1 TRADE NAME OF THE MEDICINAL PRODUCT
Gentamicin Paediatric 20mg/2ml Solution for Injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each 2ml contains 20mg of Gentamicin as Gentamicin Sulfate

Excipient with known effect:
Contains 1.6mg/ml Sodium Metabisulphite (E223). For the full list of excipients see section 6.1

3 PHARMACEUTICAL FORM
Solution for Injection. Colourless or slightly yellow solution.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications
Gentamicin is a proven bactericidal antibiotic active against a broad spectrum of gram-positive and gram-negative pathogens including Escherichia coli, klebsiella, proteus, pseudomonas aeruginosa and antibiotic resistant strains of staph. aureus. Gentamicin is often active against strains resistant to streptomycin, kanamycin and other unrelated antibiotics.

Consideration should be given to official guidance on the appropriate use of antibacterial agents.

4.2 Posology and method of administration
For paediatric use only.
Gentamicin Paediatric 20mg/2ml Solution for Injection is normally administered intramuscularly but may be given intravenously if required.

If intravenous administration is necessary the normal intramuscular dose should be given as a bolus injection into the tubing of the giving set or directly into the venous system over a period of two or three minutes. Gentamicin should not be given as a slow infusion or mixed with other drugs before use.

With either intramuscular or intravenous administration the following dosage applies.

The daily dose recommended in children with normal renal function, is 3-6mg/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 4.5-7.5mg/kg body weight per day as 1 (preferred) up to 2 single doses.

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

Gentamicin Paediatric Solution for Injection can be expected to give lower serum levels than those found in adults at equivalent dosage per body weight.

In neonates, infants and children, subsequent dosage will often need to be increased to achieve therapeutic serum levels. Peak levels should be measured about one hour after intramuscular or intravenous injection and should reach 4 micrograms/ml, but not exceed 10 micrograms/ml.

Trough levels can be measured just prior to the next injection.

In impaired renal function, the recommended daily dose has to be decreased and adjusted to the renal function. The following table for adults can serve as a guideline to these modified doses:

<table>
<thead>
<tr>
<th>Blood Urea (mg/100ml)</th>
<th>Creatinine Clearance (GFR) (ml/minute)</th>
<th>Dose and frequency of administration</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;40</td>
<td>&gt;70</td>
<td>80mg* 8 hourly</td>
</tr>
<tr>
<td>40-100</td>
<td>30-70</td>
<td>80mg* 12 hourly</td>
</tr>
<tr>
<td>100-200</td>
<td>10-30</td>
<td>80mg* daily</td>
</tr>
<tr>
<td>&gt;200</td>
<td>5-10</td>
<td>80mg* every 48 hours</td>
</tr>
<tr>
<td>Twice-weekly intermittent haemodialysis</td>
<td>&lt;5</td>
<td>80mg* after dialysis</td>
</tr>
</tbody>
</table>

*60mg if bodyweight <60kg 
(80mg=80,000 I.U.)

Route of Administration
For intramuscular or intravenous injection.

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 2µg/ml administering gentamicin twice daily and 1µg/ml for a once daily dose. Please refer to section 4.4

4.3 Contraindications:
Hypersensitivity; myasthenia gravis.

Contains sodium metabisulphite (E223). May rarely cause severe hypersensitivity

4.4 Special warnings and precautions for use
To avoid adverse events, continuous monitoring (before, during and after) of renal function (serum creatinin, creatinin clearance), control of function of vestibule and cochlea as well as hepatic and laboratory parameters is recommended.

Ototoxicity has been recorded following the use of gentamicin. Groups at special risk include patients with impaired renal function, infants and possibly the elderly. Consequently, renal, auditory and vestibular functions should be monitored in these patients and serum levels determined so as to avoid peak concentrations above 10mg/l and troughs above 2mg/l. 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.
Increased monitoring may be necessary in patients with hepatic dysfunction and impaired auditory function as these patients are at increased risk of ototoxicity.

Care should be taken in patients with conditions characterised by muscular weakness Pneumococci and haemolytic streptococci are bacteria which are not susceptible to gentamicin. Gentamicin has been shown to have a broad spectrum of activity and its use is recommended in bacterial infections where urgent, effective and often blind chemotherapy is called for. In cases of significant obesity gentamicin serum concentrations should be closely monitored and a reduction in dose should be considered.

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

4.5 Interaction with other medicinal products and other forms of interaction.

There is evidence that any potential nephro-toxicity of cephalosporins (in particular cephaloridine) may be increased in the presence of gentamicin and monitoring of kidney function is recommended if this combination is used. Gentamicin Paediatric Solution for Injection and bacteriostatic antibiotics may give an antagonistic reaction (e.g. as with chloramphenicol). In the specific case of clindamycin and lincomycin the disadvantage of antagonism may be outweighed by the addition of activity against anaerobic organisms. Gentamicin Paediatric Solution for Injection acts synergistically with penicillins and this combination is particularly useful against enterococci.

Neuromuscular blockade and respiratory paralysis have been reported from administration of aminoglycosides to patients who have received curare-type muscle relaxants during anaesthesia.

Concurrent administration of gentamicin and other potentially ototoxic or nephrotoxic drugs should be avoided. Potent diuretics such as etacrynic acid and furosemide are believed to enhance the risk of otoxicity whilst amphotericin b, cis-platinum and ciclosporin are potential enhancers of nephrotoxicity.

Gentamicin antagonizes the effect of neostigmine and pyridostigmine and there is an increased risk of ototoxicity when loop diuretics are given.

Indometacin possibly increases plasma concentrations of gentamicin in neonates.

Concurrent use with oral anticoagulants may increase the hyporthrombinanaemic effect.

Concurrent use of bisphosphonates may increase the risk of hypocalcaemia.
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
There are no proven cases of intrauterine damage caused by gentamicin. However, in common with most drugs known to cross the placenta, usage in pregnancy should only be considered in life-threatening situations where expected benefits outweigh possible risks. 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
Side-effects include vestibular damage or hearing loss, particularly after exposure to ototoxic drugs or in the presence of renal dysfunction. Nephrotoxicity (usually reversible) and occasionally acute renal failure, hypersensitivity, anaemia, blood dyscrasias, purpura, stomatitis, convulsions and effects on liver function occur occasionally.

Rarely, hypomagnesia on prolonged therapy and antibiotic–associated colitis have been reported.

Nausea, vomiting and rash have also been reported.

Central neurotoxicity, including encephalopathy, confusion, lethargy, mental depression and hallucinations, has been reported in association with gentamicin therapy but this is extremely rare.

4.9 Overdose
Haemodialysis and peritoneal dialysis will aid removal from 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
Gentamicin is an aminoglycoside antibiotic active against a broad spectrum of gram-positive and gram-negative pathogens which include *Escherichia coli*, Klebsiella, Proteus, *Pseudomonas aeruginosa* and antibiotic-resistant strains of *Staph. aureus*. Gentamicin is often active against strains resistant to Streptomycin, Kanamycin and other unrelated antibiotics.

5.2 Pharmacokinetic properties
Gentamicin is rapidly absorbed after intramuscular injection with peak serum concentrations obtained approximately one hour after intramuscular and intravenous administration. These should reach 4 micrograms/ml, and not exceed 10 micrograms/ml.

The plasma elimination half-life for Gentamicin has been reported to be 2 to 3 hours, though it may be longer in neonates and patients with renal impairment.

Gentamicin does not appear to be metabolized and is excreted virtually unchanged in the urine by glomerular filtration.

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 metabolized 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 to 0.2 L/h in neonates at a gestational age of 40 weeks.
5.3 Preclinical safety data
None stated.

6.1 List of Excipients:
Sodium metabisulphite (E223), sodium edetate, sodium citrate, citric acid, water for injection.

6.2 Incompatibilities
The following are incompatible in mixed solution with gentamicin injectables: penicillins, cephalosporins, erythromycin, lipiphysan, heparins, sodium bicarbonate.

6.3 Shelf life
2 years

6.4 Special precautions for storage
Store below 25°C. Protect from light.

6.5 Nature and contents of container
Clear glass ampoules in packs of 5 with 2ml in each ampoule.

6.6 Special precautions for disposal
None given.

7 MARKETING AUTHORISATION HOLDER
Ennogen Pharma Limited
Unit G4,
Riverside Industrial Estate,
Riverside Way,
Dartford
DA1 5BS
UK
8 MARKETING AUTHORISATION NUMBER(S)
PL 40147/0042

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
04/02/2009

10 DATE OF REVISION OF THE TEXT
11/04/2013