hearing due to antibiotic medicines, you are advised to inform your doctor or pharmacist before you take an aminoglycoside; certain mitochondrial mutations may increase your risk of hearing loss with this product. Your doctor may recommend genetic testing before administration of Amikacin.

If any of the above applies to you, talk to your doctor or nurse before using this medicine.

Other medicines and Amikacin
Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines, including medicines administered without a prescription.

Some medicines may interact with others. Tell your doctor if you are taking:
- diuretics such as furosemide or ethacrynic acid
- other medicines that may affect your kidneys or hearing such as bacitracin, cisplatin, amphotericin B, cyclosporine, tacrolimus, cephaloridine, paromomycin, viomycin, polymyxin B, colistin, vancomycin or other aminoglycosides
- penicillin type medicines
- bisphosphonates (used to treat osteoporosis and similar diseases)
- vitamin B1
- platinum compound medicines
- muscle relaxants
- indomethacin, an anti-inflammatory medicine, may increase the amount of amikacin absorbed in newborns
- ataluren (used in Duchenne muscular dystrophy, a rare genetic neuromuscular disease)

Pregnancy, breast-feeding and fertility
If you are pregnant or breast-feeding, think you may be pregnant or planning to have a baby, ask your doctor or pharmacist for advice before you are given this medicine.

Your doctor will only use this medicine if the expected benefits outweigh any potential risk to your baby.

Ask your doctor's advice before taking any medicine.

Driving and using machines
Do not drive or use machine if you experience any side effects (such as dizziness) which may lessen your ability to react.

Amikacin contains sodium metabisulfite and sodium
This medicine contains sodium metabisulfite which may rarely cause severe hypersensitivity reactions (severe allergy) and bronchospasm (difficulty breathing).
This medicine contains less than 1 mmol sodium (23 mg) per ampoule, that is to say essentially 'sodium free'.

3. How Amikacin is given

This medicine is usually given by injection into a muscle. It can also be administered intravenously (into a vein) either by injection or (after dilution) by infusion (drip).

Dose
Your doctor will work out the correct dose of amikacin for you and how often it should be given.

The dose will depend upon your weight, your age, the infection you have, how well your kidneys

are working, if you have poor hearing, and any other medicines you may be taking.
It will usually be given once or twice a day for up to 10 days.

During the course of treatment, you may undergo blood tests to monitor your kidney function and the level of amikacin in your blood, and you may be asked to provide urine samples.
You will possibly have hearing tests before and during treatment to check for signs of side effects. Your doctor may adjust your dose based on the results of these tests.

Use in children
Amikacin, like all aminoglycosides, should be used with caution in premature and neonatal (newborn) infants.

If you are given more Amikacin than you should
If you think you have been given too much of this medicine, please tell your doctor or nurse immediately.
Overdosing may cause damage to kidneys and the ear nerves or a blockage of muscle function (paralysis). In such a case the infusion of amikacin has to be stopped.

If you have any further questions on the use of this medicine, ask your doctor, pharmacist or nurse.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

If you notice any of the following severe side effects, contact your doctor immediately:
Very rare (may affect up to 1 in 10000 people)
- breathing paralysis

Not known (frequency cannot be estimated from the available data)
- swelling of the face, lips, or tongue, skin rash, difficulty breathing, as these may be signs of an allergic reaction
- ringing in your ears or loss of hearing (deafness)
- kidney problems including a reduction in urine output (acute kidney failure)
- paralysis

Other side effects include:

Uncommon (may affect up to 1 in 100 people):
- infections or growth of resistant bacteria
- nausea, vomiting
- dizinness, vertigo
- involuntary eye movements (nystagmus)
- damage to kidney tubuli, kidney impairment

Rare (may affect up to 1 in 1000 people):
- abnormal blood cell and plateles count, such as anaemia, eosinophilia, leukopaenia, granulocytopenia, thrombocytopenia
- hypomagnesaemia (low level of magnesium in your blood)
- tremor, hallucinations, headache, imbalance
- blindness, retinal infarction
- tinnitus, hearing loss
- hypotension (low blood pressure)
- itching, hives, skin rash, exanthema
- arthralgia (joint pain), muscle contractions
- decrease in the amount of urine you produce, elevated serum creatinine, albuminuria, azotemia,

urinary erythrocytes, urinary leukocytes
- pyrexia (fever)
- migraine
- respiratory function depression
- aspartate aminotransferase increased, alanine aminotransferase increased, alkaline phosphatase increased (slight and transient)

Very rare (may affect up to 1 in 10000 people):
- neuromuscular blockage
- respiratory paralysis (isolated cases) - complete or severe weakness of the muscles of breathing

Not known (frequency cannot be estimated from the available data):
- anaphylactic reaction, anaphylactic shock and anaphylactoid reaction, hypersensitivity
- paralysis
- deafness, neurosensory deafness
- apnea (disorder that causes you to stop breathing while asleep), bronchospasm
- acute kidney failure, toxic nephropathy (kidney injury due to medicines, toxic chemicals), urinary epithelium

If Amikacin is injected directly into the eye, serious vision problems may occur.

Reporting side effects
If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via HPRA Pharmacovigilance, Website: www. hpra.ie. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Amikacin

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton and label after "EXP". The expiry date refers to the last day of that month.

Store below 25°C
Do not use this medicine if you notice particles in the ampoule, or if the solution does not appear colourless to pale yellow.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help to protect the environment.

6. Contents of the pack and other information

What Amikacin contains
- The active substance is amikacin sulfate.
  Each ml of solution for injection/infusion contains 125 mg amikacin (as sulfate).
  Each ml of solution for injection/infusion contains 250 mg amikacin (as sulfate).
  Each 2 ml ampoule contains 250 mg amikacin.
  Each 2 ml ampoule contains 500 mg amikacin.
- The other ingredients are sodium citrate dihydrate, sodium metabisulfite, sulfuric acid (for pH adjustment), water for injections.

What Amikacin looks like and contents of the pack

Amikacin solution is a clear, colourless to pale yellow solution, free from visible particles in clear glass ampoules.
Pack sizes: 1 and 10 ampoules

Not all pack sizes may be marketed.

Marketing Authorization Holder
Noridem Enterprises Ltd.
Evagorou & Makariou,
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This medicine is authorised in the Member States of the European Economic Area under the following names:

Ireland	Amikacin 125 mg/ml Solution for injection/infusion
	Amikacin 250 mg/ml Solution for injection/infusion
Greece	BRUSE
	BRUSE
France	AMIKACINE NORIDEM 125 mg/mL, solution injectable/pour perfusion
	AMIKACINE NORIDEM 250 mg/mL, solution injectable/pour perfusion
Italy	Amikacina Noridem
	Amikacina Noridem
Spain	Amikacina Noridem 125 mg/ml Solución inyectable y para perfusión
	Amikacina Noridem 250 mg/ml Solución inyectable y para perfusión
Czech Republic	Amikacin Noridem
	Amikacin Noridem
Slovakia	Amikacin Noridem 125 mg/ml Injekčný/infúzny roztok
	Amikacin Noridem 250 mg/ml Injekčný/infúzny roztok
Hungary	Amikacin Noridem 125 mg/ml Oldatos injekció/infúzió
	Amikacin Noridem 250 mg/ml, Oldatos injekció/infúzió
Romania	Amikacină Noridem 125 mg/ml soluţie injectabilă/perfuzabilă
	Amikacină Noridem 250 mg/ml, soluţie injectabilă/perfuzabilă
Poland	Amikacinum Noridem
	Amikacinum Noridem

This leaflet was last revised in {MM/YYYY}

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The following information is intended for medical or healthcare professionals only:

Posology and method of administration

Amikacin is generally used in combination with other appropriate antibiotics. The dose of amikacin depends on the infection, the patient's status, and the renal function. Local guidance should be taken into consideration.

Posology

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

The status of renal function should be estimated by measurement of the serum creatinine concentration or calculation of the endogenous creatinine clearance rate. Reassessment of renal function should be made periodically during therapy. Blood urea measurement is much less reliable for this purpose.

Amikacin concentrations in serum should be measured whenever possible in order to assure adequate but not excessive levels. It is desirable to measure both peak and trough concentrations intermittently during treatment. Peak concentrations (30-90 minutes after injection) above 35 mcg/ml and trough concentrations (just prior to the next dose) above 10 mcg/ml should be avoided. The dosage should be adjusted as indicated. In patients with normal renal function, once daily dosing may be used. Peak concentrations in these cases may exceed 35 mcg/ml (see Single Daily Administration and Renal Impairment below).

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

Children aged 4 weeks to 12 years:
The recommended intramuscular or intravenous (slow intravenous infusion) dose in children with normal renal function is 15-20 mg/kg/day which may be administered as 15-20 mg/kg, once a day; or as 7.5 mg/kg 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:
An initial loading dose of 10 mg/kg followed by 7.5 mg/kg every 12 hours (see sections 4.4 and 5.2).

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

Data on single daily administration to patients with other systemic infections are limited (see also above for controlling peak and trough serum amikacin concentrations).

The duration of treatment is 7 to 10 days. In majority of cases, aminoglycosides are indicated only at the start of treatment when inoculum is potentially high and when there are uncertainties about the effectiveness of the treatment, and for a duration of treatment ≤ 5 days due to their benefit/safety ratio (bactericidal activity/toxicity correlated to the duration of treatment). The total daily dose with all modes of administration should not exceed 20 mg/kg/day. In difficult and complicated infections where treatment beyond 10 days is considered, the use of amikacin should be re-evaluated and, if continued, renal, auditory and vestibular function as well as serum amikacin levels should be monitored.
At the recommended dosage level, uncomplicated infections due to amikacin-sensitive microorganisms should respond within 24 to 48 hours. If no clear clinical response is observed after 3 to 5 days, treatment should be stopped and the susceptibility of the pathogen to the antibiotic should be re-tested. Failure to respond to infection may be due to resistance of the microorganism or the presence of septic foci requiring surgical drainage.

Impaired renal function

In patients with renal impairment reflected by creatinine clearance less than 50 mL/min, administration of the recommended total daily dose of amikacin in single daily doses is not desirable since these patients will have protracted exposure to high trough concentrations. See below for dosage adjustments in patients with impaired renal function.

For patients with impaired renal function receiving usual twice or three times daily dosing, whenever possible, serum amikacin concentrations should be monitored by appropriate assay procedures. Doses should be adjusted in patients with impaired renal function either by administering normal doses at prolonged intervals or by administering reduced doses at fixed intervals.

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 in patients with diminished renal function. These dosage schedules must be used in conjunction with careful clinical and laboratory observations of the patient and should be modified as necessary, including modification when dialysis is being performed.

Normal dosing at extended intervals

If there is no data on creatinine clearance and the patient's condition is stable, a dosage interval in hours for the normal single dose (ie that would be given to patients with normal renal function on a twice daily schedule, 7.5 mg/kg per day) can be calculated by multiplying the patient's serum creatinine by nine. For example, if the serum creatinine concentration is 2 mg/100 ml, the recommended single dose (7.5 mg/kg) should be administered every 18 hours.

Reduced dosage at fixed time intervals between dosing

When amikacin should be administered at a fixed time interval in renal impairment, the dose must be reduced. In these patients, serum amikacin concentrations should be measured to assure accurate administration and to avoid excessive serum concentrations. If serum assay determinations are not available and the patient's condition is stable, serum creatinine or serum creatinine clearance values are the most readily available indicators of the degree of renal impairment that can be used as a dosing guide.

First, initiate therapy by administering a normal dose, 7.5 mg/kg, as a loading dose. This dose is the same as the normally recommended dose which would be calculated for a patient with a normal renal function as described above.

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

Maintenance dose every 12 hours =

$$\frac{\text{observed CrCL in ml/min X calculated loading dose in mg}}{\text{Normal CrCL in ml/min}}$$

(CrCI = creatinine clearance rate)

An alternative 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 regimens are not intended to be rigid recommendations, but are provided as dosing guides when serum amikacin level measurement is not feasible.

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
Amikacin can be given intramuscularly or intravenously. **Local guidance should be taken into consideration.**

Intravenous administration
In adults can be given either as is (2-3 minutes) or by slow infusion within 30 to 60 minutes.
A slow infusion over 30 minutes in addition to serum amikacin concentrations measured 30 minutes after the end of the infusion, can be considered as an appropriate management, taking into account the pharmacokinetic/pharmacodynamic objectives and drug concentrations monitored at adequate times with a standardized approach.

Special recommendation for intravenous administration in the paediatric population
In paediatric patients, the amount of diluents used will depend on the amount of amikacin tolerated by the patient. The solution should normally be infused over a 30 to 60 minute period. Infants should receive a 1 to 2 hour infusion.

Amikacin should not be mixed with other medicines, but can be given separately according to the recommended dose and route of administration.

For instructions on the dilution of the medicinal product before administration, please refer to "Instructions on handling" section below.

Incompatibilities

This medicinal product must not be mixed with any other medicinal products (except those mentioned in section "Instructions on handling" below).

Mixing aminoglycosides with β-lactam antibiotics (penicillins or cephalosporins) in an infusion solution can lead to significant mutual inactivation. Decreased serum activity may also be observed when an aminoglycoside or a penicillin-type antibiotic is administered *in vivo* by separate route. Aminoglycoside inactivation is of clinical importance only in patients with severe renal impairment. Inactivation may persist in body fluid samples taken for assays, resulting in inaccurate aminoglycoside measurements. Samples must be handled properly (direct examination, freezing or β-lactamase effect).

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.

Overdose
In case of overdosage there is a general risk for nephro-, oto- and neurotoxic (neuromuscular blockage) reactions. Neuromuscular blockage with respiratory arrest needs appropriate treatment including application of ionic calcium (e.g. as gluconate or lactobionat in 10-20% solution). In the event of overdosage or toxic reaction, peritoneal dialysis or haemodialysis will aid in the removal of amikacin from the blood.

Amikacin levels are also reduced during continuous arteriovenous hemofiltration.
In the newborn infant, exchange transfusion may also be considered.

Instructions on handling

Intravenous administration: *Preparation of solutions*
The solution for intravenous use is prepared by adding the desired dose to 100 ml or 200 ml of sterile solvent such as sodium chloride solution or 5% dextrose in water or any other compatible solution.

Amikacin 125 mg/mL and Amikacin 250 mg/mL are diluted under aseptic conditions with:

- 5% Dextrose Injection
- 5% Dextrose and 0.2% Sodium Chloride Injection
- 5% Dextrose and 0.45% Sodium Chloride Injection
- 0.9% Sodium Chloride Injection
- Lactated Ringer's Injection
- Lactated Ringer's Injection with 5% Dextrose

In pediatric patients, the amount of fluid that will be used depends on the amount that will be tolerated by the patient. It should be sufficient in order to inject amikacin over a period of 30 to 60 minutes.

After dilution:
Diluted solutions having final concentrations below 2.5 mg/ml should be used immediately.

Chemical and physical in-use stability has been demonstrated for 24 hours at 23-27 °C under artificial light and at 2-8°C with 0.9% Sodium Chloride Injection and Lactated Ringer's Injection, at a concentration of Amikacin of 2.5 mg/mL, 5.0 mg/mL, 7.5 mg/mL and 15.0 mg/mL.

Chemical and physical in-use stability has been demonstrated for 3 hours at 23-27 °C under artificial light and for 12 hours at 2-8 °C with 5% Dextrose Injection, 5% Dextrose and 0.2% Sodium Chloride Injection, 5% Dextrose and 0.45% Sodium Chloride Injection and Lactated Ringer's Injection with 5% Dextrose, at a concentration of Amikacin of 2.5 mg/mL, 5.0 mg/mL and 7.5 mg/mL**.**

Chemical and physical in-use stability has been demonstrated for 6 hours at 23-27 °C under artificial light and for 24 hours at 2-8 °C with 5% Dextrose Injection, 5% Dextrose and 0.2% Sodium Chloride Injection, 5% Dextrose and 0.45% Sodium Chloride Injection and Lactated Ringer's Injection with 5% Dextrose, at a concentration of Amikacin of 15.0 mg/mL**.**

From a microbiological point of view, unless the method of opening precludes the risk of microbial contamination, the product should be used immediately. If not used immediately, in-use storage times and conditions are the responsibility of the user.

The medicinal product should be visually inspected for particulate matter and discoloration prior to administration.

Only clear solutions free from particles should be used.

Single use only.

Unused solution should be discarded.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements, immediately after use.