



The following information is intended for medical or healthcare professionals only:

Gentamicin 40 mg/ml Injection

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 betalactam 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.

Instructions for use, handling and disposal

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

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

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

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 (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 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.

Contraindications

Hypersensitivity to gentamicin, any other ingredients 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.

PACKAGE LEAFLET: INFORMATION FOR THE USER

Gentamicin 40 mg/ml Injection

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor.

What is in this leaflet:

- What Gentamicin Injection is and what it is used for
- What you need to know before you use Gentamicin Injection
- How to use Gentamicin Injection
- Possible side effects
- How to store Gentamicin Injection
- Contents of the pack and other information

1. WHAT GENTAMICIN INJECTION IS AND WHAT IT IS USED FOR

Gentamicin Injection is an aminoglycoside antibiotic medicine, in the form of a solution for injection (a solution which can be given as an injection).

Gentamicin Injection is used to treat a wide variety of infections such as chest, wound and blood infections.

2. WHAT YOU NEED TO KNOW BEFORE YOU USE GENTAMICIN INJECTION

Do not use Gentamicin Injection

- if you have shown signs of hypersensitivity (severe allergy) to gentamicin or any of the ingredients in this medicine on previous occasions.
- if you suffer from a disorder called myasthenia gravis which is severe weakness of some muscles

Take special care with Gentamicin Injection

- if treating premature babies
- if you are an elderly patient
- if your kidneys are not working properly
- if you have diabetes
- if you have an ear, hearing or balance disorder, a history of ear infections or if you have been treated with medicines that affect hearing in the past
- if you have a disorder which makes your muscles weak
- if you are severely overweight

Other medicines and Gentamicin injection

Take special care with Gentamicin Injection if you are taking certain other medicines, such as:

- antibiotics that also affect your kidneys or hearing, such as other aminoglycosides, cephalosporins (e.g. ceftazidime and cephalothin) and methicillin
- medicines used to thin the blood, such as warfarin and phenindione
- digoxin (a medicine used for certain heart conditions)
- amphotericin (medicine used to treat fungal infections)
- neostigmine and pyridostigmine (medicines used in the treatment of muscle weakness)
- cyclosporin (a medicine that reduces the activity of the body's immune system)
- cisplatin (anti-cancer medicine)
- some diuretics (water tablets), such as ethacrynic acid and furosemide
- muscle relaxants used during general anaesthesia (such as tubocurarine and suxamethonium)
- indomethacin (one of a group of medicines called non-steroidal anti-inflammatory agents used to treat pain and inflammations)
- bisphosphonates (a group of medicines used to treat e.g. osteoporosis)
- Botulinum Toxin (medicine used for the treatment of muscle spasticity, an involuntary flexing of the muscles).

Please tell your doctor if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.

Pregnancy, breast-feeding and fertility

Gentamicin Injection will not normally be used if you are pregnant or breast-feeding.

Driving and using machines

Do not drive if you experience any effect which may impair your ability to drive or use machines.

Important information regarding some of the ingredients of Gentamicin Injection

This medicine 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; this medicinal product contains 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.

3. HOW TO USE GENTAMICIN INJECTION

The dose of medicine given to you will depend on how serious the infection is, your age, body weight and how well your kidneys are working.

The medicine is usually injected into a muscle but may also be injected into a vein in some patients. If it is given into a vein, it can either be given as an injection or diluted and given as a slow injection via a drip (infusion). It will be given daily, with your dose given as one (preferred) or two doses.

As this medicine will be given to you whilst you are in hospital it is unlikely that you will be given too little or too much, however tell you doctor or pharmacist if you have any concerns.

The amount of gentamicin in your blood will be measured regularly to check that the correct blood levels have been achieved. Your doctor will decide, depending on your condition, how long you should receive gentamicin.

Your doctor may carry out blood tests to check your kidney and liver function before, during and after treatment with gentamicin. You may also be asked to take tests to check the drug is not affecting your hearing or balance.

4. POSSIBLE SIDE EFFECTS

Like all medicines Gentamicin Injection can cause side effects, although not everybody gets them.

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

- severe allergic reaction – you may experience a sudden itchy rash (hives), swelling of the hands, feet, ankles, face, lips, mouth or throat (which may cause difficulty in swallowing or breathing), and you may feel you are going to faint.

This is a very serious side effect. You may need urgent medical attention. This very serious side effect is rare.

If you experience any of the following tell your doctor as soon as possible:

- hearing problems (if you have this side-effect your doctor may need to change your dose or give you other treatments)
- feeling or being sick (nausea or vomiting)
- skin rash or development of raised coloured blotches which may be itchy
- purple discolouration under the skin
- fever
- sore throat
- muscle weakness
- diarrhoea
- kidney disease with symptoms such as reduced urine output
- low blood cell counts (red and white blood cells) and further blood abnormalities or disorders (known as blood dyscrasia)
- damage to the brain with signs such as seizures, confusion, lack of interest, depression and hallucinations
- liver problems

Low levels of blood electrolytes, such as calcium, magnesium and potassium have been reported due to effects on kidney function. This side effect is rare.

Your doctor may regularly carry out blood tests to check for changes in your blood cells, electrolytes (such as potassium, calcium and magnesium) in your blood, kidney and liver function and changes in some white blood cells, as well as hearing tests.

If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via

HPRA Pharmacovigilance
Earlsfort Terrace
IRL - Dublin 2
Tel: +353 1 6764971
Fax: +353 1 6762517
Website: www.hpra.ie
e-mail: medsafety@hpra.ie

By reporting side effects you can help provide more information on the safety of this medicine.

5. HOW TO STORE GENTAMICIN INJECTION

Keep out of the sight and reach of children.

Do not use Gentamicin Injection after the expiry date printed on the vial label and carton (after abbreviation e.g. EXP>}. The expiry date refers to the last day of that month.

Do not use this medicine if you notice that the solution is no longer clear and colourless or contains visible particulates. In particular, a slight yellow colouring may indicate that the medicine is not safe for use.

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

For single use only.

The vials should not be stored above 25°C.

6. CONTENTS OF THE PACK AND OTHER INFORMATION

What Gentamicin Injection contains

The active substance is gentamicin sulphate.

Each millilitre (ml) of Gentamicin Injection contains 40 milligrams (mg) of gentamicin (as sulphate)

The other ingredients are sodium metabisulphite (E223), disodium edentate, methyl

hydroxybenzoate, propyl hydroxybenzoate, sulphuric acid, sodium hydroxide and Water for Injections.

Contains preservative.

What Gentamicin Injection looks like and contents of the pack

This medicinal product is a solution for injection. It is a clear, colourless solution.

This medicine is presented in glass containers called vials. It is available in packs containing 5 x 80 mg/2 ml vials.

Marketing Authorisation holder and manufacturer responsible for batch release in the European Union

The marketing authorisation holder and manufacturer responsible for batch release in the European Union is Hospira UK Limited, Horizon, Honey Lane, Hurley, Maidenhead, SL6 6RJ, UK.

The manufacturer is Hospira Australia Pty Ltd, 1-5, 7-23 and 25-39 Lexia Place, MULGRAVE VIC 3170, Australia.

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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.

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.

Interaction with other medicinal products and other forms of interaction

- (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.

Use in 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.

Use in Lactation

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.

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.

Special Precautions for Storage

Do not store above 25°C.

Nature and Contents of Container

For single use only. Discard any unused contents.

Marketing Authorisation Holder

Hospira UK Limited
Horizon, Honey Lane, Hurley, Maidenhead, SL6 6RJ,
United Kingdom

435472

| Component Specification | |
|-------------------------|---|
| Item number: | 435472 |
| Request number: | PAR-2016-0004796 |
| Country: | Ireland |
| Ol template: | 88S078 |
| Amalia version: | 5 |
| Mulgrave version: | 4 |
| Dimensions: | 456 x 200 mm (8 panels) |
| Container(s): | vials (blistered) |
| Supplier: | Howden Printing |
| Stock: | Primapharm 40gsm / Teropaque Thin Medical 40gsm |
| Folded dimensions: | 57 x 100 mm |
| Printed both sides: | Yes |
| Perforated: | No |
| Pharma code: | 6874 - 212122122122 |
| Pharma code length: | 25 mm |
| Mulgrave 4 series no.: | 435472 |
| Colours | |
| Black: | ■ |



Requester

I have checked this artwork against the registered text including spelling, layout, size, colours, registration numbers and scientific equations, the name and address and trademarks. Also for any possible changes to related items.

This artwork is in conformance with the Marketing Authorisation and can now proceed to the printing stage.

Previous Item Number: Q79463 / 434548

Signed:

Date:

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|-----------------|-------------------|
| Technician: BC | Technician: KM |
| Date: 02/Aug/16 | Date: 30/Nov/2016 |
| Version 3 | Version 4 |
| Technician: KM | Technician: XX |
| Date: 15/Feb/17 | Date: dd/mmm/yy |
| Version 5 | Version 6 |
| Technician: XX | Technician: XX |
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| Version 7 | Version 8 |
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