Summary of Product Characteristics for Pharmaceutical Products

1. Name of the medicinal product:

Gentamicin sulfate injection 2ml:80mg

2. Qualitative and quantitative composition

1 ampoule of 2 ml solution for injection contains 80 mg of gentamicin (as sulphate)

Excipients with known effect; Sodium sulfite (E 221)

For a full list of excipients, see section 6.1

3. Pharmaceutical form

Solution for injection.
Ampoules containing a clear colourless solution.

4. Clinical particulars

4.1 Therapeutic indications

Gentamicin is bactericidal and is active against many strains of Gram-positive and Gram-negative pathogens including species of Escherichia, Enterobacter, Klebsiella, Salmonella, Serratia, Shigella, Staphylococcus aureus, some Proteus and against Pseudomonas aeruginosa. Gentamicin is often effective against strains of these organisms which are resistant to other antibiotics such as streptomycin, kanamycin and neomycin. Gentamicin is effective against penicillin-resistant Staphylococci, but rarely effective against Streptococci.

Gentamicin is indicated in the treatment of the following infections when caused by susceptible organisms.

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

***Severe Gram-Negative Infections*:**
Upper and lower urinary tract infections
Burn and wound infections
Septicaemia, Bacteraemia
Abscesses
Subacute Bacterial Endocarditis
Respiratory Tract infections (Bronchopneumonia)
Neonatal infections
Gynaecological infections

Gram-Positive Infections:

Bacteraemia
Abscesses
Accidental and operative trauma
Burns and serious skin lesions.

4.2 Posology and method of administration

Gentamicin is normally given by the intramuscular route, but can be given intravenously when intramuscular administration is not feasible, e.g. in shocked or severely burned patients. When given intravenously, the prescribed dose should be administered slowly over no less than 3 minutes directly into a vein or into the rubber tubing of a giving set. 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 normal saline or 5% glucose in water, but not solutions containing bicarbonate (see Incompatibilities P6B, 7h), and the solution infused over no longer than 20 minutes.

The same dosage schedule is recommended for intramuscular and intravenous dosing. Dosage is related to the severity of infection, the age of the patient and the patient's renal function.

The daily dose recommended in children, adolescents and adults with normal renal function, is 3-5mg/kg body weight per day as 1 (preferred) up to 2 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 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.

In impaired renal function, the recommended daily dose has to be decreased and adjusted to the renal function

Doses in Patients with Impaired Renal Function:

Dosage is adjusted for patients with renal impairment to minimise the risk of toxicity. The first dose should be as normal after this, doses should be given less frequently, the interval being determined by results of renal function tests as below:

Renal Function Tests:

Blood Urea (mg/100 ml)	Blood Urea (mmol/l)	Creatinine Clearance (GFR) (ml/min)	Dose and frequency of administration
<40	6-7	>70	80 mg* 8-hourly
40-100	6-17	30-70	80 mg* 12-hourly
100-200	17-34	10-30	80 mg* daily
>200	>34	5-10	80 mg* every 48 hours
Twice weekly intermittent haemodialysis		<5	80 mg* after dialysis

**60 mg if body weight <60 kg. Frequency of dosage in hours may also be approximated as serum creatinine (mg%) x eight or in SI units, as serum creatinine (µmol/l) divided by 11. If these dosage guides are used, peak serum levels must be measured. Peak levels of gentamicin occur approximately one hour after intra muscular injection and intravenous injection. Trough levels are measured just prior to the next injection. Assay of peak serum levels gives confirmation of adequacy of dosage and also serves to detect levels above 10 mg/l, at which the possibility of ototoxicity should be considered. One-hour concentrations of gentamicin should not exceed 10 mg/l (but should reach 4 mg/l), while the pre-dose trough concentration should be less than 2 mg/l.*

The recommended dose and precautions for intramuscular and intravenous administration are identical. Gentamicin 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 no longer than 20 minutes and in no greater volume of fluid than 100 ml.

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. Please refer to section 4.4.

4.3 Contraindications

Patients being treated with gentamicin should be under close clinical observation because of its potential toxicity.

Hypersensitivity to gentamicin, any other ingredient/excipients listed in section 6.1 or other aminoglycosides.

Myasthenia gravis.

4.4 Special warnings and precautions for use

Patients being treated with gentamicin should be under close clinical observation because of its potential toxicity.

Gentamicin should be used with caution in premature infants because of their renal immaturity, in elderly people and generally in patients with impaired renal function, diabetes, auditory vestibular dysfunctions, otitis media, a history of otitis media, previous use of ototoxic drugs and a genetically determined high sensitivity to aminoglycoside induced ototoxicity, are other main factors which may pre-dispose the patient to toxicity.

As with other aminoglycosides toxicity is related to serum concentration. At serum levels more than 10 micrograms/ml the vestibular mechanism may be affected.

Toxicity can be minimised by monitoring serum concentrations and it is advisable to check serum levels to confirm that peak levels (one hour) do not exceed 10 micrograms/ml and that trough levels (one hour before next injection) do not exceed 2 micrograms/ml when administering Gentamicin twice daily and 1µg/ml for a once daily dose.

Evidence of toxicity requires adjustment of dosage or withdrawal of the drug. As there is some evidence that the 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.

Gentamicin should be used with care in conditions characterised by muscular weakness.

In cases of significant obesity gentamicin serum concentrations should be closely monitored and a reduction in dose should be

considered.

Concurrent use of other neurotoxic and/or nephrotoxic drugs can increase the possibility of gentamicin toxicity. Co-administration with the following agents should be avoided:

Neuromuscular blocking agents such as succinylcholine and tubocurarine.
Other potentially nephrotoxic or ototoxic drugs such as cephalosporins and methicillin.
Potent diuretics such as etacrynic acid and furosemide.
Other aminoglycosides.

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.

Sulphites can cause allergic-type reactions including anaphylactic symptoms and bronchospasm in susceptible people, especially those with a history of asthma or allergy.

The ampoule stopper contains dry natural rubber (a derivative of latex), which may cause allergic reactions.

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.

Superinfection-Treatment with gentamicin 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 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).

Severe subcutaneous adverse reactions (SCARs)-serious skin reactions including Stevens-Johnson Syndrome (SJS) and toxic

epidermal necrolysis (TEN) have been reported in association with gentamicin 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

(i) Antibacterials: increased risk of nephrotoxicity with cephalosporins notably cephalothin.
(ii) Gentamicin has been known to potentiate anticoagulants such as warfarin and phenindione.
(iii) Antifungals: increased risk of nephrotoxicity with amphotericin B.
(iv) Cholinergics: antagonism of effect of neostigmine and pyridostigmine.
(v) Cyclosporin, cisplatin: increased risk of nephrotoxicity.
(vi) Cytotoxics: increased risk of nephrotoxicity and possible risk of ototoxicity with cisplatin.
(vii) Diuretics: increased risk of ototoxicity with loop diuretics.
(viii) Muscle relaxants: effect of non-depolarising muscle relaxants such as tubocurarine enhanced.
Neuromuscular blockade and respiratory paralysis have been reported from administration of aminoglycosides to patients who have received curare-type muscle relaxants during anesthesia.
(ix) Indomethacin possibly increases plasma concentrations of gentamicin in neonates.
(x) Concurrent use of bisphosphonates may increase the risk of hypocalcaemia.

4.6 Pregnancy and Lactation

Gentamicin should only be used in pregnancy if considered essential by the physician.

Use in Pregnancy:

Although no teratogenic effects have been observed, gentamicin is known to cross the placenta. Ototoxicity in the foetus is also a potential hazard. The benefits should, therefore, be weighed against such hazards to the foetus before using gentamicin during pregnancy.

Monitor: maternal serum gentamicin concentration, infant hearing and infant renal function if administered.

Use in Lactation:

Small amounts of gentamicin have been reported in breast milk. Because of the potential for serious adverse reactions to an

aminoglycoside in nursing infants, a decision should be made whether to discontinue nursing or the drug, taking into account the importance of the drug to the woman.

Monitor; the serum concentration of gentamicin in the breast-fed infant in cases of suspected severe mucosal erosion. Animal and human data suggest that if the serum gentamicin concentration in the infant exceeds 1 µg/ml either breast-feeding, gentamicin therapy may need to be discontinued, under medical supervision.

The following effects of gentamicin 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.

In the absence of gastro-intestinal inflammation, the amount of gentamicin ingested from the milk is unlikely to result in significant blood levels in breast-fed infants.

4.7 Effects on ability to drive and use machines

Caution is advised when driving and using machines in view of the possible undesired effects such as dizziness and vertigo.

4.8 Undesirable effects

Ototoxicity and nephrotoxicity are the most common side effects associated with Gentamicin therapy. Both effects are related to renal impairment and hence the dosage in such patients should be altered as suggested. In addition, there have been rare reports of changes in electrolyte balance including hypocalcaemia and hypokalaemia caused by renal tubular dysfunction.

The following CIOMS frequency rating is used, when applicable:

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).

Ear and labyrinth disorders:
Not known; Vestibular damage and ototoxicity may occur, Irreversible

hearing loss and deafness.

Renal and urinary disorders:
Nephrotoxicity. Frequency Very rare (< 1/10,000).: Acute renal failure, Fanconi-like syndrome in pati58ents treated with a prolonged course of high-dose
Not known; nephrotoxicity, usually reversible.

Immune system disorders
Not known; Hypersensitivity, anaphylactic reactions associated with gentamicin containing therapy.

Blood and lymphatic system disorder
Not known; Anemia, blood dyscrasias, granulocytopenia (reversible)

Nervous system disorders
Not known; Convulsions, central nervous system toxicity (including encephalopathy, confusion, lethargy, mental depression and hallucinations), neuromuscular blockade

Hepatobiliary disorders
Not known: Hepatic function abnormal

Metabolism and nutrition disorders
Not known; Hypomagnesaemia (on prolonged therapy)

Infections and infestations
Not known; Combinations of antibiotics containing gentamicin have been associated with rare reports of Clostridium difficile diarrhoea.

Gastrointestinal disorders
Very common; vomiting
Not known; Stomatitis, nausea,

Skin and subcutaneous tissue disorders:
Not known; Stevens-Johnson Syndrome, toxic epidermal necrosis, rash, urticaria, allergic contact dermatitis, purpura, pruritus.

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.

4.9 Overdose

As in the case of other aminoglycosides, toxicity is associated with serum levels above a critical value. In patients with normal renal function, it is unlikely that toxic serum levels (in excess of 10

micrograms/ml) will be reached after administration of recommended doses. Where higher levels occur because of renal impairment, dosage should be reduced. In the event of an overdose or toxic reaction, peritoneal dialysis or haemodialysis will lower serum gentamicin levels. Calcium salts given intravenously have been used to counter the neuromuscular blockade caused by gentamicin.

5. Pharmacological properties

5.1 Pharmacodynamic properties

Gentamicin is usually bactericidal in action.
Although the exact mechanism of action has not been fully elucidated, the drug appears to inhibit protein synthesis in susceptible bacteria by irreversibly binding to 30S ribosomal subunits. 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.

In vitro, gentamicin concentrations of 1-8 µg/ml inhibit most susceptible strains of Escherichia coli, *Haemophilus influenzae, Moraxella lacunata*, Neisseria, indole positive and indole negative Proteus, Pseudomonas (including most strains of *Ps. aeruginosa*), *Staphylococcus aureus, S. epidermidis,* and *Serratia*. However, different species and different strains of the same species may exhibit wide variations in susceptibility in vitro. In addition, in vitro susceptibility does not always correlate with in vivo activity. Gentamicin is only minimally active against Streptococci.

Natural and acquired resistance to gentamicin has been demonstrated in both gram-negative and gram-positive bacteria. Gentamicin resistance may be due to decreased permeability of the bacterial cell wall, alteration in the ribosomal binding site, or the presence of a plasmid-mediated resistance factor which is acquired by conjugation. Plasmid-mediated resistance enables the resistant bacteria to enzymatically modify the drug by acetylation, phosphorylation, or adenylation and can be transferred between organisms of the same or different species.

Resistance to other aminoglycosides and several other anti-infectives (e.g. chloramphenicol, sulphonamides, tetracycline) may be transferred on the same plasmid. There is partial cross-resistance between gentamicin and other aminoglycosides.

5.2 Pharmacokinetic properties

Absorption

Like all aminoglycoside antibiotics, gentamicin is barely absorbed by healthy intestinal mucosa after oral administration. Therefore,

therapeutic application is parenteral.

Higher peak and lower trough levels are found when the total daily dose is given as a single daily infusion. When gentamicin is administered by intravenous short infusion of 30 minutes at 4 mg/kg body weight per day in three divided doses, peak and trough gentamicin concentrations measured in adult patients were 4.7 µg/ml and 1.0 µg/ml, respectively. With the same daily dose administered once daily, peak and trough concentrations of 9.5 µg/ml and 0.4 µg/ml were measured.

Therapeutic serum concentrations generally lie between 2 and 8 µg/ml. Therapeutic peak serum concentrations are in the range of 5 – 10 µg/ml for multiple daily dosing and 20 – 30 µg/ml for once daily dosing. Maximum serum concentrations of 10 – 12 µg/ml should not be exceeded when administered conventionally, in several doses per day. Before another dose is administered, the serum concentration when administered conventionally, in several doses per day, should have fallen below 2 µg/ml.

Distribution

The distribution volume of gentamicin is about equivalent to the volume of extracellular water. In the newborn water makes up 70 to 75% of bodyweight, compared with 50 to 55% in adults. The extracellular water compartment is larger (40% of body weight compared with 25% of body weight in adults). Therefore, the volume of distribution of gentamicin per kg bodyweight is affected and decreases with increasing age from 0.5 to 0.7 L/kg for a premature newborn to 0.25 L/kg for an adolescent. The larger volume of distribution per kg bodyweight means that for adequate peak blood concentration a higher dose per kg bodyweight needs to be administered.

The distribution of gentamicin to the individual organs results in varying tissue concentrations; the highest concentrations appear in the renal tissue. Smaller concentrations are found in the liver and gall bladder, the lung and spleen.

Gentamicin crosses the placenta; the foetal concentrations can be 30% of the maternal plasma concentrations. Gentamicin is excreted in small quantities in breast milk (1/3 of the concentration is found here, as in the case of the maternal plasma).

After repeated injection of gentamicin, approximately 50% of the concentrations reached in plasma is measured in the synovial, pleural, pericardial and peritoneal fluid. The penetration of gentamicin into the cerebrospinal fluid is poor in un-inflamed

meninges. In inflamed meninges, concentrations reach up to 30% of the concentrations measured in plasma.

Plasma protein binding: less than 10%.

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. 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

There is no pre-clinical data of relevance to the prescriber which are additional to that already included in other sections of the SmPc.

6. Pharmaceutical Particulars

6.1 List of Excipients

Anhydrous sodium sulfite,
Activated Charcoal
Water for injections.

6.2 Incompatibilities

Gentamicin Injection should not be mixed with other drugs before injection and where co-administration with beta-lactams e.g. (penicillins, cephalosporins), erythromycin, sulphadiazine, furosemide, lipiphysan (a special-oil-in-water-emulsion for parenteral nutrition) or where there is combinations with heparin sodium, diazepam, furosemide it is necessary the drugs be administered separately, either as bolus injections into the tubing of the giving set or at separate sites; with adequate flushing.

In the case of carbenicillin, administration should be at a separate site.

Gentamicin is incompatible with amphotericin B, Cephalothin sodium, nitrofurantoin sodium, sulfadiazine sodium and tetracyclines.

Addition of gentamicin to solutions containing bicarbonate may lead to the release of carbon dioxide.

6.3 Shelf-Life

36 months

6.4 Special Precautions for storage

Store below 30°C.

6.5 Nature and Content of container

Liquid solution fill in to Type I glass ampoule containing 2ml of solution and packed in carton together with leaflet

6.6 Special precautions for disposal and other handling

For single use only.

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

7. Marketing Authorization Holder

Joshpa Africa Ltd.
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P.O. Box 9167-00300,
Nairobi, Kenya

8. Marketing Authorization Number

CTD9167

9. Date of first authorization/renewal of the authorization

24/02/2023

10. Date of revision of the text

10/05/2025