SUMMARY OF PRODUCT CHARACTERISTICS[SmPC]

FITZKING GENTAMYCIN SULPHATE INJECTION 80MG/2ML

1. Name of the medicinal product

FITZKING GENTAMICIN SULPHATE INJECTION 80MG/2ML

2. Qualitative and quantitative composition

Each ml contains 40 mg of gentamicin (corresponding to 67.8 mg gentamicin sulfate).

Each ampoule of 2 ml contains 80 mg of gentamicin (corresponding to 135.6 mg gentamicin sulfate).

For the full list of excipients, see section 6.1.

3. Pharmaceutical form

Solution for injection/infusion.

A clear colourless solution.

4. Clinical particulars

4.1 Therapeutic indications

Gentamicin is indicated for the treatment of the following infections in adults and children from birth when less toxic antimicrobial agents are not effective (see sections 4.4 and 5.1)

Under these conditions, Gentamicin is indicated in the treatment of the following infections:

– Complicated urinary tract infection (cUTI), including acute pyelonephritis

– Complicated intra-abdominal infection (cIAI)

– Hospital-acquired pneumonia (HAP) including ventilator-associated pneumonia (VAP)

– Broncho-pulmonary infections in patients with cystic fibrosis

– Infective endocarditis

– Burn wound infections

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

Gentamicin 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).

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

4.2 Posology and method of administration

CAUTION: In the absence of data, administration of Gentamicin solution for injection/infusion via inhalation is not recommended (see section 4.4)

Posology

The dose depends on the severity of the clinical picture, the setting, the patient's renal function and the bacterium identified.

Dosage and dosage interval should be adjusted individually in accordance with the patient's renal function, the bacterium identified and must be controlled by regular determination of the serum concentration.

The dose is expressed in terms of the patient's body weight.

Dosing regimens are identical for intravenous and intramuscular use. During treatment the patient should be sufficiently hydrated.

Adults

Gentamicin is generally used at the start of combined antibiotic treatment and for a maximum duration of 7 days, with discontinuation usually after 48 to 72 hours of treatment (i.e. when results from antimicrobial susceptibility tests become available).

The preferred dosing regimen is the single daily dose (SDD), i.e. the entire daily dose administered as a single daily injection (see section 4.4).

In certain situations the daily dose may be divided into 2 daily injections.The dose ranges from 3 to 6 mg/kg/day according to official recommendations, with the maximum dose of 6 mg/kg/day particularly recommended at the start of treatment, in severe infections and/or in cases where there is a risk of infection due to a bacterial strain with reduced sensitivity and with an increased minimum inhibitory concentration (MIC) for gentamicin.

Paediatric population

The daily recommended dose in children and adolescents with normal renal function is 3-6mg/kg body weight per day as one (preferred) up to two single doses.

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 in neonates and pre-term infants (aged 0-4 weeks old) is 4-7 mg/kg body weight per day. Due to the longer half-life, new-borns are given the required daily dose in 1 single dose.

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

There is no dose recommendation for children with impaired renal function.

The Elderly Patients

Elderly patients may be more susceptible to aminoglycoside toxicity whether secondary to previous eighth nerve 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.

Patients with Renal impairment

Since gentamicin is chiefly eliminated via the kidneys by glomerular filtration, the elimination rate depends on the patient's renal function, and the recommended daily dose must therefore be adjusted to the renal function.

The following table is a guide to recommended dosage schedules:

Blood urea (mg/100ml)	Creatinine clearance (GFR) (ml/min)	Dose and frequency of administration
<40	>70	80mg† 8-hourly
40 - 100	30 - 70	80mg† 12-hourly
100 - 200	10 - 30	80mg† daily
>200	5 - 10	80mg† every 48 hours
Twice-weekly intermittent haemodialysis	<5	80mg† after dialysis

† 60mg if body weight <60kg

If the dose is not reduced, and/or the dosage interval not lengthened, abnormally high and possibly toxic concentrations can be reached in the blood and tissues due to accumulation.

The SDD regimen and short treatment periods must be preferred (generally: 1 or 2 injections), other risk factors promoting aminoglycoside nephrotoxicity must be taken into account and monitoring of renal and auditory functions must be performed (see sections 4.4 and 4.8).

For the first injection, the dosage is identical to that of patients with normal renal function, regardless of the degree of renal impairment (including all situations involving renal replacement therapy).

Further injections at the same dose as the first injection should be performed, unless the single dose needs to be adjusted according to the peak assay.

Continuous renal replacement therapyin patients on dialysis, injections should be given 2 to 4 hours before the dialysis session to reduce the potential for toxicity.

Adjustment of treatment should be considered by performing repeated assays to determine residual levels; gentamicin may be reinjected only when levels are below the toxicity threshold.

Patients with renal impairment not receiving renal replacement therapy: no further injections should be performed while residual levels are above the toxicity threshold (see sections 4.2 and 4.4).

If the residual assay (generally performed 24 hours post-dose) is higher than the toxicity threshold, the assay must be repeated 24 hours later.

Patients with Hepatic impairment

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

Obese Patients

The dose in mg/kg must be calculated according to adjusted body weight:

Adjusted body weight = ideal weight1 + 0.43 x excess weight (Excess weight = total weight - ideal weight)

1 Lorentz formula (ideal weight expressed in kg):

Women = height (cm) – 100 – [height (cm) - 150] / 2

Men = height (cm) – 100 – [height (cm) – 150] / 4

Conditions for use of this formula:

• age over 18 years;

• height between 140 and 220 cm.

Method of administration

Administration via the intravenous route (as a 30-minute infusion) or intramuscular route.

For the intravenous infusion, the amount of gentamicin to be administered must be diluted in a solution for infusion (5% Glucose or 0.9% NaCl) at a rate of approximately 50 to 200 ml, without exceeding a maximum concentration of 10 mg/ml.

The solution for injection/infusion can be given directly intravenously without previous dilution and administered slowly (3-5 min.).

Special clinical circumstances

Therapeutic monitoring

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 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.

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.

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.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

General information

In the absence of data, Gentamicin solution for injection/infusion is not recommended for use via inhalation. Aminoglycosides must be used within a strict prescribing framework (indications restricted to severe infections or due to resistant bacteria, administration regimens must be observed) and accompanied by appropriate surveillance. Prescription of gentamicin must meet this objective.

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.

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

Concurrent use with Neurotoxic or nephrotoxic antibiotics

Simultaneous and/or sequential systemic or topical treatment with other potentially neuro- and/or nephrotoxic agents should be avoided.

Neuromuscular blockade and respiratory paralysis have been reported following administration of aminoglycosides in patients receiving non-depolarising muscle relaxants during anaesthesia. These patients must also be very closely monitored (see section 4.8).

Ototoxicity

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 and less commonly, loss of hearing (see section 4.8).

In patients with end-stage renal disease, on intermittent haemodialysis or chronic peritoneal dialysis, toxicity is mainly auditory, as the kidneys are no longer functional.

Muscular weakness

Since gentamicin has neuromuscular blocking properties, particular attention must be paid to patients with pre-existing neuromuscular disease (e.g. Parkinson's disease or myasthenia gravis). Close monitoring must always be instituted in such patients (see section 4.8).

Singe Daily Dose

SDD 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.

Impaired renal function

In the presence of acute or chronic pre-existing renal impairment, aminoglycosides should be used only when absolutely necessary. All possible non-nephrotoxic alternatives should be looked into. Dosage adjustments are required in patients with renal impairment (see section 4.2).

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).

Paediatric population

According to the data available, renal and auditory toxicities remain rare in newborns and children.

The Elderly Patients

Elderly patients can have impaired renal function that does not show up in routine analyses like BUN and serum creatinine. Creatinine clearance determination is more practicable. Checking the function is particularly important in these patients.

Patients with severe burns injuries

Patients with severe burn injuries must be monitored extra carefully due to the altered pharmacokinetics.

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

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).

4.5 Interaction with other medicinal products and other forms of interaction

• Other aminoglycosides in concomitant administration. Increased risk of nephrotoxicity and ototoxicity.

• 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.

• Ototoxic agents

Concomitant use of medicinal products with intrinsic ototoxicity increases the risk of vestibulocochlear damage. If such a combination is necessary, monitoring of auditory function must be increased. In particular, such medicines include antibiotics of the glycopeptide group, such as vancomycin and teicoplanin, aminoglycosides, cytotoxic agents such as organoplatinum compounds and loop diuretics.

• Nephrotoxic agents

Concomitant use of medicinal products with intrinsic renal toxicity increases the risk of nephrotoxicity. If such a combination is necessary, monitoring of kidney function tests must be increased. In particular, such medicines include iodinated contrast media, aminoglycosides, organoplatinum compounds, high-dose methotrexate, certain antiviral agents (e.g. the “–ciclovir” group, foscarnet), amphotericin B, pentamidine, ciclosporin or tacrolimus.

Gentamicine is usually contraindicated in patients treated with cisplatine and platinum compounds, as the nephrotoxicity of gentamicine may be increased for several weeks after the administration of cisplatine or platinum therapy.

• Polymyxin B

Additive nephrotoxic effects. If the combination cannot be avoided, the bacteriological justification for its use should be irrefutable and strict surveillance is required.

• Curare-type muscle relaxants during anaesthesia

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

• Contraceptives

In rare cases, some antibiotics for systemic use are supposedly capable of diminishing the effect of contraceptive pills. This unusual interaction is said to occur in women with high biliary excretion of steroid conjugates.

• Botulinum toxin

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

4.6 Fertility, 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 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 impairment of balance, drivers and operators of machinery should be warned of this potential risk.

4.8 Undesirable effects
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 (caused by gentamicin-resistant bacteria), 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), up to anaphylactic reactions (including anaphylactic shock)	
Metabolism and nutrition disorders			Hypokalaemia, hypocalcaemia, hypomagnesaemia, pseudo-Bartter's 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, depression	
Nervous system disorders			Polyneuropathies, peripheral paraesthesia	Encephalopathy, seizures, neuromuscular block, dizziness, impaired balance, headache (see section 4.4)	
Eye disorders				Visual disorders	
Ear and labyrinth				Vestibular damage, loss	Irreversible

disorders				of hearing, Meniere's disease, tinnitus, vertigo (see section 4.4)	hearing loss, deafness
Vascular disorders				Hypotension, hypertension	
Gastrointestinal disorders			Vomiting, nausea, increased salivation, stomatitis		
Hepatobiliary disorders			Increased aspartate aminotransferase (AST), increased alanine aminotransferase (ALT), increased alkaline phosphatase (ALP), reversible increase of serum bilirubin (all reversible)		
Skin and subcutaneous tissue disorders		Allergic skin exanthema	Skin reddening	Toxic epidermal necrolysis[2], Lyell's syndrome[2], Stevens-Johnson syndrom, Erythema multiforme[2], Alopecia	
Musculoskeletal and connective tissue disorders			Muscle pain (myalgia)	Amyostasia	
Renal and urinary disorders	Renal function impairment[2]		Blood urea nitrogen increased (reversible)	Acute renal failure, hyperphosphaturia, aminoaciduria, Fanconi-like syndrome in patients treated with a prolonged course of, high-dose treatment (see section 4.4)	
General disorders and administration site conditions			Increased body temperature	Pain at the injection site	

[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 Yellow Card Scheme at: www.mhra.gov.uk/yellowcard or search for 'MHRA Yellow Card' in the Google Play or Apple App Store. By reporting side effects you can help provide more information on the safety of this medicine.

4.9 Overdose

Gentamicin has a narrow therapeutic margin.

Symptoms

In the event of accumulation, renal damage and damage to the vestibulocochlear nerves may occur.

Treatment

Stop treatment. Provide good, preferably somewhat increased diuresis. Can be also removed from the blood by dialysis.

Monitor the serum concentration

In the event of neuromuscular blockade, administration of calcium chloride is recommended, as well as the use of artificial ventilation, if necessary.

---

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).

Mechanism of action

Gentamicin has a bactericidal effect on both the proliferation and latency of bacteria.

It forms a bond with bacterial 30S ribosomal subunits, which causes misreading of 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.

Mechanisms 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. Gentamycin often has synergistic effect when used in combination with beta-lactam therapy despite low to moderate level in vitro-resistance, such as for treatment of enterococcal species without high-level (MIC > 128) resistance.

COMMONLY SUSCEPTIBLE SPECIES

Gram-positive aerobes

Listeria monocytogenes

Staphylococcus aureus, methicillin-sensitive

Gram-negative aerobes

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 enterocolitica
Yersinia pseudotuberculosis

SPECIES FOR WHICH ACQUIRED RESISTANCE MAY BE A PROBLEM (ACQUIRED RESISTANCE ≥ 10%)

Gram-positive aerobes
Staphylococcus aureus, methicillin-resistant
Staphylococcus epidermidis
Staphylococcus haemolyticus

Gram-negative aerobes
Acinetobacter spp.
Citrobacter freundii
Morganella morganii
Proteus mirabilis
Pseudomonas aeruginosa

INHERENTLY RESISTANT SPECIES

Gram-positive aerobes
Enterococcus faecalis
Enterococcus faecium
Streptococcus spp.

Gram-negative aerobes
Burkholderia cepacia
Legionella pneumophila
Stenotrophomonas maltophilia

Anaerobes

Other
Atypical pathogens
Chlamydia spp.
Chlamydophila spp.
Mycoplasma spp.
Ureaplasma urealyticum

5.2 Pharmacokinetic properties

Absorption

At therapeutic levels and under normal physiological conditions, gentamicin binding to plasma proteins is low, ranging between 0 and 3%.

In patients with normal renal function After IM administration at the single dose of 1 mg/kg, the peak serum level, reached after 30 to 60 minutes, is approximately 4 µg/ml. Active plasma concentrations persist for about 6 hours.

After IM administration at the single dose of 160 mg, the peak serum level, reached after 30 to 60 minutes, is approximately 9 µg/ml. Active plasma concentrations persist for about 8 hours.

After IV administration by a 30-minute infusion at 4 mg/kg body weight per day, divided into 3 doses, peak and trough gentamicin concentrations measured in adults were 4.7 µg/ml and 1.0 µg/ml, respectively. At the same daily dose administered as a single dose, peak and trough concentrations of 9.5 µg/ml and 0.4 µg/ml were measured.

In patients with renal impairment the peak serum level is slightly higher and plasma concentrations are more prolonged.

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.

After parenteral administration, gentamicin is found in most tissues and biological fluids. Therapeutic levels are present in serum.

Concentrations in the renal parenchyma are much higher than the plasma levels.

Concentrations of about 40% and above are found in bronchial secretions, infected bone, synovial fluid and tissue, skin, pleura, pericardium, peritoneal cavity and ascites.

Gentamicin does not penetrate the prostate. It crosses the placental barrier.

However, it barely crosses the blood-brain barrier. Excretion into human milk is negligible.

Gentamicin diffuses through the membranes used in haemodialysis.

Paediatric population

60-90	24 hours
40-60	36 hours
20-40	48 hours
< 20	Residual levels must be determined

Biotransformation

Gentamicin does not undergo metabolic transformation

Elimination

Gentamicin is not metabolized in the body but is excreted unchanged in microbiologically active form predominantly via the kidneys. In patients with normal renal function the elimination half- life is about 2 to 3 hours.

Paediatric population

In neonates elimination rate is reduced due to 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.

5.3 Preclinical safety data

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

Genotoxicity and carcinogenic potential

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

Toxicity to reproduction

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

Disodium edetate, sodium chloride, sulfuric acid (for pH adjustment) and water for injections.

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf life
3 years.

After opening; the product must be used immediately.

Chemical and physical in-use stability has been demonstrated for 24 hours at 25°C when diluted with the infusion fluids listed in 6.6.

Chemical and physical in-use stability has also been demonstrated for 3 hours at 25°C, after 24 hours at 2-8°C when diluted with the infusion fluids listed in 6.6.

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 reconstitution and dilution have taken place in controlled validated aseptic conditions.

6.4 Special precautions for storage
Store below 30°C.

6.5 Nature and contents of container
Box of 10 colorless ampoules (glass type I).

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling
For the intravenous route, the amount of gentamicin to be administered is to be diluted in a solution for infusion (with the Glucose 5% or sodium chloride 0.9%) at a rate of 50 to 200 ml with a maximum concentration of 10 mg/ml.

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

---

7. Marketing authorisation holder

FITZKING LINK LIMITED,

15, RAMON JIMOH STREET, OFF NNPC ROAD, EJIGBO, LAGOS STATE

---

8. Marketing authorisation number

A4-3217

9. Date of first authorisation/renewal of the authorisation

06/11/2019

---

10. Date of revision of the text

06/07/2022