Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Genticin 80mg/2ml Solution for Injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 2 ml ampoule contains gentamicin sulfate equivalent to 80 mg gentamicin base.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for injection.

Each ampoule contains a sterile, clear colourless to pale yellow solution. The solution is preservative free.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Genticin Solution for Injection is indicated in adolescents, children and adults for the following:

The treatment of systemic infections due to susceptible bacteria such as, bacteraemia, septicaemia, urinary-tract infections and severe chest infections.

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

4.2 Posology and method of administration

Posology

The daily dose recommended in children, adolescents and adults with normal renal function, is 3-6 mg/kg body weight per day as 1 (preferred) up to 2 single doses.

Paediatric population (newborns and infants)
The daily dose in newborns is 4.0- 7.0 mg/kg body weight per day. Due to the longer half-life, newborns are given the required daily dose in 1 single dose.
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.

In children and in neonates, it can be expected that serum levels will be lower than those found in adults at equivalent dosage per kg body weight.

Elderly population
Adjust dosage according to weight and renal function. Older people may require lower maintenance doses than younger adults because of impaired renal function.

Serious infections
In life-threatening infections the frequency of dosage may need to be increased to 6-hourly and the quantity of each dose may also be increased at the discretion of the clinician up to a total dosage of 6 mg/kg in 24 hours. In such cases it is advisable to monitor gentamicin serum levels.

If renal function is not impaired, 160 mg once daily may be used in some cases.

Renal impairment

In cases of impaired renal function a reduction in dosage frequency is recommended. Patients with renal function impairment should be monitored in order to adjust the therapeutic concentrations in plasma, either by decreasing the dose or by increasing the dosage interval.

The most important risk factors are high total dose, long duration of therapy, raised serum level (high trough level). Dose reduction and interval prolongation are referred to as suitable solutions for managing patients with renal function impairment (see section 4.4).

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	80 mg† 8-hourly
40 – 100	30 - 70	80 mg† 12-hourly
100 – 200	10 - 30	80 mg† daily
> 200	5 - 10	80 mg† every 48 hours
Twice-weekly intermittent haemodialysis	< 5	80 mg† after dialysis

† 60mg if body weight < 60kg.

The creatinine clearance should be preferred as a parameter especially in the elderly and in patients with fluctuating serum-creatinine concentrations, as it is observed in severe infections (e.g. sepsis).

Dosage in patients undergoing haemodialysis
Gentamicin is dialysable. In the case of a 4 – 5-hour haemodialysis, a 50 - 60% reduction in concentration should be expected and in the case of an 8 –12-hour haemodialysis, a 70 - 80% reduction in concentration. The dosage must be individually adjusted after each dialysis, based on the gentamicin serum concentration at that time. The normal recommended dose after dialysis is 1 – 1.7 mg/kg body weight.

Hepatic impairment
Liver disease can be a risk factor for nephrotoxicity, so caution should be applied, regarding the dosing regimen.

In obese patients
The initial dose should be based on ideal body weight plus 40% of weight excess. Caution is advised in significant obesity as gentamicin is poorly distributed into fatty tissue. The dosage calculation should be based on an estimate of lean body weight. Serum levels should be monitored closely and the dose possibly adjusted (see section 4.4).

Method of administration

Genticin Solution for Injection is normally administered intramuscularly but may be given intravenously as a slow intravenous injection over at least 3 minutes or short infusion if required. Genticin Solution for Injection should not be given as a slow infusion or mixed with other drugs before use (see section 6.2).

Monitoring advice
Serum concentration monitoring of gentamicin is recommended, assess kidney function and hearing levels. Monitoring should occur before, after and during treatment with gentamicin. This monitoring applies to all patients, inclusive of adults, elderly, children and adolescents, including patients with liver and kidney failure. Samples are taken at the end of a dosing interval (trough level). Trough levels should not exceed 2 microgram/ml if gentamicin is administered twice daily and 1 microgram/ml for a once daily dosing.

Prolonged use of this medication should be avoided and whenever possible the treatment should not exceed 7 days.

4.3 Contraindications

Hypersensitivity to the active substance, to other aminoglycosides or to any of the excipients listed in section 6.1.

Genticin Solution for Injection is contraindicated in Myasthenia gravis.

4.4 Special warnings and precautions for use

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

Where renal function is impaired through disease or old age the frequency, but not the amount, of each dose should be reduced according to the degree of impairment (see section 4.2).

Gentamicin is excreted by simple glomerular filtration, and dosage frequency may be predicted by assessing creatinine clearance rates or blood urea and reducing the frequency accordingly. Renal impairment such as restriction of glomerular filtration is observed in approximately 10 % of patients treated with gentamicin is usually reversible. Volume depletion or hypotension and liver disease have been reported as additional risk factors for nephrotoxicity; in addition, other potential risk factors are age, hypovolaemia and shock. Clinical signs of renal damage are proteinuria, cylindruria, haematuria, oliguria, raised creatinine and urea concentrations in serum. 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.

Antibiotic-associated diarrhoea and pseudomembranous colitis, have been reported with the use of gentamicin. These diagnoses should be considered in any patient who develops diarrhoea during or shortly after treatment. It is recommended that gentamicin is discontinued if severe and/or bloody diarrhoea occurs during treatment, followed by rehydration, and appropriate therapy instituted. Drugs that inhibit peristalsis must not be given (see section 4.8).

Ototoxicity has been recorded following the use of gentamicin. Impaired hepatic function or auditory function, bacteraemia and fever have been reported to increase the risk of ototoxicity. 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 10 mg/l and troughs above 2 mg/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. Gentamicin related auditory impairment and balance impairment can sometimes be irreversible (see section 4.8).

There is an increased risk of ototoxicity in patients with mitochondrial DNA mutations (particularly the nucleotide 1555 A to G substitution in the 12S rRNA gene), even if aminoglycoside serum levels are within the recommended range during treatment. Alternative treatment options should be considered in such patients.

In patients with a maternal history of relevant mutations or aminoglycoside induced deafness, alternative treatments or genetic testing prior to administration should be considered.

Co-administration of ototoxic or nephrotoxic medicines can increase the risk nephrotoxicity and otoxicity associated with gentamicin (see section 4.5).

Caution is required in Parkinsonism and other conditions characterised by muscular weakness as gentamicin has neuromuscular blocking properties. Neuromuscular blockade and respiratory paralysis have been reported from administration of aminoglycosides to patients who have received curare-type muscle relaxants during anaesthesia. These patients should be monitored very carefully (see section 4.8).

In cases of significant obesity gentamicin serum concentrations should be closely monitored and a reduction in dose should be considered (see section 4.2).

Hypersensitivity reactions have occurred, especially after local use, and cross-sensitivity between aminoglycosides may occur. Very rarely, anaphylactic reactions to gentamicin have occurred. Some hypersensitivity reactions have been attributed to the presence of sulfites in parenteral formulations, and endotoxic shock (see section 4.8).

Gentamicin should only be used in pregnancy if considered essential by the physician (see section 4.6)

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

4.5 Interaction with other medicinal products and other forms of interaction

Gentamicin should not be used concurrently with other potentially nephrotoxic or ototoxic drug substances unless considered essential by the physician. The potential nephrotoxicity of other aminoglycosides, vancomycin, ciclosporin, cisplatin, fludarabine and amphotericin may be increased in the presence of gentamicin and monitoring of renal function is therefore recommended.

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.

Furosemide (frusemide) and piretanide may potentiate the ototoxicity of gentamicin, and etacrynic acid, which is ototoxic in its own right, should be avoided with gentamicin.

Aminoglycosides, including gentamicin, may induce neuromuscular blockade and respiratory paralysis and should therefore only be used with great caution in patients receiving curare-type muscle relaxants.

Aminoglycosides antagonise the effects of cholinergic agents such as neostigmine and pyridostigmine.

Indomethacin has been reported to increase the plasma concentrations of aminoglycosides when given concomitantly.

Bacteriostatic antibiotics may give an antagonistic interaction, but in some cases (e.g. with clindamycin and lincomycin) the disadvantage of antagonism may be outweighed by the addition of activity against anaerobic organisms. Synergistic action has been demonstrated with penicillin. However, if penicillins (such as ticarcillin) are used with gentamicin the drugs should not be physically mixed. In cases where both drugs need to be administered intravenously, patients with poor renal function should be monitored for effectiveness of the gentamicin. There should also be an intervening flush of suitable fluid between both medicinal products, or they should be given at separate sites (see section 6.2). Cross-sensitivity with aminoglycosides may occur.

Aminoglycosides such as gentamicin may increase the kidney damaging effect of methoxyflurane. When used concurrently, extremely severe nephropathies are possible. The anaesthetist should be made aware of the use of aminoglycosides before a surgical procedure.

Concurrent use with oral anticoagulants may increase the hypoprothrombinemic 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.

4.6 Fertility, pregnancy and lactation

Pregnancy
Safety for use in pregnancy has not been established. Gentamicin crosses the placenta and there is a risk of ototoxicity (auditory or vestibular nerve damage) in the foetus. Gentamicin should only be used where the seriousness of the mother's condition justifies the risk and use is considered essential by the physician. In such cases, serum gentamicin concentration monitoring is essential. Some animal studies have shown a teratogenic effect.

Breast-feeding
Gentamicin is excreted in breast milk, but is unlikely to be a hazard to the infant except in the presence of maternal renal insufficiency when breast-feeding should be avoided, as the levels in breast milk then rise appreciably. 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.

Fertility
No data available

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. In the case of administration to outpatients, caution is advised when driving and using machines in view of the possible undesired effects such as dizziness and vertigo.

4.8 Undesirable effects

As with all aminoglycosides, at critical levels gentamicin exhibits toxicity.
The following undesirable effects have been reported for gentamicin. The undesirable effects are listed according to their frequency:

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 (caused by gentamicin-resistant bacteria)

Blood and lymphatic system disorders
Uncommon: Blood dyscrasias, including pancytopenia

Very Rare: Anaemia, reversible granulocytopenia and neutropenia, have been reported infrequently. Thrombocytopenia, reticulocytopaenia, leukopaenia and eosinophilia have also been seen.

Immune system disorders
Very Rare: Hypersensitivity reactions and allergic rashes have occurred. Very rarely, anaphylactic reactions (including anaphylactic shock) to gentamicin have occurred.

Metabolism and nutrition disorders
Rare: Electrolyte disturbances (e.g. hypomagnesaemia, hypocalcaemia and hypokalaemia). Loss of appetite, weight loss, pseudo-Bartter syndrome in patients treated with high doses over a long period (more than 4 weeks).

Very rare: Hypophosphatemia

Psychiatric disorders
Very Rare: Confusion, hallucinations, mental depression

Nervous system disorders
Rare: Polyneuropathies, peripheral paraesthesias.

Very Rare: Headache, central neurotoxicity, including encephalopathy, convulsions, confusional state, lethargy, hallucinations and mental depression has been reported with gentamicin therapy, but this is extremely rare.

Gentamicin can cause neuromuscular blockade which may unmask or aggravate myasthenia gravis and cause postoperative respiratory distress.

Ear and labyrinth disorders
Not known: Irreversible hearing loss, deafness

Eye disorders
Very Rare: Visual disorders.

Vascular disorders
Very Rare: Hypotension, hypertension

Gastrointestinal system disorders
Rare: Infrequent effects reported include nausea, salivation increase, vomiting and stomatitis.
Very rare: pseudomembranous colitis.

Hepatobiliary disorders
Rare: Signs of liver dysfunction such as transient elevation of serum aminotransferase values, increased alkaline phosphatase and increased serum bilirubin concentration have been reported infrequently.

Skin and subcutaneous tissue disorders
Uncommon: Allergic skin exanthema
Rare: Skin reddening
Very rare: Toxic epidermal necrolysis, Stevens-Johnson syndrome, Alopecia, Erythema multiforme.
Not known: Rash, purpura, pruritus and urticaria have been reported.

Musculoskeletal and connective tissue disorders
Rare: myalgia
Very Rare: Amyostasia

Renal and urinary disorders
Common: Renal impairment
Rare: Blood urea nitrogen increased (reversible)
Very rare: Acute renal failure, hyperphosphaturia, aminoaciduria, Fanconi-like syndrome in patients treated with a prolonged course of high-dose.

Nephrotoxicity may occur, resulting in a gradual reduction in creatinine clearance after several days of treatment. This is usually reversible if the drug is withdrawn. Nephrotoxicity is more common if trough serum concentrations exceed 2 micrograms/ml and where there is pre-existing renal disease or concomitant treatment with other nephrotoxic agents. Renal failure, renal tubular necrosis and tubulointerstitial nephritis have been reported.

General disorders and administration site conditions
Rare: increased body temperature
Very Rare: Pain at injection site.

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:
HPRA Pharmacovigilance,
Website: www.hpra.ie.

4.9 Overdose

Gentamicin has a narrow therapeutic window, in the event of accumulation (e.g. as a result of impaired renal function), renal damage and damage to the vestibulocochlear nerve may occur.

Symptoms
Symptoms include dizziness, vertigo and hearing loss if overdose accidentally given parenterally.

Management
If the reaction is severe consider haemodialysis as treatment. Gentamicin may be removed from the body by haemodialysis or peritoneal dialysis. Calcium salts given intravenously have been used to counter the neuromuscular blockade caused by gentamicin.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group:Antibacterials for systemic use, ATC code: J01GB03

Mechanism of action
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, sulfonamides, tetracycline) may be transferred on the same plasmid.

There is partial cross-resistance between gentamicin and other aminoglycosides.

5.2 Pharmacokinetic properties

Absorption
Gentamicin is rapidly absorbed following intramuscular injection, giving peak plasma concentrations after 30 minutes - 1 hour. Effective plasma concentration is 4 – 8 microgram/ml. Effective concentrations are still present 4 hours after injection. An injection of 1 mg/kg body weight results in a peak plasma concentration of approximately 4 micrograms/ml.

Gentamicin is 70-85% bound to plasma albumin following administration.

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.

Elimination
Gentamicin is not metabolised 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. > 90% gentamicin is excreted unchanged in the urine by glomerular filtration. 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.

The elimination rate constant is:
0.02 hr^{-1} for anuric patients*
0.30 hr^{-1} normal
*therefore, in those with anuria, care must be exercised.

5.3 Preclinical safety data

There are no preclinical 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

Water for Injections
Sulfuric acid (for pH adjustment)

6.2 Incompatibilities

In general, mixing Genticin Solution for Injection with other drugs prior to administration is not advised. In particular the following are incompatible in mixed solution: penicillins, cephalosporins, erythromycin, lipiphysan, heparins and sodium bicarbonate. In the latter case 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.

Dilution in the body will obviate the danger of physical and chemical incompatibility and enable Genticin Solution for Injection 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. However, in the case of carbenicillin and gentamicin they should only be given at separate sites.

6.3 Shelf life

4 years.

6.4 Special precautions for storage

Do not store above 25°C. Do not freeze.

6.5 Nature and contents of container

Genticin Solution for Injection is available in colourless, Type 1 glass ampoules containing 2ml, in boxes of 10 ampoules.

6.6 Special precautions for disposal and other handling

For single use only.

Discard any portion of the contents remaining after use.
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Amdipharm Limited
Temple Chambers
3 Burlington Road
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8 MARKETING AUTHORISATION NUMBER

PA1142/013/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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