Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Gentamicin 20 mg/mL Solution for injection/infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each mL of solution contains 20 mg of gentamicin (as gentamicin sulfate).
Each ampoule of 2 mL solution contains 40 mg gentamicin.

Excipient(s) with known effect
Each mL solution contains 1.60 mg sodium metabisulfite

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for injection/infusion

Clear and colourless solution.

pH 3.00-5.50

Osmolality : 80 – 90 mOsm/kg

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Gentamicin is an aminoglycoside antibiotic with broad-spectrum bactericidal activity. It is indicated in adults and children including neonates.
Gentamicin is indicated for the treatment of severe infections caused by pathogens susceptible to gentamicin.

Under these conditions, gentamicin can be used for:

- urinary tract infections
- bacterial endocarditis
- intra-abdominal infections
- meningitis caused by Gram-negative pathogens
- osteomyelitis and bacterial arthritis
- management of neutropenic patients with fever that is suspected to be due to a bacterial infection
- Hospital-acquired and Ventilator-associated Pneumonia (HAP and VAP)
- listeriosis
- severe neonatal infections.

Treatment of patients with bacteraemia that occurs in association with, or is suspected to be associated with, any of the infections listed above.

Note:
Combination treatment is mainly indicated together with a beta-lactam antibiotic or with an antibiotic effective against anaerobic bacteria for life-threatening infections with an unknown pathogen, for mixed anaerobic/aerobic infections, for bacterial endocarditis, for systemic Pseudomonas infections and in neutropenic patients with fever that is suspected to be due to a bacterial infection.

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

4.2 Posology and method of administration

Posology
The dose depends on the severity of the clinical picture, the setting, the patient's renal function and the type of infection. Several presentations of gentamicin are available, some of which are more suitable for high doses to be administered intravenously. The dose is expressed in terms of the patient's body weight.

The recommended daily dose in adolescents and adults with normal renal function should preferably be given as a single dose, or else divided into 2 separate doses.
A dosing frequency of more than twice daily may be adopted for some specific pathogens or some sites of infection as recommended in national and local guidance.

Once daily dosing is not recommended in cases of endocarditis, depending on the responsible pathogens. National and local guidance on treatment with gentamicin and serum level monitoring in endocarditis should be followed.

Dose calculations should be based on ideal body weight.

Recommendations for dosage
Posology (adults and adolescents)

Recommended dose: 3 – 6 mg gentamicin / kg / day

Subsequent doses should be adjusted according to serum concentration levels (see "Monitoring advice") using local guidance or nomograms.

Dosage in impaired renal function

Gentamicin is mainly excreted by glomerular filtration. Thus, the dosage for patients with impaired renal function must be adjusted accordingly.
Dose adjustments in patients with renal impairment should also be based on therapeutic drug monitoring. For patients on once daily dose regimens, a prolongation of the dose interval is generally recommended. The initial dose interval should be at least 24 hours and extended according to the degree of renal impairment and the results of serum gentamicin monitoring. Limited data are available in patients with severe renal impairment (creatinine clearance < 30 mL / min) for once daily dose administration.

Dose adjustment
Nomograms are available for the calculation of dose or dose interval, which depends on the patient's age, weight and renal function and plasma concentrations. Local guidance should be followed where available. If nomograms or local guidance are not available the following may be used:

For dosage adjustment, there are two possibilities:

A. Prolongation of the dosing interval while maintaining the same dose (subsequent doses identical to the initial dose).

B. Reduction of the dose while maintaining the same dosing intervals (subsequent doses smaller than the initial dose).

For patients on once daily dosing, prolonging the dose interval is preferable. For patients on multiple daily dosing, reduction of the dose is preferred.

The following table provides a guideline for reducing the dose whilst maintaining the same dosing intervals (8-hour dosing interval):

Serum creatinine (mg / 100 mL)	**Creatinine clearance (mL / min / 1.73 m^2)**	**Subsequent doses (percentage of the initial dose)**
less than 1.0	more than 100	100
1.1 – 1.3	71 – 100	80

1.4 – 1.6	56 – 70	65
1.7 – 1.9	46 – 55	55
2.0 – 2.2	41 – 45	50
2.3 – 2.5	36 – 40	40
2.6 – 3.0	31 – 35	35
3.1 – 3.5	26 – 30	30
3.6 – 4.0	21 – 25	25
4.1 – 5.1	16 – 20	20
5.2 – 6.6	11 – 15	15
6.7 – 8.0	less than 10	10

It must also be remembered that renal function may change during the course of treatment.

Creatinine clearance should be preferred as a parameter especially in patients with fluctuating plasma creatinine concentrations, such as those observed in severe infections (e.g. sepsis).

If serum creatinine values only are known, creatinine clearance can be estimated using the following formulae:

Men:

$$Clcr = \frac{\text{Body weight in (kg) x (140 minus years of life)}}{72 \times \text{serum creatinine (mg / 100 mL)}}$$

or

Men:

$$Clcr = \frac{\text{Body weight in (kg) x (140 minus years of life)}}{0.814 \times \text{serum creatinine (µmol / L)}}$$

Women: 0.85 x the above value

If serum creatinine values are used for assessing renal function, these values should be taken several times, as correlation to creatinine clearance values exists only when impaired renal function remains the same.

Paediatric population

The daily dose recommended in children aged 1 year and above with normal renal function, is 3 – 6 mg / kg / day as one single dose (preferred) or two divided doses.The recommended daily dose in children after the first month of life is 4.5 – 7.5 mg / kg per day and should be preferably given as a single dose, or else divided into 2 separate doses. The recommended daily dose in newborn infants is 4 – 7 mg / kg body weight per day. Due to the longer half-life, newborn infants are given the required dose as a single dose.

Particular attention must be paid to the preparation (dilution) and amount administered. Any error, however minor, can have a major impact on the serum concentrations obtained.

Elderly

There is some evidence that elderly patients may be more susceptible to aminoglycoside toxicity whether secondary to previous auditory/vestibular impairment or borderline renal dysfunction. Accordingly, therapy should be closely monitored by frequent determination of gentamicin serum levels, assessment of renal function and signs of ototoxicity. If renal function is impaired, the daily recommended dose should be reduced and adjusted to renal function.

Hepatic impairment

In cases of hepatic impairment, gentamicin may be prescribed and no dosage adjustment is necessary.

Dosage for haemodialysis patients

Gentamicin is dialysable. A haemodialysis session lasting 4 – 5 hours or 8 – 12 hours can be expected to reduce concentrations by 50 – 60 % and 70 – 80 %, respectively. After each dialysis session, the patient must be given individual booster doses, based on current gentamicin serum concentrations. Normally, the recommended dose after dialysis is 1 – 1.7 mg / kg body weight.

As haemodialysis patients are usually on anticoagulant therapy, intramuscular injections must not be given in such cases, due to the risk of haematoma formation.

Obese patients

Dose calculations should be based on ideal body weight. In cases of significant obesity gentamicin serum concentrations should be closely monitored.

Monitoring advice
Regular serum concentration monitoring of gentamicin is recommended for all patients, and especially in the elderly, newborns, obesity and in patients with impaired renal function, as well as in patients with cystic fibrosis. Gentamicin should not be prescribed if serum concentrations cannot be monitored.

There are no universally accepted guidelines for therapeutic drug monitoring of gentamicin. Local monitoring and dose adjustment guidelines should be followed where available. The following is commonly recommended: Pre-dose ("trough level") monitoring is recommended to ensure that the interval between doses is correct. Trough levels are measured at the end of a dosing interval and should not exceed 1 mg / L for once daily dosing or 2 mg / L for multiple daily dosing. Levels in excess of these indicate the need to extend the interval between doses, not reduction of the dose.

Post-dose ("peak level") monitoring is recommended to check the adequacy of a dose or to ensure that it is not excessive and likely to cause toxicity. Peak levels should be measured one hour after an intravenous bolus or intramuscular bolus dose, or 30 minutes after the end of an infusion. A plasma concentration < 4 mg / L indicates that the dose is likely to be inadequate and a dose increase should be considered; plasma concentrations > 10 mg / L indicate an increased risk for toxicity, particularly ototoxicity, and a dose reduction should be considered.

Any change in dose should be re-assessed with pre- and post-dose levels to confirm the adequacy of the new dose and the appropriateness of the dose interval.

Method of administration

For intramuscular, intravenous injection or for intravenous infusion after dilution. The same dosage schedule is recommended for intramuscular and intravenous dosing. Intramuscular administration should be considered when the intravenous route is not possible or less appropriate for the patient.

Gentamicin can, if medically indicated, be injected directly into the vein in undiluted form; the injection must be given slowly over 2 – 3 minutes. Rapid, direct intravenous administration may give rise, initially, to potentially neurotoxic concentrations and it is essential that the prescribed dose is administered over the recommended period of time.
Alternatively the prescribed dose should be dissolved in up to 100 mL of sodium chloride 9 mg / mL (0.9 %) solution for injection or glucose 50 mg / mL (5 %) solution for injection and the solution infused over no longer than 20 minutes. The injection/infusion must not be administered together with other medicinal substances (see also section 6.2).

4.3 Contraindications

-Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- Subcutaneous administration, due to the lack of efficacy and onset of necrosis at the injection site.

4.4 Special warnings and precautions for use

Warnings
In cases of advanced renal impairment or pre-existing inner ear deafness, gentamicin should only be used for life-threatening indications. As gentamicin has neuromuscular-blocking properties, particular vigilance is required in patients with pre-existing neuromuscular disease (e.g. myasthenia gravis, Parkinson's disease). This also applies to patients concomitantly receiving muscle relaxants (e.g. with perioperative administration of gentamicin).
Diabetes, auditory vestibular dysfunctions, otitis media, a history of otitis media, previous use of ototoxic medicinal products and a genetically determined high sensitivity to aminoglycoside induced ototoxicity, are other main factors which may pre-dispose the patients to toxicity.

Renal and vestibulocochlear damage

Impaired renal function
Clinical signs of kidney damage are: proteinuria, cylindruria, haematuria, oliguria, increased blood concentrations of creatinine and urea. In isolated cases, acute kidney failure may occur (see section 4.8).

Effects on the vestibulocochlear nerves
Damage to the vestibulocochlear nerves (eighth cranial nerve), where balance and hearing are affected, is possible. Vestibular damage is the most common ototoxic reaction. Hearing loss is initially manifested by reduced high-frequency acuity and is usually irreversible.
Symptoms of ototoxicity are: dizziness, ringing/whistling noises (tinnitus), vertigo, loss of balance and less commonly, loss of hearing (see section 4.8). In patients with end-stage renal failure, on intermittent haemodialysis or chronic peritoneal dialysis, toxicity is mainly auditory, as the kidneys are no longer functional.

Paediatric population
According to the data available, renal and auditory toxicities remain rare in newborn infants and children.

Risk factors
Risks for the development of renal and auditory toxicities increase with treatment periods of more than 5 – 7 days, even in healthy subjects; the risk is greater in patients with renal impairment. Nevertheless, early toxicity can even appear with the very first doses.

Renal toxicity is independent of the peak plasma concentration obtained (C_{max}). With regard to auditory and vestibular toxicities, there is no evidence of a correlation with the peak plasma concentration level obtained, even when treatment is administered as a single daily dose.

The main risk factors for nephrotoxicity (and, in some patients, ototoxicity) are:
the most common clinical situations favouring renal hypoperfusion and accompanied by less elimination of aminoglycosides
-age > 75 years (physiological change in renal function, starting from 60 years of age),
-dehydration, often age-related,
-combination with certain medicinal products, especially loop diuretics (see section 4.5),
-left ventricular failure, hypovolaemia, state of shock,
-hypoalbuminaemia,
-grade B and C cirrhosis according to Child-Pugh's classification,

clinical situations that increase the risk of kidney damage
-pre-existing or concomitant nephropathy,
-combination with certain medicinal products (see section 4.5).

Diarrhoea associated with antibiotics and pseudomembranous colitis
Antibiotic-related diarrhoea and pseudomembranous colitis have been observed during gentamicin use. Such diagnosis must be considered in any patient developing diarrhoea during or after treatment. Gentamicin must be discontinued if severe and/or bloody diarrhoea develops during treatment and appropriate therapy must be initiated. Medicinal products that inhibit peristalsis must not be administered (see section 4.8).

Precautions

To avoid adverse drug reactions, continuous monitoring of renal function (serum creatinine, creatinine clearance before, during and after administration) and checks on vestibular and cochlear function, as well as hepatic and laboratory parameters, are recommended.

-Monitoring of serum gentamicin (Please see section 4.2).
-If possible, restrict the duration of treatment to 10 – 14 days.
-Avoid a new course of aminoglycoside therapy immediately after a previous course of aminoglycoside treatment: 7 – 14-day treatment-free interval if possible.
-If possible, no co-administration of other potential oto- and nephrotoxic substances. If this cannot be avoided, particularly close monitoring of renal function is indicated.
-Ensure adequate hydration and urine production.

Single daily dose
Data on the single daily dose (SDD) show that this method of prescription:
-optimises pharmacokinetic-pharmacodynamic parameters (see section 5.1),
-promotes tissue diffusion,
-has a clinical efficacy at least identical to that obtained following administration divided into several daily injections,
-is responsible for renal and auditory toxicities comparable to or even less than those observed with other methods of administration,
-decreases the risk for the emergence of resistant mutant strains.

This medicinal product contains:
-Sodium metabisulfite which may rarely cause severe hypersensitivity reactions and bronchospasm.
-Sodium: This medicinal product contains less than 1 mmol sodium (23 mg) per ampoule, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interactions

Concurrent administration of gentamicin and other potentially ototoxic or nephrotoxic medicinal products should be avoided. If such combinations are necessary, monitoring of auditory/renal function must be increased.

Contraindicated combinations: Other aminoglycosides in concomitant administration is contraindicated due to increased risk of nephrotoxicity and ototoxicity.

Combinations not recommended
+ Polymyxin B: Additive nephrotoxic effects. If the combination cannot be avoided, the bacteriological justification for its use should be beyond dispute and strict surveillance is required.

+ Botulinum toxin: Risk of potentiation of the effects of botulinum toxin with aminoglycosides (extrapolated from effects observed with botulism). Use another antibiotic.

Combinations requiring precautions for use
+ Cephalothin: It has been argued that cephalothin increases the nephrotoxicity of aminoglycosides.
Monitoring of renal function.

+ Non-depolarising muscle relaxants: Potentiation of non-depolarising muscle relaxants when the antibiotic is administered parenterally and/or peritoneally before, during or after the neuromuscular blocking agent.
Monitor the degree of muscle relaxation at the end of anaesthesia.

+ Loop diuretics: Increased nephrotoxic and ototoxic risks due to the aminoglycoside (functional renal impairment associated with diuretic-induced dehydration).
Combination is possible together with monitoring of hydration status, renal and vestibulocochlear functions, aminoglycoside plasma concentrations.

Combinations to be taken into account
+ Other aminoglycosides in consecutive administration: The risk of cumulative ototoxicity must be taken into account.

+ Amphotericin B, administered IV: Increased risk of nephrotoxicity.

+ Ciclosporin: Greater increase in serum creatinine than with ciclosporin alone, with an increased nephrotoxic risk.

+ Organoplatinum compounds: Additive nephrotoxic and/or ototoxic effects, especially in cases of previous renal impairment. With medicinal products containing cisplatin, it should be remembered that the nephrotoxicity of gentamicin may be increased for a further 3 to 4 weeks after administration of these substances.

+ Tacrolimus: Greater increase in serum creatinine than with tacrolimus alone (synergy of nephrotoxic effects of both substances).

+ Methoxyflurane anaesthesia: Aminoglycosides may increase the nephrotoxic effect of methoxyflurane. Extremely severe nephropathies are possible in concomitant use.

+ Indometacin: possibly increases plasma concentrations of gentamicin in neonates.

+ Anticoagulants: concurrent use with oral anticoagulants may increase the hypothrombinanaemic effect.

+ Bisphosphonates: concurrent use with bisphosphonates may increase the risk of hypocalcaemia.

+ Iodinated contrast media, methotrexate, antiviral agents (e.g. the "–ciclovir" group, foscarnet), pentamidine may increase the risk of nephrotoxicity.

+ Combination with antibiotics of the glycopeptide group, such as vancomycin and teicoplanin, would increase the risk of vestibulocochlear damage.

+ Antagonism of effect may occur with concomitant administration of gentamicin with either neostigmine or pyridostigmine.

+ Digoxin: Gentamicin has been known to increase serum digoxin levels.

Gentamicin/other antibiotics

Combination therapy with appropriate antibiotics (e.g. with beta-lactams) can lead to a synergistic effect. Synergistic effects have been described with acylamino penicillins on *Pseudomonas aeruginosa*, with ampicillin on enterococci and with cephalosporins on *Klebsiella pneumoniae*.

Specific problems of INR imbalance
Numerous cases of increased vitamin K antagonist activity have been reported in patients receiving antibiotics. The marked infectious or inflammatory context, along with the patient's age and general state, appear to be risk factors. In such circumstances, it seems difficult to distinguish whether the onset of INR imbalance is due to the infectious disease itself or its treatment. However, certain antibiotic groups are more implicated than others, especially fluoroquinolones, macrolides, cyclins, cotrimoxazole and certain cephalosporins.

4.6 Fertility, pregnancy and lactation

Pregnancy
There are no adequate data on the use of gentamicin during pregnancy. Studies in animals have shown a toxic effect on reproduction for gentamicin (see section 5.3).

Gentamicin penetrates the placental barrier and reaches measurable concentrations in foetal tissue and in the amniotic fluid. There is a potential risk that gentamicin may lead to damage of the inner ear and kidney in the foetus, hence assessment of neonatal auditory function is desirable (otoacoustic emissions).

For these reasons, gentamicin should, in principle, only be used during pregnancy for life-threatening indications and when no safer therapeutic alternatives are available.

Breastfeeding
Small amounts of gentamicin are excreted in human milk and low concentrations have been found in the serum of breastfed infants. A decision must be made whether to stop breastfeeding or whether to discontinue or not to give gentamicin.Diarrhoea and mucosal colonisation by yeast-like fungi may occur in breastfed infants. The possibility of sensitisation should be considered.

Fertility
There are no human data on the effect of gentamicin on fertility. In animals, adverse effects of gentamicin on male fertility have been documented (see section 5.3). Men should be advised not to father a child while receiving treatment and must use effective contraception during and up to 3 months after treatment. Before starting treatment, male patients should be advised to seek counselling on sperm storage.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed.

As this treatment is likely to induce impaired balance, drivers and operators of machinery should be warned of this potential risk.

4.8 Undesirable effects

Tabulated list of adverse reactions

Those adverse reactions deemed most likely to be treatment-related are listed below by organ and by frequency. Frequencies are defined as:

Very common (≥1/10);
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);
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)**	**Not known (cannot be estimated from the available data)**
Infections and infestations				Superinfection (with gentamicin-resistant germs), pseudo-membranous colitis (see section 4.4)[1]	
Blood and lymphatic system disorders		Dyscrasia		Thrombocytopenia, reticulocytopenia, leukopenia, eosinophilia, granulocytopenia, anaemia	
Immune system disorders				Hypersensitivity reactions of varying degrees of severity, ranging from rash and pruritus, drug-induced fever	

				to severe acute hypersensitivity reactions (anaphylaxis) and even anaphylactic shock	
Metabolism and nutrition disorders			Hypokalaemia, hypocalcaemia, hypomagnesaemia, Bartter's syndrome in patients treated at high doses over a long period (more than 4 weeks), loss of appetite, weight loss	Hypophosphataemia	
Psychiatric disorders				Confusion, hallucinations, depression	
Nervous system disorders			Polyneuropathies, peripheral paraesthesia	Encephalopathy, seizures, neuromuscular block, dizziness, vertigo, impaired balance, headache (see section 4.4)	Lethargy
Eye disorders				Visual disturbances	
Ear and labyrinth disorders				Vestibular damage, hearing loss, Meniere's disease, tinnitus (see section 4.4)	Irreversible hearing loss, deafness
Vascular disorders				Hypotension, hypertension	
Gastrointestinal disorders			Vomiting, nausea, increased salivation, stomatitis		
Hepatobiliary disorders			Aspartate aminotransferase (AST) increased, alanine aminotransferase (ALT) increased, alkaline phosphatase (ALP) increased, (all reversible) serum bilirubin increased		
Skin and subcutaneous tissue disorders		Allergic skin rash	Skin redness	Lyell's syndrome[2], Stevens-Johnson syndrome[2], erythema multiforme, alopecia	Urticaria, Purpura
Musculoskeletal and connective tissue disorders			Muscle pain (myalgia)	Amyostasia	
Renal and urinary disorders	Impaired renal function		Blood nitrogen increased (reversible)	Acute kidney failure, hyperphosphaturia, aminoaciduria, Fanconi syndrome in patients receiving prolonged, high-dose treatment (see section 4.4)	
General disorders and administration site conditions			Body temperature increased	Injection site pain	

[1] Generally, in these cases, other antibiotics are also involved.

[2] 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. Healthcare professionals are asked to report any suspected adverse reactions via the
HPRA Pharmacovigilance
Website: www.hpra.ie..

4.9 Overdose

Gentamicin has a narrow therapeutic index. In the event of accumulation (e.g. as a result of impaired renal function), renal damage and damage to the vestibulocochlear nerve may occur. Renal damage is correlated to trough levels of more than 4 mg / L.

Treatment in case of overdose:
Discontinue medication. There is no specific antidote. In the event of an overdose or toxic reaction, peritoneal dialysis or haemodialysis will lower serum gentamicin levels.

In the event of neuromuscular blockade (mostly caused by interactions, q.v. for details), administration of calcium chloride is appropriate; if necessary, artificial ventilation.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Aminoglycoside Antibacterials; Other aminoglycosides
ATC code: J01GB03

Mechanism of action
For gentamicin, the mechanism of action is based on interference with protein biosynthesis at the bacterial ribosome, due to interaction with the rRNA and subsequent inhibition of translation. This results in a bactericidal action. It is bactericidal with greater antibacterial activity than streptomycin, neomycin or kanamycin.

In general, Gentamicin is active against many aerobic gram-negative bacteria and some aerobic gram-positive bacteria. Gentamicin is inactive against fungi, viruses, and most anaerobic bacteria.

PK/PD relationship

Efficacy largely depends on the ratio between the peak serum concentration (C_{max}) and minimum inhibitory concentration (MIC) of the pathogen.

Mechanism of resistance
Resistance to gentamicin can be based on the following mechanisms:

- Enzymatic inactivation: Enzymatic modifications of aminoglycoside molecules are the most common mechanism of resistance. For this, acetyltransferases, phosphotransferases or nucleotidyltransferases are responsible, which are mostly plasmid-encoded.

- Reduced penetration and active efflux: These resistance mechanisms are mainly found in *Pseudomonas aeruginosa*.

- Change in target structure: Modifications within the ribosomes occur as a cause of resistance. These occur either due to mutation or the formation of methyltransferases.

Gentamicin is largely cross-resistant to other aminoglycoside antibiotics.

Breakpoints

Gentamicin is tested using the standard dilution series. The following minimum inhibitory concentrations for susceptible and resistant germs have been established:

EUCAST (European Committee on Antimicrobial Susceptibility Testing) breakpoints (version 10.0, 2020-01-01):

Pathogen	Susceptible	Resistant
Enterobacterales (systemic infections) [1]	≤ 2 mg / L	> 2 mg / L
Enterobacterales (infections originating from the urinary tract)	≤ 2 mg / L	> 2 mg / L
Pseudomonas *spp*. (systemic infections)	IE[3]	IE[3]
Pseudomonas *spp*. (infections originating from the urinary tract)	IE[3]	IE[3]
Acinetobacter *spp*. (systemic infections) [1]	≤ 4 mg / L	> 4 mg / L
Staphylococcus aureus	≤ 1 mg / L	> 1 mg / L
Coagulase-negative staphylococci	≤ 1 mg / L	> 1 mg / L
Enterococcus spp. (test for high-level aminoglycoside resistance)	Note[2]	Note[2]
Viridans group streptococci (test for high level aminoglycoside resistance)	Note[2]	Note[2]
Haemophilus influenzae	IE[3]	IE[3]
Moraxella catarrhalis	IE[3]	IE[3]
PK-PD (Non-species related) breakpoints	≤ 0.5 mg / L	> 0.5 mg / L

[1] For systemic infections, aminoglycosides must be used in combination with other active therapy. In this circumstance, the breakpoint/ECOFF in brackets can be used to distinguish between organisms with and without acquired resistance mechanisms. For isolates without resistance mechanisms, include a comment in the report: "Aminoglycosides are often given in combination with other agents, either to support the activity of the aminoglycoside or to broaden the spectrum of therapy. In systemic infections, the aminoglycoside must be supported by other active therapy." For more information, see http://www.eucast.org/guidance_documents/.

[2] Gentamicin can be used to screen for high-level aminoglycoside resistance (HLAR). Negative test: Isolates with gentamicin MIC ≤ 128 mg / L or a zone diameter ≥ 8 mm. The isolate is wild type for gentamicin and low-level intrinsic resistant. For other aminoglycosides, this may not be the case. Synergy with penicillins or glycopeptides can be expected if the isolate is susceptible to the penicillin or glycopeptide. Positive test: Isolates with gentamicin MIC > 128 mg / L or a zone diameter

[3] Insufficient evidence that the organism or group is a good target for therapy with the agent

Prevalence of acquired resistance

The prevalence of acquired resistance for individual species may vary geographically and over time.
Hence, local information on the resistance situation is required, especially for the adequate treatment of severe infections. If, based on the local resistance situation, the efficacy of gentamicin is questionable, expert therapeutic advice should be sought. Particularly in the case of serious infections or treatment failure, a microbiological diagnosis - with detection of the pathogen and its susceptibility to gentamicin - should be sought.

Commonly susceptible species
Aerobic Gram-positive micro-organisms
Staphylococcus aureus *Staphylococcus saprophyticus*°
Aerobic Gram-negative micro-organisms
Acinetobacter pittii *Citrobacter freundii* *Enterobacter aerogenes* *Enterobacter cloacae* *Escherichia coli*# *Klebsiella oxytoca* *Klebsiella pneumoniae* *Proteus vulgaris* *Proteus mirabilis* *Salmonella enterica* (Enteritis-Salmonellen) *Serratia liquefaciens*° *Serratia marcescens*

Species for which acquired resistance may be a problem
Aerobic Gram-positive micro-organisms
Staphylococcus epidermidis+
Staphylococcus haemolyticus+
Staphylococcus hominis
Aerobic Gram-negative micro-organisms
Acinetobacter baumannii
Morganella morganii
Pseudomonas aeruginosa
Inherently resistant organisms
Aerobic Gram-positive micro-organisms
Enterococcus spp.§
Streptococcus spp.§
Aerobic Gram-negative micro-organisms
Burkholderia cepacia
Legionella pneumophila
Stenotrophomonas maltophilia
Anaerobic micro-organisms
Bacteroides spp.
Clostridium difficile
Others
Chlamydia spp.
Chlamydophila spp.
Mycoplasma spp.
Ureaplasma urealyticum

° At the time of publication of the table, no current data where present. In primary literature, standard references and therapy recommendations, the susceptibility is assumed.
+ In at least one region, the resistance rate is over 50%.
§ Clinical effect proven in combination with penicillin for the therapy of enterococcal and streptococcal endocarditis, when no high grade resistance (Enterococci) exists.
 # At intensive care units, the resistance rate is ≥10%.

5.2 Pharmacokinetic properties

Absorption

Like all aminoglycoside antibiotics, there is virtually no absorption of gentamicin by healthy intestinal mucosa after oral administration. Thus, therapeutic use is parenteral, i.e. intravenous or intramuscular.

Upon intramuscular administration of 1 mg/kg body weight, mean peak gentamicin concentrations of 3.5 – 6.4 mg / L are measured after 30 – 60 minutes. After a short intravenous infusion of 15-30 minutes, serum concentrations similar to those after intramuscular administration are measured after one hour.

Therapeutic serum concentrations are generally between 2 and 8 mg / L. Peak serum concentrations of 10-12 mg / L should not be exceeded in conventional administration, several times a day. Prior to re-administration, the serum concentration should have fallen to less than 2 mg / L in patients on conventional administration, several times a day. The trough level should be less than 1 mg / L with once-daily administration.

Distribution

For gentamicin, the volume of distribution is roughly equivalent to the volume of extracellular water. In newborn infants, water accounts for 70 to 75 % of body weight, compared with 50 to 55 % in adults.

The extracellular 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 premature infants to 0.25 L / kg for adolescents. The larger volume of distribution per kg body weight in newborn infants means that, for an adequate peak concentration in blood, a higher dose per kg body weight must be administered.

Distribution of gentamicin to the individual organs leads to various tissue concentrations, with the highest concentrations present in renal tissue. Lower concentrations are found in the liver and gallbladder, lung and spleen. No gentamicin is detectable in the cerebral and nerve tissue after parenteral administration and no measurable concentrations are found in the bones during short-term treatment. Gentamicin does not penetrate the prostate.

After repeated injection of gentamicin, approximately 50 % of attainable plasma concentrations are measured in the synovial, pleural, pericardial and peritoneal fluid. Passage of gentamicin into the cerebrospinal fluid is minimal, even when the meninges are inflamed (up to 20 % of corresponding plasma concentrations).

Gentamicin crosses the placenta. Foetal concentrations may amount to 30 % of maternal plasma concentrations. Small amounts of gentamicin are excreted in human milk (where concentrations are 1/3 those in maternal plasma).

Plasma protein binding: less than 10 %.

Systemic absorption of gentamicin and other aminoglycosides has been reported after topical use on denuded skin and burns and following instillation into and irrigation of wounds, body-cavities, and joints.

Biotransformation and Elimination

Gentamicin is not metabolised in the body, but rather excreted unchanged in microbiologically active form mainly via the kidneys by glomerular filtration. The elimination half-life in patients with normal renal function is about 2 3 hours.

The elimination rate constant is:
1. 0.02 hr^{-1} for anuric patients*
2. 0.30 hr^{-1} normal
* Therefore, in those with anuria care must be exercised following the usual initial dose, any subsequent administration being reduced in-line with plasma concentrations of gentamicin.

In newborn infants, the elimination rate is reduced due to immature renal function. The mean elimination half-life is about 8 hours in newborn infants up to a gestational age of 26 to 34 weeks, compared with about 6.7 hours in newborn infants with a gestational age of 35 to 37 weeks. Accordingly, clearance values increase from about 0.05 L / h in newborn infants with a gestational age of 27 weeks to 0.2 L / h in newborn infants with a gestational age of 40 weeks.

Gentamicin accumulates in the tubular cells of the renal cortex. A terminal half-life around 100 – 150 hours results from release of gentamicin from this deep compartment.

Excretion is not dose-dependent. Well over 90 % of the substance is excreted via the kidneys. Only about 2 % of the administered dose is excreted extrarenally in patients with normal renal function. Total clearance is approximately 0.73 mL / min^{-1} / kg^{-1}. Bile concentrations are generally low, reflecting poor biliary elimination.

If renal function is impaired, the elimination half-life is prolonged depending on the degree of renal impairment. Maintenance of the usual dosage regimen leads to accumulation. Gentamicin is totally dialysable.

During extracorporeal haemodialysis, depending on the duration of dialysis, 50-80% of gentamicin is removed from the serum. Peritoneal dialysis is also possible; in which case, the elimination half-lives are between 12.5 and 28.5 hours.

5.3 Preclinical safety data

Chronic toxicity
In chronic toxicity studies (IM application) on various animal species, nephrotoxic and ototoxic effects were observed at high dosages.

Mutagenic and tumorigenic potential
Gentamicin showed no mutagenic potential in various test systems (*in vitro* and *in vivo*).

No long-term animal studies on the tumorigenic potential of gentamicin have been conducted.

Toxicity to reproduction
For the class of aminoglycoside antibiotics, there is a potential risk of inner ear and renal damage in the foetus. There are reports of foetal kidney damage in rats and guinea pigs after treatment of the dams with gentamicin.

Impairment of fertility
Gentamicin showed negative effects on sperm parameters and testis apoptosis in rats.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Disodium edetate
Sodium metabisulfite (E223)
Sodium Hydroxide 1 N (for pH-adjustment)
Sulfuric acid 0.5 M (for pH-adjustment)
Water for injections

6.2 Incompatibilities

In general, gentamicin preparations should not be mixed. In particular the following are incompatible in mixed solution with gentamicin preparations: penicillins, cephalosporins, erythromycin, heparins, sodium bicarbonate. *Dilution in the body will obviate the danger of physical and chemical incompatibility and enable gentamicin to be given concurrently with the medicinal products listed above either as a bolus injection into the drip tubing, with adequate flushing, or at separate sites. In the case of carbenicillin, administration should only be at a separate site.
*Carbon dioxide may be liberated on addition of the two solutions. Normally this will dissolve in the solution but under some circumstances small bubbles may form.

This also applies to a combination of gentamicin with diazepam, furosemide, flecainide acetate

6.3 Shelf life

3 years

After first opening, the product should be used immediately.

After dilution in sodium chloride 9 mg / mL (0.9 %) solution for injection or glucose 50 mg / mL (5 %) solution for injection:
Chemical and physical in-use stability has been demonstrated for 24 hours both at 2 – 8 °C and 23 – 27 °C. From a 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, unless dilution has taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions. Do not refrigerate or freeze.

For storage conditions after dilution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

Each ampoule of 2 mL solution for injection / infusion contains 40 mg gentamicin.
Type I, clear glass ampoules.

Pack sizes: 5, 10, 20, 25, 50 or 100 ampoules and pack sizes of 10 (2x5), 20 (4x5), 25 (5x5) or 50 (5x10) ampoules.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

This medicinal product is for single use only and contains no antimicrobial agents. Only clear solutions practically free from particles should be used.

After opening, unused portions must not be stored and should be discarded immediately.

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

7 MARKETING AUTHORISATION HOLDER

Noridem Enterprises Limited
Evagorou & Makariou
Mitsi Building 3, Office 115
1065 Nicosia
Cyprus

8 MARKETING AUTHORISATION NUMBER

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9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 12th November 2021

10 DATE OF REVISION OF THE TEXT