SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Genticin Injectable
Gentamicin 40 mg/ml Solution for Injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ampoule (2 ml) 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

Gentamicin 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
Adults
The daily recommended dose in adults with normal renal function is 3-6mg/kg body weight per day as one (preferred) up to two single doses.
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 5mg/kg in 24 hours. In such cases it is advisable to monitor gentamicin serum levels.
If renal function is not impaired, 160mg once daily may be used in some cases.

Renal impairment

In cases of impaired renal function a reduction in dosage frequency is recommended. 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	80mg† 8-hourly
40 - 100	30 - 70	80mg† 12-hourly
100 - 200	10 - 30	80mg† daily
>200	5 - 10	80mg† every 48 hours
Twice-weekly intermittent haemodialysis	<5	80mg† after dialysis

† 60mg if body weight <60kg

Paediatric population:

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

The daily dose in infants after the first month of life is 4.5-7.5mg/kg body weight per day as one (preferred) up to two single doses.

The daily dose in newborns is 4-7mg/kg body weight per day. Due to the longer half-life, newborns are given the required daily dose in one single dose.

Method of administration:

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

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 2µg/ml administering gentamicin twice daily and 1µg/ml for a once daily dose.

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

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 4.4).

4.3 Contraindications

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

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. Gentamicin is excreted by simple glomerular filtration, and dosage frequency may be predicted by assessing serum creatinine, creatinine clearance rates or blood urea and reducing the frequency accordingly. Volume depletion or hypotension and liver disease have been reported as additional risk factors for nephrotoxicity. 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.

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 10mg/l and troughs above 2mg/l when administrating Gentamicin twice daily and 1mg/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.

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. Mitochondrial mutations are rare, and the penetrance of this observed effect is unknown.

Caution is required in Parkinsonism and other 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 (see section 4.2).

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.

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).

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.

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

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.

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 and patients with poor renal function should be monitored for effectiveness of the gentamicin. Cross-sensitivity with aminoglycosides may occur.

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. 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.

Fertility

No data available

4.7 Effects on ability to drive and use machines

This medicine has no or negligible influence on the ability to drive and use machines.

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 (≥1/1,000 to <1/100)

Rare (≥1/10,000 to <1/1,000)

Very rare (<1/10,000)

Not known (cannot be estimated from the available data)

System Organ Class	Frequency	Adverse reaction
Infections and infestations	Not known	Superinfection (caused by gentamicin-resistant bacteria) Pseudomembranous colitis[1]
Blood and lymphatic system disorders	Uncommon Not known	Blood disorder Anaemia
Immune system disorders	Not known	Anaphylactic reaction (including anaphylactic

		shock) and hypersensitivity
Metabolism and nutrition disorders	Rare	Electrolyte imbalance (e.g. hypomagnesaemia, hypocalcaemia and hypokalaemia)
Psychiatric disorders	Very rare	Confusional state, hallucination and depression
Nervous system disorders	Common Very rare	Neuromuscular blockade[2] Encephalopathy, seizure
Ear and labyrinth disorders	Not known	Irreversible hearing loss, deafness
Vascular disorders	Not known	Purpura
Gastrointestinal disorders	Uncommon	Nausea, vomiting, stomatitis.
Skin and subcutaneous tissue disorders	Not known	Steven Johnson syndrome, Toxic epidermal necrosis. Rash
Renal and urinary disorders	Very rare Not known	Acute renal failure, Fanconi-like syndrome in patients treated with a prolonged course of high-dose Nephropathy toxic [3],
General disorders and administration site conditions	Very rare	Lethargy
Investigations	Uncommon	Aspartate/alanine aminotransferase increased, blood bilirubin increased

[1] usually in these cases other antibiotics are also involved.

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

[3] 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.

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 the Yellow Card Scheme Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

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 1-8µg/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 - 8µg/ml. Effective concentrations are still present 4 hours after injection. An injection of 1mg/kg body weight results in a peak plasma concentration of approximately 4 micrograms/ml.

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

T½ = 2 - 3 hours in individuals with normal kidney function, but can be increased in individuals with renal insufficiency.

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 volume of distribution (VD) is 0.3 l/kg.

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.

>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 SPC.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Water for Injection
Sulfuric acid

6.2 Incompatibilities

In general, mixing this product 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 this product 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 25ºC. Do not freeze.

6.5 Nature and contents of container

This product is available in colourless, Type I glass ampoules containing 2ml, in boxes of 10 ampoules.

6.6 Special precautions for disposal and other handling

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

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EC2M 1QS, United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

PL 20072/0056

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