Module 1	Gentamicin Injection 80mg/2ml

Summary of Product Characteristics

1. Name of drug prodcut

Trade Name: Gentamicin Injection 80mg/2ml
Strength: Gentamicin sulfate 80mg.

2. Qualitative and quantitative compositions

Each ampoule (2 mL) contains：

Gentamicin sulfate 80mg-active.

Excipients of safety concern;
Anhydrous Sodium Sulfite 2mg
Sodium Hydrogen Sulfite 2mg
Water for Injection to 2ml.

3. Pharmaceutical Form

A clear, colourless or almost colourless liquid.

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 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.

Gentamicin Injection must not be physically 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 equal 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. *Pseudomonas*	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 1 week – 1 year 1 year – 12 years	5 mg/kg/day initially 6 mg/kg/day initially 4.5 mg/kg/day initially	12 hours 12 hours 8 hours
Uncomplicated urinary tract infections	-	3 mg/kg/day initially	8-12 hours
Life threatening infections	0-7 days 1 week – 1 year 1 year – 12 years	5 mg/kg/day initially 7.5 mg/kg/day initially 6 mg/kg/day initially	12 hours 8 hours 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 (see Section 6.1 List of excipients), or patients who have experienced previous toxic reactions (ototoxicity, nephrotoxicity) resulting from aminoglycoside therapy.

4.4 Special warnings and precautions for use

Gentamicin, as with other aminoglycosides, is potentially nephrotoxic and ototoxic. 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.

Neurotoxicity

Neurotoxicity 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.

Diabetes, auditory vestibular dysfunctions, previous use of ototoxic drugs and a genetically determined high sensitivity to aminoglycoside-induced ototoxicity, are other main factors that may predispose the patient to ototoxicity.

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.

Renal and eighth cranial nerve function should be closely monitored, 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. Urine should be examined for decreased specific gravity, increased excretion of protein, and the presence of cells or casts. Serum urea, serum creatinine, or creatinine clearance should be determined periodically. 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.

Serum concentrations of aminoglycosides should be monitored to assure adequate levels and to avoid potentially toxic levels. When monitoring gentamicin peak concentrations, dosage should be adjusted so that prolonged levels above 10 micrograms/mL are avoided. When monitoring gentamicin trough concentrations, dosage should be adjusted so that levels above 2 micrograms/mL are avoided. Excessive peak and/or trough serum concentrations of aminoglycosides may increase the risk of renal and eighth cranial nerve toxicity. In the event of overdose or toxic reactions, haemodialysis may aid in the removal of gentamicin from the blood, especially if renal function is or becomes compromised. The rate of removal of gentamicin is considerably less by peritoneal dialysis than by haemodialysis.

Concurrent and/or sequential systemic or topical use of other potentially neurotoxic and/or nephrotoxic drugs can increase the possibility of gentamicin toxicity (see Section 4.5 Interactions with other medicines and other forms of interactions). Co-administration with the following agents should be avoided:

- neuromuscular blocking agents such as suxamethonium and tubocurarine
- other potentially nephrotoxic or ototoxic drugs such as cephalosporins
- potent diuretics such as etacrynic acid and furosemide
- other aminoglycosides
- amphotericin B
- cisplatin

- ciclosporin

Other factors which may increase the risk of toxicity are dehydration, advancing age and diabetes mellitus.

Patients should be well hydrated during therapy. Patients treated with aminoglycoside antibiotics, including gentamicin, by injection, irrigation or local application, should be under close clinical observation because these drugs have the inherent potential for causing neurotoxicity and nephrotoxicity, particularly if patients have pre-existing renal damage or if the drug is administered for longer periods or at higher doses than those recommended.

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 neuromuscular function. Gentamicin should be used with care in conditions characterised by muscular weakness. Gentamicin induced renal tubular dysfunction including Fanconi syndrome acquired and Pseudo-Bartter syndrome, with acid base and electrolyte disturbances has been reported in some infants, children and adults being given gentamicin injections. Muscle weakness, paraesthesias, tetany, positive Chvostek and Trousseau signs have been described in patients with hypomagnesemia, hypocalcaemia and hypokalaemia. All required appropriate corrective electrolyte therapy.

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.

Obesity

In cases of significant obesity, gentamicin serum concentrations should be closely monitored and a reduction in dose should be considered (see Section 4.2 Dose and method of administration).

Clostridioides difficile-associated diarrhoea

Clostridioides difficile-associated diarrhoea (CDAD) has been reported with the use of nearly all antibacterial agents, including gentamicin, and may range in severity from mild diarrhoea

to fatal colitis. Treatment with antibacterial agents alters the normal flora of the colon, leading to overgrowth of C. difficile. C. difficile produces toxins A and B, which contribute to the development of CDAD. Hypertoxin producing strains of C. difficile cause increased morbidity and mortality, as these infections can be refractory to antimicrobial therapy and may require colectomy. CDAD must be considered in all patients who present with diarrhoea following antibiotic use. Careful medical history is necessary since CDAD has been reported to occur over 2 months after the administration of antibacterial agents.

Use in renal impairment

Gentamicin should be used with caution generally in premature infants because of their renal immaturity, in elderly people and generally in patients with impaired renal function. In some patients with impaired renal function, there has been a transient rise in serum urea, 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.

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

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.

4.5 Interactions with other medicines and other forms of interactions

Concurrent administration of gentamicin and other potentially ototoxic or nephrotoxic drugs should be avoided. Co-administration with the following agents should be avoided:

- neuromuscular blocking agents such as suxamethonium and tubocurarine
- other potentially nephrotoxic or ototoxic drugs such as cephalosporins
- potent diuretics such as etacrynic acid and furosemide
- other aminoglycosides

- amphotericin B
- cisplatin
- ciclosporin (see Section 4.4 Special warnings and precautions for use)

Digoxin

Gentamicin has been known to increase serum digoxin levels.

Neuromuscular blocking agents or medications with neuromuscular blocking activity
Concurrent use of gentamicin with agents with neuromuscular blocking activity e.g. suxamethonium (succinylcholine), tubocurarine, decamethonium, halogenated hydrocarbon inhalation anaesthetics, opioid analgesics or massive transfusions with citrated anticoagulated blood, should be carefully monitored; neuromuscular blockade may be enhanced, resulting in skeletal muscle weakness and respiratory depression or paralysis (apnoea); caution is recommended when these medications and gentamicin are used concurrently during surgery or in the postoperative period, especially if there is a possibility of incomplete reversal of neuromuscular blockade postoperatively; treatment with anticholinesterase agents or calcium salts may help reverse the blockade.

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

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 Page 8 of 15 aminoglycosides, polymyxin B, colistin, vancomycin, amphotericin B, clindamycin, cephalosporins, cisplatin and ciclosporins.

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

Potent diuretics

If possible, do not give gentamicin in conjunction with etacrynic acid, furosemide or other potent diuretics that may themselves cause ototoxicity or enhance aminoglycoside toxicity by altering antibiotic concentrations in serum and tissue.

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 compared to patients with normal renal function. 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.

Although the inactivation of gentamicin and penicillin proceeds on an equimolar basis, in practice the penicillin is present in such an excess that only the decline in activity of gentamicin is of concern. A combination of penicillin and gentamicin is often used in the treatment of enterococcal endocarditis.

Indometacin

Indometacin possibly increases plasma concentrations of gentamicin in neonates.

Neostigmine

Antagonism of effect may occur with concomitant administration of gentamicin with neostigmine.

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

Gentamicin and other aminoglycosides are known to cross the placenta. 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 effect of gentamicin sulfate on the ability to drive or use machines has not been systematically evaluated.

4.8 Adverse effects (undesirable effects)

These effects are reported in decreasing order of seriousness within each system organ class (SOC) and absolute frequency.

Table 4: Adverse events

System Organ Class	Common (≥1/100 to <1/10)	Uncommon (≥1/1,000 to <1/100)	Rare (≥1/10,000 to <1/1,000)	Very rare (<1/10,000)	Frequency not known (cannot be estimated from the available data)
Infections and infestations				Superinfection (with gentamicin-resistant bacteria), pseudomembranous colitis*[1]	
Blood and lymphatic system effects		Dyscrasia		Thrombocytopenia, reticulocytopenia, leucopenia, eosinophilia, granulocytopenia, anaemia	
Immune system effects				Hypersensitivity reactions of varying severity, ranging from rash and itching, drug fever to severe acute hypersensitivity reactions (anaphylaxis), up to anaphylactic shock	
Metabolism and nutrition effects			Hypokalaemia, hypocalcaemia, hypomagnesaemia, pseudo-Bartter syndrome in patients treated with high doses over a long period (more than 4	Hypophosphataemia	Tetany
			weeks), loss of appetite, weight loss		
Psychiatric effects				Confusion, hallucinations, mental depression	
Nervous system effects			Polyneuropathies, peripheral paraesthesias	Encephalopathy, convulsions, neuromuscular blockage, dizziness, balance disorder, headache*	Neurotoxicity[3]
Eye effects				Visual disorders	
Ear and labyrinth effects				Vestibular damage, hearing loss, Menière's disease, tinnitus vertigo*	Irreversible hearing loss, deafness, ototoxicity
Vascular effects				Hypotension, hypertension	
Gastrointestinal effects			Vomiting, nausea, salivation increased, stomatitis, antibiotic-associated diarrhoea		

Hepatobiliary effects			Aspartate aminotransferase (AST) increased, alanine aminotransferase (ALT) increased, alkaline phosphatase (ALP) increased, serum bilirubin increased (all reversible)		Hepatic function abnormal
Skin and subcutaneous tissue effects		Allergic skin exanthema	Skin reddening	Toxic epidermal necrolysis[2], Stevens-Johnson syndrome[2], erythema multiforme[2], alopecia	
Musculoskeletal and connective tissue effects			Muscle pain (myalgia)	Amyostasia	
Renal and urinary effects	Renal function impairment*		Plasma urea increased (reversible)	Acute renal failure, hyperphosphaturia, aminoaciduria, Fanconi-like syndrome in patients treated with a prolonged course of high-dose*	Nephrotoxicity
Congenital,					Fanconi syndrome

System Organ Class	**Common** (≥1/100 to <1/10)	**Uncommon** (≥1/1,000 to <1/100)	**Rare** (≥1/10,000 to <1/1,000)	**Very rare** (<1/10,000)	**Frequency not known** (cannot be estimated from the available data)
familial and genetic disorders					acquired
General effects and administration site conditions			Increased body temperature	Pain at injection site	
Pulmonary effects	Respiratory depression, laryngeal oedema, pulmonary fibrosis				

* See also **Section 4.4 Special warnings and precautions for use**.
1 Usually in these cases other antibiotics are also involved.
2 May occur as hypersensitivity reactions.
3 Including encephalopathy, confusion, lethargy, mental depression and hallucinations.

Serious or life-threatening reactions

Nephrotoxicity (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, non-protein nitrogen, 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.

Neurotoxicity (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, which, as with the other aminoglycosides, 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.

More common reactions

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

Note: The risk of toxic reactions is low in patients with normal renal function who do not receive gentamicin at higher doses or for longer periods of time than recommended.

Other adverse reactions

Other reported adverse reactions possibly related to gentamicin include: respiratory depression, lethargy, confusion, depression, visual disturbances, decreased appetite, weight loss, hypotension, hypertension, rash, itching, urticaria, generalised burning, laryngeal oedema, anaphylactoid reactions, fever, headache, nausea, vomiting, increased salivation, stomatitis, purpura, pseudotumor cerebri, acute organic brain syndrome, pulmonary fibrosis, alopecia, joint pain, transient hepatomegaly, and splenomegaly. Page 12 of 15 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.

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. This is particularly important in patients with renal malfunction.

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* species. Some species have demonstrated resistance to aminoglycosides including *Streptococcus pneumoniae* and anaerobic organisms such as Bacteroides or *Clostridioides* species.

Clinical trials

No data available.

5.2 Pharmacokinetic properties

Absorption

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.

Gentamicin is poorly absorbed by the oral route, and only minimal amounts have been found in the blood following oral administration.

In patients with normal renal function, peak serum concentrations of gentamicin, expressed in microgram/mL, are usually about four times the single dose expressed in mg/kg; for example, an injection of gentamicin 1 mg/kg may be expected to result in peak serum concentration of approximately 4 microgram/mL. Gentamicin administered every 8 hours does not accumulate in the serum except in patients with impaired renal function in whom the serum concentration Page 13 of 15 of gentamicin is usually higher, and measurable for longer periods. When gentamicin is administered by intravenous infusion, over 1 to 2 hours, the serum concentrations are similar to those obtained with intramuscular administration. About 25 to 30% of the administered dose of gentamicin is bound by serum protein; it is released as the drug is excreted. Gentamicin is excreted principally in the urine by glomerular filtration.

Distribution

Following parenteral administration gentamicin can be detected in tissues and body fluids. Concentration in bile is low.

Gentamicin administered intramuscularly has been found in low concentrations in the cerebrospinal fluid. Gentamicin has also been found in the sputum, pleural, peritoneal, ascitic, pericardial, synovial and abscess fluids. Gentamicin crosses the peritoneal as well as the placental membranes.

Excretion

After initial administration to patients with normal renal function, 30 to 100% of the gentamicin is recoverable in the urine in 24 hours. High urine concentrations (above 100 microgram/mL) may be achieved. After several days of treatment, the amount of gentamicin excreted in the urine approaches the daily dose administered. Renal clearance of gentamicin is similar to that of endogenous creatinine. 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.

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).

Endogenous creatinine clearance rate and serum creatinine, which have high correlation with serum half-life of gentamicin, may be used as a guide for this purpose (see Section 4.2 Dosage and method of administration).

5.3 Preclinical safety data

Genotoxicity

No data available.

Carcinogenicity

No data available

6.0 Pharmaceutical particulars

6.1 **List of excipients**

Sodium sulfite: 2.4 mg
Sodium Hydrogen
sulfite: 2 mg
Water for injection
q.s…. ……2ml

6.2. Shelf-life
36 months from manufactured date

6.3 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.

6.4 Special precautions for storage

Protect from direct sunlight. Do not store above 30°C. Do not refrigerate or freeze.

6.5 Nature and contents of container <and special equipment for use, administration or implantation>

6.6 Special precautions for disposal

7.0 Marketing authorization holder

8.0 Manufacturer:

Cisen Pharmaceutical Co.,Ltd.

Site of Manufacture: Haichuan Road, Jining High＆New Technology Ind. Development Zone, Jining, Shandong Province, China.