For the use only of a Registered Medical Practitioners.

℞ Arbekacin Sulfate Injection 200mg / 4ml

Arbekem
अरबीकेम

1. Generic name
Arbekacin Sulfate Injection 200 mg/4 ml.

2. Qualitative and quantitative composition
Each 4ml contains:
Arbekacin Sulfate JP Equivalent to Arbekacin .....200 mg
Excipients.....q.s.

3. Dosage form and strength
Injection

4. Clinical particulars
4.1 Therapeutic indications
Arbekacin is indicated in following infections caused by methicillin - resistant staphylococcus aureus (MRSA).
• Pneumonia
• Sepsis

4.2 Posology and method of administration
Adults: The usual adult dosage is 150 – 200 mg/day once daily by intravenous drip.
Method of administration
Arbekacin is administered by intravenous route. It should be preferably diluted in 0.9% normal saline and can be administered by Intravenous infusion over a period of 30 min. to 2 hrs.
Patients with renal impairment
Arbekacin can be given to renally impaired patients however caution has to be exercised in terms of dosage. Thus following dosage pattern is recommended in renally impaired patients:

• **Priming dose:** 75 – 100 mg
• **Maintenance dose:** half of priming dose
• **Dosage interval:**
• 12 – 24 hours in case of Creatinine clearance 20 – 25 ml/min
• 24 – 48 hours in case of Creatinine clearance <20 ml/min

Patients with hepatic impairment
Caution is required while administering Arbekacin in patients with hepatic impairment.
Elderly
Special precaution is required when using in elderly patients with significant impairment of renal function because high serum concentration of arbekacin might cause renal or ototoxicity

4.3 Contraindications
A history of hypersensitivity or toxic reaction to any aminoglycoside

4.4 Special warnings and precautions for use
Hypersensitivity
Arbekacin should not be used in patients with history of anaphylaxis for Bacitracin and Aminoglycosides such as Kanamycin, Streptomycin, Gentamycin, Tobramycin, Amikacin, Netilmycin, and so on.
Nephrotoxicity
It is well-known that the use of aminoglycosides is associated with the occurrence of nephrotoxicity. Similarly, the major toxicity of arbekacin treatment is the risk of nephrotoxicity. In patients with renal insufficiency the dosage and dose interval should be adjusted as given in section 4.2. Posology and method of administration.
Ototoxicity
In case of patient or patient's family has difficulty in hearing or has streptomycin deafness, arbekacin should be avoided or used with caution.

4.5 Drug interactions
• It's desirable to avoid arbekacin in conjunction with blood substance such as dextran and hydroxyl ethyl starch, which may lead to renal disorder. In case of renal disorder stop administration and take a proper measure as dialysis.
• Respiratory repression caused by myo-neural blockade function may occur. Therefore when administering in conjunction with anesthetic and muscle relaxant, administer cautiously. In case of respiratory repression, take a necessary treatment such as cholinesterase inhibitor, calcium preparation etc.
• Nephrotoxicity, ototoxicity caused by conjunction with ethacrynic acid, furosemide, may be increased, avoid administering with these diuretics.
•In case of combined treatment with other aminoglycosides antibiotics (injection) to an infant, nephrotoxicity and ototoxicity can be increased.
• Combination with Ampicillin, Piperacillin, administer by separate way.
• Conjunction with nephrotoxic and ototoxic medicine such as vancomycin, antineoplastic including platinum (cisplatin, carboplatin) nephrotoxicity and ototoxicity can be increased.
• Conjunction with nephrotoxic medicine such as cyclosporine and amphotericin B, nephrotoxicity can be increased.
• Combination with sulbactam, cefoperazone, cefazolin, bromhexine HCl, hydrocortisone succinate, calcium chloride and doxorubicin chloride in same infusion, cloudiness and precipitation can appear.

4.6 Use in special populations (such as pregnant women, lactating women, paediatric patients, geriatric patients etc.)
Pregnancy
Usage for pregnant women can induce the 8th cranial—nerve disorder in fetus, Use only when the efficacy is considered to be greater than the risk of the side effect. It has induced retardation to live born infants in the experiment on rats. In case of perinatal and lactiferous phase test, weight gain repression, intake reduction, enlarged kidney were observed among litters.
Fertility
According to the result of animal (rats, rabbit) fertility test, animal weight gain repression, intake reduction, enlarged kidney were observed when used in intravenous doses (4-50mg/kg/day) or intramuscular injection (1-25mg/kg/day). With intramuscular (25mg/kg/day) high dose, live fetal reduction were observed.

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.

4.8 Undesirable effects
Summary of the safety profile
Ototoxicity & nephrotoxicity are the most serious adverse effects of aminoglycoside therapy & are more likely to occur in patients with a history of renal impairment.
Tabulated list of adverse reactions
Safety of Arbekacin in Indian patient was evaluated in a clinical trial comparing Arbekacin and Vancomycin in patients with MRSA infections. Following Adverse events were reported in study.

System Organ Class	Adverse Event
Blood and lymphatic system disorders:	Increased TLC
Nervous system disorders	Dizziness
Gastrointestinal disorders	Stomach pain, Vomiting, Diarrhoea, Hyperacidity
Hepatobiliary disorders	Raised Transaminases, Acute hepatocellular injury
Renal and urinary disorders	Pyuria, Decreased creatinine clearance
General disorders and administration site conditions	Pyrexia

4.9 Overdose
In case of overdose, renal disorder, hypoacusis, vestibular disorder, myoneural blockade, respiratory paralysis may occur. Discontinue the infusion immediately. Hemodialysis or peritoneal dialysis should be performed. For management of Myoneural blockade or respiratory paralysis cholinesterase inhibitors, calcium agents. For severe respiratory paralysis, ventilator support may be required.

5. Pharmacological properties
5. 1 Mechanism of action
Arbekacin inhibit protein synthesis in susceptible bacteria by irreversibly binding to the bacterial 30S ribosomal subunits. Specifically, Arbekacin binds to four nucleotides of 16S rRNA and a single amino acid of protein S12. This interferes with the decoding site in the vicinity of nucleotide 1400 in the 16S rRNA component of the 30S subunit. This region interacts with the wobble base in the anticodon of tRNA. This leads to misreading of mRNA, so incorrect amino acids are inserted into the polypeptide, leading to non-functional or toxic peptides and the breakup of polysomes into non-functional monosomes.

5.2 Pharmacodynamic properties
Pharmaco-therapeutic group: Antibacterial for systemic use, Aminoglycosides.
Microbiological Susceptibility
Arbekacin as well as other aminoglycosides such as gentamicin, tobramycin, dibekacin and amikacin is potentially active against *Enterobacteriaceae*, Pseudomonas aeruginosa and S. aureus. Arbekacin showed more activity than amikacin against S. aureus, Escherichia coli, Klebsiella pneumoniae, Enterobacter cloacae, Serratia marcescens, Proteus mirabilis, Proteus rettgeri, Proteus vulgaris and Morganella morganii. Arbekacin is active against E. coli, S. marcescens, K. pneumoniae, P. mirabilis and P. aeruginosa and indole-positive Proteus spp. Arbekacin was superior against kanamycin, gentamicin, tobramycin, dibekacin and amikacin resistant S. aureus. In particular this drug was active against MRSA.
Arbekacin activity was tested against 904 isolates from pneumonias in U.S. hospitalized patients (PHP) collected in 2012 from 62 U.S. medical centers and 303 multidrug-resistant (MDR) organisms collected worldwide in 2009 and 2010 from various infection types.
Susceptibility to arbekacin and comparator agents was evaluated by the reference broth micro dilution method. The four most common organisms from PHP were Staphylococcus aureus, Pseudomonas aeruginosa, Klebsiella spp., and Enterobacter spp. The highest arbekacin MIC among S. aureus isolates from PHP (43% methicillin-resistant S. aureus [MRSA]) was 4 µg/ml. Among P. aeruginosa isolates from PHP, only one had an arbekacin MIC of >16 µg/ml (MIC50 and MIC90, 1 and 4 µg/ml), and susceptibility rates for gentamicin, tobramycin, and amikacin were 88.0, 90.0, and 98.0%, respectively.
Arbekacin (MIC50, 2 µg/ml) and tobramycin (MIC50, 4 µg/ml) were the most potent aminoglycosides tested against Acinetobacter baumannii. Against Enterobacteriaceae from PHP, arbekacin and gentamicin (MIC50 and MIC90, 0.25 to 1 and 1 to 8 µg/ml for both compounds) were generally more potent than tobramycin (MIC50 and MIC90, 0.25 to 2 and 1 to 32 µg/ml) and amikacin (MIC50 and MIC90, 1 to 2 and 2 to 32 µg/ml). Arbekacin also demonstrated potent in vitro activity against a worldwide collection of well-characterized MDR Gram-negative and MRSA strain.
A study was conducted to evaluate the safety and efficacy of Arbekacin sulphate in patients with MRSA infection including septicemia and pneumonia where Vancomycin Hydrochloride is indicated. A total of 127 subjects were enrolled in the trial at 13 clinical trial sites in India. It was found that the ooverall cure rate of MRSA infection (clinical as well as microbiological cure) was comparable in both the treatment groups i.e. Arbekacin 96.8 % (61/63) & Vancomycin 100 % (64/64). Median time taken for fever clearance was 10 days in Arbekacin group whereas in Vancomycin group it was 11.5 days and it was comparable. In patients with skin and soft tissue infections, the rate of wound healing was comparable in both the groups. It was concluded that, the efficacy of Arbekacin sulphate 200 mg OD was found to be comparable to Vancomycin in terms of overall cure rate in the treatment of MRSA infections.

5.2 Pharmacokinetic properties
The pharmacokinetics of Arbekacin has been studied in not only healthy young adults but also in patients with renal dysfunction. The average peak serum concentrations were 4.2 µg/ml and 5.6 µg/ml after 30 minutes of intramuscular injection of 75 and 100 mg of Arbekacin, respectively, to 4 healthy young male adults. Regardless of the dose, 70% of the Arbekacin was excreted in the urine by 8 hours after injection. The average peak serum concentrations were 6.8µg/ml and 7.56 µg/ml after administration of 75 and 100 mg of Arbekacin, respectively, when given to 3 healthy young adults by drip infusion for 1 hour and 78.3% and 78.6% respectively of Arbekacin was excreted in the urine by 8 hours after the end of drip infusion.
The half-life of the serum concentration of Arbekacin was inversely proportional to creatinine clearance. The average peak serum concentration after 200 mg of arbekacin administration by 1 hour intravenous infusion to 5 healthy volunteers was 13.20 ± 1.37µg/ml and the average serum concentration 12 hours after administration was 0.38 ± 0.006 µg/ml. The mean urinary recovery rate after 24 hours of administration was 86.8 ± 4.94%.

6. Nonclinical properties
6.1 Animal toxicology & Pharmacology
Preclinical Safety Data
Arbekacin Sulphate Injection (200 mg Arbekacin/4 ml) diluted with water for injection was administered to rats via intravenous route at the dose levels ranging from 0 mg/kg to 50 mg/kg i.e. 0 mg/kg, 12.5 mg/kg, 25 mg/kg & 50 mg/kg body weight.
Salient features of the study were as follows:
Male & female animals from control & different dose groups survived through the dosing period of 28 days. No signs of toxicity were observed in male & female animals from different dose groups during the dosing period of 28 days. Male & female animals from control & different dose groups exhibited normal body weight gain at the end of the dosing period of 28 days.
Food intake of animals from control & different dose groups was found to be comparable throughout the dosing period of 28 days.
Haematological analysis revealed no abnormalities attributable to the treatment. Biochemical analysis revealed no abnormalities attributable to the treatment. Organ weight data of male animals revealed decreased relative weights of kidneys of animals from 25 mg/kg dose group, decreased relative weights of adrenals of animals from 25 mg/kg & 50 mg/kg dose groups & increased relative weights of spleen of animals from 12.5 mg/kg dose group. Organ weight data of female animals revealed increased relative weights of kidneys of animals from 50 mg/kg dose group. Although significant changes in organ weights were observed in animals from different dose groups, no related gross pathological or histological changes were seen, hence these findings were considered to be of no toxicological importance. Gross pathological examination did not reveal any abnormality attributable to the treatment.

7. Description
Colorless and transparent injection in colorless and transparent ampoule.

8. Pharmaceutical particulars
8.1 Incompatibilities
In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products except those mentioned in section of reconstitution.

8.2 Shelf life:
36 months.

8.3 Packaging information:
4 ml ampoule.

8.4 Storage and handling instructions
Store below 25ºC. Protected from light. Do not freeze.
Reconstitution and Dilution:
It should be diluted preferably with 0.9% normal saline
Infusion
It can be administered by intravenous infusion over 30 min. to 2 hrs.

9. Patient Counselling Information
Package leaflet: Information for the user
Arbekacin Sulphate Injection 200 mg/4 ml

Read all of this leaflet carefully before you start using 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 or pharmacist.
• If you get any side effects, talk to your doctor. This includes any possible side effects not listed in this leaflet. See section 4.
What is in this leaflet
1. What Arbekacin Injection is and what it is used for
2. What you need to know before you use Arbekacin Injection
3. How to use Arbekacin Injection
4. Possible side effects
5. How to store Arbekacin Injection
6. Contents of the pack and other information

22i. What Arbekacin injection is and what it is used for?
Arbekacin Injection is one of a group of antibiotic medicines called 'aminoglycosides'.
Arbekacin Injection is used in the treatment of serious infections caused by bacteria sensitive to arbekacin.

ii. Before you use Arbekacin Injection
Do not use Arbekacin Injection
• If you have shown signs of hypersensitivity (severe allergy) to arbekacin, or any of the other ingredients listed in section 6, in the past
• If you suffer from a disorder called myasthenia gravis (severe weakness of certain muscles of the body)
Tell your doctor if any of the above applies to you before this medicine is used.

Warnings and precautions
Talk to your doctor before using Arbekacin Injection
• If you have kidney problems
• If you have hearing difficulties or tinnitus (ringing or buzzing in the ears)
• If you have shown signs of allergy to any of the antibiotics related to arbekacin (aminoglycosides) in the past
• If you have a known allergy to sulphites
Tell your doctor if any of the above applies to you before this medicine is used.

Children
Arbekacin should be used with caution in premature and neonatal infants.

Other medicines and Arbekacin Injection
Tell your doctor if you are taking, have recently taken or might take/use any other medicines.
Special care is needed if you are taking/using other medicines, as some could interact with Arbekacin for example:
• Diuretics (water tablets) such as furosemide and ethacrynic acid
• Other antibiotics that can affect your kidneys, hearing or balance
• Anaesthetics or muscle-relaxing drugs
• Indomethacin (an anti-inflammatory medicine)
• Other antibiotics called beta-lactamases such as penicillins or cephalosporins
• Bisphosphonates; drugs used to treat loss of bone mass
• Vitamin B1 (thiamine)
• Platinum compounds used in chemotherapy such as cisplatin

Pregnancy and breast-feeding
If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor for advice before taking this medicine. Your doctor will only use this medicine if the expected benefits outweigh any potential risk to your baby.
Driving and using machines
Do not drive or use machines if you experience any side effect (e.g. dizziness) which may lessen your ability to do so.
iii. How to use Arbekacin Injection
This medicine is to be administered into a vein as an infusion (drip) over a period of 30 min. to 2 hrs
Your doctor will ensure you are well hydrated before and during treatment.
Dose
Your doctor will work out the correct dose of arbekacin for you and how often it must be given. This may require blood tests before treatment.
The dose will depend upon your age, weight, the infection you have, how well your kidneys are working, if you have poor hearing and any other medicines you may be taking.
The usual adult dosage is 150 – 200 mg/day once daily by intravenous drip
In case of renal impairment (disease) following dosage pattern is followed:
• **Priming/Staring dose:** 75 – 100 mg
• **Maintenance dose:** half of priming dose
• **Dosage interval:**
• 12 – 24 hours in case of Creatinine clearance 20 – 25 ml/min
• 24 – 48 hours in case of Creatinine clearance <20 ml/min
During treatment you may undergo blood tests and be asked to provide urine samples. You will possibly also have hearing tests before and during treatment to look for signs of side effects. Your doctor may change your dose depending upon the results of these tests.
If you are given too much or too little Arbekacin Injection
This medicine will be given to you in a hospital, under the supervision of a doctor. It is unlikely that you will be given too much or too little, however, tell your doctor or nurse if you have any concerns.
iv. Possible side effects
Like all medicines, this medicine can cause side effects, although not everybody gets them.
If any of the following happens, tell your doctor immediately as these are all serious. You may need urgent medical attention or hospitalisation.
Rare side-effects may affect up to 1 in 1,000 people are listed below:
• Ringing in your ears or loss of hearing
• Decrease in the amount of urine you produce
Not known: frequency cannot be estimated from available data are listed below:
• Severe allergic reaction - you may experience a sudden itchy rash (hives), swelling of the hands, feet, ankles, face, lips, mouth or throat (which may cause difficulty in swallowing or breathing), and you may feel you are going to faint
• Paralysis
• Deafness
• Sudden loss of breathing
• Severe kidney failure
These are serious side effects. You may need urgent medical attention.
Following are few side effects observed in clinical study done in Indian patients, which you should tell your doctor as soon as possible:
• Fever
• Dizziness (spinning sensation)
• Stomach pain
• Vomiting
• Diarrhoea
• Hyperacidity
• Acute liver injury
• Raised liver enzymes (Transaminases)
• Increased total leucocyte count
• Pus in urine
• Decreased creatinine clearance
Arbekacin may lead to changes in your kidney function. Your doctor may take blood and urine samples to monitor for changes such as increased levels of creatinine or nitrogen in the blood and protein or red/white blood cells in urine. Your doctor may also ask you to undergo hearing tests.
If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor.
v. How to store Arbekacin Injection
Keep this medicine out of the sight and reach of children.
Expiry: 36 months.

Storage
Store below 25ºC. Protected from light. Do not freeze.

vi. Contents of the pack and other information
What Arbekacin Injection contains
Each 4 ml ampoule contains Arbekacin Sulphate equivalent to Arbekacin 200 mg
Diluted solutions should be used immediately.

10. Details of manufacturer:
Made in India by:
ALKEM HEALTH SCIENCE
A Unit of Alkem Laboratories Limited, Unit-2,
Samardung, Karek Block, P.O. Namthang,
South Sikkim-737 137.

11. Details of permission or licence number with date
M.L.No. M/449/07 dated 23.12.2016

12. Date of revision:
September 2020

13. Marketed by:
Marketed by:
ALKEM LABORATORIES LTD.
ALKEM HOUSE
Senapati Bapat Marg,
Lower Parel, Mumbai - 400 013
To report a product query & adverse drug event,
please reach us at - pvglobal@alkem.com