



SUMMARY OF PRODUCT CHARACTERISTICS (SmPC)

Gentamycin Sulphate Injection

1. NAME OF THE MEDICINAL PRODUCT

{(Gentamycin Sulphate) 80mg Injection}

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

[Each 2ml ampoule contains:
Gentamycin Sulphate 80mg]

3. PHARMACEUTICAL FORM

Solution for Injection.

4. Clinical particulars

4.1 Therapeutic indications

Gentamycin is an aminoglycoside antibiotic with broad-spectrum bactericidal activity. It is indicated to treat severe infections caused by bacteria susceptible to gentamycin such as, but not limited to:

- Urinary tract infections
- Respiratory tract infections
- Intra-abdominal infections
- CNS infections
- Severe neonatal infections

It is usually active against most strains of the following organisms: *Escherichia coli*, *Klebsiella* spp., *Proteus* spp. (indole positive and indole negative), *Pseudomonas aeruginosa*, *Staphylococci*, *Enterobacter* spp., *Citrobacter* spp. and *Providencia* spp.

4.2 Posology and method of administration

Posology

Route of Administration: Parenteral

Adults

The recommended dose in adults with normal renal function is 3 – 5 mg/kg/day, depending on the severity of infection, administered as one single dose (preferred) or in two divided doses. The dose should be adjusted according to clinical response and serum concentration levels (see below). Dose calculations should be based on ideal body weight. 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 gentamycin and serum level monitoring in endocarditis should be followed.

In patients with normal renal function, 160 mg once daily may be used for the treatment of urinary tract infections.

Paediatric population

The daily dose recommended in children aged 1 year and above and adolescents with normal renal function, is 3 – 6 mg/kg/day as one single dose (preferred) or two divided doses.

The daily dose in infants after the first month of life is 4.5 – 7.5 mg/kg/day as one single dose (preferred) or two divided doses.

The daily dose in neonates and pre-term infants (aged 0 – 4 weeks old) is 4 – 7 mg/kg/day. Due to the longer half-life, newborns are given the required daily dose in one single dose.

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 gentamycin serum levels, assessment of renal function and signs of ototoxicity.

Renal impairment

In impaired renal function, the recommended daily dose has to be decreased and adjusted to the renal function. This can be achieved by reducing the dose and/or increasing the dose interval.

In all patients with renal impairment, serum gentamycin peak and trough concentration and renal function must be monitored frequently.

Nomograms are available for the calculation of dose, which depends on the patient's age, weight and renal function. No clear recommendation can be made for once daily dosing; dosing should be guided by plasma concentration levels. In patients with moderate renal impairment, in whom once daily dosing would be considered appropriate if their renal function were normal, the dose interval should be at least 24 hours and extended according to the degree of renal impairment and the results of serum gentamycin monitoring. Limited data are available in patients with severe renal impairment (creatinine clearance < 30 ml/min) after once daily

dose administration.

Method of administration

I.M/I.V Route

The recommended dose and precautions for intramuscular and intravenous administration are identical. Gentamycin when given intravenously should be injected directly into a vein or into the drip set tubing over no less than three minutes. If administered by infusion, this should be over 20 – 30 minutes and in no greater volume of fluid than 100 ml. Longer infusion times of up to 60 minutes may be used, in particular for a once daily dosing regimen. Once daily dosing should only be administered through the intravenous route

4.3 Contraindications

- Hypersensitivity to the active substance or any of the excipients.
- Myasthenia gravis

4.4 Special warnings and precautions for use

Ototoxicity and nephrotoxicity

Ototoxicity has been reported following the use of aminoglycosides, including gentamycin.

Symptoms include loss of balance and hearing loss, which may be irreversible. Important risk factors include renal impairment, high doses, prolonged duration of treatment and age (neonates/infants and possibly the elderly). Due to the potential for ototoxicity and nephrotoxicity, monitoring of vestibule, cochlea and renal function is recommended before, during and shortly after treatment (see section 4.8). Serum levels are determined so as to avoid peak concentrations above 10 mg/L and troughs above 1 mg/L when administering gentamycin once daily and 2 mg/L when administering gentamycin twice daily.

As there is some evidence that risk of both ototoxicity and nephrotoxicity is related to the level of total exposure, duration of therapy should be the shortest possible compatible with clinical recovery.

In some patients with impaired renal function there has been a transient rise in blood-urea-nitrogen which has usually reverted to normal during or following cessation of therapy. It is important to adjust the frequency of dosage according to the degree of renal function.

There have been observed cases of an increased risk of ototoxicity with aminoglycosides administered to patients with mitochondrial mutations, particularly the m.1555A>G mutation, including cases where the patient's aminoglycoside serum levels were within the recommended range. Some cases were associated with a maternal history of deafness and/or mitochondrial mutation. Mitochondrial mutations are rare, and the penetrance of this observed effect is unknown.

In cases of significant obesity gentamycin serum concentrations should be closely monitored and a

reduction in dose should be considered. To avoid adverse events, continuous monitoring (before, during and after treatment) of hepatic and laboratory parameters is also recommended.

Gentamycin should only be used in pregnancy if considered essential by the physician. Gentamycin should be used with care in conditions characterised by muscular weakness.

Superinfection

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

Pseudomembranous colitis

Diarrhoea and pseudomembranous colitis have been observed when gentamycin is combined with other antibiotics. These diagnoses should be considered in every patient that develops diarrhoea during or immediately after treatment. Gentamycin 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.

Severe subcutaneous adverse reactions (SCARs)

Serious skin reactions including Stevens-Johnson Syndrome (SJS) and toxic epidermal necrolysis (TEN) have been reported in association with gentamycin treatment. Patients should be informed about the signs and symptoms of serious skin manifestations and monitored closely. Treatment should be discontinued at the first appearance of skin rash, mucosal lesions or any other sign of skin hypersensitivity.

4.5 Interaction with other medicinal products and other forms of interaction

Ototoxicity and nephrotoxicity

Concurrent administration of gentamycin and other potentially ototoxic or nephrotoxic drugs should be avoided. Potent diuretics such as etacrynic acid and furosemide are expected to enhance the risk of ototoxicity whilst amphotericin B, cisplatin and ciclosporin are potential enhancers of nephrotoxicity.

Any potential nephrotoxicity of cephalosporins, and in particular cephaloridine, may also be increased in the presence of gentamycin. Consequently, if this combination is used monitoring of kidney function is advised.

Neuromuscular blockade

Neuromuscular blockade and respiratory paralysis have been reported from administration of aminoglycosides to patients who have received curare-type muscle relaxants during anaesthesia. Concomitant use of gentamycin with drugs with neuromuscular blocking effects, such as botulinum toxin, may increase the risk of toxicity due to enhanced neuromuscular block.

Aminoglycosides such as gentamycin can also act as neuromuscular blockers and may therefore antagonise the effects of neostigmine or pyridostigmine.

The following combinations with gentamycin may require dose adjustment:

- Concomitant use of indomethacin possibly increases plasma concentrations of gentamycin in neonates.
- Concomitant use with oral anticoagulants may decrease thrombin levels and increase the risk of bleeding.
- Concomitant use of bisphosphonates with gentamycin may increase the risk of hypocalcaemia.

4.6 Pregnancy and Lactation

Pregnancy, Lactation, Fertility:

Pregnancy

There are limited data from the use of aminoglycosides, including gentamycin, in pregnancy.

Gentamycin crosses the placenta, and there is a risk of ototoxicity (vestibulocochlear nerve damage) and/or renal damage in the fetus, as seen in animal studies (see section 5.3). Gentamycin should not be used in pregnancy, except in case of life-threatening situations where expected benefits outweigh possible risks.

In such cases, maternal serum gentamycin concentration monitoring is recommended (see section 4.2). Monitoring of the hearing and renal function of the infants is also recommended.

Lactation

Gentamycin is excreted in human breast milk and was detected in low concentrations in the serum of breast-fed infants, except in cases where the mucous membrane of the infant's stomach and intestines is severely eroded.

In cases of suspected severe mucosal erosion, if the infant is breast-fed during gentamycin treatment, it is recommended to monitor the serum concentration of gentamycin in the infant (see section 4.2). Animal and human data suggest that if the serum gentamycin concentration in the infant exceeds 1 µg/ml either breast-feeding or the gentamycin therapy may need to be discontinued, under medical supervision.

The following effects of gentamycin on the infant's normal gastrointestinal flora are possible and it is recommended to monitor the infant for possible effects such as diarrhoea, candidiasis and bloody stools.

4.7 Effects on ability to drive and use machines

None reported.

4.8 Undesirable effects

The following CIOMS frequency rating is used, when applicable: Very common ($\geq 1/10$); common ($\geq 1/100$ to $\leq 1/10$); uncommon ($\geq 1/1,000$ to $\leq 1/100$); rare ($\geq 1/10,000$ to $\leq 1/1,000$); very rare ($\leq 1/10,000$); not known (cannot be estimated from the available data).

Infections and infestations:

Not known: antibiotic-associated colitis (including pseudomembranous colitis), superinfection (caused by gentamycin-resistant bacteria)

Blood and lymphatic system disorders:

Not known: anaemia, blood dyscrasias

Immune system disorders:

Not known: hypersensitivity (see section 4.4), anaphylaxis/anaphylactic reaction (including anaphylactic shock)

Metabolism and nutrition disorders:

Not known: hypomagnesaemia on prolonged therapy

Psychiatric disorders:

Not known: depression, hallucinations, confusion

Nervous system disorders:

Not known: central neuropathy (including convulsions, lethargy, encephalopathy), peripheral neuropathy

Ear and labyrinth disorders:

Not known: vestibular damage, transitory hearing loss, irreversible hearing loss, deafness, particularly after exposure to ototoxic drugs or in the presence of renal dysfunction (see section 4.4).

Gastrointestinal disorders:

Very common: vomiting

Not known: stomatitis, nausea

Hepatobiliary disorders:

Not known: abnormal liver function, transaminases increased

Skin and subcutaneous tissue disorders:

Not known: Stevens-Johnson syndrome, toxic epidermal necrosis, rash, purpura, urticaria, pruritus

Renal and urinary disorders:

Very rare: acute renal failure, Fanconi-like syndrome in patients treated with a prolonged course of high dose

Not known: nephrotoxicity (usually reversible) has been reported.

4.9 Overdose

Haemodialysis and peritoneal dialysis will aid the removal from blood, but the former is probably more efficient. Calcium salts given intravenously have been used to counter the neuromuscular blockade caused by gentamycin.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamics properties

Pharmacotherapeutic group: {Anti-bacterials for systemic use. ATC code: {J01GB03}}

Gentamycin is a mixture of antibiotic substances produced by the growth of micromonospora purpurea. It is bactericidal with greater antibacterial activity than streptomycin, neomycin or kanamycin.

Gentamycin exerts a number of effects on cells of susceptible bacteria. It affects the integrity of the plasma membrane and the metabolism of RNA, but its most important effects is inhibition of protein

synthesis at the level of the 30s ribosomal subunit.

5.2 Pharmacokinetic properties

Absorption

Gentamycin is not readily absorbed from the gastro-intestinal tract. Gentamycin is 70 – 85% bound to plasma albumin following administration and is excreted 90% unchanged in urine. The half-life for its elimination in normal patients is 2 – 3 hours.

- Effective plasma concentration is 4 – 8 µg/ml.
- The volume of distribution (vd) is 0.3 L/kg.
- 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 gentamycin.

Paediatric population (premature infants and neonates).

Distribution

The distribution volume of gentamycin is about equivalent to the volume of extracellular water. In the newborn water makes up 70 – 75% of bodyweight, compared with 50 – 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 gentamycin per kg bodyweight is affected and decreases with increasing age from 0.5 – 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.

Elimination

Gentamycin 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 – 3 hours. 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 – 34 weeks compared with about 6.7 hours in neonates at a gestational age of 35 – 37 weeks.

Correspondingly, clearance values increase from about 0.05 L/h in neonates at a gestational age of 27 – 0.2 L/h in neonates at a gestational age of 40 weeks.

5.3 Preclinical safety data

Reproductive and developmental toxicity

The limited non-clinical literature mentions that prenatal or postnatal administration of gentamycin to rodents and guinea pigs produces developmental toxicity of the kidney and/or inner ear in fetuses and offspring.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

NA.

6.2 Incompatibilities

The ampoules used im or iv as an infusion should not be mixed with other injection solutions. In particular the following are incompatible in mixed solution with gentamycin injection:

- Penicillins
- Cephalosporins
- Erythromycin
- Heparins
- sodium bicarbonate

*Dilution in the body will obviate the danger of physical and chemical incompatibility and enable gentamycin to be given concurrently with the drugs 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

6.3 Shelf life

24 months

6.4 Special precautions for storage

Store in a cool dry place. Below 30°C.

Store in the original package in order to protect from light.

The infusion solution should not be used if crystals or precipitates are observed.

6.5 Nature and contents of container <and special equipment for use, administration or implantation>

Type I clear amber glass ampoule containing 2 ml solution for injection. Package of 10 ampoules of 2 ml.

6.6 Special precautions for disposal <and other handling>

No special requirements.

7. APPLICANT

Sifam Life Care Pharmaceutical Ltd. No. 33, Keffi Street, Nomansland, Kano State, Nigeria.