

GENTAMICIN INJECTION BP (GENTAMICIN SULFATE)

1. NAME OF THE MEDICINE

Gentamicin sulfate

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Gentamicin Injection BP is a sterile, preservative-free solution containing Gentamicin (as Sulfate) 80 mg/2 mL.

3. PHARMACEUTICAL FORM

Solution for injection.

4. CLINICAL PARTICULARS

4.1 Therapeutic 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* and *Serratia* species and *Staphylococcus* (including strains resistant to other antibiotics).

Gentamicin 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 antimicrobial 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.

4.2 Dose and method of administration

Each ampoule is for use in a single patient on one occasion only

Gentamicin is normally given by intramuscular injection. Intravenous administration may be used for particular indications when the intramuscular 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 which 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.

Gentamicin Injection must not be mixed with other drugs, but should be administered by separate infusion (see **Section 4.5 Interactions with other medicines and other forms of interactions**).

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 eight 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:

Table 1: 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. <i>Pseudomonas</i>	5 mg/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 alkalinise the patient's urine before therapy.

** Use lean bodyweight.

Paediatrics

The following table should be used as a guide:

Table 2: 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 initially	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 minimise 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:

Table 3: Approximate dosage guidelines for adult patients based on renal function

Bodyweight 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	<0.12	<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 utilised initially, however, it should be supplemented with a serum creatinine level or creatinine clearance rate whenever possible.

N.B. The standard dose of 80 mg three times a day may be inappropriate and a more appropriate dose can be calculated using a nomogram which takes into account the patient's serum creatinine levels, bodyweight and age. This dose can be adjusted if necessary following determination of serum creatinine levels. Desirable serum levels of gentamicin are 5-8 micrograms/mL as a peak and 1-2 micrograms/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.

4.3 Contraindications

Known hypersensitivity to gentamicin, any of the excipients, or patients who have experienced previous toxic reactions (ototoxicity, nephrotoxicity) resulting from aminoglycoside therapy.

4.4 Special warnings and precautions for use

Nephrotoxicity and ototoxicity

As for other aminoglycosides, patients being 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.

Patients with mitochondrial DNA mutations, particularly the nucleotide 1555 A to G substitution in the 12S rRNA gene may be at higher risk for ototoxicity, even if the patient's aminoglycoside serum levels were within the recommended range. In case of family history of aminoglycoside induced deafness or known mitochondrial DNA mutations in the 12S rRNA gene, alternative treatments other than aminoglycosides should be considered.

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 also 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, (see **Section 4.5 Interactions with other medicines and other forms of interactions**) 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.

Neuromuscular disorders

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 neuro-muscular function.

Use during anaesthesia

The possibility of prolonged or secondary apnoea should be considered if the drug is administered to anaesthetised 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.

Superinfection

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.

Allergic reactions

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

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.

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.

Effects on laboratory tests

No data available.

4.5 Interactions with other medicines and other forms of interactions

Neuromuscular blocking agents

Respiratory paralysis and prolongation of neuromuscular blockade may occur if a neuromuscular blocking agent such as succinylcholine, tubocurarine, decamethonium, halogenated hydrocarbon inhalation anaesthetics, opioid analgesics or massive transfusions with citrated anticoagulated blood are administered to a patient receiving 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.

Diuretics

Potent diuretics such as etacrynic acid or frusemide may potentiate the ototoxic effects of gentamicin.

Penicillins

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 of time. 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.

Vitamin K

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

Potential interactions

In vitro synergism and antagonism have been found between various antineoplastic agents and aminoglycosides.

4.6 Fertility, pregnancy and lactation

Effects on fertility

No data available.

Use in pregnancy – Pregnancy Category D

There is evidence of selective uptake of aminoglycosides by the fetal kidney resulting in damage (probably reversible) to immature nephrons. Eighth cranial nerve damage has also been reported following *in utero* exposure to some of the aminoglycosides. Because of their chemical similarity, all aminoglycosides must be considered potentially nephrotoxic and ototoxic to the fetus. It should also be noted that therapeutic blood concentrations in the mother do not equate with safety for the fetus.

Use in lactation

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.

4.7 Effects on ability to drive and use machines

The effects of this medicine on a person's ability to drive and use machines were not assessed as part of its registration.

4.8 Adverse effects (undesirable effects)

Serious or life-threatening reactions

Otic (see Section 4.4 Special warnings and precautions for use)

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 (see Section 4.4 Special warnings and precautions for use)

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, generalised burning, anaphylactoid reactions may occur.

Pulmonary

Respiratory depression, laryngeal oedema, pulmonary fibrosis may occur.

Gastrointestinal

Nausea, vomiting, increased salivation and stomatitis 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 hypokalaemia.

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions.

4.9 Overdose

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Mechanism of action

Class: Aminoglycoside antibiotic.

Microbiology

Gentamicin is bactericidal and acts by inhibiting protein synthesis in susceptible bacteria. Cell death results. It is active against a wide range of pathogenic Gram-negative organisms including *Escherichia coli*, *Pseudomonas aeruginosa*, *Proteus* sp. (both indole positive and indole negative), *Klebsiella*, *Enterobacter* and *Serratia* species. It is also active against some Gram-positive organisms, e.g. *Staphylococcus* sp. (including methicillin and penicillin resistant strains). *In vitro*, gentamicin is also active against *Salmonella* and *Shigella*. Some species have demonstrated resistance to aminoglycosides including *Streptococcus pneumoniae* and anaerobic organisms such as *Bacteroides* or *Clostridium* species.

Clinical trials

No data available.

5.2 Pharmacokinetic properties

Gentamicin is rapidly absorbed after intramuscular injection and peak serum levels are usually achieved within 30 to 90 minutes and are measurable for 6-8 hours. Following parenteral administration gentamicin can be detected in tissues and body fluids. Following absorption, gentamicin is widely distributed into body fluid including ascitic, pericardial, pleural, synovial and abscess fluids. Concentration in bile is low.

Gentamicin is excreted almost entirely by renal glomerular filtration, hence the half-life of the drug is prolonged in the presence of renal failure. Adjustments in the frequency of administration of gentamicin are necessary to allow for the degree of renal failure (see **Section 4.2 Dose and method of administration**). The serum half-life of gentamicin is approximately 2-3 hours in adults with normal renal function. It is prolonged in patients with impaired renal function and in premature or newborn infants.

5.3 Preclinical safety data

Genotoxicity

No data available.

Carcinogenicity

No data available.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Disodium edetate
Water for injections
Sodium hydroxide
Sulfuric acid

6.2 Incompatibilities

When gentamicin is used in combination with any other drug, mixing the drugs before administration should be avoided at all costs.

6.3 Shelf life

The expiry date can be found on the packaging.

6.4 Special precautions for storage

Store below 25°C. Protect from light. Single use only. Discard unused portion.

6.5 Nature and contents of container

Gentamicin Injection BP 80 mg in 2 mL Steriluer (10s)
Gentamicin Injection BP 80 mg in 2 mL Steriluer (50s)

Not all presentations may be available locally.

6.6 Special precautions for disposal

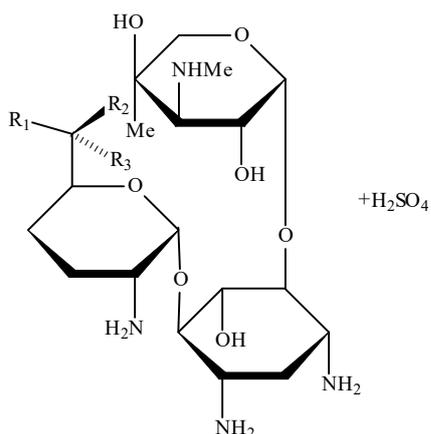
Any unused medicine or waste material should be disposed of in accordance with local requirements.

6.7 Physicochemical properties

Gentamicin sulfate is a mixture of the sulfates of antimicrobial substances produced by *Micromonospora purpurea*. The potency is not less than 590 I.U. per milligram, calculated with reference to the anhydrous substance. It is a white or almost white powder, freely soluble in water, practically insoluble in alcohol and in ether.

Chemical structure

The structural formula is represented below.



Gentamicin	R1	R2	R3
C1	Me	NHMe	H
C2	Me	NH ₂	H
C1a	H	NH ₂	H
C2a	H	NH ₂	Me

CAS number

1405-41-0

7. PRODUCT REGISTRANT

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