SUMMARY OF PRODUCT CHARACTERISTICS

1. Name of the medicinal product

Gentamicin Injection 80mg/2ml

2. Qualitative and quantitative composition

Each 2ml contains Gentamicin sulphate is equivalent to Gentamicin 80mg.

3. Pharmaceutical form

Small volume parenteral injection

4. Clinical particulars

4.1 Therapeutic indications

4.1 Therapeutic indications

Gentamicin is an aminoglycoside antibiotic with broad-spectrum bactericidal activity. It is indicated to treat severe infections caused by bacteria susceptible to gentamicin 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.

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

4.2 Posology and method of administration

ADULTS:

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

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

Urinary tract infections: As “Systemic infections”. Or, if renal function is not impaired, 160mg 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 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 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, newborns are given the required daily dose in 1 single dose.

THE 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 ototoxicity.

RENAL IMPAIRMENT:

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

Gentamicin is excreted by simple glomerular filtration and therefore reduced dosage is necessary where renal function is impaired. Nomograms are available for the calculation of dose, which depends on the patient's age, weight and renal function.

The following table may be useful when treating adults.

Blood Urea		Creatinine clearance (GFR)	Dose & frequency of administration
(mg/100ml)	(mmol/l)	(ml/min)	
< 40	6 - 7	> 70	80mg* 8 hourly

40 - 100	6 - 17	30 - 70	80mg* 12 hourly
100 - 200	17 - 34	10 - 30	80mg* daily
> 200	> 34	5 - 10	80mg* every 48 hours
Twice weekly intermittent haemodialysis		< 5	80mg* after dialysis

*60mg if body weight <60kg. 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 10mg/l, at which the possibility of ototoxicity should be considered. One hour concentrations of gentamicin should not exceed 10mg/l (but should reach 4mg/l), while the pre dose trough concentration should be less than 2mg/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 100ml.

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.

4.3 Contraindications

Hypersensitivity to the gentamicin or to any of the excipients, Myasthenia Gravis.

4.4 Special warnings and precautions for use

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.

Ototoxicity has been recorded following the use of gentamicin. Groups at special risk include patients with impaired renal function, infants and possibly the elderly.

Consequently, renal, auditory and vestibular functions should be monitored in these patients and serum levels determined so as to avoid peak concentrations above 10mg/l and troughs above 2mg/l when administrating Gentamicin twice daily and 1 mg/l for a once daily dose. 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.
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. Potent diuretics such as etacrynic acid and furosemide are believed 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 gentamicin. Consequently, if this combination is used monitoring of kidney function is advised.
Neuromuscular blockade and respiratory paralysis have been reported from administration of aminoglycosides to patients who have received curare-type muscle relaxants during anaesthesia.
Indometacin possibly increases plasma concentrations of gentamicin in neonates.
Concurrent use with oral anticoagulants may increase the hypothrombinanaemic effect.
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.

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

4.6 Fertility, pregnancy and lactation

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. 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.

4.8 Undesirable effects

Side-effects include vestibular damage or hearing loss, particularly after exposure to ototoxic drugs or in the presence of renal dysfunction. Nephrotoxicity (usually reversible) and occasionally acute renal failure, hypersensitivity, anaemia, blood dycrasias, purpura, stomatitis, convulsions and effects on liver function occur occasionally.

Rarely hypomagnesia on prolonged therapy and antibiotic–associated colitis have been reported.

Nausea, vomiting and rash have also been reported.

Central neurotoxicity, including encephalopathy, confusion, lethargy, mental depression and hallucinations, has been reported in association with gentamicin therapy but this is extremely rare.

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 gentamicin.

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5. Pharmacological properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Anti-bacterials for systemic use, ATC Code: J01GB03

Gentamicin 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.

Gentamicin 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

Gentamicin is not readily absorbed from the gastro-intestinal tract. Gentamicin 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 gentamicin.

Paediatric population (premature infants and neonates)

Distribution

The distribution volume of gentamicin 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 gentamicin 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

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 – 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 gentamicin to rodents and guinea pigs produces developmental toxicity of the kidney and/or inner ear in fetuses and offspring.

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6. Pharmaceutical particulars

6.1 List of excipients
Anhydrous sodium sulfate

H2SO4(for pH adjustment)

Water for Injection

6.2 Incompatibilities
In general, gentamicin injection should not be mixed.

In particular the following are incompatible in mixed solution with gentamicin injection:

- 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 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
3 years

6.4 Special precautions for storage
Do not store above 30°C. Do not refrigerate or freeze.

6.5 Nature and contents of container
The Gentamicin Injection 80mg/2ml is filled in 2ml ampoule vial

6.6 Special precautions for disposal and other handling
No special requirements.

7. Marketing authorisation holder

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