# ZETAMYCIN

**Ampoule**

## Composition

**Zetamycin 20 Injection**
Each ampoule of 1 ml contains Gentamicin (as sulphate) 20 mg.

**Zetamycin 40 Injection**
Each ampoule of 2 ml contains Gentamicin (as sulphate) 40 mg.

**Zetamycin 80 Injection**
Each ampoule of 2 ml contains Gentamicin (as sulphate) 80 mg.

## Action

Gentamicin is usually bactericidal in action. Although the exact mechanism of action has not been fully elucidated, the drug appears to inhibit protein synthesis in susceptible bacteria by irreversibly binding to 30S ribosomal subunits.

In general, gentamicin is active against many aerobic gram-negative bacteria and some aerobic gram-positive bacteria. Gentamicin is inactive against fungi, viruses, and most anaerobic bacteria.

In vitro, gentamicin concentrations of 1-8 µg/ml inhibit most susceptible strains of Escherichia coli, Haemophilus influenzae, Moraxella lacunata, Neisseria, indole positive and indole negative Proteus, Pseudomonas (including most strains of Ps. aeruginosa), Staphylococcus aureus, S. epidermidis, and Serratia. However, different species and different strains of the same species may exhibit wide variations in susceptibility in vitro. In addition, in vitro susceptibility does not always correlate with in vivo activity. Gentamicin is only minimally active against Streptococci.

Natural and acquired resistance to gentamicin has been demonstrated in both gram-negative and gram-positive bacteria. Gentamicin resistance may be due to decreased permeability of the bacterial cell wall, alteration in the ribosomal binding site, or the presence of a plasmid-mediated resistance factor which is acquired by conjugation. Plasmid-mediated resistance enables the resistant bacteria to enzymatically modify the drug by acetylation, phosphorylation, or adenylation and can be transferred between organisms of the same or different species. Resistance to other aminoglycosides and several other anti-infectives (e.g. chloramphenicol, sulphonamides, tetracycline) may be transferred on the same plasmid.

There is partial cross-resistance between gentamicin and other aminoglycosides.

**Pharmacokinetics**
*Absorption*
Gentamicin is rapidly absorbed following intramuscular injection, giving peak plasma concentrations after 30 minutes - 1 hour. Effective plasma concentration is 4 - 8ug/ml. Effective concentrations are still present 4 hours after injection. An injection of 1mg/kg body weight results in a peak plasma concentration of approximately 4 micrograms/ml.

Gentamicin is 70-85% bound to plasma albumin following administration.
$T_{½}$ = 2 - 3 hours in individuals with normal kidney function, but can be increased in individuals with renal insufficiency.

*Distribution*
The distribution volume of gentamicin is about equivalent to the volume of extracellular water. In the newborn water makes up 70 to 75% of bodyweight, compared with 50 to 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 to 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 volume of distribution ($^{V}_{D}$) is 0.3 1/kg

*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 to 3 hours.

> 90% Gentamicin is excreted unchanged in the urine by glomerular filtration. In neonates elimination rate is reduced due to immature renal function. Elimination half-life averages approximately 8 hours in neonates at a gestational age of 26 to 34 weeks compared with about 6.7 hours in neonates at a gestational age of 35 to 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.

## Indications

- For the treatment of infections due to one or more susceptible strains of bacteria, including *Pseudomonas aeruginosa*, *Proteus* species (indole positive and indole negative), *Escherichia coli*, *Klebsiella*, *Enterobacter*, *Serratia* species and *Staphylococcus* (including strains resistant to other antibiotics).
- Zetamycin may also be used for the treatment of the following conditions when caused by susceptible organisms: bacteraemia, respiratory tract infections, urinary tract infections, skin and skin structure infections, bone infections, peritonitis, septic abortion and burns complicated by sepsis. Aminoglycosides, including gentamicin are generally not indicated in uncomplicated initial episodes of urinary tract infection unless the causative organisms are not susceptible to less toxic antibiotics.
- In suspected or documented Gram-negative sepsis, gentamicin should be considered for initial microbial therapy. Therapy may be instituted before obtaining results of susceptibility tests. The decision to continue therapy is based on results of the susceptibility tests, the severity of the infection and risk of toxicity. If anaerobic organisms are suspected, antimicrobial therapy in addition to the gentamicin regimen should be considered.

## Contraindications

- Known hypersensitivity to gentamicin or disodium edetate.
- Patients who have experienced previous toxic reactions (ototoxicity, nephrotoxicity) resulting from aminoglycoside therapy.

## Warnings and Precautions

**Nephrotoxicity and ototoxicity**
As for other aminoglycosides, patients treated with gentamicin should be under close clinical observation during treatment because of the potential toxicity associated with their use. Gentamicin, as with other aminoglycosides, is potentially nephrotoxic and ototoxic.

Ototoxicity may be manifested by both vestibular and auditory ototoxicity. These auditory changes are generally irreversible, usually bilateral and may be partial or total. Other manifestations of neurotoxicity may include numbness; skin tingling, muscle twitching and convulsions. The risk of this toxicity is higher in patients receiving high doses, prolonged treatment, or with impaired renal function. Gentamicin should therefore be used with caution in patients with impaired renal function. In such patients, the frequency of administration should be reduced and renal function should be monitored. Prolonged concentrations above 10 microgram/mL should be avoided and trough concentrations should not exceed 2 microgram/mL In neonates, infants and children, dosage reductions may also be necessary to avoid toxicity.

Peak and trough blood levels should be constantly monitored as should renal and eighth cranial nerve function, especially in patients with known or suspected reduced renal function at onset of therapy and in those whose renal function is initially normal but who develop signs of renal dysfunction during therapy. Where possible, it is recommended that serial audiograms be obtained in patients old enough to be tested, particularly high-risk patients. Evidence of ototoxicity (dizziness, vertigo, tinnitus, roaring in the ears or hearing loss) or nephrotoxicity requires dosage adjustment or discontinuance of the drug. As with the other aminoglycosides, on rare occasions changes in renal and eighth cranial nerve function may not become manifest until soon after completion of therapy. Treatment period should not normally exceed 10-14 days.

Concurrent and/or sequential systemic or topical use of other potentially neurotoxic and/or nephrotoxic drugs, should be avoided. This includes concurrent use with potent diuretics, cephalosporins or other aminoglycosides. Other factors which may increase the risk of toxicity are dehydration and advancing age. Patients should be well hydrated during therapy.

Recent evidence suggests that neurotoxic and nephrotoxic antibiotics may be absorbed in significant quantities from body surfaces after local irrigation or application. The potential toxic effect of antibiotics administered in this fashion should be considered and inadvertent contact with the skin should be removed with water.

**Allergic reactions**
May occur after administration of gentamicin. Cross allergenicity among aminoglycosides has also been known to occur.

**Use during anesthesia**
The possibility of prolonged or secondary apnea should be considered if the drug is administered to anaesthetized patients who are concurrently receiving neuromuscular blocking agents such as suxamethonium (succinylcholine), tubocurarine or decamethonium. This also applies to patients who are receiving massive transfusions of citrated blood. If neuromuscular blockade occurs, it may be reversed by the administration of calcium salts.

Aminoglycosides should be used cautiously in patients with neuromuscular disorders such as myasthenia gravis or parkinsonism. In such cases, gentamicin may aggravate muscle weakness because of its curare-like effect on neuromuscular function.

Treatment with gentamicin may lead to an over-growth of non-susceptible organisms. If overgrowth of non-susceptible organisms occurs, appropriate therapy should be initiated.

**Paediatric use**
Gentamicin should be used with caution in premature and neonatal infants because their renal immaturity may result in the prolongation of the serum half-life of the drug and subsequent gentamicin induced toxicity.

**Use in the elderly**
Because of its toxicity, gentamicin should be used with caution in elderly patients only after less toxic alternatives have been considered and/or found ineffective. Elderly patients are more likely to have an age related decrease in renal function which may not be evident in the results of routine screening test such as serum urea or serum creatinine. A creatinine clearance determination may be more useful. Recommended doses should not be exceeded, and the patient's renal function should be carefully monitored during therapy. Elderly patients may require smaller daily doses of gentamicin in accordance with their increased age, decreased renal function, and possibly, decreased weight. In addition, loss of hearing may result even in patients with normal renal function.

**Pregnancy**
*Category D*

There is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience or studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks.

**Nursing Mothers**
Small amounts of gentamicin have been detected in breast milk. Because of the potential risk to the newborn, it is recommended that breastfeeding be discontinued during therapy unless the expected benefits outweigh any potential risk.

## Adverse Reactions

**Serious or life-threatening reactions**
***Otic:*** Serious adverse effects on both vestibular and auditory branches of the eighth cranial nerves have been reported, primarily in patients with renal impairment (especially if dialysis is required), and in patients on high doses and/or prolonged therapy. Symptoms reported include dizziness, vertigo, tinnitus, roaring in the ears and hearing loss may be irreversible. Hearing loss is usually manifested initially by diminution of high tone acuity. Other factors that may increase the risk of toxicity include excessive dosage, dehydration and previous exposure to other ototoxic drugs.

***Renal:*** Adverse renal effects have been reported, and are demonstrated by the presence of casts, cells, or protein in the urine or by rising serum urea, NPN, serum creatinine, or oliguria. They occur more frequently in patients with a history of renal impairment and in patients who have been treated for longer periods or with larger dosage than recommended.

**More common reactions**
***Neurological***: Peripheral neuropathy or encephalopathy, including numbness, skin tingling, muscle twitching, convulsions and a myasthenia gravis-like syndrome, have also been reported.

***Dermatological and hypersensitivity:*** Rash, itching, urticaria, purpura, generalized burning, anaphylactoid reactions may occur.

***Pulmonary:*** Respiratory depression, laryngeal oedema, pulmonary fibrosis may occur.

***Gastrointestinal****:* Nausea, vomiting, increased salivation and stomtatitis may also occur.

***Other adverse reactions:*** Lethargy, confusion, depression, visual disturbances, decreased appetite, weight loss, hypotension and hypertension; fever and headache, pseudotumor cerebri, acute organic brain syndrome, alopecia, joint pain, transient hepatomegaly, and splenomegaly

While local tolerance of gentamicin injection is generally excellent, there has been an occasional report of pain at the injection site. Subcutaneous atrophy or fat necrosis suggesting local irritation has been reported rarely.

**Laboratory tests**
Laboratory abnormalities possibly related to gentamicin include increased levels of serum transaminase (ALT, AST), serum LDH and bilirubin; decreased serum calcium, magnesium, sodium and potassium; anaemia, leucopenia, granulocytopenia, transient agranulocytosis, eosinophilia, increased and decreased reticulocyte counts, and thrombocytopenia. While clinical laboratory test abnormalities may be isolated findings, they may also be associated with clinically related signs and symptoms. For example, tetany and muscle weakness may be associated with hypomagnesaemia, hypocalcaemia, and Hypokalemia.

## Drug Interactions

*Penicillins and Cephalosporins*
Gentamicin is inactivated by solutions containing beta-lactam antibiotics (penicillins and cephalosporins) so the two drugs should not be administered simultaneously nor should they be combined in the intravenous fluid. The inactivation of gentamicin by penicillins may occur in vivo,

especially in patients with renal failure who maintain a higher level of the penicillin for a longer period. Therefore, when gentamicin and penicillins are used together in patients with renal failure, the time of administration of each drug should be staggered so that several hours separate each infusion.

*Diuretics*
Potent diuretics such as ethacrynic acid or frusemide may potentiate the ototoxic effects of gentamicin.

*Other neurotoxic and/or nephrotoxic agents*
Since the ototoxic or nephrotoxic effects of gentamicin may be additive, avoid concurrent or sequential use of other neurotoxic and/or nephrotoxic antibiotics, including other aminoglycosides, polymyxin B, colistin, cisplatin, vancomycin, amphotericin, clindamycin and cephalosporins.

*Neuromuscular Blocking Agents*
Respiratory paralysis and prolongation of neuromuscular blockade may occur if a neuromuscular blocking agent such as suxamethonium (succinylcholine), tubocurarine, decamethonium, halogenated hydrocarbon inhalation anesthetics, opioid analgesics or massive transfusions with citrated anticoagulated blood are administered to a patient receiving gentamicin.

*Vitamin K*
Gentamicin may inhibit the action of intravenous vitamin K upon the synthesis of clotting factors.

## Dosage and Administration

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. Zetamycin injection may be administered intramuscularly or intravenously.

Zetamycin injection should not be pre-mixed with other drugs. It should be administered separately, in accordance with the recommended route of administration and dosage schedule.

Zetamycin is normally given by IM injection. Intravenous administration may be used for particular indications when the IM route is not appropriate, the dosage is the same for either route of administration. It is desirable to measure both peak and trough serum levels during treatment.

Prior to administration, the patient's bodyweight should be measured for the correct calculation of dosage. In obese patients, the appropriate dose can be calculated by assuming the bodyweight is the patient's estimated lean bodyweight plus 40% of the excess.

Blood specimens for the determination of peak gentamicin concentrations should be obtained approximately one hour following IM administration and 30 minutes after completion of a 30-minute infusion. Blood specimens for the trough gentamicin concentration should be obtained immediately prior to the next IM or IV dose.

**Intravenous administration**
For IV administration, the prescribed dose of gentamicin may be diluted in 100-200 ml of sterile normal saline or 5% glucose in water. The concentration of gentamicin in the solution should not exceed 1 mg/ml. Infusion periods of 30 minutes to 2 hours have been advocated.

Administration of the dose by bolus injection produces serum levels that are initially in excess of what is regarded as being safe from toxic side effects. The high serum level does however rapidly fall and the potential danger or safety of this method is yet to be established.
Zetamycin must not be mixed with other drugs, but should be administered by separate infusion.

**Adults (Dosage in patients with normal renal function)**

For serious infections (Systemic and urinary tract infections): 3 mg/kg/day in three doses given every 8 hours.
Life threatening infections: Up to 5 mg/kg/day in 3 or 4 equal doses with reduction to 3 mg/kg/day as soon as clinically indicated. Doses should never exceed 5 mg/kg/day unless serum levels are monitored. The following table should be used as a guide:

***Dosage Guidelines For Adults With Normal Renal Function***

| **Type of Infection** | **Dosage** | **Time interval between doses** | **Duration of therapy** |
|---|---|---|---|
| Systemic and urinary tract infections* | 3 mg/kg/day (where bodyweight** >60 kg, usual dose is 80 mg, where bodyweight=60 kg, usual dose is 60 mg) | 8 hours | 7-10 days |
| Life threatening and respiratory tract infections and infections with relatively resistant organisms i.e. Pseudomonas | 5mg/kg/day initially then 3 mg/kg/day as soon as improvement is indicated | 6-8 hours | 7-10 days. Longer therapy may be required. If so, auditory, renal & vestibular functions should be monitored |

* Gentamicin activity is increased at pH 7.5. It may therefore be advantageous to alkalinize the patient's urine before therapy.
** Use lean bodyweight.

**Paediatrics**
The following table should be used as a guide:

***Dosage In Paediatrics With Normal Renal Function***

| **Type of Infection** | **Age** | **Dosage #** | **Dosage Interval** |
|---|---|---|---|
| Systemic infections | 0-7 days | 5 mg/kg/day initially | 12 hours |
| | 1 week - 1 year | 6 mg/kg/day initially | 12 hours |
| | 1 year - 12 years | 4.5 mg/kg/day initially | 8 hours |
| Uncomplicated urinary tract infections | - | 3 mg/kg/day | 8-12 hours |
| Life threatening infections | 0-7 days | 5 mg/kg/day initially | 12 hours |
| | 1 week - 1 year | 7.5 mg/kg/day initially | 8 hours |
| | 1 year - 12 years | 6 mg/kg/day initially | 8 hours |

# In neonates, infants and children, where possible, serum levels should be measured and the dose adjusted to provide the desired serum level.

**Dosage in patients with impaired renal function**
Dosage should be adjusted to minimize the risk of toxicity. The first dose should be as normal, e.g., 80 mg (bodyweight > 60 kg) and subsequent doses should be given less frequently, depending on the degree of renal impairment. The following table should be used as a guide:

***Approximate Dosage Guidelines For Adult Patients Based On Renal Function***

| **Body Weight of Adult Patient (kg)** | **Dose (mg)** | **Creatinine Clearance Rate (ml/min)** | **Serum Creatinine (mmol/l)** | **Serum urea (mmol/l)** | **Interval Between Doses** |
|---|---|---|---|---|---|
| Over 60 | 80 | Over 70 | Less than 12 | Less than 6.5 | 8 hours |
| | | 35-70 | 0.12-0.17 | 6.5-10 | 12 hours |
| | | 24-34 | 0.18-0.25 | 11-14 | 18 hours |
| | | 16-23 | 0.26-0.33 | 15-18 | 24 hours |
| | | 10-15 | 0.34-0.47 | 19-26 | 36 hours |
| | | 5-9 | 0.48-0.64 | 27-36 | 48 hours |
| 60 or less | 60 | (Same as above) | | | |

When only a serum urea concentration is available, this value may be utilized initially, however, it

should be supplemented with a serum creatinine level or creatinine clearance rate whenever possible.

*Note:* The standard dose of 80 mg three times daily may be inappropriate and a more appropriate dose can be calculated using a nomogram which takes into account the patient's serum creatinine levels, body weight and age. This dose can be adjusted, if necessary, following determination of serum creatinine levels. Desirable serum levels of gentamicin are 5-8 mcg/ml as a peak and a 1-2 mcg/ml as a trough.

*Note:* In children with impaired renal function serum levels should be monitored and frequency of dosage reduced if indicated.

In adults with renal failure undergoing haemodialysis, the amount of gentamicin removed from the blood may vary depending upon several factors including the dialysis method used. An eight hour haemodialysis may reduce serum concentrations of gentamicin by approximately 50%. The recommended dosage at the end of each dialysis period is 1 to 1.7 mg/kg depending upon the severity of infection.

## Over Dosage

As the drug is almost entirely eliminated by the kidneys, fluid loading may hasten its elimination following overdosage. Peritoneal dialysis or hemodialysis will also aid in the drug's removal.

## Presentation

**Zetamycin 20 Injection**
Box of 5 ampoules of 1 ml.

**Zetamycin 40 Injection**
Box of 5 ampoules of 2 ml.

**Zetamycin 80 Injection**
Box of 5 ampoules of 2 ml.