IRISH MEDICINES BOARD ACTS 1995 AND 2006

MEDICINAL PRODUCTS(CONTROL OF PLACING ON THE MARKET)REGULATIONS,2007

(S.I. No.540 of 2007)

PA0437/016/008
Case No: 2045348

The Irish Medicines Board in exercise of the powers conferred on it by the above mentioned Regulations hereby grants to

HOSPIRA UK Ltd

Queensway, **Royal Leamington Spa**, **Warwickshire CV31 3RW**, **United Kingdom**

an authorisation, subject to the provisions of the said Regulations, in respect of the product

GENTAMICIN 40 mg/ml Injection

The particulars of which are set out in Part I and Part II of the attached Schedule. The authorisation is also subject to the general conditions as may be specified in the said Regulations as listed on the reverse of this document.

This authorisation, unless previously revoked, shall continue in force from **20/02/2008** until **19/04/2009**.

Signed on behalf of the Irish Medicines Board this

_____

A person authorised in that behalf by the said Board.

Part II

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Gentamicin 40 mg/ml Injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Gentamicin Sulphate equivalent to gentamicin base 40.0 mg/ml.

For excipients, see 6.1.

3 PHARMACEUTICAL FORM

Solution for Injection

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Gentamicin is indicated in the treatment of serious systemic infections, including those of the central nervous system, due to organisms sensitive to this anti-infective.

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 2 to 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.

Adults*:*
The usual total daily dose is 180-240mg in three divided doses (3mg/kg/day).

Dosage may be increased as required up to a maximum of 5mg/kg/24 hours and the frequency increased to 6 hourly.

In the absence of renal dysfunction, a single daily dose of 160mg may be used in some cases.

Children aged 1 year to 12 years:
The usual total daily dose is 4.5mg/kg in three divided doses.

Children aged 0 to 7 days:
The usual total daily dose is 5mg/kg in two divided doses.

Children aged 7 days to 1 year:
The usual total daily dose is 6mg/kg in two divided doses.

Doses in Patients with Impaired Renal Function:
Dosage is adjusted for patients with renal impairment to minimise the risk of toxicity. 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:

Renal Function Tests:

Dose	Creatinine Clearance (ml/min)	BUN mg/ml	Interval between doses
80 mg	30-70	40-100	12 hrs
	10-30	100-200	24 hrs
	5-10	>200	48 hrs

Serum levels should be monitored daily.

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.

4.3 Contraindications

Use in patients hypersensitive to gentamicin.

Use concurrently with other potentially nephrotoxic or ototoxic drug substances.

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 predispose 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 (one hour before next injection) do not exceed 2 micrograms/ml. Evidence of toxicity requires adjustment of dosage or withdrawal of the drug.

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.

Other potentially nephrotoxic or ototoxic drugs such as cephalosporins and methicillin.

Potent diuretics such as ethacrynic acid and frusemide.

Other aminoglycosides.

4.5 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) Cyclosporin: 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.

4.6 Pregnancy and lactation

Use in Pregnancy
Gentamicin should only be used during pregnancy or lactation if considered essential by the physician.

Use in Lactation
The drug crosses the placenta and it is excreted in small amounts in breast milk.

4.7 Effects on ability to drive and use machines

Not applicable.

4.8 Undesirable effects

Ototoxicity and nephrotoxicity 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.

Other adverse reactions associated with Gentamicin therapy include nausea, vomiting, urticaria, reversible granulocytopenia, allergic contact sensitization and neuromuscular blockade.

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.

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 micrograms/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 micrograms per ml have been obtained 30 to 60 minutes after intramuscular administration of a dose equivalent to 1mg 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 micrograms 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.

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
Disodium edetate
Water for Injections
Sulphuric acid (2.5N)
Sodium hydroxide (2.5N)

6.2 Incompatibilities

Gentamicin injection should not be mixed with other drugs before injection and where co-administration of penicilins, cephalosporins, erythromycin, lipiphysan sulphadiazine, frusemide and betalactam antibiotics and heparin is necessary, the drugs should be administered separately, either as bolus injection into the tubing of the giving set or at separate sites. Gentamicin should not be added to solutions containing bicarbonate as this may lead to the release of carbon dioxide.

6.3 Shelf Life

Prior to first use:	36 months.
In use:	24 hours.

6.4 Special precautions for storage

Prior to first use: Do not store above 25°C.
In use: Following dilution in either normal saline or 5% dextrose in PVC infusion bags, chemical and physical in-use stability has been demonstrated for 7 days at 2-8°C.
However, from a microbiological point of view, 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 and would normally not be longer that 24 hours at 2-8°C, unless dilution has taken place in controlled and validated aseptic conditions.

6.5 Nature and contents of container

A clear Type I glass vial containing 6 ml with a 20mm rubber closure (S63 W44 32/50), aluminium seal and plastic flip off cap. Available in single packs and packs of 5.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

Single use only. Discard any unused contents.

For administration by intravenous infusion the prescribed dose should be dissolved in up to 100ml of normal saline or 5% glucose in water, but not solutions containing bicarbonate.

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

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Queensway
Royal Leamington Spa
Warwickshire
CV31 3RW
UK

8 MARKETING AUTHORISATION NUMBER

PA 437/16/8

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 20 April 2004

10 DATE OF REVISION OF THE TEXT

February 2008