SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

AMIKAVER 500 mg/2ml I.M./I.V. Solution for Injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active substance:
Each 2 ml ampoule contains amikacin sulfate equivalent to 500 mg amikacin.

Excipient(s):
Sodium metabisulfite…….0.0132 g
Sodium citrate……0.050 g
See 6.1 for excipients.

3. PHARMACEUTICAL FORM

IM/IV solution for Injection

4. CLINICAL PARTICULARS

4.1. Therapeutic indications:

Amikacin sulphate is an aminoglycoside antibiotic which is active against a broad spectrum of Gram-negative organisms, including *Pseudomonas* spp, *Escherichia coli*, indole-positive and indole-negative *Proteus* spp, *Klebsiella-Enterobacter-Serratia* spp, *Salmonella, Shigella, Minea-Herellae, Citrobacter freundii* and *Providencia* spp.

Many strains of these gram-negative organisms resistant to gentamicin and tobramycin may show sensitivity to amikacin *in vitro*. The principal Gram-positive organism sensitive to amikacin is *Staphylococcus aureus*, including methicillin-resistant strains. Amikacin has activity at a certain level against other Gram-positive organisms including certain strains of *Streptococcus pyogenes, Enterococci* and *Diplococcus pneumoniae*.

AMIKAVER is indicated in the short-term treatment of severe infections due to susceptible strains of Gram-negative bacteria. It may also be indicated for the treatment of known or suspected staphylococcal disease.

In the treatment, consideration should be given to official guidance on the appropriate use of antibacterial agents.

4.2. Posology and method of administration

Posology / Frequency and duration of administration

Adults and children over 12 years:

The recommended intramuscular or intravenous dosage for adults and adolescents with normal renal function (creatinine clearance ≥50 m/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 patients with endocarditis and febrile neutropenia, dosing should be twice daily, as there is not enough data to support once daily dosing.

Life-threatening infections and/or those caused by Pseudomonas

The adult dose may be increased to 500 mg every 8 hours but should neither exceed 1.5 g/day nor be administered for a period longer than 10 days. A maximum total adult dose of 15 g should not be exceeded.

Urinary tract infections (other than pseudomonal infections):

7.5 mg/kg/day in two equally divided doses (equivalent to 250 mg twice daily in adults). As the activity of amikacin is enhanced by increasing the pH, a urinary alkalizing agent may be administered concurrently.

Method of administration

For most infections the intramuscular route is preferred, but in life-threatening infections, or in patients in whom intramuscular injection is not feasible the intravenous route, either slow bolus (2 to 3 minutes) or infusion (0.25% over 30 minutes) may be used.

Intramuscular and intravenous administration

At the recommended dosage level, uncomplicated infections due to sensitive organisms should respond to therapy within 24 to 48 hours.

If no clinical response is achieved within 3 to 5 days, alternative treatment should be considered.

Intraperitoneal use

Following exploration for established peritonitis, or after peritoneal contamination due to fecal spill during surgery, AMIKAVER may be used as an irrigation agent after recovery from anesthesia in concentrations of 0.25% (2.5 mg/ml).

If instillation is desired in adults, a single dose of 500 mg is diluted in 20 ml of sterile distilled water and may be instilled through a polyethylene catheter sutured into the wound at closure. If possible, instillation should be postponed until the patient has fully recovered from the effects of anesthesia and muscle-relaxing drugs.

Other routes of administration

AMIKAVER in a concentration of 0.25% (2.5 mg/ml) may be used effectively as an irrigating solution in abscess cavities, the pleural space, the peritoneum and the cerebral ventricles.

Additional information regarding special population

Renal and hepatic insufficiency:

In order to prevent the accumulation of the drug, daily doses should be reduced and/or intervals between the doses should be prolonged in patients with impaired renal function. A recommended method for calculating the dose in patients with a known or suspected reduction in renal function is multiplying the patient's serum creatinine concentration (in mg/100 ml) by 9 and using the obtained number as a dosage interval in hours.

Serum Creatinine Concentration		**Interval between Amikacin doses of 7.5 mg/kg/IM (hours)**
1.5	X 9 =	13.5
2.0		18
2.5		22.5
3.0		27
3.5		31.5
4.0		36
4.5		40.5
5.0		45
5.5		49.5
6.0		54

As renal function may alter appreciably during therapy, the serum creatinine value should be checked frequently and the dosage regimen modified as necessary.

Pediatric population:

Children 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 patients with endocarditis and febrile neutropenia, dosing should be twice daily, as there is not enough data to support once daily dosing.

Neonates:

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

Specific recommendations for intravenous administration

In pediatric patients, the amount of diluents used is depend on the amount of amikacin tolerated by the patient. The solution should normally be administered as infusion over a 30 to 60 minute period. Infants should be administered an infusion of 1 to 2 hours.

Elderly population:

Amikacin is excreted by the renal route. Renal function should be assessed whenever possible and dosage in elderly patients should be adjusted as described under impaired renal function.

4.3. Contraindications:

Hypersensitivity to any of the components of the product.

Myasthenia gravis.

4.4. Special Warnings and Precautions for Use

Adequate hydration should be provided during amikacin treatment in patients.

In patients with impaired renal function or diminished glomerular filtration, amikacin should be used with caution. In these patients, renal function should be assessed by the usual methods prior to therapy and periodically during therapy. Daily doses should be reduced and/or the interval between doses prolonged in accordance with serum creatinine concentrations to avoid accumulation of abnormally high blood levels and to minimize the risk of ototoxicity.

As with other aminoglycosides, ototoxicity and/or nephrotoxicity may occur due to amikacin use; precautions on dosage and adequate hydration should be implemented.

If symptoms of renal irritation (albumin, cylindrical and red or white blood cells) are observed, hydration should be increased; also a reduction in dosage may be appropriate. These findings are usually eliminated when treatment is completed. In cases of azotemia, or if a progressive decrease in urinary output occurs, treatment should be discontinued.

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 such as streptomycin, dihydrostreptomycin, gentamicin, tobramycin, kanamycin, bekanamycin, neomycin, polymyxin B, colistin, cephaloridine, or viomycin should be considered with caution, as additional toxicity may occur.

In these patients amikacin should be used only if, in the opinion of the physician, therapeutic advantages outweigh the potential risks.

Aminoglycosides should be used with caution in patients with muscular disorders such as parkinsonism, since these drugs may impair neuromuscular conduction. High doses given during surgery led to a temporary myasthenic syndrome.

This product contains 13.2 mg of sodium metabisulphite. In rare cases, it can cause severe allergic reactions (possibly delayed) and bronchospasm.

This medicinal product contains sodium of less than 1 mmol (23 mg) in each dose, i.e. it is essentially sodium-free.

Pediatric use

Aminoglycosides should be used with caution in premature infants and neonates because of the renal immaturity of these patients and the resulting prolongation of serum half-life of these drugs.

The intraperitoneal use of amikacin is not recommended in young children.

4.5. Interaction with other medicinal products and other forms of interaction

Concurrent use with other potentially nephrotoxic or ototoxic agents should be avoided. Where this is not possible, patients should be monitored carefully. The risk of ototoxicity is increased when amikacin is used in conjunction with rapidly acting diuretic drugs, particularly when the diuretic is administered intravenously. Such agents include furosemide and ethacrynic acid which are themselves ototoxic agents. Irreversible deafness may result.

The use of amikacin is not recommended in patients under the influence of anesthetics or muscle-

relaxing drugs (including ether, halothane, d-tubocurarine, succinylcholine and decamethonium) as neuromuscular blockade and consequent respiratory depression may occur.

In neonates, indomethacin may increase the plasma concentration of amikacin.

In patients with severely impaired renal function, a reduction in activity of aminoglycosides may occur with concomitant use of penicillin-type drugs.

4.6. Pregnancy and lactation

General recommendation

Pregnancy category: D

Women of childbearing potential/Birth-control/Contraception

If amikacin is used during pregnancy or if the patient becomes pregnant while using this drug, the patient should be apprised of the potential hazard to the fetus.

Pregnancy

There are limited data on use of aminoglycosides in pregnancy. Aminoglycosides can cause fetal 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 fetus or neonates have not been reported in pregnant women treated with other aminoglycosides, the potential for harm exists.

Lactation

It is not known whether amikacin is excreted in breast milk. A decision must be made on whether to discontinue the breast-feeding or treatment.

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

Reproductivity/Fertility

No studies on this subject have been performed.

4.7. Effects on ability to drive and use machines

Any effect has not been stated.

4.8. Undesirable effects

The following terms and frequencies are used for the undesirable effects related to the use AMIKAVER:

Very common (≥/10), common (≥1/100, <1/10), uncommon (≥1/1.000, <1/100), rare (≥1/10.000, <1/1.000), very rare (<1/10.000), and not known (cannot be estimated from the available data)

Nervous system disorders:

Unknown: Acute muscular paralysis

Eye disorders:

Unknown: Retinal toxicity following intravitreal amikacin injection

Ear and labyrinth disorders:

Unknown: Tinnitus, dizziness, reversible or irreversible deafness

Respiratory, thoracic and mediastinal disorders:

Unknown: Apnea, bronchospasm

Gastrointestinal disorders:

Unknown: Nausea and vomiting

Skin and subcutaneous tissue disorders:

Unknown: Severe hypersensitivity reactions

Renal and urinary disorders:

Unknown: Urinary symptoms related to renal irritation (serum creatinine levels increased, albuminuria, cylindrical and red or white blood cells), azotemia and oliguria

General disorders and administration site conditions:

Unknown: Rash, drug fever, headache, paresthesia, eosinophilia, arthralgia, anemia and hypotension

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorization of the medicinal product is very important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Health care professionals should report any suspected adverse reaction to Turkish Pharmacovigilance Center (TUFAM). (www.titck.gov.tr; e-mail: tufam@titck.gov.tr; phone: 0 800 314 00 08; fax: 0 312 218 35 99)

4.9. Overdose and its management

In the event of overdosage or toxic reaction, peritoneal dialysis or hemodialysis will aid in the removal of amikacin from the blood.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacotherapeutic group: Aminoglycoside antibacterials, ATC code: 01GB06

Amikacin sulphate *is an aminoglycoside antibiotic which is active against a broad spectrum of Gram-negative organisms, including Pseudomonas* spp*, Escherichia coli*, indole-positive and indole-negative *Proteus* spp*, Klebsiella-Enterobacter-Serratia* spp*, Salmonella, Shigella, Minea-Herellae, Citrobacter freundii* and *Providencia* spp.

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5.2. Pharmacokinetic properties

General properties

Absorption:

AMIKAVER is rapidly absorbed after intramuscular injection. Peak serum levels of approximately 11 mg/l and 23 mg/l are reached one hour after i.m. doses of 250 mg and 500 mg respectively. Levels observed 10 hours after injection are 0.3 mg/l and 2.1 mg/l respectively.

Distribution:

Single doses of 500 mg administered to normal adults as an intravenous infusion over a period of 30 minutes produce a mean peak serum concentration of 38 mg/l at the end of the infusion. Repeated infusions do not cause drug accumulation.

AMIKAVER has been detected in cerebrospinal fluid, pleural fluid, and amniotic fluid and in the peritoneal cavity following parenteral administration.

Data from multiple daily dosing studies show that spinal fluid levels in normal infants are approximately 10 to 20% of the serum concentrations and may reach 50% in meningitis.

Biotransformation:

20% or less is bound to serum protein and serum concentrations remain in the bactericidal range for sensitive organisms for 10 to 12 hours.

AMIKAVER diffuses readily through extracellular fluids and is excreted in the urine unchanged, primarily by glomerular filtration. Half-life in individuals with normal renal functions is two to three hours.

Elimination:

Following intramuscular administration of a 250 mg dose, about 65% is excreted in 6 hours and 91% within 24 hours. The average urinary concentrations are 563 mg/l in the first 6 hours and 163 mg/L over 6 to 12 hours. The mean urine concentration following a 500 mg intramuscular dose is average 832 mg/l in the first 6 hours.

Intramuscular and intravenous administration

In neonates and particularly in premature infants, the renal elimination of amikacin is reduced.

In a single study in newborns (postnatal age: 1-6 days) grouped according to birth weights (<2000, 2000-3000 and >3000 g), amikacin was administered by intramuscular and/or intravenous route 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 were determined as 0.3 ml/kg and
0.5 mg/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 cause accumulation after 5 days.

5.3. Preclinical safety data

No further relevant information.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Sodium metabisulfite Sodium citrate dihydrate Water for injection

Sulphuric acid (for pH adjustment)

6.2. Incompatibilities

Not applicable.

6.3. Shelf-life

24 months.

6.4. Special precautions for storage

It should be stored at between 15 °C-30 °C. The ampule should not be frozen.

6.5. Nature and contents of container

Box contents one ampule of 2 ml colorless, glass ampule (hydrolytic grade, type I)

6.6. Disposal of medicinal products and special precautions

Any unused product or waste material should be disposed of in accordance with "Regulation on Control of Medical Wastes" and "Regulation on Control of Packaging and Packaging Wastes".

7. MARKETING AUTHORIZATION HOLDER

Name : OSEL İlaç Sanayi ve Ticaret A.Ş.
Address : Akbaba Mah, Maraş Cad. No:52 Beykoz/İstanbul
Tel : 0 (216) 320 45 50
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8. MARKETING AUTHORIZATION NUMBER(S)

192/2

9. DATE OF FIRST AUTHORIZATION/RENEWAL OF THE AUTHORIZATION

Date of first authorization: 30.06.1999
Date of renewal of the authorization: 24.05.2005

10. DATE OF REVISION OF THE SPC