

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Gentamicin 40 mg/ml Injection, vials

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

1 ml of solution for injection contains 40 mg of gentamicin (as sulphate).

1 vial of 2 ml solution for injection contains 80 mg of gentamicin (as sulphate).

Contains approximately 3.6 mg Methyl Hydroxybenzoate per 2 ml vial.

Contains approximately 0.4 mg Propyl Hydroxybenzoate per 2 ml vial.

Contains approximately 6.4 mg Sodium Metabisulphite per 2 ml vial.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for injection (Injection)

Clear, colourless solution.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Gentamicin is indicated for 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

Gentamicin is normally given by the intramuscular route, but can be given intravenously when intramuscular administration is not feasible, e.g. in shocked or severely burned patients. When given intravenously, the prescribed dose should be administered slowly over no less than 3 minutes directly into a vein or into the rubber tubing of giving set. Rapid, direct intravenous administration may give rise, initially, to potentially neurotoxic concentrations and it is essential that the prescribed dose is administered over the recommended period of time. Alternatively the prescribed dose should be dissolved in up to 100 ml of normal saline or 5% glucose in water, but not solutions containing bicarbonate, and the solution infused over a period of less than 20 minutes.

The same dosage schedule is recommended for intramuscular and intravenous dosing. Dosage is related to the severity of infection, the age of the patient and the patient's renal function.

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.

The daily dose in infants after the first month of life is 4.5-7.5 mg/kg body weight per day as 1 (preferred) up to 2 single doses.

The daily dose in newborns is 4-7 mg/kg body weight per day. Due to the longer half-life, newborns are given the required daily dose in 1 single dose.

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

The first dose should be as normal – after this, doses should be given less frequently, the interval being determined by results of renal function tests as below:

| Blood urea mg/100 ml (mmol/l) | Creatinine clearance (GFR) (ml/min) | Dose and frequency of administration |
|---|--|---|
| <40 (6-7) | >70 | 80 mg* 8-hourly |
| 40-100 (6-17) | 30-70 | 80 mg* 12-hourly |
| 100-200 (17-34) | 10-30 | 80 mg* daily |
| >200 (>34) | 5-10 | 80 mg* every 48 hours |
| Twice weekly intermittent haemodialysis | <5 | 80 mg* after dialysis |

*60 mg if body weight <60 kg. Frequency of dosage in hours may also be approximated as serum creatinine (mg%) x eight or in SI units, as serum creatinine ($\mu\text{mol/l}$) divided by 11. If these dosage guides are used, peak serum levels must be measured. Peak levels of gentamicin occur approximately one hour after intra muscular injection and intravenous injection. Trough levels are measured just prior to the next injection. Assay of peak serum levels gives confirmation of adequacy of dosage and also serves to detect levels above 10 mg/l, at which the possibility of ototoxicity should be considered. One hour concentrations of gentamicin should not exceed 10 mg/l (but should reach 4 mg/l), while the pre-dose trough concentration should be less than 2 mg/l.

The same dosage schedule is recommended for intramuscular and intravenous dosing. 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 100 ml.

Peak levels in infants and young children:

Peak serum levels are reached in 1 hour and dosage should be adjusted to achieve levels of more than 4 micrograms/ml, but not exceed 10 micrograms/ml.

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

4.3 Contraindications

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

Myasthenia gravis.

Gentamicin should be used with caution in premature infants because of their renal immaturity, in elderly people and generally in patients with impaired renal function.

Diabetes, auditory vestibular dysfunctions, otitis media, a history of otitis media, previous use of ototoxic drugs and a genetically determined high sensitivity to aminoglycoside induced ototoxicity, are other main factors which may pre-dispose the patients to toxicity.

4.4 Special warnings and precautions for use

Patients being treated with gentamicin should be under close clinical observation because of its potential toxicity.

As with other aminoglycosides toxicity is related to serum concentration. With 6-8 hourly dosing, serum levels more than 10 micrograms/ml may be associated with effects on the vestibular mechanism. Toxicity can be minimised by monitoring serum concentrations and it is advisable to check serum levels to confirm that peak levels (one hour) do not exceed 10 micrograms/ml and that trough levels do not exceed 2 micrograms/ml for twice daily administration of gentamicin and 1 microgram/ml for a once daily dose.

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. Evidence of toxicity requires adjustment of dosage or withdrawal of the drug.

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

In cases of significant obesity gentamicin serum concentrations should be closely monitored and a reduction in dose should be considered.

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 should not be used concurrently with other nephrotoxic or ototoxic drug substances unless considered essential by the physician. Concurrent use of other neurotoxic and/or nephrotoxic drugs can increase the possibility of gentamicin toxicity. Co-administration with the following agents should be avoided.

- Neuromuscular blocking agents such as succinylcholine and tubocurarine.
- Potent diuretics such as ethacrynic acid and furosemide.
- Other aminoglycosides.
- Other potentially nephrotoxic or ototoxic drugs such as methicillin.
- Great caution should be taken when administering cephalosporin antibiotics such as ceftazidime with gentamicin. Co-administration of gentamicin with cephalosporins should be avoided as this combination of drugs can increase the possibility of gentamicin toxicity and increase the nephrotoxic effect of gentamicin.

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).

Exposure to antimicrobial agents is one primary risk factor in the development of *Clostridium difficile* - associated diarrhoea. Though this diarrhoea is more frequently associated with the use of clindamycin, ampicillin and cephalosporins, cases involving prior exposure to combination therapy with gentamicin have also been reported.

Sulphites can cause allergic-type reactions including anaphylactic symptoms and bronchospasm in susceptible people, especially those with a history of asthma or allergy.

This medicinal product contains:

- Sodium metabisulphite, which may rarely cause severe hypersensitivity (allergy) reactions and bronchospasm (difficulty in breathing).
- Methylhydroxybenzoate and propylhydroxybenzoate, which may cause allergic reactions (possibly delayed), and exceptionally, bronchospasm (difficulty in breathing)
- Sodium hydroxide (less than 1 mmol sodium (23 mg) per dose, i.e. essentially 'sodium- free')

The vial stopper contains dry natural rubber (a derivative of latex), which may cause allergic reactions.

4.5 Interaction with other medicinal products and other forms of interactions

(i) Antibacterials: increased risk of nephrotoxicity with *cephalosporins notably cephalothin*.

(ii) Gentamicin has been known to potentiate anticoagulants such as warfarin and phenindione.

- (iii) Antifungals: increased risk of nephrotoxicity with amphotericin.
- (iv) Cholinergics: antagonism of effect of neostigmine and pyridostigmine.
- (v) Ciclosporin, cisplatin: increased risk of nephrotoxicity.
- (vi) Cytotoxics: increased risk of nephrotoxicity and possible risk of ototoxicity with cisplatin.
- (vii) Diuretics: increased risk of ototoxicity with loop diuretics.
- (viii) Muscle relaxants: effect of non-depolarising muscle relaxants such as tubocurarine enhanced. Neuromuscular blockade and respiratory paralysis have been reported from administration of aminoglycosides to patients who have received curare-type muscle relaxants during anaesthesia.
- (ix) Digoxin: Gentamicin has been known to increase serum digoxin levels.
- (x) Indomethacin possibly increases plasma concentrations of gentamicin in neonates.
- (xi) Concurrent use of bisphosphonates may increase the risk of hypocalcaemia.
- (xii) 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

Gentamicin is known to cross the placenta. Ototoxicity in the foetus is also a potential hazard. The benefits should, therefore, be weighed against such hazards to the foetus before using gentamicin during pregnancy. Some animal studies have shown a teratogenic effect. Gentamicin is therefore not recommended in pregnancy unless considered essential by the physician.

Breast-feeding

Small amounts of gentamicin have been reported in breast milk. Because of the potential for serious adverse reactions to an aminoglycoside in nursing infants, a decision should be made whether to discontinue nursing or the drug, taking into account the importance of the drug to the woman. In the absence of gastro-intestinal inflammation, the amount of gentamicin ingested from the milk is unlikely to result in significant blood levels in breast-fed infants.

4.7 Effects on ability to drive and use machines

Not applicable.

4.8 Undesirable effects

Ototoxicity (including neurosensory deafness) and nephrotoxicity (including acute tubular necrosis) are the most common side effects associated with gentamicin therapy. Both effects are related to renal impairment and hence the dosage in such patients should be altered as suggested. In addition, there have been rare reports of changes in electrolyte balance including hypomagnesaemia, hypocalcaemia and hypokalaemia caused by renal tubular dysfunction.

Ear and labyrinth disorders:

Vestibular damage or hearing loss may occur, particularly after exposure to ototoxic drugs or in the presence of renal dysfunction. Frequency Unknown (cannot be estimated from the available data): Irreversible hearing loss, deafness.

Renal and urinary disorders:

Frequency Very rare (< 1/10,000): Acute renal failure. Fanconi-like syndrome in patients treated with a prolonged course of high-dose.

Immune system disorders:

Frequency unknown: Anaphylactic reaction (including anaphylactic shock) and hypersensitivity.

Blood and lymphatic system disorders:

Anaemia, blood dyscrasias, granulocytopenia (reversible).

Nervous system disorders:

Convulsions, central nervous system toxicity (including encephalopathy, confusion, lethargy, mental depression and hallucinations), neuromuscular blockade.

Hepatobiliary disorders:

Hepatic function abnormal.

Metabolism and nutrition disorders:

Hypomagnesaemia (on prolonged therapy).

Infections and infestations:

Combinations of antibiotics containing gentamicin have been associated with rare reports of *Clostridium difficile* diarrhoea.

Frequency unknown: Superinfection (caused by gentamicin-resistant bacteria), Pseudomembranous colitis

Gastrointestinal disorders:

Stomatitis, nausea, vomiting.

Skin and subcutaneous tissue disorders:

Urticaria, allergic contact dermatitis, purpura

Frequency unknown: Steven Johnson syndrome, Toxic epidermal necrosis

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

As in the case of other aminoglycosides, toxicity is associated with serum levels above a critical value. In patients with normal renal function it is unlikely that toxic serum levels (in excess of 10 micrograms/ml) will be reached after administration of recommended doses. Where higher levels occur because of renal impairment, dosage should be reduced. In the event of an overdose or toxic reaction, peritoneal dialysis or haemodialysis will lower serum gentamicin levels. Calcium salts given intravenously have been used to counter the neuromuscular blockade caused by gentamicin.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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, sulphonamides, tetracycline) may be transferred on the same plasmid.

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

5.2 Pharmacokinetic properties

Gentamicin and other aminoglycosides are poorly absorbed from the gastro-intestinal tract but are rapidly absorbed after intramuscular injection. Average peak plasma concentrations of about 4 µg per ml have been obtained 30 to 60 minutes after intramuscular administration of a dose equivalent to 1 mg of gentamicin per kg body-weight although there may be considerable individual variation and higher concentrations in patients with renal failure. Similar concentrations are obtained after intravenous administration. Several doses are required before equilibrium concentrations are obtained in the plasma and this may represent the saturation of binding sites in body tissues such as the kidney. Binding of gentamicin to plasma proteins is usually low.

Following parenteral administration gentamicin and other aminoglycosides diffuse mainly into extracellular fluids and factors which affect the volume of distribution will also affect plasma concentrations.

However, there is little diffusion into the cerebrospinal fluid and even when the meninges are inflamed effective concentrations may not be achieved; diffusion into the eye is also poor. Aminoglycosides diffuse readily into the perilymph of the inner ear. Gentamicin crosses the placenta but only small amounts have been reported in breast milk.

Systemic absorption of gentamicin and other aminoglycosides has been reported after topical use on denuded skin and burns and following instillation into and irrigation of wounds, body-cavities, and joints.

The plasma elimination half-life for gentamicin has been reported to be 2 to 3 hours though it may be considerably longer in neonates and patients with renal impairment. Gentamicin and other aminoglycosides do not appear to be metabolised and are excreted virtually unchanged in the urine by glomerular filtration. At steady-state at least 70% of a dose may be recovered in the urine in 24 hours and urine concentrations in excess of 100 µg per ml may be obtained. However, gentamicin and the other aminoglycosides appear to accumulate in body tissues to some extent, mainly in the kidney, although the relative degree to which this occurs may vary with different aminoglycosides. Release from these sites is slow and aminoglycosides may be detected in the urine for up to 20 days or more after administration ceases. Small amounts of gentamicin appear in the bile.

Paediatric patients – premature infants and neonates

Distribution

The distribution volume of gentamicin is about equivalent to the volume of extracellular water. In the newborn water makes up 70 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. 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 weeks to 0.2 L/h in neonates at a gestational age of 40 weeks.

5.3 Preclinical safety data

There is 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

Sodium metabisulphite, E223
Disodium edetate
Methyl hydroxybenzoate, E218
Propyl hydroxybenzoate, E216
Water for Injections
Sulphuric acid (2.5N) (for pH adjustment)
Sodium hydroxide (2.5N) (for pH adjustment)

6.2 Incompatibilities

Gentamicin Injection should not be mixed with other drugs before injection and where co-administration of penicillins, cephalosporins, erythromycin, lipiphysan, sulphadiazine, furosemide (frusemide) and beta lactam antibiotics and heparin is necessary, the drugs should be administered separately, either as bolus injections into the tubing of the giving set or at separate sites. Addition of gentamicin to solutions containing bicarbonate may lead to the release of carbon dioxide.

6.3 Shelf life

Unopened: 3 years.

6.4 Special precautions for storage

Do not store above 25°C.

Unused portions of opened vials must not be stored and should be discarded immediately.

6.5 Nature and contents of container

80 mg/2 ml - Clear, Type I glass vials in packs of 5 vials.

For single use only. Discard any unused contents.

6.6 Special precautions for disposal

Syringes, vials that are either empty or have remaining solution should be carefully discarded in a thick plastic bag or impervious container, and incinerated.

7 MARKETING AUTHORISATION HOLDER

Pfizer Healthcare Ireland
9 Riverwalk
National Digital Park
Citywest Business Campus
Dublin 24
Ireland

8 MARKETING AUTHORISATION NUMBER

PA0822/203/001

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