# SUMMARY OF PRODUCT CHARACTERISTICS

## 1. NAME OF THE MEDICINAL PRODUCT

Gentamicin B. Braun 3 mg/ml

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

*Gentamicin B. Braun 3 mg/ml, solution for infusion:*

1 ml of solution for infusion contains gentamicin sulphate equivalent to 3 mg gentamicin.
1 bottle of 80 ml contains 240 mg of gentamicin.
1 bottle of 120 ml contains 360 mg of gentamicin.

Excipients:
283 mg (12 mmol) of sodium (as chloride) per 80 ml bottle.
425 mg (18 mmol) of sodium (as chloride) per 120 ml bottle.

For the full list of excipients, see section 6.1.

## 3. PHARMACEUTICAL FORM

Solution for infusion.
A clear colourless aqueous solution.

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

For the treatment of serious infections caused by susceptible microorganisms.

Gentamicin B. Braun 3 mg/ml should for all indications, except complicated urinary tract infections, only be used in combination with other relevant antibiotics (predominantly together with a beta-lactam antibiotic or with an antibiotic effective against anaerobic bacteria).

Under these conditions, Gentamicin B. Braun 3 mg/ml may be used in:
- Complicated and recurrent urinary tract infections
- Nosocomial lower respiratory tract infections including severe pneumonia
- Intraabdominal infections including peritonitis
- Skin and soft tissue infections including severe burns
- Septicaemia including bacteraemia
- Treatment of bacterial endocarditis
- Treatment of surgical infections

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

### 4.2 Posology and method of administration

**Posology**

**Dosage in patients with normal renal function**

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 1 (preferred) up to 2 single doses.
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 in 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 weakened immunity (e.g. neutropenia), severe renal failure, ascites, bacterial endocarditis, patients with extensive burns (more than 20% of the skin), and in pregnancy.

The duration of treatment should be limited to 7 – 10 days. A longer duration of treatment may be necessary in difficult and complicated infections.

**Paediatric population**
The daily dose in newborns is 4 – 7 mg/kg body weight per day. Due to the longer half-life, newborns 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 1 (preferred) up to 2 single doses.
The daily dose recommended in older children with normal renal function is 3 – 6 mg/kg body weight per day as 1 (preferred) up to 2 single doses.

One 80 ml bottle of Gentamicin 3 mg/ml solution for infusion contains 240 mg gentamicin. To avoid overdosing especially in children, Gentamicin 3 mg/ml solution for infusion should not be administered to children who need less than 240 mg gentamicin per dose.

**Dosage in patients with renal impairment**

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 prolongation 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 organisms of different patients. Therefore gentamicin serum levels should be determined in the given patient, so that the dosage can then 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 equation may be used:

| Normal dose interval × (normal creatinine clearance/creatinine clearance of the patient) = 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 (ml/min) | Dose and dosage interval |
|---|---|---|
| < 6.7 | > 72 | 80 mg* every 8 hours |
| 6.7 – 16.7 | 30 – 72 | 80 mg* every 12 hours |
| 16.7 – 33.3 | 12 – 30 | 80 mg* every 24 hours |
| > 33.3 | 6 – 12 | 80 mg* every 48 hours |

*In case 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 may be taken as a rough guide for the measurement of the reduced dose that should be administered every 8 hours.

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).

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

| Normal dose × creatinine clearance of the patient/normal creatinine clearance (100 ml/min) = subsequent dose. |
|---|

*Reduced dose at normal dose interval (8-hourly):*

| Serum creatinine (mg/100 ml) | Approximate rate of creatinine clearance (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 |

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

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

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, 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 may require lower maintenance doses than younger adults because of impaired renal function.

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

In patients with impaired hepatic function no dose adjustment is necessary.

Monitoring advice:
Serum concentration monitoring of gentamicin is recommended, especially in elderly, in newborns and in patients with impaired renal function. Blood samples are taken before the start of the next dosage interval (trough level). 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 B. Braun 3 mg/ml solution for infusion is administered by intravenous infusion over a period of 30 – 60 minutes. Gentamicin B. Braun 3 mg/ml is not suitable for intramuscular or slow intravenous injection.

Only for intravenous use.

## 4.3 Contraindications

- Hypersensitivity to the active substance, other aminoglycosides or to any of the excipients listed in section 6.1.
- Myasthenia gravis.

## 4.4 Special warnings and precautions for 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 physician. 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 also section 4.8).

*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 also section 4.8).

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 also section 4.8).

*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 common 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 common hearing loss.

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 (see also section 4.8).

*Ototoxicity*
There is an increased risk of ototoxicity in patients with mitochondrial DNA mutations (particularly the nucleotide 1555A to G substitution in the 12S rRNA gene), even if aminoglycoside serum levels are within the recommended range during treatment. Alternative treatment options should be considered in such patients.
In patients with a maternal history of relevant mutations or aminoglycoside induced deafness, alternative treatments or genetic testing prior to administration should be considered.

*Antibiotic-associated diarrhoea, pseudomembranous colitis*
Diarrhoea and pseudomembranous colitis have been observed when gentamicin is combined with other antibiotics. These diagnoses should be considered in every patient that develops diarrhoea during or immediately after treatment. Gentamicin should be discontinued if the patient suffers severe diarrhoea and/or

bloody diarrhoea during treatment and an appropriate treatment should be initiated. Drugs that inhibit peristalsis should not be administered (see section 4.8).

*Pregnancy and lactation*
Gentamicin should be used in pregnancy and during lactation only after careful benefit risk assessment (see section 4.6).

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.

*Monitoring*

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

*Super-infections*
Treatment with gentamicin may produce an excessive growth of drug-resistant microorganisms. If this happens, an appropriate treatment should be initiated.

*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 instructions 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.

*Excipients*
This medicinal product contains 283 mg/ 425 mg of sodium per 80 ml/120 ml bottle solution for infusion, equivalent to 14.2 %/ 21.3 % of the WHO recommended maximum daily intake of 2 g sodium for an adult.

## 4.5 Interactions with other medicinal products 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.

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 drugs***

Because of the increased risk of undesired effects, careful monitoring is required of patients being treated concurrently or sequentially with potentially nephrotoxic or ototoxic drugs such as e.g. amphotericin B, colistin, ciclosporin, cisplatin, vancomycin, streptomycin, viomycin, aminoglycosides, some cephalosporins, and loop diuretics such as ethacrynic acid and frusemide.

In the case of drugs 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 Pregnancy and lactation

*Pregnancy*

There are no adequate data from the use of gentamicin in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3). Gentamicin crosses the placenta. Because of the potential risk of inner ear and renal damage to the fetus, gentamicin should not be used in pregnancy unless in case of a life-threatening indication and if no other treatment options are available.

In case of exposition to gentamicin during pregnancy, monitoring of hearing and renal function of the newborn 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.

## 4.7 Effects on ability to drive and using machines

No studies on the effects on the ability to drive and use machines have been performed. In the case of administration to outpatients, caution is advised when driving and using machines in view of the possible undesired effects such as dizziness and vertigo.

## 4.8 Undesirable effects

Under certain conditions gentamicin shows ototoxic and/or nephrotoxic effects. Renal impairment is commonly observed in patients treated with gentamicin and is usually reversible upon withdrawal of the drug. In most cases nephrotoxicity is associated with an excessively high dosage or prolonged treatment, pre-existing renal abnormalities or associated with other substances reported to be nephrotoxic.

The adverse reactions considered at least possibly related to treatment are listed below by body system organ class and absolute frequency. Frequencies are defined as
very common (≥1/10);
common (≥1/100 to <1/10);
uncommon (≥1/1000 to <1/100);
rare (≥1/10 000 to <1/1000);
very rare (<1/10 000),
not known (cannot be estimated from the available data).

| **System 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 (caused by gentamicinresistant bacteria), pseudomembranous colitis |
| **Blood and lymphatic system disorders** | | Dyscrasia | | Thrombocytopaenia, reticulocytopaenia, leukopaenia, eosinophilia, granulocytopaenia, anaemia | |
| **Immune system disorders** | | | | | Anaphylactic reaction (including anaphylactic shock) and hypersensitivity |
| **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 | |
| **Psychiatric disorders** | | | | Confusion, hallucinations, mental depression | |
| **Nervous system disorders** | | | Polyneuropathies, peripheral paraesthesias | Encephalopathy, convulsions, neuromuscular blockage, dizziness, balance disorder, headache (see also section 4.4) | |
| **Eye disorders** | | | | Visual disorders | |
| **Ear and labyrinth disorders** | | | | Vestibular damage, hearing loss, Meniére`s disease, tinnitus, vertigo (see also section 4.4) | Irreversible hearing loss, deafness |
| **Vascular disorders** | | | | Hypotension, hypertension | |
| **Gastrointestinal disorders** | | | Vomiting, nausea, salivation increased, | | |

| | | | | | |
|---|---|---|---|---|---|
| | | | stomatitis | | |
| **Hepatobiliary disorders** | | | Aspartate aminotransferase (AST) increased, Alanine aminotransferase (ALT) increased, alkaline phosphatase (ALP) increased, reversible increase of serum bilirubin (all reversible) | | |
| **Skin and subcutaneous tissue disorders** | | Allergic skin exanthema | Skin reddening | Erythema multiforme[1], Alopecia | Steven Johnson syndrome, Toxic epidermal necrolysis |
| **Musculoskeletal and connective tissue disorders** | | | Muscle pain (myalgia) | Amyostasia | |
| **Renal and urinary disorders** | Renal function impairment | | Blood urea nitrogen increased (reversible) | Acute renal failure, hyperphosphaturia, aminoaciduria, Fanconi-like syndrome in patients treated with a prolonged course of high-dose, see also section 4.4. | |
| **General disorders and administration site conditions** | | | Increased body temperature | Pain at injection site | |

[1] May occur as hypersensitivity reactions.

**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. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form https://sideeffects.health.gov.il

### 4.9 Overdose

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.

**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

Pharmacotherapeutic group: Other aminoglycosides, ATC code: J01GB03

Gentamicin is an aminoglycoside antibiotic extracted from *Micromonospora purpurea*. It represents a mixture of the structurally very similar homologues gentamicin C1, C1a and C2. The gentamicin homologue C2 is classified as the component with the highest toxicity. The antibacterial activity of gentamicin sulphate is determined both on the basis of units and also on the basis of mass (weight). The following relationships apply:

1 mg is equivalent to 628 I.U. or 1 I.U. is equivalent to 0.00159 mg gentamicin sulphate.

For its international standard substance, the WHO specifies a specific activity of 614 I.U./mg gentamicin sulphate.

Mechanism of action:
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.

PK/PD relationship
The aminoglycosides show a concentration dependent anti-bacterial effect.
Gentamicin and other aminoglycosides show a clear post-antibiotic effect *in vitro* and *in vivo* in most experimental models of infection. Provided sufficiently high doses are administered, these drugs are therefore efficacious against infections with many susceptible micro-organisms even if the concentration in plasma and tissues remains below the MIC during part of the dosage interval. The post-antibiotic effect permits the dosage interval to be extended without loss of efficacy against most Gram-negative bacilli.

Mechanism of resistance
Resistance may be due to a failure of permeation, low affinity for the bacterial ribosome or inactivation of gentamicin by microbial enzymes. The emergence of resistance during therapy is unusual.

Breakpoints

According to EUCAST, the following limit values apply for gentamicin:

| **Pathogen** | **Susceptible** | **Resistant** |
|---|---|---|
| Enterobacteriaceae | ≤ 2 mg/l | > 4 mg/l |
| Pseudomonas *spp*. | ≤ 4 mg/l | > 4 mg/l |
| Acinetobacter *spp*. | ≤ 4 mg/l | > 4 mg/l |
| Staphylococcus *spp*. | ≤ 1 mg/l | > 1 mg/l |
| *Non-species related breakpoints** | ≤ 2 mg/l | > 4 mg/l |

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. As necessary, expert advice should be sought when the local prevalence of resistance is such that the utility of the agent in at least some types of infections is questionable. Especially in such circumstances, samples should be obtained in order to identify the causal micro-organism and to measure its sensitivity to gentamicin.

| **Commonly susceptible species (according to EUCAST)** |
|---|
| **Aerobic Gram-positive micro-organisms** |
| *Listeria monocytogenes* |
| *Staphylococcus aureus (MSSA)* |
| **Aerobic Gram-negative micro-organisms** |
| *Campylobacter coli* |
| *Campylobacter jejuni* |
| *Citrobacter koseri* |

| |
|---|
| *Enterobacter aerogenes* |
| *Enterobacter cloacae* |
| *Escherichia coli* |
| *Francisella tularensis* |
| *Klebsiella oxytoca* |
| *Klebsiella pneumoniae* |
| *Proteus vulgaris* |
| *Salmonella enterica subsp. enterica* |
| *Serratia marcescens* |
| *Yersinia enterolitica* |
| *Yersinia pseudotuberculosis* |
| **Species for which acquired resistance may be a problem** |
| **Aerobic Gram-positive micro-organisms** |
| *Staphylococcus aureus (MRSA)* |
| *Staphylococcus epidermidis* |
| *Staphylococcus haemolyticus* |
| *Staphylococcus hominis* |
| **Aerobic Gram-negative micro-organisms** |
| *Acinetobacter spp.* |
| *Citrobacter freundii* |
| *Morganella morganii* |
| *Proteus mirabilis* |
| *Pseudomonas aeruginosa* |
| **Inherently resistant organisms** |
| **Aerobic Gram-positive micro-organisms** |
| *Enterococcus faecalis* |
| *Enterococcus faecium* |
| *Streptococcus spp.* |
| **Aerobic Gram-negative micro-organisms** |
| *Burkholderia cepacia* |
| *Legionella pneumophila* |
| *Stenotrophomonas maltophilia* |
| **Anaerobic micro-organisms** |
| *Bacteroides spp.* |
| *Clostridium difficile* |
| **Others** |
| **Atypical pathogens** |
| *Chlamydia spp.* |
| *Chlamydophila spp.* |
| *Mycoplasma spp.* |
| *Ureaplasma urealyticum* |

Abbreviations:
MSSA = Methicillin-sensitive Staphylococcus aureus,
MRSA = Methicillin-resistant Staphylococcus aureus

Infections caused by Streptococci or Enterococci:

Aminoglycosides are suitable combination partners for other antibiotics against Gram-positive cocci. For some indications (septicaemia, endocarditis), synergistic effects with beta-lactams have been described. This synergy is abolished when Streptococci or Enterococci present a high level acquired resistance to gentamicin.

Other notes:
Synergistic effects have been described with acylamino penicillins (e.g. piperacillin) 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 bodyweight, compared with 50 to 55% in adults. The extracellular water compartment is larger (40% of body weight compared with 25% of body weight in adults). Therefore, the volume of distribution of gentamicin per kg bodyweight is affected and decreases with increasing age from 0.5 to 0.7 l/kg for a premature newborn to 0.25 l/kg for an adolescent. The larger volume of distribution per kg bodyweight means that for adequate peak blood concentration a higher dose per kg bodyweight needs to be administered.

The 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 organism but is excreted unchanged in microbiologically active form.

**Elimination**

Gentamicin is eliminated unchanged in microbiologically active form principally in the urine 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 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. Adherence to the standard treatment program results in accumulation of the drug.

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-lifes are between 12.5 and 28.5 hours and 25% of the dose is removed within 48 to 72 hours (see section 4.2).

### 5.3 Preclinical safety data

**Chronic toxicity**
In studies on chronic toxicity (i.m. application) carried out on various animal species, nephrotoxic and ototoxic effects were observed at high dosages.

**Mutagenic and carcinogenic potential**
Gentamicin was not mutagenic in *in vitro* and *in vivo* tests. There are no long-term studies on animals on the carcinogenic potential of gentamicin.

**Reproductive toxicity**
There is a potential risk of inner ear and renal damage to the fetus as was observed for the class of aminoglycoside antibiotics. Fetal renal abnormalities have been documented in rats and guinea pigs after administration of gentamicin to the dams.

## 6. PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients

For Gentamicin B. Braun 3 mg/ml:
Disodium edetate
Sodium chloride
Water for injections

### 6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products. On no account may aminoglycosides be mixed in an infusion solution with beta-lactam antibiotics (e.g. penicillins, cephalosporins), erythromycin, or lipiphysan (A special oil-in-water-emulsion for parenteral nutrition) as this may cause physico-chemical inactivation. This also applies to a combination of gentamicin with diazepam, furosemide, flecainide acetate or heparin sodium.

The following active substances or solution for reconstitution/dilution should not be administered simultaneously:
Gentamicin is incompatible with amphotericin B, cephalothin sodium, nitrofurantoin sodium, sulfadiazine sodium and tetracyclines.
Addition of gentamicin to solutions containing bicarbonate may lead to the release of carbon dioxide.

### 6.3 Shelf life

The expiry date of the product is indicated on the packaging materials.

*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

Do not store above 25˚c.

### 6.5 Nature and contents of container

For Gentamicin B. Braun 3 mg/ml:
Bottles of low-density polyethylene containing 80 ml (3 mg/ml) and 120 ml (3 mg/ml).
10 x 80 ml
20 x 80 ml
10 x 120 ml
20 x 120 ml

Not all package sizes may be marketed.

### 6.6 Special precautions for disposal

Gentamicin B. Braun 3 mg/ml 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. MANUFACTURER

B.Braun Melsungen AG, Carl-Braun str. 1, D-34212 Melsungen, Germany

## 8. REGISTRATION HOLDER

Lapidot Medical Import and Marketing Ltd.
8 Hashita St. Industrial Park Caesarea, 38900, Israel

## 9. MARKETING AUTHORISATION NUMBER

Gentamicin B. Braun 3 mg/ml Registration no.: 148 90 33563 00

*Revised in August 2025.*