For the use only of a Registered Medical Practitioners or a Hospital or a Laboratory

Arbekacin Sulfate Injection 200 mg/4 ml **Zabicase**

1. Name of the medicinal product

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. Pharmaceutical form

Colorless and transparent injection in colorless and transparent ampoule.

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 Interaction with other medicinal products and other forms of interaction

- 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 Fertility, pregnancy and lactation

Pregnancy

Usage for pregnant women can induce the 8th cranial—nerve disorder in foetus, 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 Pharmacodynamic properties

General properties

Pharmaco-therapeutic group: Antibacterial for systemic use, Aminoglycosides.

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 nonfunctional or toxic peptides and the breakup of polysomes into nonfunctional monosomes.

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 microdilution 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 overall 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%.

5.3 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.

6. Pharmaceutical particulars

6.1 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.

6.2 Shelf life

36 months.

Diluted solutions should be used immediately.

6.3 Special precautions for storage

The Arbekacin drug has to be stored at 25^0C. Protected from light. Do not freeze.

6.4 Nature and contents of container

Each 4 ml ampoule contains Arbekacin Sulfate equivalent to Arbekacin 200 mg.

6.5 Special precautions for disposal and other handling

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.

7. Marketed BY:

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8. Date of revision: November 2019