Summary of Product Characteristics for Pharmaceutical Products

1. Name of the medicinal product:

Karemycin

2. Qualitative and quantitative composition

Gentamicin injection 80mg /2mL

Each ampoule contains Gentamicin Sulfate equivalent to Gentamicin 80mg

3. Pharmaceutical form

Solution for injection.
Colorless to yellowish or yellowish green clear liquid.

4. Clinical particulars

4.1 Therapeutic indications

Karemycin is an aminoglycoside antibiotic with broad-spectrum bactericidal activity. It is indicated to treat severe infections caused by bacteria susceptible to gentamicin such as, but not limited to:

- Urinary tract infections
- Respiratory tract infections
- Intra-abdominal infections
- CNS infections
- Severe neonatal infections

It is usually active against most strains of the following organisms*: Escherichia coli, Klebsiella* spp*., Proteus* spp. (indole positive and indole negative), *Pseudomonas aeruginosa*, Staphylococci*, Enterobacter* spp., *Citrobacter* spp. and *Providencia* spp.

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

4.2 Posology and method of administration

The recommended dose in adults with normal renal function is 3 – 5 mg/kg/day, depending on the severity of infection, administered as one single dose (preferred) or in two divided doses.
The doses should be adjusted according to clinical response and serum concentration levels (see below). Dose calculations should be based on ideal body weight. A dosing frequency of more than twice daily may be adopted for some specific pathogens or some sites of infection as recommended in national and local guidance.

Once daily dosing is not recommended in cases of endocarditis, depending on the responsible pathogens. National and local guidance on treatment with gentamicin and serum level monitoring in endocarditis should be followed. In patients with normal renal function, 160 mg once daily may be used for the treatment of urinary tract infections.

Paediatric population
The daily dose recommended in children aged 1 year and above and adolescents with normal renal function, is 3 – 6 mg/kg/day as one single dose (preferred) or two divided doses. The daily dose in infants after the first month of life is 4.5 – 7.5 mg/kg/day as one single dose (preferred) or two divided doses. The daily dose in neonates and pre-term infants (aged 0 – 4 weeks old) is 4 – 7 mg/kg/day. Due to the longer half-life, newborns are given the required daily dose in one single dose.

Elderly
There is some evidence that elderly patients may be more susceptible to aminoglycoside toxicity whether secondary to previous auditory/vestibular impairment or borderline renal dysfunction. Accordingly, therapy should be closely monitored by frequent determination of gentamicin serum levels, assessment of renal function and signs of ototoxicity.

Renal impairment
In impaired renal function, the recommended daily dose has to be decreased and adjusted to the renal function. This can be achieved by reducing the dose and/or increasing the dose interval. In all patients with renal impairment, serum gentamicin peak and trough concentration and renal function must be monitored frequently (see below)

Nomograms are available for the calculation of dose, which depends on the patient's age, weight and renal function. Local guidance should be followed where available.

No clear recommendation can be made for once daily dosing; dosing should be guided by plasma concentration levels. In patients with moderate renal impairment, in whom once daily dosing would be considered appropriate if their renal function were normal, the dose interval should be at least 24 hours and extended according to the degree of renal impairment and the results of serum gentamicin monitoring. Limited data are available in patients with severe renal impairment (creatinine clearance < 30 ml/min) after once daily dose administration.

Renal Function Tests:

Blood Urea (mg/100 ml)	Blood Urea (mmol/l)	Creatinine Clearance (GFR) (ml/min)	Dose and frequency of administration

<40	6-7	>70	80 mg* 8-hourly
40-100	6-17	30-70	80 mg* 12-hourly
100-200	17-34	10-30	80 mg* daily
>200	>34	5-10	80 mg* every 48 hours
Twice weekly intermittent haemodialysis		<5	80 mg* after dialysis

**60 mg if body weight < 60 kg.*

Monitoring advice

Regular serum concentration monitoring of gentamicin is recommended for all patients, especially in the elderly, newborns, obesity and in patients with impaired renal function, as well as patients with cystic fibrosis. Gentamicin should not be prescribed if serum concentrations cannot be monitored.

There are no universally accepted guidelines for therapeutic drug monitoring of gentamicin. Local monitoring and dose adjustment guidelines should be followed where available. Pre-dose ("trough level") monitoring is recommended to ensure that the interval between doses is correct. Trough levels are measured at the end of a dosing interval and should not exceed 1 µg/L for once daily dosing or 2 µg/L for multiple daily dosing. Levels in excess of these indicate the need to extend the interval between doses, not reduction of the dose. Post-dose ("peak level") monitoring is recommended to check the adequacy of a dose or to ensure that it is not excessive and likely to cause toxicity. Peak levels should be measured one hour after an intravenous bolus or intramuscular bolus dose, or 30 minutes after the end of an infusion. A plasma concentration < 4 mg/L indicates that the dose is likely to be inadequate and a dose increase should be considered; plasma concentrations > 10 mg/L indicate an increased risk for toxicity, particularly ototoxicity, and a dose reduction should be considered. Any change in dose should be re-assessed with pre- and post-dose levels to confirm the adequacy of the new dose and the appropriateness of the dose interval.

Method of administration

The recommended dose and precautions for intramuscular and intravenous administration are identical. Gentamicin when given intravenously should be injected directly into a vein or into the drip set tubing over no less than three minutes. If administered by infusion, this should be over no longer than 20 – 30 minutes and in no greater volume of fluid than 100 ml. Once daily dosing should only be administered through the intravenous.

4.3 Contraindications

• Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
• Myasthenia gravis.

4.4 Special warnings and precautions for use

Ototoxicity and nephrotoxicity

Ototoxicity has been reported following the use of aminoglycosides, including gentamicin. Symptoms include loss of balance and hearing loss, which may be irreversible (see section 4.8). Important risk factors include renal impairment, high doses, prolonged duration of treatment and age (neonates/infants and possibly the elderly). Due to the potential for ototoxicity and nephrotoxicity, monitoring of vestibule, cochlea and renal function is recommended before, during and shortly after treatment (see section 4.8). Serum levels are determined so as to avoid peak concentrations above 10 mg/L and troughs above 1 mg/L when administering gentamicin once daily and 2 mg/L when administering gentamicin twice daily.

As there is some evidence that risk of both ototoxicity and nephrotoxicity is related to the level of total exposure, duration of therapy should be the shortest possible compatible with clinical recovery. In some patients with impaired renal function there has been a transient rise in blood- urea-nitrogen which has usually reverted to normal during or following cessation of therapy. It is important to adjust the frequency of dosage according to the degree of renal function.

To avoid adverse events, continuous monitoring (before, during and after treatment) of hepatic and laboratory parameters is also recommended.

Gentamicin should only be used in pregnancy if considered essential by the physician (see section 4.6).

Gentamicin should be used with care in conditions characterised by muscular weakness. In cases of significant obesity gentamicin serum concentrations should be closely monitored and a reduction in dose should be considered

There have been observed cases of an increased risk of ototoxicity with aminoglycosides administered to patients with mitochondrial mutations, particularly the m.1555A>G mutation, including cases where the patient's aminoglycoside serum levels were within the recommended range. Some cases were associated with a maternal history of deafness and/or mitochondrial mutation. Mitochondrial mutations are rare, and the penetrance of this observed effect is unknown.

Superinfection-Treatment with gentamicin may produce an excessive growth of drug-resistant micro-organisms. If this happens, an appropriate treatment should be initiated.

Pseudomembranous colitis- Diarrhoea and pseudomembranous colitis have been observed when gentamicin is combined with other antibiotics. These diagnoses should be considered in every patient that develops diarrhoea during or immediately after treatment. Gentamicin should be discontinued if the patient suffers severe diarrhoea and/or bloody diarrhoea during treatment and an appropriate treatment should be initiated. Drugs that inhibit peristalsis should not be administered (see section 4.8).

Severe subcutaneous adverse reactions (SCARs)-serious skin reactions including Stevens-Johnson Syndrome (SJS) and toxic epidermal necrolysis (TEN) have been reported in association with gentamicin treatment. Patients should be informed about the signs and symptoms of serious skin manifestations and monitored closely. Treatment should be discontinued at the first appearance of skin rash, mucosal lesions or any other sign of skin hypersensitivity.

4.5 Interaction with other medicinal products and other forms of interaction

Concurrent administration of gentamicin and other potentially ototoxic or nephrotoxic drugs should be avoided. Potent diuretics such as etacrynic acid and furosemide are believed to enhance the risk of ototoxicity whilst amphotericin B, cisplatin and ciclosporin are potential enhancers of nephrotoxicity.

Any potential nephrotoxicity of cephalosporins, and in particular cephaloridine, may also be increased is in the presence of gentamicin. Consequently, if this combination is used monitoring of kidney function advised.

Neuromuscular blockade and respiratory paralysis have been reported from administration of aminoglycosides to patients who have received curare-type muscle relaxants during anaesthesia.

Indomethacin possibly increases plasma concentrations of gentamicin in neonates.

Concurrent use with oral anticoagulants may increase the hypothrombinanaemic effect.

Concurrent use of bisphosphonates may increase the risk of hypocalcaemia.

Concurrent use of the Botulinum Toxin and gentamicin may increase the risk of toxicity due to enhanced neuromuscular block.

Antagonism of effect may occur with concomitant administration of gentamicin with either neostigmine or pyridostigmine.

4.6 Pregnancy and Lactation

Pregnancy
There are no proven cases of intrauterine damage caused by gentamicin. However, in common with most drugs known to cross the placenta, usage in pregnancy should only be considered in life threatening situations where expected benefits outweigh possible risks.

Monitor: maternal serum gentamicin concentration, infant hearing and infant renal function if administered.

Breast-feeding
In the absence of gastro-intestinal inflammation, the amount of gentamicin ingested from the milk is unlikely to result in significant blood levels in breast-fed infants.

Monitor; the serum concentration of gentamicin in the breast-fed infant in cases of suspected severe mucosal erosion. Animal and human data suggest that if the serum gentamicin concentration in the infant exceeds 1 µg/ml either breast-feeding, gentamicin therapy may need to be discontinued, under medical supervision.

The following effects of gentamicin on the infant's normal gastrointestinal flora are possible and it is recommended to monitor the infant for possible effects such as diarrhoea, candidiasis and bloody stools.

In the absence of gastro-intestinal inflammation, the amount of gentamicin ingested from the milk is unlikely to result in significant blood levels in breast-fed infants.

4.7 Effects on ability to drive and use machines

Caution is advised when driving and using machines in view of the possible undesired effects such as dizziness and vertigo.

4.8 Undesirable effects

The following CIOMS frequency rating is used, when applicable:

very common (≥1/10);

common (≥1/100 to <1/10);

uncommon (≥1/1000 to <1/100);

rare (≥1/10 000 to <1/1000);

very rare (<1/10 000),

not known (cannot be estimated from the available data).

System disorders:
Not known: hypersensitivity, anaphylaxis/anaphylactic reaction (including anaphylactic shock)

Metabolism and nutrition disorders:
Not known: hypomagnesaemia on prolonged therapy

Psychiatric disorders: Not known: depression, hallucinations, confusion

Nervous system disorders:
Not known: central neuropathy (including convulsions, lethargy, encephalopathy), peripheral neuropathy

Ear and labyrinth disorders:
Not known: vestibular damage, transitory hearing loss, irreversible hearing loss, deafness, particularly after exposure to ototoxic drugs or in the presence of renal dysfunction (see section 4.4).

Gastrointestinal disorders:
Very common: vomiting
Not known: stomatitis, nausea

Hepatobiliary disorders.
Not known: abnormal liver function, transaminases increased

Skin and subcutaneous tissue disorders:
Not known: rash, purpura, urticaria, pruritus

Renal and urinary disorders:
Very rare: acute renal failure, Fanconi-like syndrome in patients treated with a prolonged course of high dose
Not known: nephrotoxicity (usually reversible) has been reported.

4.9 Overdose

Haemodialysis and peritoneal dialysis will aid the removal from blood but the former is probably more efficient. Calcium salts given intravenously have been used to counter the neuromuscular blockade caused by gentamicin.

5. Pharmacological properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antibacterials for systemic use, ATC Code: J01GB03

Gentamicin is a mixture of antibiotic substances produced by the growth of micromonospora purpurea. It is bactericidal with greater antibacterial activity than streptomycin, neomycin or kanamycin. Gentamicin exerts a number of effects on cells of susceptible bacteria. It affects the integrity of the plasma membrane and the metabolism of RNA, but its most important effects is inhibition of protein synthesis at the level of the 30s ribosomal subunit.

5.2 Pharmacokinetic properties

Absorption
Gentamicin is not readily absorbed from the gastro-intestinal tract. Gentamicin is 70 – 85% bound to plasma albumin following administration and is excreted 90% unchanged in urine. The half-life for its elimination in normal patients is 2 – 3 hours.

Effective plasma concentration is 4 – 8 µg/ml.
The volume of distribution (vd) is 0.3 l/kg.
The elimination rate constant is:
1. 0.02 hr-1 for anuric patients*
2. 0.30 hr-1 normal

Therefore, in those with anuria care must be exercised following the usual initial dose, any subsequent administration being reduced in-line with plasma concentrations of gentamicin.

Paediatric population (premature infants and neonates)

Distribution

The distribution volume of gentamicin is about equivalent to the volume of extracellular water. In the newborn water makes up 70 – 75% of bodyweight, compared with 50 – 55% in adults. The extracellular water compartment is larger (40% of body weight compared with 25% of body weight in adults). Therefore, the volume of distribution of gentamicin per kg bodyweight is affected and decreases with increasing age from 0.5 – 0.7 l/kg for a premature newborn to 0.25 l/kg for an adolescent. The larger volume of distribution per kg bodyweight means that for adequate peak blood concentration a higher dose per kg bodyweight needs to be administered.

The distribution of gentamicin to the individual organs results in varying tissue concentrations; the highest concentrations appear in the renal tissue. Smaller concentrations are found in the liver and gall bladder, the lung and spleen.

Gentamicin crosses the placenta; the foetal concentrations can be 30% of the maternal plasma concentrations. Gentamicin is excreted in small quantities in breast milk (1/3 of the concentration is found here, as in the

case of the maternal plasma).

After repeated injection of gentamicin, approximately 50% of the concentrations reached in plasma is measured in the synovial, pleural, pericardial and peritoneal fluid. The penetration of gentamicin into the cerebrospinal fluid is poor in un-inflamed meninges. In inflamed meninges, concentrations reach up to 30% of the concentrations measured in plasma.

Plasma protein binding: less than 10%.

Elimination

Gentamicin is not metabolized in the body but is excreted unchanged in microbiologically active form predominantly via the kidneys. In patients with normal renal function the elimination half- life is about 2–3 hours. In neonates' elimination rate is reduced due to immature renal function. Elimination half-life averages approximate 8hours neonates at a gestational age of 26 –34 weeks compared with about 6.7 hours in neonates at a gestational age of 35 – 37 weeks. Correspondingly, clearance values increase from about 0.05 l/h in neonates at a gestational age of 27 to 0.2 L/h in neonates at a gestational age of 40 weeks

5.3 Preclinical safety data

Not applicable.

6. Pharmaceutical Particulars

6.1 List of Excipients

Anhydrous Sodium sulfate
Water for injection

6.2 Incompatibilities

In general, gentamicin injection should not be mixed. In particular the following are incompatible in mixed solution with gentamicin injection

- Penicillins
- Cephalosporins
- Erythromycin
- Heparins
- Sodium bicarbonate

*Dilution in the body will obviate the danger of physical and chemical incompatibility and enable gentamicin to be given concurrently with the drugs listed above either as a bolus injection into the drip tubing, with adequate flushing, or at separate sites.

In the case of carbenicillin, administration should only be at a separate site.
*Carbon dioxide may be liberated on addition of the two solutions. Normally this will dissolve in the solution but under some circumstances small bubbles may form.

6.3 Shelf-Life

3 years

6.4 Special Precautions for storage

Do not store above 30°C.
Do not refrigerate or freeze.

6.5 Nature and Content of container

2mL USP type I glass amber ampoules, 10 amps/tray, 10 trays/box, 200 boxes/ carton.

6.6 Special precautions for disposal and other handling

No special requirements.

7. Marketing Authorization Holder

Karemax Industrial Limited
Address. Floor 1 No 4 Building No 501
Jinwan Rd Pudong
District Shanghai 20000 China
E-Mail. Admin@Karemax.Net
Call Us. +86-021-58880331.

8. Marketing Authorization Number

CTD8735

9. Date of first authorization/renewal of the authorization

21/08/2023

10. Date of revision of the text

11/05/2025