767+768/12612384/0113

Directions for Use

B. Braun Melsungen AG, 34209 Melsungen, Germany

Gentamicin B. Braun 1 mg/ml

solution for infusion

Gentamicin B. Braun 3 mg/ml

solution for infusion

Composition

Gentamicin B. Braun 1 mg/ml:

1 ml of solution for infusion contains gentamicin sulphate equivalent to 1 mg gentamicin.
1 bottle of 80 ml contains 80 mg of gentamicin.

Excipients:

283 mg (12 mmol) of sodium (as chloride) per 80 ml bottle
Water for injections

Gentamicin B. Braun 3 mg/ml:

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.
Disodium edetate
Water for injections

Pharmaceutical form

Solution for infusion
A clear colourless aqueous solution

Pharmaco-therapeutic group

Other aminoglycosides, ATC code: J01GB03

Indications

For the treatment of serious infections caused by susceptible microorganisms.

Gentamicin B. Braun 1 mg/ml and 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 1 mg/ml and 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.

Contraindications

- Hypersensitivity to gentamicin or other aminoglycosides or to any of the excipients
- Myasthenia gravis.

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 "Dosage").

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 "Undesirable effects").

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 "Undesirable effects").

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 "Undesirable effects").

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 "Undesirable effects").

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. Drugs that inhibit peristalsis must not be given (see section 4.8).

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.

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.

Cross resistance and hypersensitivity to aminoglycosides may occur.

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.

Gentamicin B. Braun 1 mg/ml: This medicinal product contains 283 mg of sodium per bottle solution for infusion. To be taken into consideration by patients on a controlled sodium diet.
Gentamicin B. Braun 3 mg/ml: This medicinal product contains 283 mg/425 mg of sodium per 80 ml/120 ml bottle solution for infusion. To be taken into consideration by patients on a controlled sodium diet.

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 oxotoxic 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.

Other forms of interaction

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 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.

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.

Lactation

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 lactation 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.

Driving 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.

Dosage

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 intake 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 (see section 4.4).

Paediatric patients

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 bottle of Gentamicin 1 mg/ml solution for infusion (Gentamicin 3 mg/ml solution for infusion) contains 80 mg gentamicin (240 mg gentamicin) To avoid overdosing especially in children, Gentamicin 1 mg/ml solution for infusion (Gentamicin 3 mg/ml solution for infusion) should not be administered to children who need less than 80 mg gentamicin (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. This is why gentamicin serum levels should be determined and the dosage for the given patient can then be adapted.

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2 Seiten

Gentamicin B. Braun 1+3 mg/ml
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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/s)	Dose and dosage interval
< 6.7	> 1.2	80* mg every 8 hours
6.7 – 16.7	0.5 – 1.2	80* mg every 12 hours
16.7 – 33.3	0.2 – 0.5	80* mg every 24 hours
> 33.3	0.1 – 0.2	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. Samples are taken at the end of a dosing interval (trough level). Trough levels should not exceed 2 µg/ml administering gentamicin twice daily and 1 µg/ml for a once daily dose.

Method of administration

Only for intravenous use.

Gentamicin B. Braun 1 mg/ml solution for infusion and Gentamicin B. Braun 3 mg/ml solution for infusion is administered by intravenous infusion over a period of 30 – 60 minutes. Gentamicin B. Braun 1 mg/ml and Gentamicin B. Braun 3 mg/ml are not suitable for intramuscular or slow intravenous injection.

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 **"Interactions"**), the administration of calcium chloride is advisable and artificial respiration if required.

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).

Additional adverse events of unknown incidence include:

Infections and infestations:	
Very rare	Superinfection (with gentamicin-resistant germs), pseudomembranous colitis (see also section "Special warnings and precautions for use")[1]
Blood and lymphatic system disorders:	
Uncommon	Dyscrasia
Very rare	Thrombocytopaenia, reticulocytopaenia, leukopaenia, eosinophilia, granulocytopaenia, anaemia
Immune system disorders:	
Very rare	Hypersensitivity reactions of varying severity, ranging from rash and itching, drug fever to severe acute hypersensitivity reactions (anaphylaxis), up to anaphylactic shock[7]
Metabolism and nutrition disorders:	
Rare	Hypokalaemia, hypocalcaemia, hypomagnesaemia, pseudo-Bartter syndrome in patients treated with high doses over a long period (more than 4 weeks), loss of appetite
Very rare	Hypophosphataemia
Psychiatric disorders:	
Very rare	Confusion, hallucinations, mental depression
Nervous system disorders:	
Rare	Polyneuropathies, peripheral paraesthesias
Very rare	Encephalopathy, convulsions, neuromuscular blockage, dizziness, vertigo, equilibrium disorder, headache (see also section "Special warnings and precautions for use")
Eye disorders:	
Very rare	Visual disorders
Ear and labyrinth disorders:	
Very rare	Vestibular damage, hearing loss, Meniére`s disease, tinnitus (see also section "Special warnings and precautions for use")
Vascular disorders:	
Very rare	Hypotension, hypertension
Gastrointestinal disorders:	
Rare	Vomiting, nausea, salivation increased, stomatitis,
Skin and subcutaneous tissue disorders:	
Uncommon	Allergic skin exanthema
Rare	Skin reddening
Very rare	Toxic epidermal necrolysis[2], Stevens-Johnson syndrome[2], Erythema multiforme[2], Alopecia
Musculoskeletal and connective tissue disorders:	
Rare	Muscle pain (myalgia)
Very rare	Amyostasia
Renal and urinary disorders:	
Common	Renal function impairment
Very rare	Acute renal failure, hyperphosphaturia, aminoaciduria, Fanconi-like syndrome in patients treated with a prolonged course of high-dose
	See also section "Special warnings and precautions for use"
General disorders and administration site conditions:	
Rare	Increased body temperature
Very rare	Pain at injection site
Investigations:	
Rare	Aspartate aminotransferase (AST) increased, Alanine aminotransferase (ALT) increased, alkaline phosphatase (ALP) increased, blood urea nitrogen increased (all reversible), weight loss

[1] Usually in these cases other antibiotics are also involved.
[2] May occur as hypersensitivity reactions.

Note:

Patients should inform their doctor or pharmacist if they notice any side effect not mentioned in this leaflet.

Expiry date

The product must not be used beyond the expiry date stated on the labelling.

Instructions for storage / use / handling

Do not store above 25°C.

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

For single use only. 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.

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 further information please refer to section "dosage".

Licence number

Gentamicin B. Braun 1 mg/ml Registration no.: 149 06 33562 00
Gentamicin B. Braun 3 mg/ml Registration no.: 148 90 33563 00

Manufacturer:

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License Holder:

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