Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Gentamicin 10 mg/ml solution for injection or infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

1 ml of solution for injection or infusion contains gentamicin sulfate equivalent to 10 mg gentamicin.
Each ampoule (2ml) contains Gentamicin Sulfate Ph Eur equivalent to 20mg Gentamicin.
This medicine contains 0.78 mg of sodium per ampoule; it is essentially sodium free.
This medicine contains 3.2 mg of sodium metabisulfite

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for Injection or Infusion.
Clear, colourless solution, having pH ranging from 3.0 to 5.5.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Indications: gentamicin is indicated in bacteraemia, urinary tract infections, chest infections, severe neonatal infections and other serious systemic infections due to susceptible organisms, in adults and children including neonates.
Please see section 5.1.
Consideration should be given to official local guidance on the appropriate use of antibacterial agents.

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 daily 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, 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 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 body weight per day as 1 single dose (preferred) or up to 2 single doses.

The daily dose in neonates is 4-7 mg/kg body weight per 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:

Gentamicin 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	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 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 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*

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 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. Please refer to section 4.4

4.3 Contraindications

Hypersensitivity to the active substance(s) or to any of the excipients listed in section 6.1;
myasthenia gravis.

4.4 Special warnings and precautions for use

In patients with advanced renal impairment or with pre-existing inner ear deafness, gentamicin should be used only if its use is considered essential by the physician. The frequency or dose of administration should be reduced in patients with impaired renal function (see section 4.2).

Renalimpairment
Renal impairment such as restriction of glomerular filtration is observed in approximately 10% of patients treated with gentamicin and is usually reversible. The most important risk factors are high total dose, long duration of therapy, raised serum level (high trough level); 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 isolated cases, acute renal failure may occur. (See also section 4.8)

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 (see section 4.8). 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 4.8). Serum levels are determined so as to avoid peak concentrations above 10mg/L and troughs above 1 mg/L when administering gentamicin once daily and 2mg/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 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.

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.

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.

In cases of significant obesity gentamicin serum concentrations should be closely monitored and a reduction in dose should be considered. To avoid adverse events, continuous monitoring (before, during and after treatment) of hepatic an laboratory parameters is also recommended.

Neuromusculardisorders
Since gentamicin has neuromuscular blocking properties, particular caution should be exercised in patients with pre- existing neuromuscular diseases (e.g. Parkinson's disease). Particularly careful monitoring is mandatory. (See also section 4.8.)

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 also be monitored very carefully. (See also section 4.8.)

Effect on vestibulocochlearnerve
Damage to the vestibulocochlear nerve (eighth cranial nerve), whereby both balance and hearing may be affected, is possible. Vestibular damage is the most common ototoxic reaction. Hearing loss is manifested initially by diminution of high-tone acuity and is usually irreversible. Important risk factors are pre-existing renal impairment or a history of damage to the eighth cranial nerve; in addition, the risk increases in proportion to the level of the total and daily dose or by association with potentially ototoxic substances. Symptoms of ototoxic effects are: dizziness, ringing/roaring in the ears (tinnitus), vertigo and less common hearing loss.
With gentamicin the vestibular mechanism may be affected if trough levels of 2 µg/ml are exceeded. This is usually reversible if observed promptly and the dose adjusted. (See also section 4.8)

Antibiotic-associateddiarrhoea,pseudomembranouscolitis
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 patients 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).

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

Pregnancy and lactation
Gentamicin should be used in pregnancy and during lactation only after careful benefit risk assessment (see section 4.6).

Once dailydosing ofgentamicin in elderlypatients:
There is limited experience with once daily dosing of gentamicin in elderly patients. Once daily dosing of gentamicin may not be suitable and therefore, close monitoring is warranted in these patients.

Excipients
This medicine contains 0,78 mg of sodium per ampoule (less than 23 mg per ampoule), i.e. it is essentially sodium free.
Sodium metabisulphite, one of the excipients of this medicinal product, may rarely cause severe hypersensitivity reactions and bronchospasm.
Cross-allergenicity/-resistance
Cross resistance and hypersensitivity to aminoglycosides may occur.

Monitoring
To avoid adverse events, continuous monitoring (before, during and after treatment) of renal function (serum creatinin, creatinin clearance), control of function of vestibule and cochlea as well as hepatic and laboratory parameters is recommended.
In order to reduce the risk of nephrotoxicity and ototoxicity, the following instructions should be considered:

- Regular assessment of auditory, vestibular and renal function is particularly necessary in patients with additional risk factors. Impaired hepatic function or auditory function, bacteraemia and fever have been reported to increase the risk of ototoxicity. Volume depletion or hypotension and liver disease have been reported as additional risk factors for nephrotoxicity.
- Monitoring of renal function before, during and after treatment.
- Dosage strictly according to creatinine clearance (or serum creatinine concentration). In patients with impaired renal function, the dosage must be adjusted according to renal performance (see section 4.2).
- In patients with impaired renal function additionally receiving gentamicin locally (inhalation, intratracheal, instillation),the amount of gentamicin absorbed after local administration must also be taken into account for dose adjustment of systemic treatment.
- Monitoring of serum gentamicin concentrations during therapy in order to avoid that peak levels exceed 10 µg/ml (toxic threshold for the cochleo-vestibular system) with conventional multiple daily dosing or trough levels exceed 2 µg/ml (see section 4.2) when administrating gentamicin twice daily and 1 mg/l for a once daily dosing.
- In patients with pre-existing inner ear damage (hearing impairment or balance function impairment), or where treatment is long-term, additional monitoring of the balance function and hearing is required.
- Prolonged treatment should be avoided. If possible, the duration of therapy should be limited to 7 – 10 days (see section 4.2).
- Avoid therapy with aminoglycosides immediately subsequent to previous aminoglycoside treatment; if possible, there should be an interval of 7 – 14 days between treatments.
- If possible, avoid concurrent administration of other potentially ototoxic and nephrotoxic substances. If this is unavoidable, particular careful monitoring of renal function is indicated (see section 4.5).
- Ensure adequate hydration and urine production.

4.5 Interaction with other medicinal products and other forms of interaction

Muscle relaxants and ether
The neuromuscular blocking activity ofaminoglycosides is enhanced by ether and muscle relaxants.
If gentamicin is administered during orimmediately after surgery, the neuromuscular blockade may be enhanced and prolonged ifnon-depolarising muscle relaxants areused. Theseinteractions may causeneuromuscular blockage and respiratory paralysis**.**Because of theincreased risk, such patients should be monitored with particular care.
Injection with calcium chloridemay reverse theneuromuscular blockade due to aminoglycosides but should be undertaken with caution.

Methoxyflurane anaesthesia
Aminoglycosides may increase the kidney damaging effect of methoxyflurane. When used concurrently, extremely severe nephropathies arepossible. The anaesthetist should be made aware of the use ofaminoglycosides before a surgical procedure.

Potentially nephrotoxic or ototoxic drugs
Concurrent administration of gentamicin and other potentially ototoxic or nephrotoxic drugs should be avoided whenever possible. Where co- administration is considered necessary, because of the increased risk ofundesired effects, careful monitoring is required ofpatients being treated concurrently orsequentially with potentially nephrotoxic or ototoxicdrugs such as:

- Antibacterials: somecephalosporins notably cephalotin and cephaloridine, colistin, vancomycin, viomycin, other aminoglycosides such as streptomycin
- Antifungals: amphotericin B
- Loop diuretics such as ethacrynic acid and frusemide
- Cytotoxics: cisplatin. It must benoted that thenephrotoxicity ofgentamicin can be increased even 3 to 4 weeks after these substances are administered.
- Anti suppressant: ciclosporin

Other antibiotics
Areduction in gentamicin serum half-life has been reported in patients with severe renal impairment receiving carbenicillin concomitantly with gentamicin.
Indometacin
Indometacin possibly increases plasma concentrations of gentamicin in neonates.
Oral anticoagulants
Concurrent use with oral anticoagulants may increase the hypothrombinanaemic effect.
Bisphosphonates
Concurrent use of bisphosphonates may increase the risk of hypocalcaemia.
Cholinergics
Antagonism of effect may occur with concomitant administration of gentamicin with either neostigmine or pyridostigmine. Concurrent use of 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 adequate data from the use of gentamicin in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3). Gentamicin crosses the placenta. Because of the potential risk of inner ear and renal damage to the fetus, gentamicin should not be used in pregnancy unless in case of a life-threatening indication and if the benefit outweighs the risk.
In case of exposition to gentamicin during pregnancy, monitoring of hearing and renal function of the newborn is recommended.

Breast-feeding
Gentamicin is excreted in human breast milk and was detected in low concentrations in serum of breast-fed 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 possibleundesired 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:
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 (frequency cannot be estimated from the available data).

System Organ	Common	Uncommon	Rare	Very rare	Frequency

Class	(≥1/100 to <1/10)	(≥1/1000 to <1/100)	(≥1/10 000 to <1/1000)	(<1/10 000)	**not known** (cannot be estimated from the available data)
Infections and infestations				Superinfection (with gentamicin-resistant germs), pseudomembranous colitis (see also section 4.4)1	
Blood and lymphatic system disorders		Dyscrasia		Thrombocytopaenia, reticulocytopaenia, leukopaenia, eosinophilia, granulocytopaenia, anaemia	
Immune system disorders				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			Hypokalaemia, hypocalcaemia, hypomagnesaemia, pseudo-Bartter syndrome in patients treated with high doses over a long period (more than 4 weeks), loss of appetite, weight loss	Hypophosphataemia	
Psychiatric disorders				Confusion, hallucinations, mental depression	
Nervous system disorders			Polyneuropathies, peripheral paraesthesias	Encephalopathy, convulsions, neuromuscular blockage, dizziness, balance disorder, headache (see also section 4.4)	
Eye disorders				Visual disorders	
Ear and labyrinth disorders				Vestibular damage, hearing loss, Meniére`s disease, tinnitus vertigo (see also section 4.4)	Irreversible hearing loss, deafness
Vascular disorders				Hypotension, hypertension	
Gastrointestinal disorders			Vomiting, nausea, salivation increased, stomatitis		
Hepatobiliary disorders			Aspartate aminotransferase (AST) increased, Alanine aminotransferase (ALT) increased, alkaline phosphatase (ALP) increased, reversible increase of serum bilirubin (all reversible)		

Skin and subcutaneous tissue disorders		Allergic skin exanthema	Skin reddening	Toxic epidermal necrolysis, Stevens-Johnson syndrome, Erythema multiforme, Alopecia	
Musculoskeletal and connective tissue disorders			Muscle pain (myalgia)	Amyostasia	
Renal and urinary disorders	Renal function impairment[2]		Blood urea nitrogen increased (reversible)	Acute renal failure, hyperphosphaturia, aminoaciduria, Fanconi- like syndrome in patients treated with a prolonged course of high-dose, see also section 4.4.	
General disorders and administration site conditions			Increased body temperature	Pain at injection site	

1. Usually in these cases other antibiotics are also involved.
2. May occur as hypersensitivity reactions

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

Haemodialysis and peritoneal dialysis will aid removal from the blood but the former is probably more efficient.
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 thehighest toxicity. The antibacterial activity ofgentamicin sulphate is determined both on thebasis of units and also on thebasis ofmass (weight).

Mechanism of action:
Gentamicin has bactericidal efficacy both in theproliferation and in theresting stage ofbacteria. It forms a bond with theproteins of the 30S subunits of thebacterial 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 ofinfection. 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 thedosage interval to beextended without loss ofefficacy against most Gram-negative bacilli.

Mechanism of resistance

Resistance may be due to a failure of permeation, lowaffinity for thebacterial ribosome or inactivation ofgentamicin by microbial enzymes. The emergence of resistance during therapy is unusual.

Breakpoints

According to EUCAST, the following limit values apply for gentamicin:

Pathogen	**Susceptible**	**Resistant**
Enterobacteriaceae	2 mg/l	> 4 mg/l
Pseudomonas *spp.*	4 mg/l	> 4 mg/l
Acinetobacter *spp.*	4 mg/l	> 4 mg/l
Staphylococcus *spp.*	1 mg/l	> 1 mg/l
Non-species related breakpoints *	2 mg/l	> 4 mg/l

The prevalence of acquired resistance may vary geographically and with time for selected species and local information on resistance is desirable, particularly when treating severe infections. As necessary, expert advice should be sought when the local prevalence ofresistance is such that theutility of the agent in at least sometypes of infections is questionable. Especially in such circumstances, samples should beobtained in order to identify the causal micro- organism and to measure its sensitivity to gentamicin.

Commonly susceptible species (according to EUCAST)
Aerobic Gram-positive micro-organisms
Listeria monocytogenes
Staphylococcus aureus (MSSA)
Aerobic Gram-negative micro-organisms
Campylobacter coli
Campylobacter jejuni
Citrobacter koseri
Enterobacter aerogenes
Enterobacter cloacae
Escherichia coli
Francisella tularensis
Klebsiella oxytoca
Klebsiella pneumoniae
Proteus vulgaris
Salmonella enterica subsp. enterica
Serratia marcescens
Yersinia enterolitica
Yersinia pseudotuberculosis
Species for which acquired resistance may be a problem
Aerobic Gram-positive micro-organisms
Staphylococcus aureus (MRSA) *Staphylococcus epidermidis*
Staphylococcus haemolyticus *Staphylococcus hominis*
Aerobic Gram-negative micro-organisms
Acinetobacter spp.
Citrobacter freundii
Morganella morganii
Proteus mirabilis

Pseudomonas aeruginosa
Inherently resistant organisms
Aerobic Gram-positive micro-organisms
Enterococcus faecalis
Enterococcus faecium
Streptococcus spp.
Aerobic Gram-negative micro-organisms
Burkholderia cepacia
Legionella pneumophila
Stenotrophomonas maltophilia
Anaerobic micro-organisms
Bacteroides spp.
Clostridium difficile
Others
Atypical pathogens
Chlamydia spp.
Chlamydophila spp.
Mycoplasma spp.
Ureaplasma urealyticum

Abbreviations:
MSSA = Methicillin-sensitive *Staphylococcusaureus,*
MRSA = Methicillin-resistant *Staphylococcus aureus*

Infections caused by Streptococci or Enterococci:
Aminoglycosides are suitable combination partners forother antibiotics against Gram-positive cocci. For some indications (endocarditis), synergistic effects with beta-lactams have been described. This synergy is abolished when Streptococci or Enterococci present a high level acquired resistance to gentamicin.

Other notes:
Synergistic effects have been described with acylamino penicillins (e.g. piperacillin) on Pseudomonas aeruginosa and with cephalosporins on Klebsiella pneumoniae.

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 asingle daily infusion. When gentamicin is administered by intravenous short infusion of 30 minutes at 4 mg/kg body weight per day in threedivided 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 andtrough concentrations of 9.5 µg/mland 0.4 µg/mlwere measured.

Therapeutic serumconcentrations 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/mlfor once daily dosing. Maximum serum concentrations of 10 – 12 µg/ml should not be exceeded when administered conventionally, inseveral 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 ofextracellular water. In thenewborn 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/kgfor an adolescent. The larger volume of distribution per kg bodyweight means that for adequate peak blood concentration ahigher dose per kg bodyweight needs to beadministered.

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

Gentamicin crosses the placenta; thefoetal 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 ofgentamicin into the cerebrospinal fluid is poor in un-inflamed meninges. In inflamed meninges, concentrations reach up to 30% of theconcentrations measured in plasma.

Plasma protein binding:less than 10%.

Biotransformation
Gentamicin is not metabolised in the organism but is excreted unchanged in microbiologically activeform.

Elimination
Gentamicin is eliminated unchanged in microbiologically active form principally in theurine by glomerular filtration. The dominant elimination half-life in patients with normal renal function is around 2 – 3 hours. Elderly patients eliminate gentamicin more slowly than youngeradults.

5.3 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 apotential risk ofinner ear and renal damage to the fetus as was observed for the class ofaminoglycoside antibiotics. Fetal renal abnormalities have been documented in rats and guinea pigs after administration ofgentamicin to thedams.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium Metabisulfite (E223)
Sulfuric Acid (10%) or Sodium Hydroxide (for pH adjustment)
Water for Injections

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

24 months
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 hours at 25°C.

Chemical and physical in-use stability has been demonstrated for 24 hours at 25°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

Do not store above 25°C. Do not refrigerate or freeze. Store in the original package in order to protect from light.
For storage conditions after dilution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

Type I glass ampoules containing 2 ml of solution for injection or infusion.
Gentamicin 10mg/ml solution for Injection or Infusion is supplied in packs of 5 ampoules.

6.6 Special precautions for disposal and other handling

Gentamycin can be diluted with 0.9% sodium chloride or 5% glucose solution.
For single use only
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Pinewood Laboratories Ltd
Ballymacarbry
Clonmel
Co. Tipperary
Ireland

8 MARKETING AUTHORISATION NUMBER

PA0281/242/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 13th March 2015
Date of last renewal: 28th October 2019

10 DATE OF REVISION OF THE TEXT

February 2024