SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Gentamicin 40mg/ml Solution for Injection or Infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

1 ml of solution for injection or infusion contains gentamicin sulfate equivalent to 40 mg gentamicin.

Each ampoule (2ml) contains Gentamicin Sulfate Ph Eur equivalent to 80mg 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 auditory/vestibular 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/I)	(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

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.

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 and laboratory parameters is also recommended.

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

Gentamicin should be used with care in conditions characterised by muscular weakness.

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.

Superinfection

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

Pseudomembranous colitis

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).

Severe subcutaneous adverse reactions (SCARs)

Serious skin reactions including Stevens-Johnson Syndrome (SJS) and toxic epidermal necrolysis (TEN) have been reported in association with gentamicin treatment. Patients should be informed about the signs and symptoms of serious skin manifestations and monitored closely. Treatment should be discontinued at the first appearance of skin rash, mucosal lesions or any other sign of skin hypersensitivity.

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.

4.5 Interaction with other medicinal products and other forms of interaction

Ototoxicity and nephrotoxicity

Concurrent administration of gentamicin and other potentially ototoxic or nephrotoxic drugs should be avoided. Potent diuretics such as etacrynic acid and furosemide are expected 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

Neuromuscular blockade and respiratory paralysis have been reported from administration of aminoglycosides to patients who have received curare-type muscle relaxants during anaesthesia. Concomitant use of gentamicin with drugs with neuromuscular blocking effects, such as botulinum toxin, may increase the risk of toxicity due to enhanced neuromuscular block.

Aminoglycosides such as gentamicin can also act as neuromuscular blockers and may therefore antagonise the effects of neostigmine or pyridostigmine.

The following combinations with gentamicin may require dose adjustment:

- Concomitant use of indomethacin possibly increases plasma concentrations of gentamicin in neonates
- Concomitant use with oral anticoagulants may decrease thrombin levels and increase the risk of bleeding.
- Concomitant use of bisphosphonates with gentamicin may increase the risk of hypocalcaemia

4.6 Fertility, pregnancy and lactation

Pregnancy

There are limited data from the use of aminoglycosides, including gentamicin, in pregnancy.

Gentamicin crosses the placenta, and there is a risk of ototoxicity (vestibulocochlear nerve damage) and/or renal damage in the fetus, as seen in animal studies (see section 5.3). Gentamicin should not be used in pregnancy, except in case of life-threatening situations where expected benefits outweigh possible risks.

In such cases, maternal serum gentamicin concentration monitoring is recommended (see section 4.2). Monitoring of the hearing and renal function of the infants is also recommended.

Breast-feeding

Gentamicin is excreted in human breast milk and was detected in low concentrations in the serum of breast-fed infants, except in cases where the mucous membrane of the infant’s stomach and intestines is severely eroded.

In cases of suspected severe mucosal erosion, if the infant is breast-fed during gentamicin treatment, it is recommended to monitor the serum concentration of gentamicin in the infant (see section 4.2). Animal and human data suggest that if the serum gentamicin concentration in the infant exceeds 1 µg/ml either breast-feeding or the gentamicin therapy may need to be discontinued, under medical supervision.

The following effects of gentamicin on the infant's normal gastrointestinal flora are possible and it is recommended to monitor the infant for possible effects such as diarrhoea, candidiasis and bloody stools.

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

The following CIOMS frequency rating is used, when applicable:
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 (cannot be estimated from the available data).

Infections and infestations:

Not known: antibiotic-associated colitis (including pseudomembranous colitis), superinfection (caused by gentamicin-resistant bacteria)

Blood and lymphatic system disorders:

Not known: anaemia, blood dyscrasias

Immune system disorders:

Not known: hypersensitivity (see section 4.4), anaphylaxis/anaphylactic reaction (including anaphylactic shock)

Metabolism and nutrition disorders:

Not known: hypomagnesaemia on prolonged therapy

Psychiatric disorders:

Not known: depression, hallucinations, confusion

Nervous system disorders:

Not known: central neuropathy (including convulsions, lethargy, encephalopathy), peripheral neuropathy

Ear and labyrinth disorders:

Not known: vestibular damage, transitory hearing loss, irreversible hearing loss, deafness, particularly after exposure to ototoxic drugs or in the presence of renal dysfunction (see section 4.4).

Gastrointestinal disorders:

Very common: vomiting

Not known: stomatitis, nausea

Hepatobiliary disorders:

Not known: abnormal liver function, transaminases increased

Skin and subcutaneous tissue disorders:

Not known: Stevens-Johnson syndrome, toxic epidermal necrosis, rash, purpura, urticaria, pruritus

Renal and urinary disorders:

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

Not known: nephrotoxicity (usually reversible) has been reported.

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 national reporting system, by the Yellow Card Scheme at: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

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 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.

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 of resistance is such that the utility of the agent in at least some types of infections is questionable. Especially in such circumstances, samples should be obtained 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 pneumonia
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 *Staphylococcus aureus,*
MRSA = Methicillin-resistant *Staphylococcus aureus*

Infections caused by Streptococci or Enterococci:
Aminoglycosides are suitable combination partners for other 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 a single daily infusion. When gentamicin is administered by intravenous short infusion of 30 minutes at 4 mg/kg body weight per day in three divided 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 and trough concentrations of 9.5 µg/ml and 0.4 µg/ml were measured.

Therapeutic serum concentrations 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/ml for once daily dosing. Maximum serum concentrations of 10 – 12 µg/ml should not be exceeded when administered conventionally, in several 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 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 distribution of gentamicin to the individual organs results in varying tissue concentrations; the highest concentrations appear in the renal tissue. Smaller concentrations are found in the liver and gall bladder, the lung and spleen.

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

Plasma protein binding: less than 10%.

Biotransformation

Gentamicin is not metabolised in the organism but is excreted unchanged in microbiologically active form.

Elimination

Gentamicin is eliminated unchanged in microbiologically active form principally in the urine 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 younger adults.

5.3 Preclinical safety data

Reproductive and development 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.

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 h at 25ºC.

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

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 25ºC. 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 2ml of solution for injection or infusion.

Gentamicin 40mg/ml solution for Injection or Infusion is supplied in packs of 5 or 10 ampoules.

6.6 Special precautions for disposal

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

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8 MARKETING AUTHORISATION NUMBER(S)

PL 29831/0660

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

14/11/2024

10 DATE OF REVISION OF THE TEXT

14/11/2024