SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE FINISHED PHARMACEUTICAL PRODUCT

Genta-SSP (Gentamycin Sulfate Injection 40 mg/ml BP)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 ml of solution for injection contains 40 mg of gentamicin (as sulphate).
1 ampoule of 2 ml solution for injection contains 80 mg of gentamicin (as sulphate).
For excipient, see 6.1.

3. PHARMACEUTICAL FORM

Solution for injection (IM/IV). Ampoule containing a clear colorless solution.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

Gentamicin is bactericidal and is active against many strains of Gram-positive and Gramnegative 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

Adults:

Systemic infections: if renal function is not impaired, 3-5 mg/kg/day in divided doses according to severity of infection, adjusting according to clinical response and body weight.

Serious infections: if renal function is not impaired, 5mg/kg/day in divided doses at six or eight hourly intervals. The total daily dose may be subsequently increased or decreased as clinically indicated.

Urinary tract infections: as 'systemic infections'. Or, if renal function is not impaired, 160 mg once daily may be used.

Paediatric Patients:

The daily dose recommended in children (aged 1 year and above) and adolescents with normal renal function, is: 3-6 mg/kg/day as 1 single dose (preferred) or up to 2 single doses.

The daily dose in infants after the first month of life is: 4.5-7.5 mg/kg/day as 1 single dose (preferred) or up to 2 single doses.

The daily dose in neonates is 4-7 mg/kg/day. Due to the longer half-life, neonates are given the required daily dose in 1 single dose.

Elderly:

There is some evidence that 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 toxicity.

Renal impairment:

Gentamicine is excreted by simple glomerular filtration. In impaired renal function, the recommended daily dose has to be decreased and adjusted to the renal function.

Nomograms are available for the calculation of the dose, which depends on the patient's age, weight, and renal function.

The following table may be useful when treating adults

Blood Urea		**Creatine clearance**	**Dose and frequency of administration**
(mg/100ml)	**(mmol/l)**	**(GFR) (ml/min)**	
< 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 creatine (mg%) x eight or in SI units, as serum creatine (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 intramuscular injectable and intravenous injectable. Trough levels are measured just prior to the next injectable.

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. 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 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 Gentamicine twice daily and 1 µg/ml for a once daily dose.

Method of administration

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 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

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

- Hypersensitivity to gentamicin, any other ingredient listed on 6.1. or other aminoglycosides.
- Myasthenia gravis.

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.

4.4. Special warnings and precautions for use

Ototoxicity and nephrotoxicity

Ototoxicity has been reported following the use of aminoglycosides, including gentamicin. 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 1.8.1.4.8). Serum levels are determined so as to avoid peak concentrations above 10 mg/L and troughs above 1 mg/L when administering gentamicin once daily and 2 mg/L when administering gentamicin 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 bloodurea-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.

To avoid adverse events, continuous monitoring (before, during and after treatment) of hepatic and laboratory parameters is also recommended.

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

4.5. Interaction with other medicinal products and other forms of interaction

Concurrent administration of gentamicin and other potentially ototoxic or nephrotoxic drugs should be avoided.

- Antibacterials: increased risk of nephrotoxicity with cephalosporins notably cephalothin.
- Gentamicin has been known to potentiate anticoagulants such as warfarin and phenindione.
- Antifungals: increased risk of nephrotoxicity with amphotericin B.
- Cholinergics: antagonism of effect of neostigmine and pyridostigmine.
- Cyclosporin, cisplatin: increased risk of nephrotoxicity.
- Cytotoxics: increased risk of nephrotoxicity and possible risk of ototoxicity with cisplatin.
- Diuretics: increased risk of ototoxicity with loop diuretics.
- 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.
- Indomethacin possibly increases plasma concentrations of gentamicin in neonates.
- Concurrent use of bisphosphonates may increase the risk of hypocalcaemia.
- Concurrent use of the Botulinum Toxin and gentamicin may increase the risk of toxicity due to enhanced neuromuscular block.

4.6. Fertility, pregnancy and lactation

Pregnancy

There are no proven cases of intrauterine damage caused by gentamicin. However, in common with most drugs known to cross the placenta, usage in pregnancy should only be considered in life threatening situations where expected benefits outweigh possible risks.

Breast-feeding

Gentamicin is excreted in human breast milk and was detected in low concentrations in serum of breastfed 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

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

4.8. Undesirable effects

Under certain conditions gentamicin shows ototoxic and/or nephrotoxic effects. Renal impairment is commonly observed in patients treated with gentamicin and is usually reversible upon withdrawal of the drug. In most cases nephrotoxicity is associated with an excessively high dosage or prolonged treatment, pre-existing renal abnormalities or associated with other substances reported to be nephrotoxic.

The adverse reactions considered at least possibly related to treatment are listed below by body system organ class and absolute frequency.

Frequencies are defined as:

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 (frequency cannot be estimated from the available data).

Infections and Infestations:

Very rare: Superinfection (with gentamicin-resistant germs), pseudomembranous colitis[1].

Blood and Lymphatic system disorders:

Uncommon: Dyscrasia.

Very rare: Thrombocytopaenia, reticulocytopaenia, leukopaenia, eosinophilia, granulocytopaenia, anaemia.

Immune system disorders:

Very rare: Hypersensitivity reactions of varying severity, ranging from rash and itching, drug fever to severe acute hypersensitivity reactions (anaphylaxis), up to anaphylactic shock.

Metabolism and Nutrition disorders:

Rare: Hypokalaemia, hypocalcaemia, hypomagnesaemia, PseudoBartter's syndrome in patients treated with high doses over a long period (more than 4 weeks), loss of appetite,

weight loss.

Very rare: Hypophosphataemia.

Psychiatric disorders:

Very rare: Confusion, hallucinations, mental depression.

Nervous system disorders:

Rare: Polyneuropathies, peripheral paraesthesias.

Very rare: Encephalopathy, convulsions, neuromuscular blockage, dizziness, balance disorder, headache.

Eye disorders:

Very rare: Visual disorders.

Ear and Labyrinth disorders:

Very rare: Vestibular damage, hearing loss, Meniére`s disease, tinnitus, vertigo.

Vascular disorders:

Very rare: Hypotension, hypertension.

Gastrointestinal disorders:

Rare: Vomiting, nausea, increased salivation, stomatitis.

Hepatobiliary disorders:

Rare: Increased Aspartate aminotransferase (AST), increased Alanine aminotransferase (ALT), increased alkaline phosphatase (ALP), reversible increase of serum bilirubin (all reversible).

Skin and Subcutaneous tissue disorders:

Uncommon: Allergic skin, exanthema.

Rare: Skin reddening.

Very rare: Toxic epidermal necrolysis, Stevens-Johnson syndrome, Erythema multiforme, Alopecia.

Musculoskeletal and Connective tissue disorders:

Rare: Muscle pain (myalgia).

Very rare: Amyostasia.

Renal and Urinary disorders:

Common: Renal function impairment[2].

Rare: Increased blood urea nitrogen (reversible).

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

General disorders and administration site conditions:

Rare: Increased body temperature.

Very rare: Pain at injection site.

1 Usually in these cases other antibiotics are also involved.

2 May occur as hypersensitivity 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

Pharmacotherapeutic group: Antibacterial for systemic use.

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 bactericidal efficacy both in the proliferation and in the resting stage of bacteria.

It forms a bond with the proteins of the 30S subunits of the bacterial ribosomes, which causes “misreading” of the 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.

Mechanism 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.

5.2. Pharmacokinetic properties

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.

5.3. 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 halflife 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.

5.4. Preclinical safety data

Chronic toxicity

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

Mutagenic and carcinogenic potential

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

Reproductive toxicity

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

Water for Injections BP

Sodium Hydroxide BP

Hydrochloric acid BP

Sodium bisulfite BP

6.2. Incompatibilities

In general, gentamicin should not be mixed with other medicinal products. In particular the

following are incompatible in mixed solution with gentamicin injection: beta-lactam antibiotics (e.g. penicillins, cephalosporins), erythromycin, or lipiphysan (a special oil-in-water-emulsion for parenteral nutrition) as this may cause physico-chemical inactivation. This also applies to a combination of gentamicin with diazepam, furosemide, flecainide acetate or heparin sodium. Dilution in the body will obviate the danger of physical and chemical incompatibility and enable gentamicin 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.

The following active substances or solution for reconstitution/dilution should not be administered simultaneously:

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

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

6.3. Shelf life

3 years

After first opening: from the microbiological point of view, the product should be used immediately.

After dilution: when diluted with 0.9% sodium chloride or 5% glucose solution, gentamicin is stable for 24 h at 30°C.

Chemical and physical in-use stability has been demonstrated for 24 hours at 30°C.

From a microbiological point of view, unless the method of opening/dilution precludes the risk of microbial contamination, 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.

6.4. Special precautions for storage

Store below 30º C. Do not refrigerate or freeze. Store in the original package in order to protect from light.

6.5. Nature and contents of container

The primary packaging material for storage of Gentamicin Injection is 2 ml of Type I amber glass ampoule.

Pack sizes: 10 ampoules of Gentamicin Injection are packed in a paperboard box.

6.6. Special precautions for disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER

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8. NUMBER(S) IN THE NATIONAL REGISTER OF FINISHED PHARMACEUTICAL PRODUCTS

07077/07914/NMR/2019

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

04/02/2022

10. DATE OF REVISION OF THE TEXT

04/08/2028