SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

Gentamicin 1 mg/mL Solution for Infusion B Braun

Gentamicin 3 mg/mL Solution for Infusion B Braun

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Gentamicin 1 mg/mL Solution for Infusion B Braun

1 mL of solution for infusion contains gentamicin sulphate equivalent to

1 mg gentamicin. One bottle of 80 mL contains 80 mg of gentamicin (as sulphate)

Gentamicin 3 mg/mL Solution for Infusion B Braun

1 mL of solution for **Gentamicin 3 mg/mL Solution for Infusion B Braun**

infusion contains gentamicin sulphate equivalent to

3 mg gentamicin. One bottle of 80 mL contains 240 mg of gentamicin (as sulphate). One bottle of 120 mL contains 360 mg of gentamicin (as sulphate).

Excipient(s) with known effect:

283 mg (12 mmol) of sodium (as chloride) per 80 mL bottle 1mg/mL or 3mg/mL solution

425 mg (18 mmol) of sodium (as chloride) per 120 mL bottle 3mg/mL solution

For full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Gentamicin 1 mg/mL Solution for Infusion B Braun;

Gentamicin 3 mg/mL Solution for Infusion B Braun

Solution for infusion

Clear solution

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

Gentamicin Solution for Infusion B.Braun solution for infusion is indicated for the following conditions, when caused by susceptible organisms, when less toxic antimicrobial agents are not effective:

- Acute and chronic urinary tract infections;
- Severe systemic infections, e.g. sepsis, peritonitis, meningitis;
- Bone and soft tissue infections, e.g. acute osteomyelitis, wound and soft tissue infections; infected burns
- Nosocomial lower respiratory tract Infections including severe pneumonia

Gentamicin Solution for Infusion B Braun should be used for all indications, only in combination with other relevant antibiotics (predominantly together with a beta- lactam antibiotic or with an antibiotic effective against anaerobic bacteria), except complicated urinary tract infections.

Consideration should be given to South African official guidance on the appropriate use of antibacterial medicines.

4.2. Posology and method of administration

Posology

Adults and adolescents

Treatment of bacterial infections.

The daily dose recommended in adolescents and adults with normal renal function, is 3 – 6 mg/kg body weight per day as one (preferred) up to two divided doses (12 hourly).

A maximum daily dose of 6 mg/kg may be needed for the treatment of serious infections and when the susceptibility of the pathogen is relatively poor.

Gentamicin has a long-lasting post-antibiotic effect (see section 5.1). Recent *in vitro* and *in vivo* studies show that the uptake of aminoglycosides into the renal cortex is limited and hence, with higher peak serum

gentamicin levels (after single daily dosing) less aminoglycoside is stored in the kidneys than with conventional multiple dosing.

In the case of combination treatment (e.g. with a beta-lactam antibiotic in the normal dosage) it is also possible to administer the total daily dose as a single dose once a day.

Due to the requirement for dose adjustments once daily dosing of gentamicin is not recommended for patients with compromised immunity (e.g. neutropenia), severe renal failure, ascites, bacterial endocarditis, patients with extensive burns (more than 20 % of the skin), and in pregnancy.

Paediatric population

The daily dose in new-borns is 4 – 7 mg/kg body weight per day. Due to the longer half-life, new-borns are given the required daily dose in 1 single dose.

The daily dose in infants after the first month of life is 4.5 – 7.5 mg/kg body weight per day as a single dose (preferred) or divided into 2 single doses.

The daily dose recommended in older children with normal renal function is 3 – 6 mg/kg body weight per day as a single dose (preferred) or divided into 2 single doses.
One 80 mL bottle of **Gentamicin 1 mg/mL Solution for Infusion B Braun** contains 80 mg gentamicin and one 80 mL bottle of **Gentamicin 3 mg/mL Solution for Infusion B Braun** contains 240 mg gentamicin. To avoid overdosing especially in children, the required volume should be calculated according to the posology and should be administered with the required technique. The unused volume shall be discarded (see section 6.6).

Duration of treatment:

In all cases, the general duration of treatment Is 7 to 10 days. When treatment exceeds this period, and in the administration of high dosage levels, it is advisable to monitor renal, auditory and vestibular functions (see section 4.4).

Patients with impaired renal function:

In impaired renal function, the recommended daily dose has to be decreased and adjusted to the renal function.

Patients with renal function impairment should be monitored in order to adjust the therapeutic concentrations in plasma, either by decreasing the dose or by increasing the dosage interval (see section 4.4).

Dose reduction and interval extension are equivalently suitable solutions.

Nonetheless, it should be remembered that doses determined in the way described below are only approximate and that the same dose may lead to different concentrations in the body of different patients. Therefore gentamicin serum levels should be determined in the given patient, so that the dosage can be adapted accordingly.

1) Extension of dosage interval at the normal dose:

Since the gentamicin clearance is directly proportional to the creatinine clearance, the following approximate formula may be used:

$$\text{Normal dose interval} \times \frac{\text{creatinine clearance}_{\text{normal}}}{\text{creatinine clearance}_{\text{patient}}} = \text{Subsequent dose interval}$$

Based on a normal creatinine clearance of 100 mL/min and a creatinine clearance of **30 mL/min** in the patient, the application interval with a constant dose would in this case be **26 hours** (8 × 100/30 [h]).

Normal dose (80 mg) at extended dose interval:

Blood urea (mmol/L)	Creatinine clearance or Glomerular Filtration Rate (GFR) (mL/min)	Dose and dosage interval
< 6.7	> 72	80 mg* every 8 hours
6.7 – 16.7	30 – 72	80 mg* every 8 hours
16.7 – 33.3	12 – 30	80 mg* every 8 hours
> 33.3	6 – 12	80 mg* every 8 hours

*If the patient's weight is < 60 kg the dose should be decreased to 60 mg.

2) Reduction of dose at the normal dose interval:

After the usual initial dose, dividing the normal recommended dose by the serum creatinine level may be taken as a rough guide for determination of the reduced dose that should be administered every 8 hours.

So e.g. 30 mg may therefore be administered every 8 hours to a patient weighing 60 kg with a serum creatinine level of 2.0 mg/100 mL after an initial dose of 60 mg (1 mg/kg; 60:2).

Reduced dose at normal dose interval (8-hourly)

Serum creatinine (mg/100 mL)	Approximate creatinine clearance or GFR (mL/min)	Percentage of the normal dose
≤ 1.0	> 100	100
1.1 – 1.3	70 – 100	80
1.4 - 1.6	55 – 70	65
1.7 – 1.9	45 – 55	55
2.0 – 2.2	40 – 45	50
2.3 – 2.5	35 – 40	40
2.6 – 3.0	30 – 35	35
3.1 – 3.5	25 – 30	30

3.6 – 4.0	20 – 25	25
4.1 – 5.1	15 – 20	20
5.2 – 6.6	10 – 15	15
6.7 – 8.0	< 10	10

Alternatively, after the usual initial dose, subsequent doses every 8 hours may be calculated according to the formula:

$$\text{Normal dose interval} \times \frac{\text{creatinine clearance}_{\text{actual}}}{\text{creatinine clearance}_{\text{normal (=100mL/ min)}}} = \text{Subsequent dose interval}$$

Creatinine clearance should be preferred as a parameter especially in the elderly and in patients with fluctuating serum creatinine levels, as is observed in severe infections (e.g. sepsis).

It should be emphasised that renal function may change during therapy with gentamicin.

It is important to recognise that deteriorating renal function may require a greater reduction of dosage than that specified in the above guidelines for patients with stable renal impairment.

Other special patient populations

Dosage in patients undergoing haemodialysis

Gentamicin is dialysable. In the case of a 4 – 5-hour haemodialysis, a 50 – 60 % reduction in concentration should be expected and in the case of an 8 – 12-hour haemodialysis, a 70 – 80 % reduction in concentration.

The dosage must be individually adjusted after each dialysis session, based on the gentamicin serum concentration at that time.

The normal recommended dose after dialysis is 1 – 1.7 mg/kg body weight.

Elderly patients

Elderly patients may require lower maintenance doses than younger adults because of impaired renal function. There is limited experience with once daily dosing of gentamicin in elderly patients. Once daily dosing of gentamicin may not be suitable and therefore, close monitoring is warranted in these patients (see Section 4.5)

Obese patients

In obese patients the initial dose should be based on ideal body weight plus 40 % of weight excess.

Critically ill patients

Critically ill patients might need higher doses than the maximum daily dose of 6 mg/kg bodyweight to achieve target peak concentration. Monitoring of plasma gentamicin concentration in this patient group is strongly recommended to avoid suboptimal peak concentrations.

Patients with impaired hepatic function

No dose adjustment is necessary.

Monitoring advice

Serum concentration of gentamicin should be monitored, to ensure efficacy and avoid toxicity especially in elderly, in new-borns, obese patients, in patients with cystic fibrosis, burns, major surgery, spinal cord injury, in patients with impaired renal function and critically ill patients, due to the increased risk of over- or underdosing. Target peak concentration depends on the indication and site of infection.
Blood samples are taken before the start of the next dosage interval for trough level.

When monitoring gentamicin peak concentration for toxicity, dosage should be adjusted so that prolonged levels above 12mcg/mL are avoided. Trough levels should not exceed 2 µg/mL when administering gentamicin twice daily and 1 µg/mL for a once daily dose. Please refer to section 4.4.

Method of administration

Gentamicin 1 mg/mL Solution for Infusion B Braun and **Gentamicin 3 mg/mL Solution for Infusion B Braun** are administered by intravenous infusion over a period of 30 – 60 minutes. Gentamicin 1 mg/mL and 3 mg/mL solutions for infusion are not suitable for intramuscular or slow intravenous injection.

Do not add other medicines together with Gentamicin Sulphate solution in the Infusion.

4.3. Contraindications

Gentamicin Solution for Infusion B Braun is contraindicated:

- Hypersensitivity to gentamicin or any component listed in section 6.1.
- In patients with a known history of allergy to other aminoglycosides.
- In patients with myasthenia gravis

4.4. Special warnings and precautions for use

Prescribers must adhere to the principles of antibiotic stewardship.

Patients treated with aminoglycosides should be under close clinical observation because of the potential toxicity associated with their use.

In patients with advanced renal impairment or with pre-existing inner ear deafness, gentamicin should be used only if its use is considered essential by the medical practitioner. The frequency or dose of administration should be reduced in patients with impaired renal function (see section 4.2).

Renal impairment

Renal impairment such as restriction of glomerular filtration is observed in approximately 10 % of patients treated with gentamicin and is usually reversible. The most important risk factors are high total dose, long duration of therapy, raised serum level (high trough level); in addition, other potential risk factors are age, hypovolaemia and shock. Clinical signs of renal damage are: proteinuria, cylindruria, haematuria, oliguria, raised creatinine and urea concentrations in serum. In isolated cases, acute renal failure may occur. (See section 4.8.).

Renal 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. Blood urea, serum creatinine, or creatinine clearance should be determined periodically. When feasible, (see Section 4.2)

Evidence of nephrotoxicity requires dosage adjustment or discontinuance of gentamicin. As with the other aminoglycosides, less frequently changes in renal function may not become manifest until soon after completion of therapy.

Neuromuscular disorders

Since gentamicin has neuromuscular blocking properties, particular caution should be exercised in patients with pre-existing neuromuscular diseases (e.g. Parkinson's disease). Particularly careful monitoring is mandatory. (See section 4.8.)

Gentamicin Solution for Infusion B Braun is contraindicated in myasthenia gravis.

Neuromuscular blockade and respiratory paralysis have been reported from administration of aminoglycosides to patients who have received curare-type muscle relaxants during anaesthesia. These patients should also be monitored very carefully. (See section 4.8.)

Neurotoxicity

Neurotoxicity manifested by ototoxicity, both vestibular and auditory (see below), can occur in patients treated with gentamicin sulphate, primarily those with pre-existing renal damage and in patients with normal renal function treated with higher doses and/or for longer periods than recommended. Aminoglycoside-induced ototoxicity is usually irreversible.

Other manifestations of neurotoxicity may include numbness, skin tingling, muscle twitching and convulsions.

Effect on vestibulocochlear nerve

Damage to the vestibulocochlear nerve (eighth cranial nerve), whereby both balance and hearing may be affected, is possible. Vestibular damage is the most frequent ototoxic reaction. Hearing loss is manifested initially by diminution of high-tone acuity and is usually irreversible. Important risk factors are pre-existing renal impairment or a history of damage to the eighth cranial nerve; in addition, the risk increases in proportion to the level of the total and daily dose or by association with potentially ototoxic substances. Symptoms of ototoxic effects are: dizziness, ringing/roaring in the ears (tinnitus), vertigo and – less frequently – hearing loss.

It is recommended that serial audiograms be obtained in patients old enough to be tested, particularly high-risk patients. Evidence of ototoxicity requires dosage adjustment or discontinuance of gentamicin. Less frequently changes eighth cranial nerve function may not become manifest until soon after completion of therapy.

With gentamicin the vestibular mechanism may be affected if trough levels of 2 µg/mL are exceeded. This is usually reversible if observed promptly and the dose adjusted. 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. (See also section 4.8.)

Antibiotic-associated diarrhoea, pseudomembranous colitis

Antibiotic-associated diarrhoea and pseudomembranous colitis have been reported with the use of gentamicin.

These diagnoses should be considered in any patient who develops diarrhoea during or shortly after treatment. Gentamicin should be discontinued if severe and/or bloody diarrhoea occurs during treatment and appropriate therapy instituted. Medicines that inhibit peristalsis must not be given (see section 4.8).

Treatment with gentamicin may produce excessive growth of drug-resistant microorganisms.

Once daily dosing of gentamicin in elderly patients

There is limited experience with once daily dosing of gentamicin in elderly patients. Once daily dosing of gentamicin may not be suitable and therefore, close monitoring is warranted in these patients.

Due to the requirement for dose adjustments, once daily dosing of gentamicin is also not recommended for patients with compromised immunity (e.g. neutropenia), severe renal failure, ascites, bacterial endocarditis, patients with extensive burns (more than 20 % of the skin), and in pregnancy.

Monitoring

To avoid adverse events, continuous monitoring (before, during and after treatment) of renal function (serum creatinine, creatinine clearance), control of function of vestibule and cochlea as well as hepatic and laboratory parameters is recommended.

Excipients

80 mL bottle 1mg/mL or 3 mg /mL solution of gentamicin sulphate: This medicinal product contains 283 mg of sodium per 80 mL bottle solution for infusion, equivalent to 14.2 % of the WHO recommended maximum daily intake of 2 g sodium for an adult.

120 mL bottle 3 mg/mL solution of gentamicin sulphate: This medicinal product contains 425 mg of sodium per 120 ml bottle solution for infusion, equivalent to 21.3 % of the WHO recommended maximum daily intake of 2 g sodium for an adult.

Add Cross-allergenicity/-resistance

Cross-resistance and hypersensitivity to aminoglycosides may occur.

Nephrotoxicity and ototoxicity

In order to reduce the risk of nephrotoxicity and ototoxicity, the following should be considered:

- Regular assessment of auditory, vestibular and renal function is particularly necessary in patients with additional risk factors. Impaired hepatic function or auditory function, bacteraemia and fever have been reported to increase the risk of ototoxicity. Volume depletion or hypotension and liver disease have been reported as additional risk factors for nephrotoxicity.
- Monitoring of renal function before, during and after treatment.
- Dosage strictly according to creatinine clearance (or serum creatinine concentration). In patients with impaired renal function, the dosage must be adjusted according to renal performance (see section 4.2).
- In patients with impaired renal function additionally receiving gentamicin locally (inhalation, intratracheal, instillation), the amount of gentamicin absorbed after local administration must also be taken into account for dose adjustment of systemic treatment.
- Monitoring of serum gentamicin concentrations during therapy in order to avoid that peak levels exceed 10-12 µg/mL (toxic threshold for the cochleo-vestibular system) with conventional multiple daily dosing or trough levels exceed 2 µg/mL (see section 4.2).
- In patients with pre-existing inner ear damage (hearing impairment or balance function impairment), or where treatment is long-term, additional monitoring of the balance function and hearing is required.
- Prolonged treatment should be avoided. If possible, the duration of therapy should be limited to 7 – 10 days (see section 4.2).
- Avoid therapy with aminoglycosides immediately subsequent to previous aminoglycoside treatment; if possible, there should be an interval of 7 – 14 days between treatments.
- If possible, avoid concurrent administration of other potentially ototoxic and nephrotoxic substances. If this is unavoidable, particular careful monitoring of renal function is indicated (see section 4.5).
- Ensure adequate hydration and urine production as risk of toxicity is enhanced by dehydration.

- In the event of 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 lower by peritoneal dialysis than it is by haemodialysis.

4.5. Interaction with other medicines and other forms of interaction

Muscle relaxants and ether

The neuromuscular blocking activity of aminoglycosides is enhanced by ether and muscle relaxants.
If gentamicin is administered during or immediately after surgery, the neuromuscular blockade may be enhanced and prolonged if non-depolarising muscle relaxants are used. These interactions may cause neuromuscular blockage and respiratory paralysis. Because of the increased risk, such patients should be monitored with particular care. Large doses of Gentamicin Solution for Infusion B Braun should not be administered concurrently with neuromuscular blocking medicines.
Injection with calcium chloride may reverse the neuromuscular blockade due to aminoglycosides.

Methoxyflurane anaesthesia

Aminoglycosides may increase the kidney damaging effect of methoxyflurane. When used concurrently, extremely severe nephropathies are possible. The anaesthetist should be made aware of the use of aminoglycosides before a surgical procedure.

Potentially nephrotoxic or ototoxic medicines

Because of the increased risk of undesired effects, concurrent administration of Gentamicin Solution for Infusion B.Braun with potentially nephrotoxic or ototoxic medicines such as e.g. amphotericin B, colistin, ciclosporin, cisplatin, vancomycin, polymyxin B, streptomycin, neomycin, other aminoglycosides, some cephalosporins (e.g. ceophaloridine), and loop diuretics such as ethacrynic acid and furosemide should be avoided.
In the case of medicines containing cisplatin, it must be noted that the nephrotoxicity of gentamicin can be increased even 3 to 4 weeks after these substances are administered.

Other antibiotics

A reduction in gentamicin serum half-life has been reported in patients with severe renal impairment receiving carbenicillin concomitantly with gentamicin.

4.6. Fertility, pregnancy and lactation

Pregnancy

Aminoglycosides may cause foetal harm if administered to a pregnant woman, **t**here are however no adequate data from the use of gentamicin in pregnant women. Studies in animals have shown reproductive toxicity. Gentamicin crosses the placenta. Because of the potential risk of inner ear and renal damage to the foetus, gentamicin should not be used in pregnancy except in case of a life-threatening indication and if no other treatment options are available.

In case of exposure to gentamicin during pregnancy, monitoring of hearing and renal function of the new-born is recommended.

Breast-feeding

Gentamicin is excreted in human breast milk and was detected in low concentrations in serum of breast-fed children. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from gentamicin therapy. Diarrhoea and fungus infection of the mucous membranes could occur in the breast-fed infant, so that nursing might have to be discontinued. The possibility of sensitisation should be borne in mind.

Fertility

No data available.

4.7. Effects on ability to drive and use machines

In the case of administration to outpatients, caution is advised when driving and using machines in view of the possible undesirable effects such as dizziness and vertigo.

4.8. Undesirable effects

Tabulated list of adverse reactions

System Organ Class	Frequency Category
Infections and infestations	
Superinfection (with gentamicin-resistant microorganisms), pseudomembranous colitis (see section 4.4)	Less Frequent
Blood and lymphatic disorders:	
Dyscrasia, Thrombocytopenia, reticulocytopenia, leukopenia, eosinophilia, granulocytopenia, anaemia, purpura	Less frequent
Immune system disorders	
Hypersensitivity reactions of varying severity, ranging from rash and itching, medicine fever to severe acute hypersensitivity reactions (anaphylaxis), up to anaphylactic shock. Hypersensitivity reactions, especially after local use; cross-sensitivity between aminoglycosides may occur; anaphylactic reactions have occurred. Some hypersensitivity reactions have been attributed to the presence of sulphites in parenteral formulations	Less frequent
Metabolism and nutrition disorders	
Hypokalaemia, hypocalcaemia, hypomagnesaemia, pseudo-Bartter syndrome in patients treated with high doses over a long period (more than 4 weeks), loss of appetite, weight loss. Hypophosphataemia	Less frequent
Psychiatric disorders	
Confusion, hallucinations, mental depression	Less frequent
Nervous system disorders:	
Polyneuropathies, peripheral paraesthesias	Less frequent
Encephalopathy, convulsions, neuromuscular blockage, respiratory depression, muscular paralysis, dizziness, balance disorder, headache, (see also section 4.4)	Less frequent
Eye disorders:	

Visual disorders	Less frequent
Subconjunctival injection of gentamicin may lead to pain, hyperaemia and conjunctival oedema, while severe retinal ischaemia has followed intra-ocular injection	Frequency unknown
Ear and labyrinth disorders	
Ototoxicity (both vestibular and auditory)	Frequent
Vestibular damage, hearing loss, Meniére's disease, tinnitus vertigo	Less frequent
tinnitus vertigo (see section 4.4)	
Irreversible hearing loss, deafness	Frequency unknown
Vascular disorders :	
Hypotension, hypertension	Less frequent
Gastrointestinal disorders:	
Vomiting, nausea, salivation increased, stomatitis	Less frequent
Hepato-biliary disorders	
Aspartate aminotransferase (AST) increased, alanine aminotransferase (ALT) increased, alkaline phosphatase (ALP) increased, serum bilirubin increased (all reversible)	Less frequent
Skin and subcutaneous tissues disorders:	
Allergic skin exanthema, Skin reddening Toxic epidermal necrolysis, Stevens-Johnson syndrome, erythema multiforme, alopecia	Less Frequent
Musculoskeletal and connective tissue disorders	
Muscle pain (myalgia), Amyostasia	Less Frequent
Renal and urinary disorders	
Nephrotoxicity, Renal function impairment (see section 4.4)	Frequent

Blood urea increased (reversible), Acute renal failure, hyperphosphaturia, aminoaciduria, Fanconi-like syndrome in patients treated with a prolonged course of high-dose (see section 4.4)	Less frequent
General disorders and administration site conditions:	
Increased body temperature, Pain at injection site, endotoxic shock	Less frequent
Electrolyte disturbances (notably hypermagnesaemia, but also hypocalcaemia and hypokalaemia) have occurred	Frequency unknown

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation 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 to SAHPRA via the '6.04 Adverse Drug Reactions Reporting Form'. Found under SAHPRA's publications: https://www/sahpra.org.za/Publications/Index/8

4.9. Overdose

Symptoms and treatment

Symptoms

Gentamicin has a narrow therapeutic window. In the event of accumulation (e.g. as a result of impaired renal function), renal damage and damage to the vestibulocochlear nerve may occur: In patients with renal impairment, gentamicin serum blood levels in excess of 12 ug/mL may result In ototoxicity. This is reversible if timeously observed and the dose is suitably adjusted. See also Section 4.4).

Treatment in the event of overdose

Discontinue medication. There is no specific antidote. Gentamicin can be removed from the blood by haemodialysis (elimination is more slowly and discontinuous with peritoneal dialysis).

Treatment of neuromuscular blockade

In the event of neuromuscular blockade (usually caused by interactions, see section 4.5), the administration of calcium chloride is advisable and artificial respiration if required.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

A.20.1.1 Broad and medium spectrum antibiotics

Pharmacotherapeutic group: Other aminoglycosides, ATC code: J01GB03

Mechanism of action

Gentamycin, an aminoglycoside, binds to the prokaryotic ribosome, inhibiting protein synthesis in susceptible bacteria. Gentamicin has bactericidal efficacy both in the proliferation and in the resting stage of bacteria. It forms a bond with the proteins of the 30S subunits of the bacterial ribosomes, which causes “misreading” of the mRNA.

Gentamicin has a wide range of activity against both Gram-positive and Gram-negative organisms.

Bacteria resistant to one aminoglycoside may be resistant to one or more other aminoglycosides.

The prevalence of **acquired resistance** may vary geographically and with time for selected species and local information on resistance is desirable, particularly when treating severe infections.

Inherently resistant organisms

Aerobic Gram-positive micro-organisms:

Most enterococcal species (including *Enterococcus faecalis, E. faecium, and E.durans*), most streptococcal species (including *Streptococcus pneumoniae* and the Group D *streptococci*)

Aerobic Gram-negative micro-organisms:

Burkholderia cepacia, Legionella pneumophila, Stenotrophomonas maltophilia

Anaerobic micro-organisms

Bacteroides spp., *Clostridium difficile*

Atypical pathogens

Chlamydia spp., Chlamydophila spp., Mycoplasma spp. Mycoplasma spp.

Aminoglycosides are known to be not effective against *Salmonella and Shigella*

Interaction with other antimicrobials

In vitro studies show that an aminoglycoside combined with an antibiotic that interferes with cell wall synthesis may act synergistically against some enterococcal strains. The combination of gentamicin and penicillin G has a synergistic bactericidal effect against strains of *Enterococcus faecalis, E. faecium* and *E. durans*. An enhanced killing effect against many of these strains has also been shown *in vitro* with combinations of gentamicin and ampicillin, carbenicillin, nafcillin or oxacillin. Synergistic effects have been described with acylamino penicillins (e.g. piperacillin, carbenicillin) on *Pseudomonas aeruginosa* and with cephalosporins on *Klebsiella pneumoniae*.

5.2. Pharmacokinetic properties

Absorption

Like all aminoglycoside antibiotics, gentamicin is barely absorbed by healthy intestinal mucosa after oral administration. Therefore therapeutic application is parenteral.

Higher peak and lower trough levels are found when the total daily dose is given as a single daily infusion. When gentamicin is administered by intravenous short infusion of 30 minutes at 4 mg/kg body weight per day in three divided doses, peak and trough gentamicin concentrations measured in adult patients were 4.7 µg/mL and 1.0 µg/mL, respectively. With the same daily dose administered once daily, peak and trough concentrations of 9.5 µg/mL and 0.4 µg/mL were measured.

Therapeutic serum concentrations generally lie between 2 and 8 µg/mL. Therapeutic peak serum concentrations are in the range of 5 – 10 µg/mL for multiple daily dosing and 20 – 30 µg/mL for once daily dosing. Maximum serum concentrations of 10 – 12 µg/mL should not be exceeded when administered

conventionally, in several doses per day. Before another dose is administered, the serum concentration when administered conventionally in several doses per day, should have fallen below 2 µg/mL.

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 body weight, 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 body weight 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 body weight means that for adequate peak blood concentration a higher dose per kg body weight 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 %.

Biotransformation

Gentamicin is not metabolised in the body but is excreted unchanged in microbiologically active form.

Elimination

Gentamicin is eliminated unchanged in microbiologically active form predominantly via the kidneys by glomerular filtration. The dominant elimination half-life in patients with normal renal function is around 2 – 3 hours.

Elderly patients eliminate gentamicin more slowly than younger adults.
Children have a shorter half-life of gentamicin and higher clearance rates compared to adult patients.

In neonates up to three weeks of age, the serum half-life is extended by about 1/3 and the elimination rate is reduced because of 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.

An accumulation of gentamicin occurs in the tubular cells of the renal cortex. A terminal half-life of 100 – 150 hours results from a release of gentamicin from this deep compartment.
Elimination occurs independent of dose. Far in excess of 90 % of the substance is eliminated via the kidneys. Only about 2 % of the dose administered is excreted extrarenally in normal renal function. The total clearance is approximately 0.73 mL × min^{-1}× kg^{-1}.

In patients with impaired renal function the elimination half-life is prolonged depending on the degree of renal impairment. The more severe the impairment, the slower the clearance. Adherence to the standard treatment programme results in accumulation of the medicine.

Linearity

Gentamicin is dialysable.

During extracorporeal haemodialysis, depending on the duration of the dialysis, 50 % - 80 % of the gentamicin is removed from the serum. Peritoneal dialysis is also possible; here the elimination half-lives are between 12.5 and 28.5 hours and 25 % of the dose is removed within 48 to 72 hours (see section 4.2).

Special Populations

Renal impairment

(See section 4.4)

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Gentamicin 1 mg/mL Solution for Infusion B Braun

Sodium chloride, water for injection

Gentamicin 3 mg/mL Solution for Infusion B Braun

Disodium edetate, sodium chloride, water for injection

6.2. Incompatibilities

This medicinal product must not be mixed with other medicinal products.

The following active substances or solutions for reconstitution/dilution should not be administered simultaneously: Gentamicin is incompatible with amphotericin B, cephalothin sodium, nitrofurantoin sodium, sulfadiazine sodium and tetracyclines.

6.3. Shelf life

3 years

After first opening

From the microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2 to 8°C.

6.4. Special precautions for storage

Store at or below 25 °C.

Keep in original packaging until required for use.

KEEP OUT OF REACH OF CHILDREN.

6.5. Nature and contents of container

Gentamicin 1 mg/mL Solution for Infusion B Braun

10/20 x 80 mL are packed in low density polyethylene containers. The container is already hermetically closed before the closure system is applied. Additional closure cap on top of the sealed polyethylene containers is made of polyethylene. Between the polyethylene container and closure cap exists an elastomeric disk.

Gentamicin 3 mg/mL Solution for Infusion B Braun

10/20 x 80 mL or 10/20 x 120 mL are packed in low density polyethylene containers. The container is already hermetically closed before the closure system is applied. Additional closure cap on top of the sealed polyethylene containers is made of polyethylene. Between the polyethylene container and closure cap exists an elastomeric disk.

Not all packs or pack sizes are necessarily marketed

6.6. Special precautions for disposal of a used medicine or waste materials derived from such medicine and other handling of the product

Gentamicin 1 mg/mL Solution for Infusion B Braun and Gentamicin 3 mg/mL Solution for Infusion B Braun is a ready-to-use formulation and should not be diluted prior to administration.

The solution should be administered with sterile equipment using an aseptic technique. The equipment should be primed with the solution in order to prevent air entering the system.

For single use only. Do not re-connect partially used containers.

Unused solution should be discarded.

The solution is to be inspected visually for particulate matter and discoloration prior to administration. The solution should only be used if the solution is clear and free from particles.

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

7. NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION

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8. REGISTRATION NUMBER

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10. DATE OF REVISION OF TEXT